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CYTOKINES AND OROFACIAL PAIN

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SUMMARY:

El dolor es una parte integral de la práctica odontológica y médica actual, y siempre es necesario entenderlo para tratarlo de la mejor manera posible.

El dolor puede ser nociceptivo o neuropático; también puede definirse como agudo o crónico, asociado a la inflamación. Para entender el dolor, es necesario comprender la respuesta inflamatoria.

Pueden describirse dos tipos diferentes de dolor orofacial: dolor relacionado con los dientes o dolor no relacionado con los dientes. La odontología se centrará en el dolor orofacial; de hecho, es necesario estudiar los mecanismos y qué proteínas o moléculas están implicadas.

Las citoquinas y el dolor orofacial están estrechamente relacionados con la respuesta inflamatoria.

Las citoquinas son proteínas implicadas en la inflamación que van a intervenir en los lugares de las lesiones, patologías o zonas dolorosas. Ante un estímulo doloroso, tendremos una respuesta inflamatoria. Se han descrito dos tipos de citoquinas, que pueden tener funciones pro o anti-inflamatorias. Trabajan conjuntamente en los focos de la inflamación.

Forman parte de una compleja maquinaria que funciona como un todo en respuesta a la inflamación, el dolor o el daño tisular. Las citoquinas se activan en respuesta a un estímulo y se reclutan y producen en el lugar de la lesión. Su implicación se ha descrito en el trastorno temporo-mandibular, la caries dental, la pulpitis, la artrosis y muchas más patologías orofaciales que producen dolor. Cada tipo de citoquina se reclutará en función de la afectación. Trabajan en equipo. En el caso de una sobreproducción de estas últimas, tendremos una inflamación de larga duración. En esta situación, en lugar de tener las funciones restauradoras habituales, podrían dañar los órganos. Deberían investigarse más a fondo para que sirvan de herramienta diagnóstica y terapéutica.

ABSTRACT

Pain is an integral part of today's dental and medical practice, and there is always a need to understand it to treat it in the best way possible.

Pain can be nociceptive or neuropathic; it can also be defined as acute or chronic, associated with inflammation. In order to understand pain, there is the need to understand the inflammatory response.

Two different orofacial pain types can be described: pain related to teeth or pain unrelated to teeth. The dentistry focus will be on orofacial pain; indeed, it is necessary to study the mechanisms and what proteins or molecules are involved. Cytokines and orofacial pain are closely linked to the inflammatory response.

Cytokines are proteins involved in inflammation that will be intervening at sites of injuries, pathologies, or painful areas. In response to a painful stimulus, we will have an inflammatory response. Two types of cytokines have been described, which can have either have pro- or anti-inflammatory functions. They will work together on inflammation sites.

They are part of a complex machinery that works as a whole in response to inflammation, pain or tissue damage. Cytokines are activated in response to a stimulus and will be recruited and produced at the injury site. Their involvement has been described in Temporo-mandibular disorder, dental caries, pulpitis, osteoarthritis and many more orofacial pathologies producing pain. Each type of cytokine will be recruited depending on the affectation. They work as a team. In the case of an overproduction of the latter, we will have a long-lasting inflammation. In this situation, instead of having the usual restoring functions, they could damage organs. They should be further investigated to serve as a diagnostic and therapeutic tool.

ABREVIATIONS :

High-threshold mechanoreceptors (HTM), Polymodal nociceptors (PMN), Osteoarthritis (OA), Neuropathic orofacial pain (NOP), Temporo-mandibular joint (TMJ), Temporo-mandibular disorder (TMD), Central nervous system (CNS), Peripheral nervous system

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1 Introduction:

This essay will focus on the relationship between cytokines and orofacial pain, particularly how cytokines modulate orofacial pain. In order to explain the link between them, there will be the need to describe and have complete knowledge of each of them separately. With the aim of understanding the relationship between cytokines and orofacial pain, it will be necessary to describe the pain pathways and their origins in order to link them to cytokines.

The acute inflammatory process can be linked to pain, redness, loss of function, swelling and heat. Inflammation is not necessarily acute it can also be silent or also known as chronic. In response to a stimulus, the inflammatory process could take place in different structures of our bodies, for example in cartilage, bone, skin, ligaments, joints, muscle or teeth.

We can encounter different types of pain, being acute, chronic, inflammatory, arthritis, neuropathic and nociceptive that will all be preceded by an inflammation process. (1)

These types of pain may course with allodynia which is caused by a stimulus that in normal condition will not produce pain and hyperalgesia which is a greater sensitivity to pain. One or the other is reversible with the elimination of the painful stimulus. (2)

Orofacial pain is mostly described as having a link to trigeminal nerve injury or with orofacial inflammation. The pain can be either acute or chronic they will produce different pain syndromes like arthritis, fibromyalgia, back and neck pain, migraine. (1) (3)

Pain can be found in different sorts but more specifically as neuropathic pain, nociceptive or inflammatory pain. (4)

Orofacial pain comprises pain triggered in the oral cavity, face, neck, trigeminal nerve, and temporomandibular disorders (TMD), which is the main common orofacial pain. (5)

Disregarding the origin and type of pain the emergence is the inflammatory process, for our system to inform about a potential o real damage and to take any action to solve and cure it.

It will require the intervention of basic mechanism which includes neurons, more specifically type Aδ and group C, action potential, synaptic transmission. (1)(4)

Regarding the type Aδ and C neurons, they are sensory neurons, they are located peripherally and they will respond to a thermal, mechanical, and chemical stimulus. (6)

Cytokines are small proteins that play an important role in pain, inflammatory diseases and also tumor necrosis. They have different forms of actions through receptors to act on the regulation of cell growth, maturation or cell response. (4) Cytokines are produced by different cells of our body that have immune or non-immune activity. We can find them under different names such as chemokines, interleukins (ILs) or interferons (IFNs). (4) Cytokines will have a different response according to the inflammatory stimulus. (4)

Cytokines are based on immune response, which is what this essay will be focusing more specifically on their response to orofacial pain.

We can find cytokines that are mediators of innate immunity:

- TNF-a,
- IL-1,
- IL-10,
- IL-12,
- INF-a

and mediators of adaptive immunity:

- IL-2
- IL-4
- IL-5
- TGF-b
- IL-10

There are also mediators of hematopoiesis (granulocyte, macrophages).

They are defined more commonly as pro-inflammatory or anti-inflammatory cytokines. (7) Cytokines can be differentiated as pro-inflammatory that will induce and enhance the inflammatory response or anti-inflammatory that can diminish inflammation and trigger the healing process. In the pro-inflammatory cytokines, we will find the TFN-a, IL-6 and IL-1b, IL-23, IL-17, IL-2, CCL2 that are associated with hyperalgesia. (3)(5)(8) In the anti-inflammatory we can find the IL-4, IL-10, IL-13. We will take into consideration that some cytokines can be either pro or anti-inflammatory, for example IL-6. (3)(9)(10)

2 Objectives:

The main objective of this essay is:

- To understand the relationship between cytokines and orofacial pain

The secondary objectives are:

- To understand the physiology of orofacial pain.
- To understand the functioning of cytokines.
- To understand why cytokines are important for dental pathology.

In the intention to describe and understand the involvement of cytokines in orofacial pain. This essay will be subdivided into different parts in order to first understand pain itself and to be able to focus and gain knowledge and understanding of orofacial pain. Cytokines need to be described and separated depending on their subgroups, either as pro-inflammatory or anti-inflammatory or the one that combines both functions. We will center our attention on the main cytokines involved in inflammation, pain, tissue regeneration.

As an opening, we will review how cytokines in this day and age are used in orofacial pain management. On account of most of the studies found the experiences were performed on mice or rats, further investigations should apply today's knowledge to a human being.

3 Materials & Methods:

To perform this essay, I based my research on scientific articles, scientific books and formerly conducted studies. I used different websites to find information and studies supporting my subject. Of those websites I searched articles on:

- Cochrane, https://www.cochranelibrary.com
- PubMed, https://pubmed.ncbi.nlm.nih.gov
- Medline, https://www.nlm.nih.gov
- Crai library (UEM), https://web-uem.bibliocrai.universidadeuropea.es/recursos-digitales/bases-de-datos
- Google Scholar, https://scholar.google.com

On different days specific keywords were used in order to educate myself on this precise subject. Keywords chosen were "cytokines and pain", "cytokines", "orofacial pain", "cytokines and orofacial pain", "physiology of pain", "periodontitis", "trigeminal nucleus", "osteoarthritis" (OA), "pulpitis and cytokines". My criteria of exclusion were any articles published before 2005 regarding "physiology of pain", all the other keywords were only selected from 2000 to the present time. As inclusion criteria, the two languages selected were English and French.

Using the keyword "cytokines pain" we found 5,660 results out of which only 3 articles were selected, as inclusion criteria: language French or English and as time laps from 2010 to 2021. While information was gathered from each article, the research was also focused on the

articles used and cited by the authors. Some of the following journals have been distinguished as having a potentially significant outcome for this review: International Journal of Molecular Sciences, Journal of pain research, Journal of Neuroinflammation, Journal of Oral Science, The Journal of Headache and Pain, British Journal of Anesthesia, Progress in Neuro-Psychopharmacology & Biological Psychiatry, The journal Cytokine, International Journal of Oral Science.

4 Discussion

This essay will be divided into several parts to be able to answer our main objective which is: to understand the relationship between cytokines and orofacial pain.

4.1 Pain

4.1.1 Physiology of pain

Pain has been described before by many. It will be perceived as an undesirable feeling coming from physical and psychological response to an injury, for example, bruise, cut, burn, hit, and so on; as an important type of pain for our study nerve injury should be integrated. (11) Physical pain can be divided into two types nociceptive or neuropathic pain. The main purpose of the painful response is to either hinder or stop the damages that are taking place at a certain moment in a very specific part of our bodies, for example when taking our hands off a burning element the pain is produced by the sensation of extreme heat at the level of the hand. (4) Guidelines, definitions and descriptions of pain have been cited by the International Association for the Study of Pain (IASP), used by many references and articles in their descriptions of pain. (4)

Pain can be defined as acute or chronic, it will depend on the stimulus, whether it is continuous or not, on the duration of it, and the intensity. (12) Each and every stimulus will lead to pain perception produced by a painful stimulus that will or will not last in time. (12) We individualized the type of pain more precisely depending on if it is considered as acute or chronic; explaining these differences will be more focused in our case on how orofacial pain is differentiated between those concepts. (13) This means that for example acute pain will be more linked to tooth pain for example caries, pulp inflammation, periodontal disease (except chronic periodontitis). (13) Regarding chronic pain we will do the acknowledgment of muscle pain, muscle dysplasia, Temporo-mandibular disorders TMD, masticatory disorder, nerve injury and neck pain. (13)

Pain in its pathological meaning will be outlined by an extreme response to a low pain threshold to a noxious stimulus and it will be considered as neuropathic or inflammatory pain. (14)

The painful stimulus will gather two specific types of fiber: Aδ fibers and C fibers. They will be activated by nociceptors which remain silent in the absence of a stimulus. (4) The fibers are also established as axons which can be differentiated into myelinated or unmyelinated. (4) The Aδ are myelinated axons expressed as fast-conducting fibers, they will be mobilized by heat and mechanoreceptors. (12) On the other hand C fibers are non-myelinated fibers thus slow-conducting and will have a reduced field to receive painful impulses. (12)(6)

Pain will use different pathways to create a correct interpretation by the nervous system, we will find many receptors for pain. This essay will be focused on nociceptors which are activated by painful stimulus in response to actual or hypothetical harm. (4) Several types of nociceptors can be encountered; there is two main groups which will include other subgroups

of receptors, first the high-threshold mechanoreceptors (HTM) and second the polymodal nociceptors (PMN) which include cytokines.

The PMN will acknowledge any inputs related to tissue-damaging injuries. (11) We can find the nociceptors in the skin, joints and viscera, they will be encountered in fluctuating amounts depending on their location. (12)

Generally pain pathway follows a certain order, the information sent from the epidermis or dermis will transmit through motor neurons the information to the brain and spinal cord, which then will create an adequate response. (4)

The basic mechanisms of pain will include three main events, transduction, transmission and modulation, those three mechanisms will be activated in the presence of a noxious stimulus. (4) In the description of the physiology of pain, we should also describe the types of pain and what they might be associated to. (4) Pain physiology is including many participants as the central nervous system (CNS), peripheral nervous system (PNS), neurons, axons (Group A and C), action potential, synaptic transmission. (4) The CNS and PNS are both included in the machinery of pain. Neurons are the first components that will link and transmit the information to the PNS and CNS. (4) Concerning which neurons, the sensory will receive the information from the skin and tissue and the motor will obtain the response from the brain and create a response. (4)

The axons which are also nerve fibers are the main conducting channel, they will conduct action potentials. (4) The interesting axons in the case of pain are type Aδ for thermal and mechanical nociceptors and Type C for carrying nociceptive information. (4) The action potential will create the synaptic transmission which will allow the release of their content into the neurotransmitters. (4)

Concerning the type of pain nociceptive pain is a response to a potentially harmful stimulus, when activated we will observe the recruitment of Aδ fibers and C fibers. (4) Whereas neuropathic pain is closely related to a nerve injury, which is often related as allodynia. A stimulus provoking pain when it is not supposed to is described as allodynia. (4)
Inflammatory pain can be classified into acute or chronic and it is a natural response to an harmful stimulus so the body can engage a reparative response. (4)(15)

4.1.2 Orofacial pain

Orofacial pain has been defined by many, in different scientific and medical fields. This essay will focus on the definition given by the American Academy of Orofacial Pain (AAOP) they interpret it as "pain conditions that are associated with the hard and soft tissues of the head, face, neck, and all the intraoral structures". (16)
Orofacial pain can be first differentiated as dental-related or non-dental-related. In the case that it is dentally related it can be originated from different conditions: long-term tooth clenching, caries, fracture, demineralization, pulpar, trauma, tooth-wear, periodontal pathologies, pericoronitis, cracked tooth syndrome. (5)(17) In comparison non-dental related could be any pain related to facial muscle including masseter, sternocleidomastoid muscle, temporalis muscle, orbicularis oculi and the buccinator, nerve injury, headache, Temporo-mandibular disorders (TMD), mucosal, sino-nasal, salivary gland disease, idiopathic facial pain, myofascial pain, headache, fibromyalgia. (5)(17)
Neuropathic orofacial pain (NOP) can occur due to many pathologies such as infections that can be from either virus or bacteria, nerve injury, dental pain or disorders including periodontal diseases. (15) NOP can be associated with pathology normally painful or from a non-painful stimulus. (15)

To understand neuropathic pain there is the need to have a further look at the pathway. Neuropathic pain is yet to be fully understand but it is transcribed as stimuli coming from a site of injury or not. (15) The central nervous system plays a key role in neuropathic pain and we will also have increased stimulus at the neuronal level. (5)(17)

TMD pain is the most common and known orofacial pain so far it includes myalgia, muscle pain in the jaw, pain on palpation and can induce reduced mouth opening and headache. (15)(18)

The orofacial muscle pain includes TMD myalgia with jaw muscle pain that is increased by function, pain on palpation, pain referral, restricted mouth opening, and headache. (18)

Orofacial pain can be very limiting in any aspect of the daily habits of people. (18) For example, headache and limit mouth opening or even myalgia will have a real impact on the day-to-day habit. (18) It will have an impact on the psychological, physical, social interaction of the patient, which can also create emotional distress. (18)

Orofacial pain is mostly incapacitating in its chronic form. (18) Chronic is defined as sustained prolonged pain, which can on a long-term basis create depression, fatigue and psychological distress as some of those myalgias can have an ectopic origin. (18) In many studies the fact that women were more inclined to suffer from orofacial pain was supported. (19)

In the description of orofacial pain we should include another specific type of pain also known as atypical odontalgia which is a sub-form of idiopathic orofacial pain that will subsist for a long time, indeed considered as chronic pain. (20) Orofacial pain described as osteoarthritis (OA) is the most common chronic disease of the joint that leads to pain. (21) In this study the interest will be focused on the OA of the Temporo-mandibular joint (TMJ) which is a part of the orofacial area. (21)

Regarding OA of the TMJ, this type of orofacial pain will be highly related to inflammatory and anti-inflammatory cytokines, as its sustained action during its degenerative process it will be producing persistent pain also described as chronic orofacial pain. (21)(22)

Neuropathic orofacial pain (NOP) is considered as a decapacitating pathology, even if the understanding of this pathology is still at the beginning of the process, it has been recently discovered that glial cells were involved in NOP. (15)

Concerning the dental field one of the most frequent painful diseases appearing after the progression of caries into pulpitis, we can also consider periodontitis as painful in its early stages it is described as the inflammation of the tissues we will in the last part of our discussion describe how this pathology can be directly linked to cytokines. (23)

4.2 Cytokines

4.2.1 Cytokine classification

In the human body we will be facing two very important types of cytokines the pro-inflammatory and the anti-inflammatory cytokines. The main purpose of cytokines is to create an equilibrium between their functions in favor of protecting our human body and immune system. Cytokines are described as modulators of immunity and are made up of proteins. Literature has described that they can have either an autocrine, paracrine and endocrine activity in order to maintain the body in equilibrium. (9)(24) The regulation of the expression of cytokines will be done by post-transcriptional mechanisms. (25)

Cytokines are emitted in the body in response to a painful, immune or inflammatory stimulus by neurons, microglia, astrocytes and also T-cells which will trigger a painful stimulus. (26)

In response to this specific stimulus, the cytokines will produce through binding at the

membrane receptor a catabolic or anabolic response, mainly in response to mechanical load. (21)

Cytokines will be activated and will give a response when the body will be in an imbalanced state which can be described as inflammation, pain, injury, joint destruction or overload. (21) Cytokines work as a team depending on the disease or inflammatory process we will have more predominant behavior as pro- or anti-inflammatory cytokines. (27)

Cytokines have pleiotropic and redundancy properties, meaning they can produce different actions on different targets and also different cytokines can have the same effects on a different target. Cytokines possess synergism and antagonism properties, synergism is defined as the combined effect of several cytokines on one target and antagonism in the sense that one cytokine can inhibit the other. (28) Cytokines will bound to the extracellular receptor, those receptors will play a major role in the transduction of signals and immune response. (28) Cytokines regulation is occurring at several levels first at the production level, during the maturation and during cell signaling and bounding to receptors. (29) In the case that we will be facing a disparity between cytokines, it will lead to an excessive inflammatory response. (29)

Cytokines are released through several pathways, through classic secretion, exocytosis, vesicular release. (30) Each cytokine should be studied one by one in order to understand their pathways of secretion by the cells of the immune system. (30) It appears that their production and excretion are directly related to the cell type they are produced by. (30)

4.2.2 Pro-inflammatory or inflammatory cytokines

The pro-inflammatory or also known as inflammatory cytokines are as indicated cytokines of the inflammation. Inflammatory cytokines have a varying effect and result in the immunological and inflammation response of the body. Their excessive production during sustained inflammatory processes could lead to inflammation, fever, tissue destruction, organ function impairment and in some cases death. (14)

In the pro-inflammatory cytokines the ones described by articles and which are interesting for our essay are: IL-1β, TNF-α, IL-6, IL-17 and IL-18. (21)

Pro-inflammatory cytokines	Functions
IL-1β and TNF-α	Pro-inflammatory, will induce proliferation and cell apoptosis. Increase the cartilage degradation and bone resorption. Stimulate other cells to produce more pro-inflammatory cytokines.
IL-6	Involved in the immune system. Regulator of acute phase response and inflammation. Generated from infectious sites. Cytokine production.
IL-17	Role of host defense in infectious disease and promote inflammatory processes. Play a role in some types of arthritis.
IL-18	Role in lupus erythematosus, macrophage activation syndrome, rheumatoid arthritis, Crohn's disease, psoriasis, and graft-versus-host disease.

Table 1: Pro-inflammatory cytokines action (31)(32)

TNF-α presence is observed in most of our body tissues, it is a major pro-inflammatory cytokine expressed in nociceptive conditions. (33)(21)(34) TNF-α will create sensitization of the neurons in close relation to the trigeminal ganglion. (33)(21)(34) TNF-α cytokines are

discharged by monocytes, macrophages, eosinophils, glial cells, neurons, myocytes; they will then produce allodynia and have a direct impact on muscles. (24)

IL-1 are pro-inflammatory cytokines emitted by monocytes, macrophages, non-immune-cells and will give rise to hyperalgesia and sensitization. (24)

IL-6 are considered as both pro-inflammatory and anti-inflammatory cytokines which are engendered by monocytes, macrophages, eosinophils, glial cells, myocytes. (24) IL-6 will trigger a powerful inflammatory reaction and also hyperalgesia in the orofacial area and muscles of the head and neck. (24)

IL-1β cytokines are most described in scientific literature it is formed of 269 amino acids and it will be creating a cytosolic precursor protein. (21)(35) IL-1β cytokines have a pleiotropic action, in other terms in its cascade can produce a different mechanism of action than the one it is specifically known for. (21) Therefore it is described as having many regulatory effects on sleep, temperature and homeostasis. (21)(35)

It should be taken into account that one of the most important cytokines is IL-6, known to be depending on its sub-group either pro-or anti-inflammatory cytokine. (10) Cytokine IL-6 will indeed play a role in inflammation, infection but also will have a purpose in metabolic regulation, regenerative and neural processes. (10) Cytokines IL-6 have an important role in the following type of pain: neuropathic pain, pain from nerve injury, nociceptive and they also play a role in allodynia and hyperalgesia. (14)

4.2.3 Anti-inflammatory cytokines

Anti-inflammatory cytokines have the capacity to control and regulate the response of the pro-inflammatory cytokines, they are considered immunoregulatory. (9) They indeed have a role in the immune response of the human body inhibiting the synthesis of pro-inflammatory cytokines. (9)(21) In the anti-inflammatory cytokines we can find the interleukin IL-1 receptor antagonist, IL-4, IL-6, IL-10, IL-11and IL-13. (9)(21) Their fundamental role is to limit any excessive inflammatory process that could, in the end, result in a tissue injury caused by the sustained action of the pro-inflammatory cytokines. (9) They have the function to regulate the pro-inflammatory response but they also can enhance their anti-inflammatory response. (34)

Anti-inflammatory cytokines	Functions
IL-4	Inhibitory effect on the expression and release of pro-inflammatory cytokines. Able to block or suppress IL-1, TNF-α, IL-6, IL-8 and other inflammatory proteins. Role in fertility and pregnancy
IL-6	It will decrease the pro-inflammatory cytokines IL-1 and TNF. Involved in the immune and regenerative system.
IL-10	Role in fertility and pregnancy, immune suppression, play a role in uncontrolled inflammation.
IL-11	Role in airway diseases
IL-13	Role in airway diseases, regulation of cell-mediated immunity.

Table 2: Anti-inflammatory cytokines actions (9)

The anti-inflammatory cytokines will work as a helper of the virus or bacteria to hide and escape from the clearance work of the body. (9) In the case of a higher than the normal number of anti-cytokines present at the site we were to see a profuse inflammation. (9) An

intense inflammation will engender an unbalance in the body hemostasis and then the body will not be able to wash away the virus or bacteria. (9)

Regarding the main anti-cytokines, IL-4 is made of 129 amino-acids, their production and apparition at the site of the injury will be traduced by a protective mechanism. (21)

4.3 The role of cytokines in orofacial pain

This essay describes how cytokines have a role in the day-to-day pathologies and pain felt in the orofacial area, which is important for us dentists to understand as it is the area we are focused on.

Further investigation will be necessary as the function and mechanism of cytokines are still considered as highly complex as it is taking part in a bigger response of our body involving glial, immune and neuronal activity.

Regarding the pro-inflammatory cytokines IL-1β they are described as having a role inducing painful feelings and also inflammatory and immune implication. (35) IL-1β action is mainly understood as intra-cellular signal protein, one of its principal activity will be as pro-nociceptive mediator inducing painful response. (35) IL-1β has an important role in pain induction, acute pain, the maintenance of chronic pain for example in nerve injuries. (35) As described previously, cytokine IL-1β is not only present in the PNS but also found in the CNS. (35) It has been detailed that it can also be acting in any stage of the regulation of the inflammatory response either augmenting it or reducing it. (35) IL-1β will operate on the neuronal and non-neuronal cellular circuit of pain creating more neuronal excitability and persistent pain. (35) It will subsequently create hyperalgesia and central sensitization which will explain painful and inflammatory reactions in the body. (35)

There is a relationship between the immune and the nervous system that will impact the maintenance or disappearance of neuropathic pain and pro-inflammatory cytokines. (35)
The clinical field has described the role of cytokines in inflammation that to some extent can lead to pain and other disorders generating pain. (21) In the interesting case of the joint pathology of the TMJ it can be described as OA. (21) OA is considered as a syndrome that will induce chronic orofacial pain, located in the TMJ area. In the case of the orofacial area during the transmission of the signals, they will be activation of IL-1β, TNF-α, IL-6, IL-15, IL-17 and IL-18 which are part of the pro-inflammatory cytokines. (21) These cytokines will have an impact on the extra-cellular pathway including the binding of the cytokines and at the same time it will recruit the necessary molecules regarding inflammation. (21) In further description of OA and cytokines correlation it has been observed that during the inflammatory process the chondrocytes, synovial and inflammatory cells of the Temporo-mandibular joint (TMJ) will in response produce TNF-α in the early onset of the inflammation. (22) The inflammatory process will activate nociceptors for induction of TMJ pain and in the case that it is not controlled could lead to tissue damage. (22)
Painful signaling in the orofacial area will, in many occasions, come from the trigeminal nucleus which is highly related to the trigeminal nerve. (22) The inflammatory process of the TMJ in the case of OA will create a neuropathic sensitization which in its pathways will recruit pro-inflammatory cytokines. (22) It has been described that more than one cytokine is present during the inflammation process, they work as a team. (21) IL-1β involvement in OA will act as a blockage in the restorative process of hemostasis in the joint because of the autocrine capacity it will in a cascade manner recruit further pro-inflammatory cytokines such as TNF-α, IL-6, IL-18. (21)

Cytokines present in our body are not necessarily active at any given time, but they are available, they are recruited when a painful stimulus occurs. (36) It is possible that they will be recruited in a higher number the longer the painful stimulus is present in the body. (36) Their recruitment will depend on the neuronal sensitization, and their specific threshold. (36) Is our body sensitive to pain only when it is alert and awake or is it susceptible to weaken up in the middle of the night by a throbbing pain? The answer is yes. Many have been woken up by a toothache or other type of orofacial pain because our body is in permanent functioning trying to stay in an equilibrium state. (17) Sleep is known as a recovery period for the human body. This is the reason why when lacking sleep the body is more sensitive to exterior stimulus, it will decrease the efficiency of our immune system directly related to cytokines (TNF-α, IL-6, IL-5, IL-1β). (17) There is a direct impact of sleep on immunity and vice versa, lack of sleep will alter cytokine levels, as an inflammatory response to pain will impair sleep. (17) Further findings should demonstrate the precise role of cytokines on sleep. (17) The relationship between cytokines and the nociceptors will lead to an over-production of IL-1β and indeed create hypersensitivity and increase production of other cytokines during a painful long-lasting stimulus. (17) The more severe the chronic orofacial pain pathology the higher the cytokines levels will be in the body, in response to this long-lasting well situated painful stimulus. (17) The higher the cytokines levels, the more important the sleep disturbance will be. (17)

As described by investigators, to understand the relationship between orofacial pain and cytokines, we need to follow the pathways the pain activation will go along with. It is observed that a painful stimulus will include the action of neurons and glial cells. The route of transmission will be based on the equilibrium between the excitatory and inhibitory actions of the neurons. (4)(15)

Describing orofacial pathology we can focus on nerve damage first. Schwann cells are responsible for the release in the body of cytokines, and more specifically TNF-α, IL-6, IL-15. (15) Cytokines have a role in increasing neuronal excitability in their inflammatory response to painful stimulus as it is oral or coming from other parts in the human body. (15)
In all the orofacial pain model described in the first part we are now going to center our attention on neuropathic pain. (15) Neuropathic pain is considered as a chronic type of pain that will at the site of the injury recruit cytokines IL-1β, TNF-α. (15)
It has been highlighted that allodynia and hyperalgesia are mechanisms involving sensory neurons that will lead to the inflammatory process and then a recruiting of cytokines in their proceeding. (34) In some cases of inflammation, it will be observed that anti-inflammatory cytokines will not have a reversing effect on the activity of pro-inflammatory cytokines recruited at the site of the injury but instead will be magnifying their action. (34)
The immune response is highly related to pro-inflammatory and anti-inflammatory cytokines. (9) In the case of extreme and lasting injuries, the pathogens have learned to adapt in order to use our immune response to their advantage. The process of anti-cytokines will create alterations in the cytokines chain of action, which is particularly relevant in chronic orofacial pain. In the case that it is misdiagnosed the therapeutic therapy will not produce the expected response. (9)
Recent studies have established the relationship between pathological pain which includes neuropathic pain, allodynia, hyperalgesia and inflammatory pain. (14) Inflammatory cytokine IL-6, which plays an important role as a regulator in our body regarding pain. (14)
In the TMD we need also to include masticatory myofascial pain, as it is related to neuromuscular function which is directly correlated to cytokines that will do the junction between the immune and nervous system. (24)

Describing orofacial pain and cytokines relationship there is the need to observe the pathway and signal produced in painful situation. (24) When located in the orofacial region, it will involve the trigeminal ganglion which will transmit the sensory painful information to the central nervous system. (24)

Pro-inflammatory and anti-inflammatory cytokines work in tandem while occurring pain or inflammation. The pro-inflammatory cytokines will be in charge of transmission of pain and inflammation. (24) The anti-inflammatory cytokines will enter into action to restore the normal function and repair damaged tissue; the level of cytokines will depend on the implication required depending on the injury. (24)

Orofacial pain, as described in the first part of our discussion, is closely related to allodynia and hyperalgesia; lateral facial skin will produce allodynia. (52) The pathway followed by the allodynia process is integrating. Microglia will express cytokines IL-1b; and is induced in another part of the body -in this case, inflammation of the trapezius muscle; thus is understood as an ectopic pain. (52) Microglia activation will recruit pro-inflammatory cytokines that directly coincide what pain pathologies. (52) Orofacial pain is emerging from inflammatory pain more often located in areas of the face, head and neck. (52)

Concerning orofacial pain headache is the most common orofacial pain encountered in society nowadays. (37) It has been recently linked that some diseases like the SARS-CoV-2 will have a relation with the trigeminal nerve ending that will directly recruit more pro-inflammatory cytokines, at the painful site. (37) There is also a direct link to fever-induced pain as we know, when fever is present it will recruit pro-inflammatory cytokines in its course of action. (37)

When describing the actions of IL-6 cytokines, it has been observed that it plays many roles, for example in our immune system but also as a regenerative agent in bone hemostasis.

However, the important case of our study is the neural function. The strong implication of IL-6 in inflammation and chronic pain makes it a marker of pain and should be studied as a source of possible therapy. (10) Chronic pain also defined by neuropathic pain is a process produced by lesions in the nervous system, it is observed in many patients presenting or not any other pathology. (14) IL-6 will play a major role in this type of pain as it is a peripheral nerve injury and IL-6 is directly recruited for this kind of lesions. (14) IL-6 are recruited in periodontal disease, oral mucosal inflammation, gingivitis, periodontitis, pulpitis, oral Lichen planus. (38) Considering inflammatory pain associated with hyperalgesia and distinguished by the sensitization of our nociceptive neurons. It has been discovered that we will have recruitment of cytokines, and more specifically IL-1β, TNF-α and IL-6. This supports the relationship between cytokines and orofacial pain. (14) In further studies regarding neuropathic pain the trigeminal ganglia involvement should be put under the light, it has been demonstrated that the closest to the inflammatory process the higher levels of IL-10 will be encountered. (39) It has also been described that trigeminal neuropathic pain will decrease the threshold for pain in the orofacial area, it has been then linked that neuropathic pain will produce an increase of cytokines present in the body. (39)

Maintaining our attention on the trigeminal nerve possible pathologies we will now focus on trigeminal neuralgia and the involvement in hemifacial spasm. This pathology will produce painful stimuli in the orofacial area. (40) Cytokines have been studied for their association long-lasting pain in the neural system. (40)It has been described that their inflammatory action is capable of inducing a painful sensation, but depending on their action could also induce analgesia. (40) The production of the opposite effect is the pleiotropic characteristic of cytokines. (28) The increase of the presence of cytokines concerning trigeminal neuralgia has

been associated more specifically to IL- 1β, IL-6, IL-8 and TNF-α with a higher predominance for IL-6. (40)

The cytokines are complex inflammatory actors, to further understand why they would be pro- or anti-inflammatory, the activating signal, the nature of the produced cytokines, the timing, their sequence of actions should be taken into consideration. (41)

In today's practice the most predominant pathology seen is dental caries. Dental caries is an inflammatory disease with a multifactorial etiology, it is produced by an unbalance between pathological and protective factors. (42)

Pathological factors are bacteria, reduced salivary function and protective factors are proteins, fluoride, calcium. (42) The evolution of dental caries caused by bacteria will induce the innate and adaptive immune response. (42) During the immune response there will be the release of cytokines IL-6, IL-4, IL-1β, TNF-α. (42)

Cytokines will produce a positive effect on the dental tissue. The fact that cytokines have restoring effects can make us believe that in some situations they will produce a restoration of the balance after an injury or bacterial invasion. (43)(42)

Centering the last part of our discussion on the real impact and relationship between dental orofacial pain and cytokines. (23) The most common dental pathology is dental caries, it has been seen that it can lead to pulpitis in some cases depending on the extent. Dental caries is an inflammatory disease induced by bacteria. (42) Dental pathology shows similar patterns of pro-inflammatory cytokine activation. (44) Dental caries will show a significant increase in IL-1β, IL-2, IL-4 and IL-6 compared to healthy teeth. (44)

Pulpitis is known as one of the most predominant dental diseases that will require an emergency visit to the dentist due to the intensity of the pain. (23)(16) The apparition of

pulpitis is directly related to a site of infection of the host. (23)(16) The infection will indeed result in the production of an inflammatory process triggered by both pain and the immune response of the host. (23)(16)

Regarding some of the latest findings, the inflammatory cytokines involved in pulp diseases such as pulpitis, play a role at the starting point of the inflammatory process triggered by the bacterial invasion of the pulp tissue. (23) Bacterial invasion can also in the case of pulpitis produce inflammation and tissue damage. Nonetheless, they produce a protective immune response for the host. Regarding the most prevalent cytokines acting in the case of pulpitis the presence of IL-1, IL-6, IL-2 IL-1β, IL-8 was recorded. (23) In this case, IL-1 is observed only in inflamed pulps as IL-2 and IL-6 are seen in both healthy and inflamed pulps. (23)

TNF-α is upregulated in the patient who had caries that lead to pulpitis, they are secreted by odontoblasts. (45) The cytokines expression could help in the diagnosis of certain dental diseases through their salivary biomarkers. (23)(45)

Nevertheless, we can find other pathologies in the oral cavity such as periodontal diseases. Periodontal disease includes gingivitis and periodontitis, one or the other is related to inflammation of oral tissues. (46)

In the case of gingivitis which is the inflammation of the gingiva, this will result in an inflammatory response. (42) In the case of this response being amplified it can lead to the destruction of periodontal tissues or periodontitis. (42)

Periodontitis is an unresolved chronic inflammation of the periodontal tissues. (44)

More specifically chronic periodontitis is an inflammatory disease that will include many orofacial structures, such as periodontal ligament, gingiva, cementum, and alveolar bone. (47)(48) The pain expressed while the inflammatory process is taking place is what will in the

purpose of this essay explain the link between orofacial pain and cytokines which are the main parts of the inflammatory response. (47)(48) In a patient suffering from periodontitis IL-1, TNF-α, IL-6 will be detected in their pro-inflammatory forms and will in their action recruit IL-10 in the long-lasting inflammatory period. (48) Chronic periodontitis is distinguished by an unbalanced action of the inflammatory cytokines in both innate immunity and acquired immunity facing this disease. (48) The anti-inflammatory cytokines involved are IL-35, IL-10 and IL-12. (48)(49) They will have a preservative function and will have a prominent imbalance with pro-inflammatory cytokines in the specific case of pro-inflammatory cytokines. (49)

Lastly in our quest to restore masticatory function with implants, the dentist can be confronted to peri-implantitis which is not necessarily defining an implant failure. (50) Peri-implantitis is any infection along its course will produce inflammatory response and pain. (50) Similarities between periodontal diseases and peri-implantitis have been acknowledged as they will both induce an immune response from the host. (50) The painful feeling that peri-implantitis will induce can be associated with inflammation of the surrounding soft tissues. (51) The inflammatory process could create bone destruction when it is maintained for a long period of time. (51) During the inflammatory response to peri-implantitis, cytokines will have a damaging action of those we can encounter TNF-α as the most present, IL-4, IL-10, IL-12. (50)(51) Their presence will depend on the inflammatory stage of the disease, it is supposed that after removal of the causing agent their level will return to normal in their dormant situation. (50)(51) During the prolonged action of TNF-α, IL- 1β, IL-6, the more nociceptors will be sensitized the longer the painful stimulus and pain sensation around the implant will last. (51) The study conducted by Tariq Abduljabbar and collaborators in 2013 has reflected that it has been found before by other scientists that cytokines and the pain described by the

patient as it is symptomatic or not will boost the presence of cytokines in the salivary medium. (51) Indeed they found elevated levels in the case of injury as if it is mucosa-related or bone-related, even nerve damage can be involved. (51) This study is self-limiting because the cytokines salivary levels will depend on more factors than just the pain experienced by the patient in response to an inflammatory process. (51) The need for further investigation regarding how cytokines are expressed depending on the pain felt by the patient remains a field that needs to be further understood and discovered. (51) Nevertheless, the study concluded that the cytokines TNF-α, IL- 1β, IL-6 were encountered in significantly higher levels in a patient presenting peri-implantitis than the patient considered having a healthy implant healing. (51)

It has been understood before in this essay that dental pain like pulp pathologies pain is not always described in the exact area as it can be diffused, this is why ectopic pain should be considered as an important part of inflammatory processes. (52) Microglia is the main producer of pro-inflammatory cytokines TNF-α, IL- 1β, IL-6 most common inflammatory cytokines understood and studied so far. (52) It is concluded that there is a positive relationship between orofacial pain as it is ectopic or localized and the painful process producing an inflammatory response of the cytokines by the microglia. (52)

5 Conclusion

Cytokines are closely related to the immune response of the body and also to the inflammatory response as they can induce or stop it. The understanding of orofacial pain needs to rely on the understanding of the pain pathway which includes the first stimulus, glia, neurons, cytokines considered as regulating factors of immunity because all of them will be described in the orofacial pain disorders and functioning. (15) We can link orofacial pain and cytokines as they are proteins that will be recruited at the site of the injury. (15)

To this day, the understanding of the relationship between orofacial pain and cytokines is still unsolved. Because orofacial pain can be very debilitating, we need further investigation to be able to help the population. It has been discovered in the past years that pain was related closely to the inflammatory process this is why we need a further investigation that will give an understanding of this relationship and how it could be developed and used by Science in order to decrease the pain in the patient suffering from orofacial pain. (53)

6 Limitations & future perspectives:

It was observed along with this work of investigation that writing articles with proper study of data were time and money-consuming. In the case of this essay, the limitations were the impossibility of animal study and founding. Studies on animals need to respect the guidelines of the health institutes of the country concerned. In order to properly realized any study on animals on humans, it would require a time-lapse of at least 12 months. Cytokines have a broad way of acting in the body and it will be interesting to study them further in their action for the management of chronic pain. Cytokines could in the future be used as a diagnostic tool in the evolution of dental pathologies.

Cytokines as receptors from anti-inflammatory pain medication should be considered in the future in order to reduce the opioid intake in the population and then it could in this way decrease addiction to opioids that is more and more frequent nowadays. (24)

The option of therapeutic blockage of IL-6 is included in the response to chronic pain. Chronic pain is for many patients a day to day suffering, and in order to alleviate their pain, the blockage of IL-6 agents should be explored. (10)

7 RESPONSIBILITY

This bibliographic review gave me a broader view on orofacial pain and all the characteristics and regions it includes, it was eye-opening on the fact that orofacial pain should not be only considered as dental pain. In the future, I will be able to diagnose orofacial pain and have the necessary knowledge to send my patients to the proper specialist that will guide them towards healing. Reading the latest reviews was vital to understand how much more we still have to discover about the functioning of the human body, and how pain management can be improved. I hope that in the future I will be able to prescribe cytokine therapy medications to my patients as a replacement for opioids in the treatment of pain.

8 References

1. Omoigui S. The biochemical origin of pain: The origin of all pain is inflammation and the inflammatory response. Part 2 of 3 - Inflammatory profile of pain syndromes. Med Hypotheses. 2007;69(6):1169–78.
2. Dinakar P, Stillman AM. Pathogenesis of Pain. Semin Pediatr Neurol [Internet]. 2016;23(3):201–8. Available from: http://dx.doi.org/10.1016/j.spen.2016.10.003
3. Shinoda M, Kubo A, Hayashi Y, Iwata K. Peripheral and Central Mechanisms of Persistent Orofacial Pain. Front Neurosci. 2019;13(November):1–10.
4. Yam MF, Loh YC, Tan CS, Adam SK, Manan NA, Basir R. General pathways of pain sensation and the major neurotransmitters involved in pain regulation. Int J Mol Sci. 2018;19(8).
5. Louca Jounger S, Christidis N, Svensson P, List T, Ernberg M. Increased levels of intramuscular cytokines in patients with jaw muscle pain. J Headache Pain. 2017;18(1).
6. MD CEA, Andrew Dubin MD M, Julie G. Pilitsis MD P. Pain Management Secrets FOURTH EDITION. 2018;
7. Ramani T, S.Auletta C, Weinstock D, Mounho-Zamora B, C. Ryan P, W.Salcedo T, et al. Cytokines: The Good, the Bad and the Deadly. Int J Toxicol. 2015;34(4).
8. Shinoda M, Hayashi Y, Kubo A, Iwata K. Pathophysiological mechanisms of persistent orofacial pain. J Oral Sci. 2020;62(2):131–5.
9. Opal SM, DePalo VA. Anti-inflammatory cytokines. Chest [Internet]. 2000;117(4):1162–72. Available from: http://dx.doi.org/10.1378/chest.117.4.1162
10. Scheller J, Chalaris A, Schmidt-Arras D, Rose-John S. The pro- and anti-inflammatory properties of the cytokine interleukin-6. Biochim Biophys Acta - Mol Cell Res. 2011;1813(5):878–88.

11. Steeds CE. The anatomy and physiology of pain. Surgery [Internet]. 2016;34(2):55–9. Available from: http://dx.doi.org/10.1016/j.mpsur.2015.11.005

12. Voscopoulos C, Lema M. When does acute pain become chronic? Br J Anaesth. 2010;105:i69–85.

13. Häggman-Henrikson B, Liv P, Ilgunas A, Visscher CM, Lobbezoo F, Durham J, et al. Increasing gender differences in the prevalence and chronification of orofacial pain in the population. Pain. 2020;161(8):1768–75.

14. Zhou YQ, Liu Z, Liu ZH, Chen SP, Li M, Shahveranov A, et al. Interleukin-6: An emerging regulator of pathological pain. J Neuroinflammation [Internet]. 2016;13(1):1–9. Available from: http://dx.doi.org/10.1186/s12974-016-0607-6

15. Hossain MZ, Unno S, Ando H, Masuda Y, Kitagawa J. Neuron-Glia crosstalk and neuropathic pain: Involvement in the modulation of motor activity in the Orofacial region. Int J Mol Sci. 2017;18(10).

16. Fan W, Zhu X, He Y, Li H, Gu W, Huang F, et al. Peripheral sympathetic mechanisms in orofacial pain. J Pain Res. 2018;11:2425–31.

17. Park J, Chung J. Inflammatory Cytokines and Sleep Disturbance in Patients with Temporomandibular Disorders. J Oral Facial Pain Headache. 2016;30(1):27–33.

18. Boggero I, Rojas-Ramirez M, de Leeuw R, Carlson C. Satisfaction with Life in Orofacial Pain Disorders: Associations and Theoretical Implications. J Oral Facial Pain Headache. 2016;30(2):99–106.

19. Honda Y, Handa T, Fukuda K ichi, Koukita Y, Ichinohe T. Comparison of risk factors in patients with acute and chronic orofacial pain. Anesth Prog. 2018;65(3):162–7.

20. Baad-Hansen L, Benoliel R. Neuropathic orofacial pain: Facts and fiction. Cephalalgia. 2017;37(7):670–9.

21. Wojdasiewicz P, Poniatowski ŁA, Szukiewicz D. The role of inflammatory and anti-inflammatory cytokines in the pathogenesis of osteoarthritis. Mediators Inflamm. 2014;2014.

22. Sperry MM, Kartha S, Winkelstein BA, Granquist EJ. Experimental Methods to Inform Diagnostic Approaches for Painful TMJ Osteoarthritis. J Dent Res. 2019;98(4):388–97.

23. Khorasani MMY, Hassanshahi G, Brodzikowska A, Khorramdelazad H. Role(s) of cytokines in pulpitis: Latest evidence and therapeutic approaches. Cytokine [Internet]. 2020;126(October 2019):154896. Available from: https://doi.org/10.1016/j.cyto.2019.154896

24. Ayoub S, Berbéri A, Fayyad-Kazan M. Cytokines, Masticatory Muscle Inflammation, and Pain: an Update. J Mol Neurosci. 2020;70(5):790–5.

25. Bak RO, Mikkelsen JG. Regulation of cytokines by small RNAs during skin inflammation. J Biomed Sci. 2010;17:53:1–19.

26. Clark AK, Old EA, Malcangio M. Neuropathic pain and cytokines: Current perspectives. J Pain Res. 2013;6:803–14.

27. Chen Z, Bozec A, Ramming A, Schett G. Anti-inflammatory and immune-regulatory cytokines in rheumatoid arthritis. Nat Rev Rheumatol [Internet]. 2019;15(1):9–17. Available from: http://dx.doi.org/10.1038/s41584-018-0109-2

28. Liu Y, Soumelis V, Ito T, Wang Y, Malefyt RDW, Omori M, et al. TSLP : An Epithelial Cell Cytokine that Regulates T Cell Differentiation by Conditioning Dendritic Cell Maturation. Annu Rev Immunol. 2007;

29. Palomo J, Dietrich D, Martin P, Palmer G, Gabay C. The interleukin (IL)-1 cytokine family - Balance between agonists and antagonists in inflammatory diseases. Cytokine [Internet]. 2015;76(1):25–37. Available from:

http://dx.doi.org/10.1016/j.cyto.2015.06.017

30. Stanley AC, Lacy P. Pathways for cytokine secretion. Physiology. 2010;25(4):218–29.

31. Tanaka T, Narazaki M, Kishimoto T. IL-6 in Inflammation, Immunity, and Disease. 2014;6(Kishimoto 1989):1–16.

32. Onishi RM, Gaffen SL. Interleukin-17 and its target genes: Mechanisms of interleukin-17 function in disease. Immunology. 2010;129(3):311–21.

33. Rachel E Miller, Miller RJ, Malfait A-M. OSTEOARTHRITIS JOINT PAIN: THE CYTOKINE CONNECTION. Cytokine [Internet]. 2014;70(2):185–93. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3624763/pdf/nihms412728.pdf

34. Basu P, Hornung RS, Averitt DL, Maier C. Euphorbia bicolor (Euphorbiaceae) latex extract reduces inflammatory cytokines and oxidative stress in a rat model of orofacial pain. Oxid Med Cell Longev. 2019;2019.

35. Ren K, Torres R. Role of interleukin-1β during pain and inflammation. Brain Res Rev [Internet]. :57–64. Available from: http://dx.doi.org/10.1016/j.earlhumdev.2015.09.003%5Cnhttp://dx.doi.org/10.1016/j.earlhumdev.2014.01.002%5Cnhttp://dx.doi.org/10.1016/S0378-3782(12)70006-3%5Cnhttp://www.sciencedirect.com/science/article/pii/S2341287914000763%5Cnhttp://dx.doi.org/10.1016/

36. Afroz S, Arakaki R, Iwasa T, Oshima M, Hosoki M, Inoue M, et al. CGRP induces differential regulation of cytokines from satellite glial cells in trigeminal ganglia and orofacial nociception. Int J Mol Sci. 2019;20(3).

37. Bolay H, Gül A, Baykan B. COVID-19 is a Real Headache! Headache. 2020;60(7):1415–21.

38. Nibali L, Fedele S, D'Aiuto F, Donos N. Interleukin-6 in oral diseases: A review. Oral

Dis. 2012;18(3):236–43.

39. Iwasa T, Afroz S, Inoue M, Arakaki R, Oshima M, Raju R, et al. IL-10 and CXCL2 in trigeminal ganglia in neuropathic pain. Neurosci Lett [Internet]. 2019;703(December 2018):132–8. Available from: https://doi.org/10.1016/j.neulet.2019.03.031

40. Liu MX, Zhong J, Xia L, Dou NN, Li ST. A correlative analysis between inflammatory cytokines and trigeminal neuralgia or hemifacial spasm. Neurol Res [Internet]. 2019;41(4):335–40. Available from: https://doi.org/10.1080/01616412.2018.1564188

41. Cavaillon J. Pro- versus anti-inflammatory cytokines : Myth or reality PRO- versus ANTI-INFLAMMATORY CYTOKINES : Cell Mol Biol. (July 2001).

42. Gornowicz A, Bielawska A, Bielawski K, Grabowska SZ, Wójcicka A, Zalewska M, et al. Pro-inflammatory cytokines in saliva of adolescents with dental caries disease. Ann Agric Environ Med. 2012;19(4):711–6.

43. Farges JC, Alliot-Licht B, Renard E, Ducret M, Gaudin A, Smith AJ, et al. Dental Pulp Defence and Repair Mechanisms in Dental Caries. Mediators Inflamm. 2015;2015.

44. Taso E, Stefanovic V, Gaudin A, Grujic J, Maldonado E, Petkovic-Curcin A, et al. Effect of dental caries on periodontal inflammatory status: A split-mouth study. Arch Oral Biol [Internet]. 2020;110:104620. Available from: https://doi.org/10.1016/j.archoralbio.2019.104620

45. Hall BE, Zhang L, Sun ZJ, Utreras E, Prochazkova M, Cho A, et al. Conditional TNF-α Overexpression in the Tooth and Alveolar Bone Results in Painful Pulpitis and Osteitis. J Dent Res. 2016;95(2):188–95.

46. Naruishi K, Nagata T. Biological effects of interleukin-6 on Gingival Fibroblasts: Cytokine regulation in periodontitis. J Cell Physiol. 2018;233(9):6393–400.

47. de Avila ED origatt., de Molon RS ca., de Godoi Gonçalves DA parecid., Camparis

CM ari. Relationship between levels of neuropeptide Substance P in periodontal disease and chronic pain: a literature review. J Investig Clin Dent. 2014;5(2):91–7.

48. Cardoso EM, Reis C, Manzanares-Céspedes MC. Chronic periodontitis, inflammatory cytokines, and interrelationship with other chronic diseases. Postgrad Med [Internet]. 2018;130(1):98–104. Available from: https://doi.org/10.1080/00325481.2018.1396876

49. Pan W, Wang Q, Chen Q. The cytokine network involved in the host immune response to periodontitis. Int J Oral Sci [Internet]. 2019;11(3). Available from: http://dx.doi.org/10.1038/s41368-019-0064-z

50. Duarte PM, de Mendonça AC, Máximo MBB, Santos VR, Bastos MF, Nociti FH. Effect of Anti-Infective Mechanical Therapy on Clinical Parameters and Cytokine Levels in Human Peri-Implant Diseases. J Periodontol. 2009;80(2):234–43.

51. Abduljabbar T, Vohra F, Ullah A, Alhamoudi N, Khan J, Javed F. Relationship between self-rated pain and peri-implant clinical, radiographic and whole salivary inflammatory markers among patients with and without peri-implantitis. Clin Implant Dent Relat Res. 2019;21(6):1218–24.

52. Kiyomoto M, Shinoda M, Honda K, Nakaya Y, Dezawa K, Katagiri A, et al. P38 Phosphorylation in Medullary Microglia Mediates Ectopic Orofacial Inflammatory Pain in Rats. Mol Pain. 2015;11(1):1–11.

53. L.Hung A, Lim M, L.Doshi T. Targeting cytokines for treatment of neuropathic pain. Physiol Behav. 2017;176(5):139–48.

9 ANNEXES:

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The Biochemical Origin of Pain: The origin of all Pain is Inflammation and the Inflammatory Response. PART 2 of 3 – Inflammatory Profile of Pain Syndromes

Sota Omoigui, MD
Division of Inflammation and Pain Research, L.A Pain Clinic, 4019 W. Rosecrans Ave, Hawthorne, CA 90250, Tel: (310) 675 9121 Fax: (310) 675 7989, medicinechief@aol.com

Abstract

Every pain syndrome has an inflammatory profile consisting of the inflammatory mediators that are present in the pain syndrome. The inflammatory profile may have variations from one person to another and may have variations in the same person at different times. The key to treatment of Pain Syndromes is an understanding of their inflammatory profile. Pain syndromes may be treated medically or surgically. The goal should be inhibition or suppression of production of the inflammatory mediators and inhibition, suppression or modulation of neuronal afferent and efferent (motor) transmission. A successful outcome is one that results in less inflammation and thus less pain. We hereby describe the inflammatory profile for several pain syndromes including arthritis, back pain, neck pain, fibromyalgia, interstitial cystitis, migraine, neuropathic pain, complex regional pain syndrome / reflex sympathetic dystrophy (CRPS/RSD), bursitis, shoulder pain and vulvodynia. These profiles are derived from basic science and clinical research performed in the past by numerous investigators and will be updated in the future by new technologies such as magnetic resonance spectroscopy. Our unifying theory or law of pain states: The origin of all pain is inflammation and the inflammatory response. The biochemical mediators of inflammation include cytokines, neuropeptides, growth factors and neurotransmitters. Irrespective of the type of pain whether it is acute or chronic pain, peripheral or central pain, nociceptive or neuropathic pain, the underlying origin is inflammation and the inflammatory response. Activation of pain receptors, transmission and modulation of pain signals, neuro plasticity and central sensitization are all one continuum of inflammation and the inflammatory response. Irrespective of the characteristic of the pain, whether it is sharp, dull, aching, burning, stabbing, numbing or tingling, all pain arise from inflammation and the inflammatory response. We are proposing a re-classification and treatment of pain syndromes based upon their inflammatory profile.

Keywords

inflammation; cytokine; interleukin 1 beta; tumor necrosis factor alpha; sympathetic nerve block; sympathectomy; lumbar block; stellate ganglion; non-steroidal anti-inflammatory drugs (NSAIDs); Steroid; Etanercept; Anakinra; Oxcarbazepine; Ketamine; arthritis; migraine; Complex Regional

Correspondence to: Sota Omoigui.

The paper is not under consideration elsewhere and none of the paper's contents have been previously published. All authors have read and approved the manuscript. Work was done at the L.A. Pain Clinic. The study was not supported by any grant. There is no conflict of interest.

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Seminars in
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Pathogenesis of Pain

Pradeep Dinakar, MD, MS, FAAP,[*,†] and Alexandra Marion Stillman, MD[‡]

The pathogenesis of pain sensation includes mechanisms that result in acute or chronic pain. Pain itself is described as an unpleasant sensory and emotional experience beginning with a peripheral stimulus that undergoes a physiological process ultimately resulting in the sensation of pain. Biologists recognize pain to be a common sign of potential tissue damage. Hence, pain sensation is protective in function. However, pathologic states of pain exist secondary to disruption of the nociceptive process both peripherally and centrally or secondary to psychological conditions. It is essential to identify these aberrant states of pain and distinguish them from situations of potential tissue damage. Chronic pain is defined as pain that exceeds 3 or 6 months duration. This article is an overview of the essential neuroanatomy and neurophysiology of normal pain nociception, its clinical implications, and the development of persistent and pathological pain conditions following improperly or poorly treated pain.
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Epidemiology of Pain

Acute and chronic pain places a significant clinical, economic, and social burden on the humanity.[1] Pain is the most common reason for a physician visit. The Institute of Medicine states that more than a 100 million Americans suffer from chronic pain.[2] Lost work-time exceeds 50 million days, and lost productivity is 61.2 billion dollars per year.[3] The total direct and indirect costs of persistent pain is placed at $560-$635 billion annually, which far exceeds the cost of any of the other 6 major diseases including cardiovascular ($309 billion), neoplasms ($243 billion), injury and poisoning ($205 billion), endocrine, nutritional, and metabolic ($127 billion), gastrointestinal ($112 billion), and pulmonary ($112 billion) as published by the National institute of Health (NIH) statistics.[4] It is also the most common cause of disability. The comorbidities associated with pain, add to the burden of patients and families. These include opioid overuse, misuse, dependence and addiction, depression, poor social relationships, and financial hardship.

From the *Department of Anesthesiology, Boston Children'sHospital, Harvard Medical School, Boston, MA.
†Department of Anesthesiology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA.
‡Cognitive Neurology Division, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA.
Address reprint requests to Pradeep Dinakar, MD, MS, FAAP, Pain Treatment Service, Department of Anesthesiology, Boston Children'sHospital, 333, Longwood Avenue, Boston, MA 02115. E-mail: Pradeep.dinakar@childrens.harvard.edu

Pediatric pain incidence and prevalence are increasingly pertinent as there is growing evidence that untreated or poorly treated pain in childhood predisposes to adult pain.[5,6] Pain in children not only affects their potential academically, socially, and physically but also burdens the family financially with lost parental income. Low back pain, headaches, and abdominal pain are the most prevalent pain complaints in children. In children, the median 1-year incidence is 22.4%, and 1-month prevalence is 22.9%. Median 1-month prevalence of headache is 47.5%, abdominal pain 12%, and whole body pain 2.9%.[7]

Process of Nociception

This section reviews the mechanisms that result in acute and chronic pain. The process by which the unpleasant noxious stimulus from the periphery is transmitted through the spinal cord and to various areas of the central nervous system resulting in the physiological sensation of pain and associated negative emotional response and memory, ultimately results in the sensation of pain.

Development of Nociception and Pain Perception

The widespread view maintained till recently was that the pain sensation was diminished or even absent in the fetus, newborn, and infant stage of human development. This was attributed to the lack of development of the nervous system including the

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Peripheral and Central Mechanisms of Persistent Orofacial Pain

*Masamichi Shinoda†, Asako Kubo†, Yoshinori Hayashi and Koichi Iwata**

Department of Physiology, Nihon University School of Dentistry, Tokyo, Japan

Neuroplastic changes in the neuronal networks involving the trigeminal ganglion (TG), trigeminal spinal subnucleus caudalis (Vc), and upper cervical spinal cord (C1/C2) are considered the mechanisms underlying the ectopic orofacial hypersensitivity associated with trigeminal nerve injury or orofacial inflammation. It has been reported that peripheral nerve injury causes injury discharges in the TG neurons, and a barrage of action potentials is generated in TG neurons and conveyed to the Vc and C1/C2 after trigeminal nerve injury. Long after trigeminal nerve injury, various molecules are produced in the TG neurons, and these molecules are released from the soma of TG neurons and are transported to the central and peripheral terminals of TG neurons. These changes within the TG cause neuroplastic changes in TG neurons and they become sensitized. The neuronal activity of TG neurons is further accelerated, and Vc and C1/C2 neurons are also sensitized. In addition to this cascade, non-neuronal glial cells are also involved in the enhancement of the neuronal activity of TG, Vc, and C1/C2 neurons. Satellite glial cells and macrophages are activated in the TG after trigeminal nerve injury and orofacial inflammation. Microglial cells and astrocytes are also activated in the Vc and C1/C2 regions. It is considered that functional interaction between non-neuronal cells and neurons in the TG, Vc, and C1/C2 regions is a key mechanism involved in the enhancement of neuronal excitability after nerve injury or inflammation. In this article, the detailed mechanisms underlying ectopic orofacial hyperalgesia associated with trigeminal nerve injury and orofacial inflammation are addressed.

Keywords: orofacial ectopic pain, trigeminal ganglion, trigeminal spinal subnucleus caudalis and upper cervical spinal cord, satellite cell, macrophage, microglia, astrocyte

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***Correspondence:**
Koichi Iwata
iwata.kouichi@nihon-u.ac.jp

†These authors have contributed equally to this work

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INTRODUCTION

Trigeminal nerve injury and orofacial inflammation are known to frequently cause persistent pain that can spread to adjacent orofacial regions innervated by the uninjured trigeminal nerve branches. Peripheral and central mechanisms are considered to be involved in the persistent ectopic orofacial pain associated with trigeminal nerve injury or orofacial inflammation (Imbe et al., 2001).

Abbreviations: ATP, adenosine triphosphate; BDNF, brain-derived neurotrophic factor; CCL2, chemokine C–C motif ligand 2; CGRP, calcitonin gene-related peptide; DRG, dorsal root ganglion; ERK, extracellular signal-regulated kinase; FKN, fractalkine; GFAP, glial fibrillary acidic protein; iNOS, inducible nitric oxide synthase; LIF, leukemia inhibitory factor; MAPK, mitogen-activated protein kinase; Nav, voltage-gated sodium channel; NGF, nerve growth factor; nNOS, neuronal nitric oxide synthase; NOS, nitric oxide synthase; RVM, rostro-ventral medulla; SGC, satellite glial cell; SP, substance P; TG, trigeminal ganglion; TNF, tumor necrosis factor; TNFR, TNF receptor; Vc, trigeminal spinal subnucleus caudalis; Vi, trigeminal subnucleus interpolaris.

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Review

General Pathways of Pain Sensation and the Major Neurotransmitters Involved in Pain Regulation

Mun Fei Yam [1,2,*], Yean Chun Loh [2], Chu Shan Tan [2], Siti Khadijah Adam [1], Nizar Abdul Manan [1] and Rusliza Basir [1,*]

[1] Department of Human Anatomy, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Serdang 43400, Malaysia; sk.adam@upm.edu.my (S.K.A.); nizar@upm.edu.my (N.A.M.)
[2] Department of Pharmacology, School of Pharmaceutical Sciences, Universiti Sains Malaysia, Minden 11800, Malaysia; lyc14_pha052@student.usm.my (Y.C.L.); chushan@usm.my (C.S.T.)
* Correspondence: yammunfei@usm.my (M.F.Y.); rusliza@upm.edu.my (R.B.); Tel.: +60-465-345-86 (M.F.Y.); +60-389-472-448 (R.B.)

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Abstract: Pain has been considered as a concept of sensation that we feel as a reaction to the stimulus of our surrounding, putting us in harm's way and acting as a form of defense mechanism that our body has permanently installed into its system. However, pain leads to a huge chunk of finances within the healthcare system with continuous rehabilitation of patients with adverse pain sensations, which might reduce not only their quality of life but also their productivity at work setting back the pace of our economy. It may not look like a huge deal but factor in pain as an issue for majority of us, it becomes an economical burden. Although pain has been researched into and understood by numerous researches, from its definition, mechanism of action to its inhibition in hopes of finding an absolute solution for victims of pain, the pathways of pain sensation, neurotransmitters involved in producing such a sensation are not comprehensively reviewed. Therefore, this review article aims to put in place a thorough understanding of major pain conditions that we experience—nociceptive, inflammatory and physiologically dysfunction, such as neuropathic pain and its modulation and feedback systems. Moreover, the complete mechanism of conduction is compiled within this article, elucidating understandings from various researches and breakthroughs.

Keywords: pain sensitization; neurotransmitters; nociceptive; inflammatory; neuropathic; presynaptic and postsynaptic; pain transmission; neurons; synaptic transmission

1. Introduction

Pain is considered to be a human primate instinct and can be defined as a distressing sensation, as well as an emotional experience that is linked to actual or potential tissue damage, with the sole purpose of notifying the body's defence mechanism to react towards a stimulus in order to avoid further tissue damages. The sensation of pain is associated with the activation of the receptors in the primary afferent fibers, which is inclusive of the unmyelinated C-fiber and myelinated Aσ-fiber. Both nociceptors remain silent during homeostasis in the absence of pain and are activated when there is a potential of noxious stimulus. The perception of a series of sensory events is required for the brain in order to detect pain and produce a response towards the threat. There are generally three main stages in the perception of pain. The first stage is pain sensitivity, followed by the second stage where the signals are transmitted from the periphery to the dorsal horn (DH), which is located in the spinal cord via the peripheral nervous system (PNS). Lastly, the third stage is to perform the transmission of the signals to the higher brain via the central nervous system (CNS). Typically, there are two routes for signal transmissions to be conducted: ascending and descending pathways. The pathway that goes

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RESEARCH ARTICLE Open Access

Increased levels of intramuscular cytokines in patients with jaw muscle pain

S. Louca Jounger[1,2*], N. Christidis[1,2], P. Svensson[1,2,3], T. List[2,4] and M. Ernberg[1,2]

Abstract

Background: The aim of this study was to investigate cytokine levels in the masseter muscle, their response to experimental tooth-clenching and their relation to pain, fatigue and psychological distress in patients with temporomandibular disorders (TMD) myalgia.

Methods: Forty women, 20 with TMD myalgia (Diagnostic Criteria for TMD) and 20 age-matched healthy controls participated. Intramuscular microdialysis was performed to sample masseter muscle cytokines. After 140 min (baseline), a 20-minute tooth-clenching task was performed (50% of maximal voluntary contraction force). Pain (Numeric rating scale 0–10) and fatigue (Borg's Ratings of Perceived Exertion 6–20) were assessed throughout microdialysis, while pressure-pain thresholds (PPT) were assessed before and after microdialysis. Perceived stress (PSS-10) and Trait Anxiety (STAI) were assessed before microdialysis.

Results: The levels of IL-6, IL-7, IL-8 and IL-13 were higher in patients than controls (Mann Whitney *U*-test; *P*'s < 0.05) during the entire microdialysis. IL-6, IL-8 and IL-13 changed during microdialysis in both groups (Friedman; *P*'s < 0.05), while IL-1β, IL-7 and GM-CSF changed only in patients (*P*'s < 0.01). IL-6 and IL-8 increased in response to tooth-clenching in both groups (Wilcoxon test; *P*'s < 0.05), while IL-7, IL-13 and TNF increased only in patients (*P*'s < 0.05). Patients had higher pain and fatigue than controls before and after tooth-clenching ($P < 0.001$), and lower PPTs before and after microdialysis ($P < 0.05$). There were no correlations between cytokine levels, pain or fatigue. Also, there were no differences in stress or anxiety levels between groups.

Conclusions: In conclusion, the masseter levels of IL-6, IL-7, IL-8 and IL-13 were elevated in patients with TMD myalgia and increased in response to tooth-clenching. Tooth-clenching increased jaw muscle pain and fatigue, but without correlations to cytokine levels. This implies that subclinical muscle inflammation may be involved in TMD myalgia pathophysiology, but that there is no direct cause-relation between inflammation and pain.

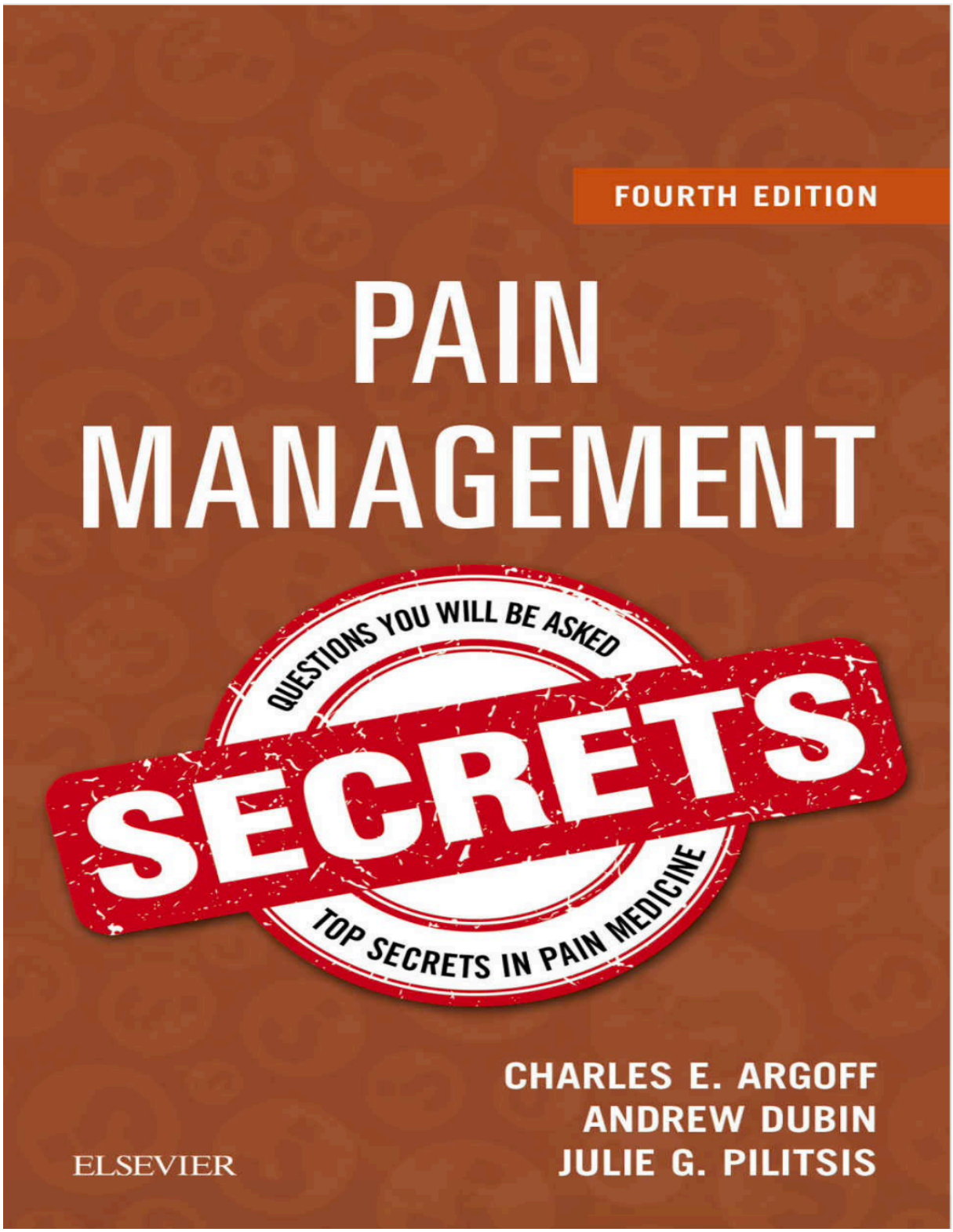
Keywords: Cytokines, Bruxism, Masseter muscle, Myalgia, Temporomandibular disorders (TMD)

Background

Temporomandibular disorders (TMD) are the most common chronic pain conditions in the orofacial region, affecting approximately 10–15% of the adult population [1] and twice as many women as men [2]. The most common subtype is TMD myalgia with jaw muscle pain that is increased by function, pain on palpation, pain referral, restricted mouth opening, and headache [3, 4]. The etiology of TMD and the higher prevalence among women is not well understood.

One hypothesis is that excessive tooth-clenching/grinding might contribute by disturbing the local blood flow in overloaded muscles, leading to ischemia [5]. Epidemiological studies show greater odds of having TMD myalgia when self-reported tooth-clenching is present [6–8]. Ischemia releases neuroactive and inflammatory biomarkers, such as neuropeptides, bradykinin, protons, serotonin (5-HT), glutamate and cytokines that may activate and sensitize nociceptors on peripheral sensory afferents to induce muscle pain and allodynia [9, 10]. Repeated muscle activity may then maintain chronic muscle pain by temporal summation [11]. Previous studies have shown that intense chewing induced pain and fatigue in pain-free healthy participants with similar, but

* Correspondence: sofia.louca@ki.se
[1]Section for Orofacial Pain and Jaw Function, Department of Dental Medicine, Karolinska Institutet, SE 14104, Huddinge, Sweden
[2]Scandinavian Center for Orofacial Neurosciences (SCON), Huddinge, Sweden
Full list of author information is available at the end of the article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ACT Annual Meeting Session Overview Article

Cytokines: The Good, the Bad, and the Deadly

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Thulasi Ramani[1], Carol S. Auletta[1], Daniel Weinstock[2], Barbara Mounho-Zamora[3], Patricia C. Ryan[4], Theodora W. Salcedo[5], and Gregory Bannish[1]

Abstract

Over the past 30 years, the world of pharmaceutical toxicology has seen an explosion in the area of cytokines. An overview of the many aspects of cytokine safety evaluation currently in progress and evolving strategies for evaluating these important entities was presented at this symposium. Cytokines play a broad role to help the immune system respond to diseases, and drugs which modulate their effect have led to some amazing therapies. Cytokines may be "good" when stimulating the immune system to fight a foreign pathogen or attack tumors. Other "good" cytokine effects include reduction of an immune response, for example interferon β reduction of neuron inflammation in patients with multiple sclerosis. They may be "bad" when their expression causes inflammatory diseases, such as the role of tumor necrosis factor α in rheumatoid arthritis or asthma and Crohn's disease. Therapeutic modulation of cytokine expression can help the "good" cytokines to generate or quench the immune system and block the "bad" cytokines to prevent damaging inflammatory events. However, care must be exercised, as some antibody therapeutics can cause "ugly" cytokine release which can be deadly. Well-designed toxicology studies should incorporate careful assessment of cytokine modulation that will allow effective therapies to treat unmet needs. This symposium discussed lessons learned in cytokine toxicology using case studies and suggested future directions.

Keywords

cytokines, biotherapeutics, immunomodulators, cytokine release syndrome, biomarkers

Introduction

Cytokine Explosion: Rocking the World of Toxicology (Thulasi Ramani and Carol S. Auletta, Huntingdon Life Sciences)

This symposium began with a thorough overview of cytokine biology and a discussion of the role of cytokines in the regulation of the immune system. Strategies for developing cytokine-targeted therapies were presented and included a discussion of regulatory guidelines and preclinical development strategies. Nonclinical development was discussed further in a presentation on safety evaluation of cytokine therapeutics with illustrations of translation of preclinical data to the clinic. Subsequent presentations summarized special considerations required in designing and interpreting nonclinical safety studies for biologics that either induce cytokines or block a key cytokine pathway as part of their mechanism of action and a thorough discussion of cytokine release syndrome with suggestions for predicting and managing this adverse immune-modulated reaction. A separate presentation reviewed the importance of including biomarkers for evaluation of immunotoxicity in development strategies. Illustrative case studies were included throughout.

Therapeutic Cytokine-Blocking Antibodies (Daniel Weinstock, Janssen Research and Development)

Introduction to anticytokines therapy

Understanding the structure, function, and biology of cytokines is essential for developing a rational strategy to intervene in cytokine-mediated disease processes. Knowledge of regulatory guidance and a case-by-case application to those principles is required for successful development of anticytokine therapeutics.

Cytokine comes from the Greek root words "cyto" for cell and "kinos" for movement. Cytokines are small proteins

[1] Huntingdon Life Sciences, Somerset, NJ, USA
[2] Janssen R&D, LLC, Spring House, PA, USA
[3] ToxStrategies, Inc, Bend, Oregon, USA
[4] MedImmune, Gaithesburg, MD, USA
[5] Bristol Myers Squibb Company, New Brunswick, NJ, USA

Corresponding Author:
Thulasi Ramani, Huntingdon Life Sciences, 100 Mettlers Road, Somerset, NJ 08873, USA.
Email: ramanit@princeton.huntingdon.com

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Review

Pathophysiological mechanisms of persistent orofacial pain

Masamichi Shinoda, Yoshinori Hayashi, Asako Kubo, and Koichi Iwata

Department of Physiology, Nihon University School of Dentistry, Tokyo, Japan

(Received September 12, 2019; Accepted October 31, 2019)

Abstract: Nociceptive stimuli to the orofacial region are typically received by the peripheral terminal of trigeminal ganglion (TG) neurons, and noxious orofacial information is subsequently conveyed to the trigeminal spinal subnucleus caudalis and the upper cervical spinal cord (C1-C2). This information is further transmitted to the cortical somatosensory regions and limbic system via the thalamus, which then leads to the perception of pain. It is a well-established fact that the presence of abnormal pain in the orofacial region is etiologically associated with neuroplastic changes that may occur at any point in the pain transmission pathway from the peripheral to the central nervous system (CNS). Recently, several studies have reported that functional plastic changes in a large number of cells, including TG neurons, glial cells (satellite cells, microglia, and astrocytes), and immune cells (macrophages and neutrophils), contribute to the sensitization and disinhibition of neurons in the peripheral and CNS, which results in orofacial pain hypersensitivity.

Keywords; orofacial pain, spinal trigeminal nucleus, trigeminal ganglion, upper cervical spinal cord

Introduction

Physiological pain induced by noxious stimuli plays an important role in the body's defense mechanism and is essential for supporting several life processes. Alternatively, chronic pathological pain is induced by non-noxious stimuli or persistent spontaneous pain hypersensitivity, leading to the impairment of processes involved in the body's defense mechanism. Pathological orofacial pain conditions, such as trigeminal neuralgia, burning mouth syndrome, myofascial pain syndrome, and temporomandibular joint dysfunction, are considered variations of chronic pain, and they can be addressed by therapeutic intervention. Nevertheless, several aspects regarding the pathogenetic mechanisms of these variations remain unclear, and, consequently, a number of clinicians struggle to control abnormal pain hypersensitivity.

Orofacial inflammation, trigeminal nerve disturbances, and oral cancer are known to underlie nociceptive trigeminal neuronal hyperexcitability, leading to orofacial pain hypersensitivity, which is induced by various molecular signaling mechanisms that are closely associated with several mediators released from immune or glial cells [1,2]. Furthermore, the trigeminal sensory nucleus complex consists of the main trigeminal sensory nucleus and trigeminal spinal nuclei. The main sensory nucleus receives information regarding touch, pressure, and vibration from the craniofacial region. The trigeminal spinal nucleus is located caudally to the main trigeminal sensory nucleus and receives sensory information from the face and oral cavity. The ophthalmic, maxillary, and mandibular trigeminal nerves terminate the trigeminal spinal nucleus, which is essentially divided into three subnuclei: oralis, interpolaris, and caudalis (Vc). The mandibular, ophthalmic, and maxillary projections are predominantly located in the dorsal, ventral, and medial regions of the body, respectively. Nociceptive input from the orofacial region terminates in the Vc as well as the upper cervical spinal cord (C1-C2) [3]. Since the cellular organization of the Vc is similar to that of the spinal dorsal horn, the Vc is also referred to as the medullary dorsal horn. Pathological plastic changes in the trigeminal neuronal circuitries lead to orofacial pain hypersensitivity.

Recent studies have demonstrated that neuronal hyperexcitability in the orofacial pain transmission pathway contributes to persistent orofacial pain mechanisms following orofacial pathogenesis [4-6]. This pathway extends from the orofacial region to the pain information-processing region in the cerebrum and is associated with the pathological plastic changes in satellite glial cells in the trigeminal ganglion (TG), secondary neurons, microglia, and astrocytes in the Vc and C1-C2. This review utilizes the latest available studies to outline the mechanisms behind pain abnormalities that occur in the orofacial region.

Local pathological changes contribute to nociceptive neuronal hyperexcitability

Dental pulpitis, periodontitis, and pericoronitis lead to the infiltration of inflammatory cells along with the release and promotion of several inflammatory mediators, such as nerve growth factor (NGF) and tumor necrosis factor-alpha (TNFα), in inflammatory sites [7,8]. TNFα signaling via TNF receptor-1 (TNFR-1) and TNF receptor-2 (TNFR-2), which are expressed in nociceptive endings, sensitize voltage-gated sodium channel 1.8 (Nav 1.8) by activating the protein kinase C, which results in the predisposition to generate action potentials [9,10]. The transient receptor potential (TRP) channel superfamily plays an important role in functions associated with sensing pain [11]. Furthermore, TRP vanilloid 1 (TRPV1) is activated in the presence of high-temperature conditions (>42°C), low pH, capsaicin, and vanilloid, while TRPA1 is activated by low temperatures (<15°C) and in the presence of numerous chemical irritants [12]. Facial inflammation subsequently reduces the acidity in the inflamed site, which increases TRPV1 expression in nociceptors. TRPV1 activation facilitates the intracellular influx of Ca^{2+}, which sensitizes TRPA1, leading to orofacial cold hypersensitivity [13].

To the contrary, heat hypersensitivity following a facial skin incision is induced by the sensitization of TRPV1 through protein kinase A signaling and is facilitated by activating TRPA1 in the TG neurons that innervate the facial skin surrounding the incision [14]. Alternatively, there is a notable upregulation of artemin (ATN) mRNA expression, a member of the glial cell line-derived neurotrophic factor family, in the epithelial cells of tongue mucosa sampled from patients with burning mouth syndrome [5]. ATN signal upregulation, facilitated by the phosphorylation of p38 mitogen-activated protein kinase (MAPK) in the tongue mucosa, produces heat hypersensitivity in the tongue due to the hyperexpression of TRPV1 in nociceptors that innervate the tongue [5,15]. The p75 neurotrophin receptor ($p75^{NTR}$) and tyrosine kinase receptor A (TrkA) act as NGF receptors in the primary nociceptive neurons [16]. NGF signaling via $p75^{NTR}$ and TrkA, which are expressed in nociceptive endings, has been reported to enhance the tetrodotoxin-resistant sodium current density and decrease the threshold potential of Nav 1.8, which is etiologically associated with inflammatory mechanical allodynia [17,18].

Furthermore, the NGF/TrkA complex is formed after NGF successfully binds to TrkA at the nociceptor endings and is internalized in the endings to be retrogradely transported to the soma of the primary neuron [19]. Neuronal firing induces NGF secretion into the extracellular space *in vitro*, which increases the concentration of NGF in the culture medium [20,21]. Following local orofacial inflammation, NGF secreted from the TG neurons innervating the inflamed site binds to NGF receptors expressed in other TG neurons. This subsequently leads to an increased expression of TRPV1 within the intact TG neurons innervating the intact sites, which

Correspondence to Dr. Masamichi Shinoda, Department of Physiology, Nihon University School of Dentistry, 1-8-13 Kanda-Surugadai, Chiyoda-ku, Tokyo 101-8310, Japan
Fax: +81-3-3219-8341 E-mail: shinoda.masamichi@nihon-u.ac.jp

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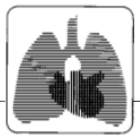

impact of basic research on tomorrow's medicine

Anti-Inflammatory Cytokines*

Steven M. Opal, MD; and Vera A. DePalo, MD

The anti-inflammatory cytokines are a series of immunoregulatory molecules that control the proinflammatory cytokine response. Cytokines act in concert with specific cytokine inhibitors and soluble cytokine receptors to regulate the human immune response. Their physiologic role in inflammation and pathologic role in systemic inflammatory states are increasingly recognized. Major anti-inflammatory cytokines include interleukin (IL)-1 receptor antagonist, IL-4, IL-6, IL-10, IL-11, and IL-13. Specific cytokine receptors for IL-1, tumor necrosis factor-α, and IL-18 also function as proinflammatory cytokine inhibitors. The nature of anti-inflammatory cytokines and soluble cytokine receptors is the focus of this review. The current and future therapeutic uses of these anti-inflammatory cytokines are also reviewed. ***(CHEST 2000; 117:1162–1172)***

Key words: anti-inflammatory cytokines; cytokines; inflammation; sepsis; septic shock

Abbreviations: GM-CSF = granulocyte-macrophage colony-stimulating factor; IFN-γ = interferon-γ; IL = interleukin; IL-1ra = IL-1 receptor antagonist; LPS = lipopolysaccharide; MHC = major histocompatibility complex; MIP = macrophage inflammatory protein; NF-κB = nuclear factor κB; TGF-β = transforming growth factor-β; Th = T helper cells; TNF = tumor necrosis factor

The human immune response is regulated by a highly complex and intricate network of control elements. Prominent among these regulatory components are the anti-inflammatory cytokines and specific cytokine inhibitors. Under physiologic conditions, these cytokine inhibitors serve as immunomodulatory elements that limit the potentially injurious effects of sustained or excess inflammatory reactions. Under pathologic conditions, these anti-inflammatory mediators may either (1) provide insufficient control over proinflammatory activities in immune-mediated diseases or (2) overcompensate and inhibit the immune response, rendering the host at risk from systemic infection.[1,2]

A dynamic and ever-shifting balance exists between proinflammatory cytokines and anti-inflammatory components of the human immune system. The regulation of inflammation by these cytokines and cytokine inhibitors is complicated by the fact that the immune system has redundant pathways with multiple elements having similar physiologic effects. Furthermore, with the potential exception of interleukin (IL)-1 receptor antagonist (IL-1ra), all the anti-inflammatory cytokines have at least some proinflammatory properties as well. The net effect of any cytokine is dependent on the timing of cytokine release, the local milieu in which it acts, the presence of competing or synergistic elements, cytokine receptor density, and tissue responsiveness to each cytokine.[3] This is what makes the study of cytokine biology so fascinating (and so frustrating as well!).

Perturbations of this regulatory network of cytokines by genetic, environmental, or microbial elements may have highly deleterious consequences.[4–8] The major anti-inflammatory cytokines and their specific roles in human disease will be the focus of this brief review. These inhibitory cytokines have already proven to be efficacious in a variety of clinical conditions marked by excess inflammation. Their potential therapeutic use in numerous other inflammatory states will also be described.

The principal anti-inflammatory cytokines and cytokine inhibitors are listed in Tables 1, 2. The functional definition of an anti-inflammatory cytokine in this review is the ability of the cytokine to inhibit the synthesis of IL-1, tumor necrosis factor (TNF), and other major proinflammatory cytokines.

*From the Infectious Disease Division and Critical Care Division, Brown University School of Medicine, Providence, RI.
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Correspondence to: Steven M. Opal, MD, Infectious Disease Division, Memorial Hospital of Rhode Island, 111 Brewster St, Pawtucket, RI 02860; e-mail: Steven_Opal@brown.edu

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Review

The pro- and anti-inflammatory properties of the cytokine interleukin-6

Jürgen Scheller [a], Athena Chalaris [b], Dirk Schmidt-Arras [b], Stefan Rose-John [b,*]

[a] Institute of Biochemistry and Molecular Biology II, Medical Faculty, Heinrich-Heine-University, Düsseldorf, Germany
[b] Institute of Biochemistry, Christian-Albrechts-University, Olshausenstrasse 40, D-24098 Kiel, Germany

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ABSTRACT

Interleukin-6 is a cytokine not only involved in inflammation and infection responses but also in the regulation of metabolic, regenerative, and neural processes. In *classic signaling*, interleukin-6 stimulates target cells via a membrane bound interleukin-6 receptor, which upon ligand binding associates with the signaling receptor protein gp130. Gp130 dimerizes, leading to the activation of Janus kinases and subsequent phosphorylation of tyrosine residues within the cytoplasmic portion of gp130. This leads to the engagement of phosphatase Src homology domains containing tyrosin phosphatase-2 (SHP-2) and activation of the ras/raf/Mitogen-activated protein (MAP) kinase (MAPK) pathway. In addition, signal transducer and activator of transcription factors are recruited, which are phosphorylated, and consequently dimerize whereupon they translocate into the nucleus and activate target genes. Interestingly, only few cells express membrane bound interleukin-6 receptor whereas all cells display gp130 on the cell surface. While cells, which only express gp130, are not responsive to interleukin-6 alone, they can respond to a complex of interleukin-6 bound to a naturally occurring soluble form of the interleukin-6 receptor. Therefore, the generation of soluble form of the interleukin-6 receptor dramatically enlarges the spectrum of interleukin-6 target cells. This process has been named *trans-signaling*. Here, we review the involvement of both signaling modes in the biology of interleukin-6. It turns out that regenerative or anti-inflammatory activities of interleukin-6 are mediated by *classic signaling* whereas pro-inflammatory responses of interleukin-6 are rather mediated by *trans-signaling*. This is important since therapeutic blockade of interleukin-6 by the neutralizing anti-interleukin-6 receptor monoclonal antibody tocilizumab has recently been approved for the treatment of inflammatory diseases.

1. Introduction

Functional pleiotropy and redundancy are characteristic features of cytokines, which include interleukins, interferons, colony-stimulating factors, and many growth factors. Cytokines are produced by many different cell types and often show overlapping activities regulating proliferation or differentiation, depending on the type and developmental state of the target cells involved. The cytokines interleukin-6 (IL-6), IL-1, and TNFα are elevated in most, if not all, inflammatory states and have been recognized as targets of therapeutic intervention. This review will focus on the cytokine IL-6, for which also numerous activities outside of the immune system are known. Interestingly, it has been recognized that, although mostly regarded as a pro-inflammatory cytokine, IL-6 also has many regenerative or anti-inflammatory activities. The molecular mechanism of how one cytokine can act in a pro- and anti-inflammatory way is starting to emerge and will be discussed in this review article.

2. IL-6 family of cytokines

Members of the interleukin 6 (IL-6) family of cytokines include IL-6, IL-11, leukemia inhibitory factor (LIF), oncostatin M (OSM), ciliary inhibitory factor (CNTF), cardiotropin-1 (CT-1), cardiotrophin-like related cytokine and stimulating neurotrophin-1/B-cell stimulating factor 3 (NNT-1), neuropoietin (NPN), IL-27, and IL-31. With the exception of IL-31, all IL-6 type cytokines share the membrane glycoprotein gp130 as a common receptor and signal transducer subunit (reviewed in references 1 and 2). IL-6 and IL-11 initially bind to the membrane bound α receptors IL-6 receptor (IL-6R) or IL-11R, respectively. Subsequently, IL-6/IL-6R or IL-11/IL-11R complexes associate with gp130, leading to gp130-homodimer formation and signal initiation. Viral IL-6 (vIL-6) from the human herpes virus 8 (HHV-8) also signals via a gp130 homodimer but without the need of the αIL-6R [3]. LIF, CNTF, OSM, CT-1, NPN, and NNT-1 signal via gp130/LIF-R-heterodimeric receptor complexes [4]. In addition, OSM signals via a

Abbreviations: ADAM, a disintegrin and metalloprotease; AOM, azoxymethane; CBM, cytokine-binding module; DSS, dextran sodium sulfate; Ig, immunoglobulin; IL, interleukin; mAb, monoclonal antibody; mb, membrane bound; R, receptor; STAT, signal transducer and activator of transcription; TNF, tumor necrosis factor; wt, wild type

* Corresponding author.
E-mail addresses: jscheller@uni-duesseldorf.de (J. Scheller), rosejohn@biochem.uni-kiel.de (S. Rose-John).

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The anatomy and physiology of pain

Charlotte E Steeds

Abstract

Pain is an unpleasant experience that results from both physical and psychological responses to injury. A complex set of pathways transmits pain messages from the periphery to the central nervous system, where control occurs from higher centres. Primary afferent pain fibres synapse with second-order neurons in the dorsal horn of the spinal cord. Ascending spinothalamic and spinoreticular tracts convey pain up to the brain, where pain signals are processed by the thalamus and sent to the cortex. Descending tracts, via the midbrain periaqueductal grey and nucleus raphe magnus, have a role in pain modulation. When nerves are damaged, neuropathic pain results and various mechanisms have been proposed for how this takes place. These mechanisms involve both peripheral and central sensitization.

Keywords Central sensitization; gate-control theory; neuropathic pain; nociception; pain pathways; peripheral sensitization; somatic pain; visceral pain

What is pain?

In 1996 the International Association for the Study of Pain (IASP) defined pain as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage'. This statement requires further explanation as it encompasses some important concepts. Pain is a subjective experience, which cannot be easily measured. It requires consciousness. Describing pain as an 'experience' separates pain from 'nociception'. Nociception is the neural process involving the transduction and transmission of a noxious stimulus to the brain via a pain pathway. Pain is the result of a complex interplay between signalling systems, modulation from higher centres and the unique perception of the individual.

We learn about pain when we experience injury in early life. Scientists recognize that stimuli that cause pain are likely to be damaging to (or likely to damage) tissue. However, many people report pain in the absence of tissue damage or any likely pathophysiological cause; usually this happens for psychological reasons. Patients misunderstand the relationship between tissue damage and pain, but sometimes healthcare professionals get it wrong too. If someone says they are in pain, regardless of whether a damaging stimulus can be identified, or not, what they are experiencing should be accepted as pain.

If a person experiences pain as a result of a particular activity, they usually stop doing that activity, because they identify pain as a warning sign that harm is occurring. However, if the pain continues, the person can do less and less. At this point pain is not providing the person with a useful signal since the likelihood of injury occurring with the activity has ceased. In fact lack of activity may now be becoming physically and psychologically bad for the patient. The continuing pain is distressing for the patient and the dissociation between pain and tissue damage is confusing.

The IASP definition avoids tying pain to the stimulus. In this article, although we will look at nociceptive pathways, it is important to recognize that the whole experience of pain is far more than physical stimuli triggering neural signals.

Pain pathways

Pain receptors and primary afferents

Nociceptors are receptors in tissues which are activated specifically by painful stimuli. This 'noxious' information is transduced by the receptors into an electrical signal and transmitted from the periphery to the central nervous system along axons. There are two types of nociceptors:

- high-threshold mechanoreceptors (HTM), which respond to mechanical deformation
- polymodal nociceptors (PMN), which respond to a variety of tissue-damaging inputs:
  - hydrogen ions (protons)
  - 5-hydoxytryptamine (5-HT)
  - cytokines
  - bradykinin
  - histamine
  - prostaglandins
  - leucotrienes.

These inflammatory mediators bathe the nociceptors, activating and sensitizing them. Prostaglandins and bradykinin sensitize nociceptors to activation by low-intensity stimuli. Histamine and 5-HT cause pain when directly applied to nerve endings. Hydrogen ions and 5-HT act directly on ion channels on the cell membrane, but most of the others bind to membrane receptors and activate second-messenger systems via G proteins.

Nociceptors are therefore the free nerve endings of nerve fibres. There are two main fibre types: Aδ and C fibres. A comparison of the properties of these pain fibres is shown in Table 1. These primary afferent nerve fibres have cell bodies in either the dorsal root ganglia or trigeminal ganglion and terminate in the dorsal horn of the spinal cord. Although all pain fibres terminate in the dorsal horn, their route to this end-point varies. Most enter the dorsal horn in the ventro-lateral bundle of the dorsal root (Figure 1). They travel just lateral to the larger-diameter myelinated Aβ fibres, which respond to non-painful stimuli such as vibration and light touch. However, 30% of the C fibres enter the spinal cord via the ventral root. Once they have entered the spinal cord the nerve roots may bifurcate into ascending and descending branches, which can enter the dorsal horn one or two segments higher or lower than the segment of origin.

The spinal cord and the gate-control theory

The dorsal horn of the spinal cord is the site where the primary afferent fibres synapse with second-order neurons. It is also where complex interactions occur between excitatory and inhibitory interneurons and where descending inhibitory tracts from higher centres exert their effect (Figure 2).

Charlotte E Steeds *BSc MBBS FFARSCI is a Locum Consultant in Anaesthesia and Pain Medicine at University Hospitals Bristol, UK.*

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When does acute pain become chronic?

C. Voscopoulos and M. Lema*

Department of Anesthesiology, Critical Care, and Pain Medicine, University at Buffalo, Buffalo, NY, USA

* Corresponding author. E-mail: mlema@buffalo.edu

Key points

- The transition from acute to chronic pain occurs in discrete pathophysiological steps involving multiple signalling pathways.
- The duration and intensity of the initial stimulus leads to both peripheral and central sensitization that synergistically exacerbate pain perception.
- A multimodal therapeutic approach is best suited to target the complex mechanisms leading to the transition from acute to chronic pain.

Summary. The transition from acute to chronic pain appears to occur in discrete pathophysiological and histopathological steps. Stimuli initiating a nociceptive response vary, but receptors and endogenous defence mechanisms in the periphery interact in a similar manner regardless of the insult. Chemical, mechanical, and thermal receptors, along with leucocytes and macrophages, determine the intensity, location, and duration of noxious events. Noxious stimuli are transduced to the dorsal horn of the spinal cord, where amino acid and peptide transmitters activate second-order neurones. Spinal neurones then transmit signals to the brain. The resultant actions by the individual involve sensory-discriminative, motivational-affective, and modulatory processes in an attempt to limit or stop the painful process. Under normal conditions, noxious stimuli diminish as healing progresses and pain sensation lessens until minimal or no pain is detected. Persistent, intense pain, however, activates secondary mechanisms both at the periphery and within the central nervous system that cause allodynia, hyperalgesia, and hyperpathia that can diminish normal functioning. These changes begin in the periphery with upregulation of cyclo-oxygenase-2 and interleukin-1β-sensitizing first-order neurones, which eventually sensitize second-order spinal neurones by activating *N*-methyl-D-aspartic acid channels and signalling microglia to alter neuronal cytoarchitecture. Throughout these processes, prostaglandins, endocannabinoids, ion-specific channels, and scavenger cells all play a key role in the transformation of acute to chronic pain. A better understanding of the interplay among these substances will assist in the development of agents designed to ameliorate or reverse chronic pain.

Keywords: analgesia; cyclo-oxygenase-2; hyperalgesia; microglia; neuroplasticity; nociception; pain; postoperative pain; post-surgical chronic pain; sensitization

Pain-related problems account for up to 80% of visits to physicians. The epidemiological significance of chronic pain after surgery is enormous.[1] The prevalence of chronic pain can range from 10.1% to 55.2% of the populations studied.[2] Current theories propose that a prolonged experience of acute pain in which long-standing changes are seen within and external to the central nervous system (CNS) creates chronic pain with a histological and pathological basis.[3] Furthermore, chronic pain development after surgery likely occurs as a result of complex biochemical and pathophysiological mechanisms that differ in type among different surgical procedures. This article focuses on how postoperative, traumatic, and neuropathic nociception are generated and inter-related, with the goal of providing a deeper understanding of how long-term pain develops so that we can prevent and treat it more effectively, in the hope of stimulating more research and inquiry.

Mechanism for acute pain generation: peripheral effects and spinal and central effects

The generation of acute surgical pain can be summarized in the following way. Surgery-associated tissue injury is interpreted neuraxially in the same way as trauma-associated injury. Pain sensation varies according to the intensity, quality, and duration of stimuli. Surgery sets off a cascade of inter-related events designed to fight infection, limit further damage, and initiate repair. It involves nociception, inflammation, and nerve cell remodelling. Pro-inflammatory cytokines, chemokines, and neurotrophins induce both peripheral and central nerve sensitization to heighten pain awareness in order to limit further injury to the affected area. In the generation of pain, multiple pain systems are known to be activated.

Research Paper

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OPEN

Increasing gender differences in the prevalence and chronification of orofacial pain in the population

Birgitta Häggman-Henrikson[a,b], Per Liv[c], Aurelia Ilgunas[a,b], Corine M. Visscher[d], Frank Lobbezoo[d], Justin Durham[e], Anna Lövgren[b,*]

Abstract

Although a fluctuating pattern of orofacial pain across the life span has been proposed, data on its natural course are lacking. The longitudinal course of orofacial pain in the general population was evaluated using data from routine dental check-ups at all Public Dental Health services in Västerbotten, Sweden. In a large population sample, 2 screening questions were used to identify individuals with pain once a week or more in the orofacial area. Incidence and longitudinal course of orofacial pain were evaluated using annual data for 2010 to 2017. To evaluate predictors for orofacial pain remaining over time, individuals who reported pain on at least 2 consecutive dental check-ups were considered persistent. A generalized estimating equation model was used to analyze the prevalence, accounting for repeated observations on the same individuals. In total, 180,308 individuals (equal gender distribution) were examined in 525,707 dental check-ups. More women than men reported orofacial pain (odds ratio 2.58, 95% confidence interval [CI] 2.48-2.68), and there was a significant increase in the prevalence of reported pain from 2010 to 2017 in both women and men. Longitudinal data for 135,800 individuals were available for incidence analysis. Women were at higher risk of both developing orofacial pain (incidence rate ratio 2.37; 95% CI 2.25-2.50) and reporting pain in consecutive check-ups (incidence rate ratio 2.56; 95% CI 2.29-2.87). In the northern Swedish population studied, the prevalence of orofacial pain increases over time and more so in women, thus indicating increasing differences in gender for orofacial pain.

Keywords: Chronic pain, Facial pain, Gender, Orofacial pain, Temporomandibular disorders, Incidence, Prevalence

1. Introduction

Chronic pain is related to a broad range of interacting external and internal factors. The complex interplay between such factors determines the susceptibility for an individual to develop a chronic pain condition. The enigma of pain with regard to chronification and treatment resistance has led to the concept of "stickiness" being proposed, which incorporates how an event or perturbation may influence the development of chronicity in vulnerable individuals.[5] For the individual, chronic pain often has a detrimental impact on the quality of life.[8,42] Furthermore, chronic pain incurs substantial societal costs, especially in the context of the global burden of pain where pain related to the musculoskeletal system has been identified as a key element.[4]

Orofacial pain with a prevalence of 10% to 15% in the adult population[23,25] is one of the most common causes of chronic pain after back, neck, and knee pain.[7,51] Acute pain in the orofacial area is often tooth related,[24] whereas chronic orofacial pain is most commonly related to musculoskeletal disorders, temporomandibular disorders (TMDs).[31] Temporomandibular disorder is the umbrella term embracing pain and dysfunction that involves the masticatory muscles, the temporomandibular joint, and associated structures.[11,24] The economic burden on society from orofacial pain is substantial[10]; this stresses the importance of enhancing understanding of its natural course. The incidence and prevalence of TMD pain have been investigated in adults overall,[12] adults aged 18 to 44,[44] and in adolescents.[22] From early adolescence, the prevalence of orofacial pain increases and more so in girls,[22,35] and it is twice as high in adult women compared with men.[12,25] It was suggested that development of TMD pain in adolescence may reflect an underlying vulnerability for musculoskeletal pain.[22]

The biopsychosocial model, as a concept, is firmly embedded in the understanding and assessment of chronic pain. Thus, psychosocial factors have been shown to have a strong association with the development and persistence of orofacial pain[13,44] and common comorbidities in chronic pain conditions. In light of reports of increasing prevalence of psychosocial factors such as stress, depression, and anxiety in the general population, especially in young adults and adolescents,[46] it is reasonable to assume that this trend may also be reflected as an increase in the prevalence of orofacial pain.

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[a] Department of Orofacial Pain and Jaw Function, Faculty of Odontology, Malmö University, Malmö, Sweden, [b] Department of Odontology/Clinical Oral Physiology, Faculty of Medicine, University of Umeå , Umeå , Sweden, [c] Section of Sustainable Health, Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden, [d] Department of Orofacial Pain and Dysfunction, Academic Centre for Dentistry Amsterdam (ACTA), University of Amsterdam and Vrije Universiteit, Amsterdam, the Netherlands, [e] Centre for Oral Health Research, School of Dental Sciences, Newcastle University, Newcastle, United Kingdom

**Corresponding author. Address: Department of Clinical Oral Physiology, Faculty of Medicine, University of Umeå, Umeå 901 87, Sweden. Tel.: + 46 70 310 32 14. E-mail address: anna.lovgren@umu.se (A. Lövgren).*

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REVIEW Open Access

Interleukin-6: an emerging regulator of pathological pain

Ya-Qun Zhou[1], Zheng Liu[2], Zhi-Heng Liu[3], Shu-Ping Chen[1], Man Li[4], Allahverdi Shahveranov[5], Da-Wei Ye[5*] and Yu-Ke Tian[1]

Abstract

Interleukin-6 is an inflammatory cytokine with wide-ranging biological effects. It has been widely demonstrated that neuroinflammation plays a critical role in the development of pathological pain. Recently, various pathological pain models have shown elevated expression levels of interleukin-6 and its receptor in the spinal cord and dorsal root ganglia. Additionally, the administration of interleukin-6 could cause mechanical allodynia and thermal hyperalgesia, and an intrathecal injection of anti-interleukin-6 neutralizing antibody alleviated these pain-related behaviors. These studies indicated a pivotal role of interleukin-6 in pathological pain. In this review, we summarize the recent progress in understanding the roles and mechanisms of interleukin-6 in mediating pathological pain associated with bone cancer, peripheral nerve injury, spinal cord injury, chemotherapy-induced peripheral neuropathy, complete Freund's adjuvant injection, and carrageenan injection. Understanding and regulating interleukin-6 could be an interesting lead to novel therapeutic strategies for pathological pain.

Keywords: Interleukin-6, Bone cancer pain, Neuropathic pain, Inflammatory pain

Background

Pathological pain is characterized by a low threshold and an exaggerated response to noxious stimuli, and it can be categorized as cancer pain, neuropathic pain, or inflammatory pain [1, 2]. Although physiological pain is essential for the elimination of damaging stimuli, pathological pain significantly affects the quality of life [3–5]. Currently, pathological pain is thought to be mainly induced by a combination of peripheral drives and central processing [6–9]. Despite growing knowledge of the mechanisms of pathological pain, this type of pain still represents a major challenge in clinical practice and basic science. Cytokines have been reported to participate in the regulation of numerous cellular functions including the inflammatory response and expression of cell surface proteins [10–12]. In addition, we previously reported that several cytokines could potentially serve as targets for the management of bone cancer pain (BCP) [13–19]. Recently, mounting evidence has suggested that one cytokine in particular, interleukin-6 (IL-6), may play a critical role in the development of pathological pain [20–24].

IL-6 is an inflammatory cytokine with wide-ranging biological effects. It was first described as B-stimulatory factor 2, which induces B lymphocytes to produce immunoglobulin [25]. IL-6 exerts its biological effect on target cells by interacting with the non-signaling membrane-bound IL-6 receptor (mIL-6R) [26, 27]. The IL-6 and mIL-6R complex then associates with the signal transducing membrane protein gp130, promoting its dimerization and the subsequent activation of intracellular signaling including the Janus-activated kinase/signal transducer activator of transcription (JAK/STAT), mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK), and phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) signaling pathways [28–30]. This manner of IL-6 signaling is often referred to as "classical IL-6 signaling." gp130 is expressed by almost all cells in the body, whereas the mIL-6R has a highly restricted expression profile, and is mainly expressed by hepatocytes, neutrophils, monocytes/macrophages and certain other leukocytes [31, 32]. Only cells expressing mIL-6R can bind and respond to IL-6. Thus, until the discovery of a naturally occurring soluble form of IL-6R (sIL-6R), it was difficult to understand how

* Correspondence: dy0711@gmail.com
[5]Cancer Center, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China
Full list of author information is available at the end of the article

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Review

Neuron–Glia Crosstalk and Neuropathic Pain: Involvement in the Modulation of Motor Activity in the Orofacial Region

Mohammad Zakir Hossain [1,*], Shumpei Unno [1], Hiroshi Ando [2], Yuji Masuda [3] and Junichi Kitagawa [1]

[1] Department of Oral Physiology, School of Dentistry, Matsumoto Dental University, 1780 Gobara Hirooka, Shiojiri, Nagano 399-0781, Japan; unno_shumpei@po.mdu.ac.jp (S.U.); kitagawa@po.mdu.ac.jp (J.K.)
[2] Department of Biology, School of Dentistry, Matsumoto Dental University, 1780 Gobara, Hirooka, Shiojiri, Nagano 399-0781, Japan; andohiroshi@po.mdu.ac.jp
[3] Institute for Oral Science, Matsumoto Dental University, 1780 Gobara, Hirooka, Shiojiri, Nagano 399-0781, Japan; masuday@po.mdu.ac.jp
* Correspondence: zakir@po.mdu.ac.jp; Tel./Fax: +81-263-51-2053

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Abstract: Neuropathic orofacial pain (NOP) is a debilitating condition. Although the pathophysiology remains unclear, accumulating evidence suggests the involvement of multiple mechanisms in the development of neuropathic pain. Recently, glial cells have been shown to play a key pathogenetic role. Nerve injury leads to an immune response near the site of injury. Satellite glial cells are activated in the peripheral ganglia. Various neural and immune mediators, released at the central terminals of primary afferents, lead to the sensitization of postsynaptic neurons and the activation of glia. The activated glia, in turn, release pro-inflammatory factors, further sensitizing the neurons, and resulting in central sensitization. Recently, we observed the involvement of glia in the alteration of orofacial motor activity in NOP. Microglia and astroglia were activated in the trigeminal sensory and motor nuclei, in parallel with altered motor functions and a decreased pain threshold. A microglial blocker attenuated the reduction in pain threshold, reduced the number of activated microglia, and restored motor activity. We also found an involvement of the astroglial glutamate–glutamine shuttle in the trigeminal motor nucleus in the alteration of the jaw reflex. Neuron–glia crosstalk thus plays an important role in the development of pain and altered motor activity in NOP.

Keywords: satellite glial cells; microglia; astroglia; neuropathic orofacial pain; orofacial motor activity

1. Introduction

Chronic pain is a major public health problem that has a significant impact on both the individual and community [1,2]. Acute pain is beneficial as it warns against impending or current tissue damage, whereas in contrast, there appear to be no beneficial functions of chronic pain [3]. Neuropathic pain, a type of chronic pain, can result from nerve injury, inflammation, or diseases of the peripheral or central nervous systems, and is characterized by spontaneous pain (ongoing or episodic), pain resulting from stimuli that would not normally provoke pain (allodynia), and exaggerated pain responses to noxious stimuli (hyperalgesia) [3,4]. Neuropathic pain in the head, neck, face, oral or perioral regions is termed neuropathic orofacial pain (NOP) [3–5]. The etiology of NOP can include systemic diseases (e.g., diabetes), viral infections (e.g., herpes zoster), nerve compression, and injury to peripheral nerves during dental operative procedures, such as tooth extraction, root canal treatment and dental implant surgery [6,7]. Neuropathic pain is associated with dysfunction throughout the pain pathway, including the nociceptors, the peripheral ganglia, the brainstem or the spinal cord,

Inflammatory Cytokines and Sleep Disturbance in Patients with Temporomandibular Disorders

Ji Woon Park, DDS, PhD
Assistant Professor
Orofacial Pain Clinic
Department of Oral Medicine and Oral Diagnosis
School of Dentistry and Dental Research Institute
Seoul National University
Seoul, Korea

Jin Woo Chung, DDS, PhD
Professor
Orofacial Pain Clinic
Department of Oral Medicine and Oral Diagnosis
School of Dentistry and Dental Research Institute
Seoul National University
Seoul, Korea

Correspondence to:
Dr Jin Woo Chung
Orofacial Pain Clinic, Department of Oral Medicine and Oral Diagnosis
School of Dentistry and Dental Research Institute, Seoul National University
28 Yunkeun-Dong, Chongro-Ku, Seoul 110-749, Korea
Fax: +82-2-744-9135
Email: jwchung@snu.ac.kr

Aims: To assess the degree and interrelationship of sleep disturbance and plasma cytokine levels in temporomandibular disorder (TMD) pain patients. **Methods:** Forty female TMD patients and 20 age-, sex-, and body mass index (BMI)–matched healthy subjects were enrolled. TMD was diagnosed using the Research Diagnostic Criteria for TMD. The TMD patients were classified as having low or high disability according to Graded Chronic Pain Scale findings. The Pittsburgh Sleep Quality Index (PSQI) and Epworth Sleepiness Scale (ESS) were used to measure sleep quality. Plasma concentrations of interleukin (IL)-1β, IL-6, IL-10, tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP) were measured from blood samples collected between 9 am and noon. Statistical analyses included Kruskal-Wallis and one-way analysis of variance tests to compare results between different groups and multivariate general linear models to evaluate the effect of sleep status on cytokine levels. **Results:** The high-disability group had the highest PSQI and ESS scores ($P < .001$). Plasma levels of IL-1β, IL-6, IL-10, and TNF-α were significantly higher in the patient groups, with the high-disability group exhibiting the highest values ($P \leq .001$). The plasma cytokine levels were significantly correlated with PSQI scores ($P < .05$). Plasma levels of IL-10 and TNF-α were significantly associated with the disability level after adjusting for both sleep indices (both $P < .05$). **Conclusion:** Patients with TMD, especially those with high disability, had elevated plasma cytokine levels and increased ESS and PSQI scores suggestive of sleep disturbance. *J Oral Facial Pain Headache 2016;30:27–33. doi: 10.11607/ofph.1367*

Keywords: *cytokine level, pain, sleep disturbance, temporomandibular disorders*

Sleep was once considered a passive state with low physiologic importance but is now recognized as a dynamic and active state that is essential for the normal functioning of an individual.[1] Furthermore, the association between disturbed sleep and chronic pain syndromes, including fibromyalgia, myofascial pain, and tension-type headache, is now well known.[2,3] A study comparing patients with temporomandibular disorders (TMD), fibromyalgia, or chronic fatigue syndrome showed that sleep disturbances were reported by approximately two-thirds of TMD patients, more than half of whom reported fatigue lasting longer than 6 months.[4] Moreover, TMD patients had a high degree of primary insomnia and associated hyperalgesia outside the orofacial region. These results suggest that disturbed sleep may eventually increase pain levels in patients with pain disorders by means of central sensitization.[5]

The mechanisms by which abnormal sleep affects pain are still unclear. Decreased sleep time impairs the immune response, and immune reactions affect sleep time and quality.[6] Changes in sleep duration alter the level of inflammatory cytokines such as C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), and interleukin (IL)-1β, IL-5, and IL-6.[7–9] Furthermore, elevated levels of CRP and IL-6 after prolonged sleep deprivation have been found to increase pain sensitivity in healthy subjects,[10] and patients with disorders highly associated with sleep problems (eg, fibromyalgia, chronic low back pain, chronic fatigue syndrome) have been found to have altered cytokine levels.[11–13] These findings suggest

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Satisfaction with Life in Orofacial Pain Disorders: Associations and Theoretical Implications

Ian A. Boggero, MS [Graduate Student]
Department of Psychology, University of Kentucky, Lexington, Kentucky, USA

Marcia V. Rojas-Ramirez, DDS, MS [Resident]
Orofacial Pain Clinic, University of Kentucky, Lexington, Kentucky, USA

Reny de Leeuw, DDS, PhD, MPH [Professor]
Orofacial Pain Clinic, University of Kentucky, Lexington, Kentucky, USA

Charles R. Carlson, PhD [Professor]
Department of Psychology, University of Kentucky, Lexington, Kentucky, USA

Abstract

Aims—To test if patients with masticatory myofascial pain, local myalgia, centrally mediated myalgia, disc displacement, capsulitis/synovitis, or continuous neuropathic pain differed in self-reported satisfaction with life. The study also tested if satisfaction with life was similarly predicted by measures of physical, emotional, and social functioning across disorders.

Methods—Satisfaction with life, fatigue, affective distress, social support, and pain data were extracted from the medical records of 343 patients seeking treatment for chronic orofacial pain. Patients were grouped by primary diagnosis assigned following their initial appointment. Satisfaction with life was compared between disorders, with and without pain intensity entered as a covariate. Disorder-specific linear regression models using physical, emotional, and social predictors of satisfaction with life were computed.

Results—Patients with centrally mediated myalgia reported significantly lower satisfaction with life than did patients with any of the other five disorders. Inclusion of pain intensity as a covariate weakened but did not eliminate the effect. Satisfaction with life was predicted by measures of physical, emotional, and social functioning, but these associations were not consistent across disorders.

Conclusions—Results suggest that reduced satisfaction with life in patients with centrally mediated myalgia is not due only to pain intensity. There may be other factors that predispose people to both reduced satisfaction with life and centrally mediated myalgia. Furthermore, the results suggest that satisfaction with life is differentially influenced by physical, emotional, and social functioning in different orofacial pain disorders.

Correspondence to: Ian A. Boggero, Department of Psychology, University of Kentucky, 111-B Kastle Hall, Lexington, KY 40506-0044, USA, ian.boggero@uky.edu.

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Comparison of Risk Factors in Patients With Acute and Chronic Orofacial Pain

Yoshifumi Honda, DDS,* Toshiyuki Handa, DDS, PhD,† Ken-ichi Fukuda, DDS, PhD,‡ Yoshihiko Koukita, DDS, PhD,§ and Tatsuya Ichinohe, DDS, PhD¶

*Department of Dental Anesthesiology, Tokyo Dental College, Japan, †Assistant Professor, Department of Dental Anesthesiology, Tokyo Dental College, Japan, ‡Professor, Division of Special Needs Dentistry and Orofacial Pain, Department of Oral Health and Clinical Science, Tokyo Dental College, Japan, §Clinical Professor, Department of Dental Anesthesiology, Tokyo Dental College, Japan, and ¶Professor, Department of Dental Anesthesiology, Tokyo Dental College, Japan

Management of patients with orofacial pain may benefit from a better understanding about patient factors that may lead pain chronicity. In this study, we retrospectively compared physical and psychological factors in patients with acute and chronic orofacial pain. We analyzed data from 854 patients presenting to the Orofacial Pain Center, Department of Dental Anesthesiology, Tokyo Dental College, Suidobashi Hospital between April 2010 and March 2014. We categorized patients into the acute group if their condition had persisted <6 months and the chronic group if their condition had lasted 6 months or longer, based on the classification by the International Association for the Study of Pain. The retrospective data were analyzed by using univariate analysis on background factors from a health questionnaire, pain evaluation sheet, and psychological test completed at the time of presentation. Multiple logistic regression was applied on these factors. Our results suggest that female gender and high trait anxiety may be involved in orofacial pain becoming chronic.

Key Words: Chronic pain; Psychological distress; Myofascial pain; Neuropathic pain; Glossodynia.

A number of studies have reported that pain is a risk factor for depression and/or anxiety.[1–4] It is estimated that approximately 70% of patients with chronic pain have depression and/or anxiety.[5–7] Various physical, psychological, and social factors are involved in chronic pain,[8] increasing the complexity of the clinical condition. It has been reported that anxiety and depression have a negative impact on treatment for chronic pain.[9] There are various chronic pain conditions occurring in the orofacial region, including neuropathic pain, myofascial pain/temporomandibular joint (TMJ) syndrome, and glossodynia.[10,11] Correct diagnosis can be difficult due to the complex anatomy and neurophysiology of the orofacial complex, as well as numerous biopsychosocial factors.[12,13]

Although previous research into the psychological state of patients with chronic orofacial pain focused on particular diseases or compared chronic pain patients with healthy individuals,[14–16] few studies in the dental field have compared the characteristics of patients with acute or chronic pain. Treatment of patients with orofacial pain may benefit from a better understanding regarding various elements of patients' backgrounds, which might lead to pain chronicity. We therefore retrospectively compared physical and psychological variables in patients with acute and chronic orofacial pain presenting to a hospital orofacial pain center.

METHODS

Subjects

Data from patients presenting with pain in the orofacial region visiting the Orofacial Pain Center, Department of Dental Anesthesiology, Tokyo Dental College Suidobashi Hospital between April 2010 and March 2014 were involved in this retrospective study. This study was approved by the Tokyo Dental College Ethics Committee (approval number 500). The requirement for written informed consent was waived by the Tokyo Dental College Ethics Committee because this study was performed by using epidemiological methodology.

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Address correspondence to Dr Yoshifumi Honda, Department of Dental Anesthesiology, Tokyo Dental College, 101-0061, Japan; hondayoshifumi@tdc.ac.jp.

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Review

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SAGE

Neuropathic orofacial pain: Facts and fiction

Lene Baad-Hansen[1,2] and Rafael Benoliel[3]

Abstract

Definition and taxonomy: This review deals with neuropathic pain of traumatic origin affecting the trigeminal nerve, i.e. painful post-traumatic trigeminal neuropathy (PTTN).

Symptomatology: The clinical characteristics of PTTN vary considerably, partly due to the type and extent of injury. Symptoms involve combinations of spontaneous and evoked pain and of positive and negative somatosensory signs. These patients are at risk of going through unnecessary dental/surgical procedures in the attempt to eradicate the cause of the pain, due to the fact that most dentists only rarely encounter PTTN.

Epidemiology: Overall, approximately 3% of patients with trigeminal nerve injuries develop PTTN. Patients are most often female above the age of 45 years, and both physical and psychological comorbidities are common.

Pathophysiology: PTTN shares many pathophysiological mechanisms with other peripheral neuropathic pain conditions.

Diagnostic considerations: PTTN may be confused with one of the regional neuralgias or other orofacial pain conditions. For intraoral PTTN, early stages are often misdiagnosed as odontogenic pain.

Pain management: Management of PTTN generally follows recommendations for peripheral neuropathic pain.

Expert opinion: International consensus on classification and taxonomy is urgently needed in order to advance the field related to this condition.

Keywords

Painful post-traumatic trigeminal neuralgia (PTTN), atypical odontalgia, neuropathic pain, orofacial pain

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Definition and taxonomy

This review deals primarily with the taxonomy, symptomatology, epidemiology, pathophysiology, diagnosis and management of the condition termed painful post-traumatic trigeminal neuropathy (PTTN) as defined (Section 13.1.2.3) in the International Classification of Headache Disorders (ICHD-3 beta) published in 2013 (1). In addition, we will review related entities such as atypical odontalgia (AO) (2), an orofacial pain condition without well-established diagnostic criteria and with significant gaps in the understanding of its pathophysiology. Originally, diagnostic criteria for AO did not include the evaluation of signs of nerve damage even though the condition was hypothesized to be neuropathic (2–7). However, at present, many consider AO as a subform of persistent idiopathic facial pain (PIFP) (ICHD 13.11), where sensory disturbances have been excluded and a neuropathic background is therefore unlikely in such patients (1). Thus, it is important to distinguish between "early criteria" AO (subsequently referred to as *early criteria AO*) (2) and "PIFP subform" AO (1). For the latter, the reader is referred to the article by Gaul and Benoliel in the present issue of *Cephalalgia*. The Classification of Chronic Pain by the International Association for the Study of Pain (IASP) is discussing the terminology for the

[1]Section of Orofacial Pain and Jaw Function, Department of Dentistry and Oral Health, Aarhus University, Aarhus, Denmark
[2]Scandinavian Center for Orofacial Neurosciences (SCON), Denmark/Sweden
[3]Rutgers School of Dental Medicine, Rutgers State University of New Jersey, Newark, NJ, USA

Corresponding author:
Lene Baad-Hansen, Section of Orofacial Pain and Jaw Function, Department of Dentistry and Oral Health, Aarhus University, Vennelyst Boulevard 9, DK-8000 Aarhus C, Denmark.
Email: lene.hansen@dent.au.dk

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Review Article

The Role of Inflammatory and Anti-Inflammatory Cytokines in the Pathogenesis of Osteoarthritis

Piotr Wojdasiewicz, Łukasz A. Poniatowski, and Dariusz Szukiewicz

Department of General and Experimental Pathology, Second Faculty of Medicine, Medical University of Warsaw, Pawińskiego 3c, 02-106 Warsaw, Poland

Correspondence should be addressed to Dariusz Szukiewicz; dszukiewicz@hotmail.com

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Osteoarthritis (OA) is the most common chronic disease of human joints. The basis of pathologic changes involves all the tissues forming the joint; already, at an early stage, it has the nature of inflammation with varying degrees of severity. An analysis of the complex relationships indicates that the processes taking place inside the joint are not merely a set that (seemingly) only includes catabolic effects. Apart from them, anti-inflammatory anabolic processes also occur continually. These phenomena are driven by various mediators, of which the key role is attributed to the interactions within the cytokine network. The most important group controlling the disease seems to be inflammatory cytokines, including IL-1β, TNFα, IL-6, IL-15, IL-17, and IL-18. The second group with antagonistic effect is formed by cytokines known as anti-inflammatory cytokines such as IL-4, IL-10, and IL-13. The role of inflammatory and anti-inflammatory cytokines in the pathogenesis of OA with respect to inter- and intracellular signaling pathways is still under investigation. This paper summarizes the current state of knowledge. The cytokine network in OA is put in the context of cells involved in this degenerative joint disease. The possibilities for further implementation of new therapeutic strategies in OA are also pointed.

1. Introduction

The most common chronic and currently regarded as potentially irreversible disease that affects the joints is osteoarthritis (OA) [1, 2]. The constantly growing number of causes for the development of the disease includes, for example, genetic predisposition, aging, obesity, trauma, and other systemic diseases (Figure 1). Although we are dealing with a diverse aetiology, which is most often the result of a number of overlapping factors, processes occur during the development of the pathomechanisms of disease at the tissue, cellular and ultrastructural level that gradually take a similar nature, resulting in the phenotypic image of OA. According to the latest medical knowledge, the participation of the immune system in the development and progression of OA is one of the key elements in the pathogenesis of the disease [3]. Currently, many independent authors are focused on identifying and describing the factors responsible for the development of inflammatory processes involved in OA [4]. An analysis of the ever-increasing number of reports directs attention to the special role of the cytokine network in the pathogenesis of OA. During the progression of OA, the production and operation of various cytokines can vary depending on the duration and severity of the disease [5]. The most important effect that cytokines have involves disturbing the catabolism and anabolism processes, particularly important in tissues that are often subject to high mechanical load, such as human joints [6]. As a result of disrupting the said balance, there is a progressive degeneration of articular cartilage performing a key role in the biomechanics of each joint and other components of the joint, which results in the development of a difficult-to-interrupt disease process that involves both inflammatory, degradation, and production processes, which together lead to a gradual loss of joint function and pain. Due to the effect of cytokines in the context of an inflammatory disease such as OA, they can be divided into inflammatory and anti-inflammatory [7]. It should be noted that the pathophysiological processes occurring in the joint affected by OA

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Experimental Methods to Inform Diagnostic Approaches for Painful TMJ Osteoarthritis

M.M. Sperry[1], S. Kartha[1], B.A. Winkelstein[1,2], and E.J. Granquist[3]

Abstract

Temporomandibular joint (TMJ) osteoarthritis (OA) is a degenerative disease of the joint that can produce persistent orofacial pain as well as functional and structural changes to its bone, cartilage, and ligaments. Despite advances in the clinical utility and reliability of the Diagnostic Criteria for Temporomandibular Disorders, clinical tools inadequately predict which patients will develop chronic TMJ pain and degeneration, limiting clinical management. The challenges of managing and treating TMJ OA are due, in part, to a limited understanding of the mechanisms contributing to the development and maintenance of TMJ pain. OA is initiated by multiple factors, including injury, aging, abnormal joint mechanics, and atypical joint shape, which can produce microtrauma, remodeling of joint tissues, and synovial inflammation. TMJ microtrauma and remodeling can increase expression of cytokines, chemokines, and catabolic factors that damage synovial tissues and can activate free nerve endings in the joint. Although studies have separately investigated inflammation-driven orofacial pain, acute activity of the trigeminal nerve, or TMJ tissue degeneration and/or damage, the temporal mechanistic factors leading to chronic TMJ pain are undefined. Limited understanding of the interaction between degeneration, intra-articular chemical factors, and pain has further restricted the development of targeted, disease-modifying drugs to help patients avoid long-term pain and invasive procedures, like TMJ replacement. A range of animal models captures features of intra-articular inflammation, joint overloading, and tissue damage. Although those models traditionally measure peripheral sensitivity as a surrogate for pain, recent studies recognize the brain's role in integrating, modulating, and interpreting nociceptive inputs in the TMJ, particularly in light of psychosocial influences on TMJ pain. The articular and neural contributors to TMJ pain, imaging modalities with clinical potential to identify TMJ OA early, and future directions for clinical management of TMJ OA are reviewed in the context of evidence in the field.

Keywords: pain, inflammation, central nervous system, animal models, joint diseases, cartilage

Introduction

Temporomandibular joint (TMJ) disorders are very common, with over 70% of the population reporting signs or symptoms (Scrivani et al. 2008). Fifteen percent of TMJ disorder (TMD) cases present as aggressive disease that is recalcitrant to therapies and lead to the development of chronic centralized pain, making TMDs the second most common musculoskeletal pain condition (National Institute of Dental and Craniofacial Research [NIDCR] 2014). Since nomenclature and terminology of TMJ disorders overlap and are used interchangeably, it is helpful to establish common terms. Internal TMJ derangement is defined by articular disc displacement (Fig. 1), pain, and joint dysfunction. Degenerative joint disease of the TMJ can occur secondary to internal derangement of the disc (Tanaka et al. 2008). Using the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) for clinical and research taxonomy, degenerative joint disease is "a degenerative disorder involving the joint characterized by deterioration of articular tissue with concomitant osseous changes in the condyle and/or articular eminence" (Schiffman et al. 2014).

Osteoarthritis (OA) describes joint degeneration with synovitis, cartilage degeneration, and subchondral bone remodeling (Fig. 1) along with joint pain (Wang et al. 2015). For TMJ disease, findings of condylar degeneration and disc displacement often occur *without* pain, and most patients experience brief pain and dysfunction (Scrivani et al. 2008). For example, anteriorly displaced discs are found in 20% of healthy, asymptomatic individuals (Haiter-Neto et al. 2002). In mild and transient pain, conservative medical management has favorable outcomes (NIDCR 2014). However, for some patients with a recalcitrant clinical course, adaptive mechanisms fail without any pathophysiological reason (Tanaka et al. 2008; Harper

[1]Department of Bioengineering, University of Pennsylvania, Philadelphia, PA, USA
[2]Department of Neurosurgery, University of Pennsylvania, Philadelphia, PA, USA
[3]Oral & Maxillofacial Surgery, University of Pennsylvania School of Medicine, Philadelphia, PA, USA

A supplemental appendix to this article is available online.

Corresponding Author:
E.J. Granquist, Oral & Maxillofacial Surgery, University of Pennsylvania School of Medicine, 3400 Spruce Street, 5th Floor White Building, Philadelphia, PA 19104, USA.
Email: Eric.Granquist@uphs.upenn.edu

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Review article

Role(s) of cytokines in pulpitis: Latest evidence and therapeutic approaches

Mohammad M.Y. Khorasani[a], Gholamhossein Hassanshahi[b,c], Aniela Brodzikowska[d], Hossein Khorramdelazad[b,c,e,*]

[a] Department of Endodontics, School of Dentistry, Rafsanjan University of Medical Sciences, Rafsanjan, Iran
[b] Molecular Medicine Research Center, Research Institute of Basic Medical Sciences, Rafsanjan University of Medical Sciences, Rafsanjan, Iran
[c] Department of Immunology, School of Medicine, Rafsanjan University of Medical Sciences, Rafsanjan, Iran
[d] Department of Conservative Dentistry, Medical University of Warsaw, Miodowa 18, 00-246 Warsaw, Poland
[e] Department of Immunology, School of Medicine, Iran University of Medical Sciences, Tehran, Iran

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ABSTRACT

Pulpitis is known as a typical inflammation of dental pulp tissue, and microorganisms of the oral microbiome are involved in this opportunistic infection. Studies indicated that several factors related to host response have a crucial role in pulpitis. Among these factors, inflammatory mediators of the immune system such as cytokines and chemokines contribute to pulpal defense mechanisms. A wide range of cytokines have been observed in dental pulp and these small molecules are able to trigger inflammation and participate in immune cell trafficking, cell proliferation, inflammation, and tissue damage in pulp space. Therefore, the aim of this review was to describe the role of cytokines in the pathogenesis of pulpitis.

1. Introduction

Pulpitis is one of the common dental disorders associated with tooth pulp inflammation [1]. In fact, microorganisms in normal flora of the mouth initiate immune responses [2]. Dental caries, trauma, dentinal cracks, unprotected main apical foramen, and dentinal tubules are important factors for microbial entry into the dental pulp and its infection [3,4]. On the other hand, immune responses are one of the main factors involved in inflammation in damaged tooth tissues. A verity of immune and non-immune cells including macrophages, dendritic cells (DCs), odontoblasts, and endothelial cells which express toll-like receptors (TLRs) as innate immune receptors in pulp tissue are able to recognize pathogen-associated molecular pattern molecules (PAMPs) and initiate immune responses [5,6]. Cytokines and chemokines are small molecule immune mediators that play an important role in growth, proliferation, differentiation, and chemotaxis due to triggerring immune responses [7,8]. These proteins are generally divided into two types, inflammatory and anti-inflammatory, and numerous studies showed that the main mediators of inflammatory responses in inflamed dental tissue and periapical lesions are monocyte chemoattractant protein-1 (MCP-1/CCL2), monocyte chemoattractant protein-2 (MCP-2/CCL8), interleukin-8 (IL-8), macrophage inflammatory protein-1 alpha (MIP-1α), macrophage inflammatory protein-1 beta (MIP-1β), CXCL10, CCL5 are [9–12]. Clinical pulpal conditions are categorized into four classes (normal, reversibly inflamed, irreversibly inflamed, and necrotic) regarding the status and symptoms of patients and examinations [13,14]. In order to determine reversible pulpitis, histological findings have shown lack of bacteria, presence of localized coagulation, and necrosis turned into fluid adjacent to irritant. However, histologic hallmarks of irreversible pulpitis are presence of bacteria or their by-products in the dental pulp, infiltration of immune cells such as neutrophils, acute inflammation, principally in the pulp tissue, under the lesion [15]. Additionally, case history, clinical and radiographic examination are potential procedures for pulpal inflammation diagnosis. Patients suffer from severe pain in both reversible and irreversible pulpitis [16]. The pulp's reaction to thermal stimulus used to differentiate between reversible and irreversible pulpitis and almost half of the patients with irreversible pulpitis do not feel pain [16]. Furthermore, in reversible pulpitis, the pulp is able to recover after elimination of the relevant stimulus whereas in irreversible pulpitis, removal of the stimulant does not help the patient, and only pulpectomy can end the pain. Accordingly, given the importance of the immune system and its components in inflammation of the dental tissue, this review was designed to summarize the role of cytokines in the pathogenesis of pulpitis.

* Corresponding author at: Molecular Medicine Research Center, Research Institute of Basic Medical Sciences, Rafsanjan University of Medical Sciences, Rafsanjan, Iran.
E-mail address: khorramdelazad@gmail.com (H. Khorramdelazad).

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Cytokines, Masticatory Muscle Inflammation, and Pain: an Update

Sara Ayoub[1] · Antoine Berbéri[2] · Mohammad Fayyad-Kazan[3,4]

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Abstract
Cytokines are proteins secreted by diverse types of immune and non-immune cells and play a role in the communication between the immune and nervous systems. Cytokines include lymphokines, monokines, chemokines, interleukins, interferons, colony stimulating factors, and growth factors. They can be both pro- and anti-inflammatory and have autocrine, paracrine, and endocrine activities. These proteins are involved in initiation and persistence of pain, and the progress of hyperalgesia and allodynia, upon stimulating nociceptive sensory neurons, and inducing central sensitization. The objective of this review is to discuss several types of pro- and anti-inflammatory mediators and their relation with inflammatory pain in masticatory muscles.

Keywords Cytokine · Inflammation · Pain · Hyperalgesia · Allodynia · Masticatory muscle

Introduction

Temporomandibular disorder (TMD) is a general term that refers to the pain and dysfunction of the temporomandibular joint (TMJ) and/or masticatory myofascial pain (MMP) (Scrivani et al. 2008). According to the Headache Classification Subcommittee of the International Headache (2004), TMD was classified as one subtype of secondary headache disorders (Headache Classification Subcommittee of the International Headache 2004). Mastication is a neuromuscular function, during which, all stomatognathic apparatus components are engaged, mainly the masticatory muscles (Lewin 1985). There are two types of primary masticatory muscles: (1) those implicated in jaw closure include the temporalis, masseter, and medial pterygoids; and (2) the lateral pterygoids which are involved in protrusion and opening of the mandible (Alomar et al. 2007). MMP, a major clinical issue, results from abnormal activity, including bruxism and/or prolonged clenching (Bender 2012). This MMP, often occurring with or without muscle injury or inflammation, has been related to central sensitization mechanism (Rammelsberg et al. 2003). In general, this pain interferes with normal muscle functions including limited range of motion or decreased bite force (Wang et al. 2017). The primary afferent neurons that have cell bodies found in the trigeminal ganglion (TG) are responsible for transmitting the sensory information, including pain, from the orofacial area to the central nervous system (CNS) (Fried et al. 2001). Therefore, a better understanding of the inflammatory biomarkers involved in MMP is necessary toward obtaining a better treatment plan.

During inflammatory response, certain inflammatory cytokines secreted by distinct cell populations, mainly immune cells, are associated with the development and persistence of pain behavior (Watkins et al. 2003). Pro- and anti-inflammatory cytokines are small signaling proteins that are secreted by immune cells and promote the interaction and communication between cells. They can act on the same cells that secrete them (autocrine signaling), on neighboring cells (paracrine signaling), or on distant target cells (endocrine signaling) (Vacchelli et al. 2013). Currently, more than 130 different cytokines have been characterized. Cytokines are pleiotropic, i.e., one cytokine can affect the activity of multiple cell types, and different cell populations can secrete the same cytokine (Miller et al. 2009b). In physiological or pathological phenomena, cytokines are secreted "by" and "in" peripheral

✉ Mohammad Fayyad-Kazan
mfayyadk@gmail.com; m.fayyadk@ul.edu.lb

Sara Ayoub
sara.ayoub.1@ul.edu.lb

Antoine Berbéri
aberberi@ul.edu.lb

[1] Department of Prosthodontics, Faculty of Dental Medicine, Lebanese University, Hadath, Beirut, Lebanon

[2] Department of Oral and Maxillofacial Surgery, Faculty of Dental Medicine, Lebanese University, Hadath, Beirut, Lebanon

[3] Laboratory of Cancer Biology and Molecular Immunology, Faculty of Sciences-I, Lebanese University, Hadath, Beirut, Lebanon

[4] Department of Natural Sciences, School of Arts and Sciences, Lebanese American University, Beirut, Lebanon

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REVIEW Open Access

Regulation of cytokines by small RNAs during skin inflammation

Rasmus O Bak and Jacob G Mikkelsen*

Abstract
Intercellular signaling by cytokines is a vital feature of the innate immune system. In skin, an inflammatory response is mediated by cytokines and an entwined network of cellular communication between T-cells and epidermal keratinocytes. Dysregulated cytokine production, orchestrated by activated T-cells homing to the skin, is believed to be the main cause of psoriasis, a common inflammatory skin disorder. Cytokines are heavily regulated at the transcriptional level, but emerging evidence suggests that regulatory mechanisms that operate after transcription play a key role in balancing the production of cytokines. Herein, we review the nature of cytokine signaling in psoriasis with particular emphasis on regulation by mRNA destabilizing elements and the potential targeting of cytokine-encoding mRNAs by miRNAs. The proposed linkage between mRNA decay mediated by AU-rich elements and miRNA association is described and discussed as a possible general feature of cytokine regulation in skin. Moreover, we describe the latest attempts to therapeutically target cytokines at the RNA level in psoriasis by exploiting the cellular RNA interference machinery. The applicability of cytokine-encoding mRNAs as future clinical drug targets is evaluated, and advances and obstacles related to topical administration of RNA-based drugs targeting the cytokine circuit in psoriasis are described.

Introduction

Cytokines are intercellular signaling proteins that serve as key modulators of the immune system and inflammation. Cells respond to extracellular stress or stimuli by operating intracellular signaling cascades that coordinate cellular gene expression through complex networks of kinase activation, protein phosphorylations, and activation of DNA-binding proteins that translate signals at the cell surface to actions of transcriptional regulation of cellular genes. Cytokines modulate the communication between cells of the immune system and between immune cells and differentiated somatic cells. Upon binding to their cognate receptor on the cell surface, cytokines trigger transcriptional changes and balance cellular activities ranging from growth to differentiation and cell survival. Cytokine-directed transcriptional induction of yet other cytokines may further enhance the innate immune response in an increasingly entangled network of signals.

Genome-wide association studies have shown that mutations of genes encoding cytokines, cytokine receptors, or downstream players in the cellular signaling cascades associated with autoimmune disease. Effectors of the different signaling cascades and the transcriptional regulation operated through these pathways have been reviewed at numerous occasions. In this review, we concentrate exclusively on the posttranscriptional mechanisms that act together to balance the expression of cytokines during inflammation. The discovery of RNA interference and the regulatory actions of small RNAs have unveiled a new world of posttranscriptional regulation and yet new layers of complexity in cellular signaling pathways that are in play during inflammation. Small non-coding RNA species, produced from intronic and intergenic regions across the mammalian genome, are key players in post-transcriptional regulatory pathways of gene expression. MicroRNAs (miRNAs) interact with mRNAs and trigger translational suppression or mRNA degradation through recruitment of cellular proteins. Short-lived RNA transcripts, such as several cytokine-encoding mRNAs, contain RNA destabilizing elements and regulatory miRNA binding motifs that may in concert contribute to stringent regulation of cytokine production. Dysregulated cytokine production is a hallmark of tissues affected by chronic inflammatory disease, and

* Correspondence: giehm@humgen.au.dk
[1] Department of Human Genetics, University of Aarhus, DK-8000 Aarhus C, Denmark
Full list of author information is available at the end of the article

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REVIEW

Neuropathic pain and cytokines: current perspectives

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Anna K Clark
Elizabeth A Old
Marzia Malcangio

Wolfson Centre for Age Related Diseases, King's College London, London, UK

Abstract: Neuropathic pain represents a major problem in clinical medicine because it causes debilitating suffering and is largely resistant to currently available analgesics. A characteristic of neuropathic pain is abnormal response to somatic sensory stimulation. Thus, patients suffering peripheral neuropathies may experience pain caused by stimuli which are normally nonpainful, such as simple touching of the skin or by changes in temperature, as well as exaggerated responses to noxious stimuli. Convincing evidence suggests that this hypersensitivity is the result of pain remaining centralized. In particular, at the first pain synapse in the dorsal horn of the spinal cord, the gain of neurons is increased and neurons begin to be activated by innocuous inputs. In recent years, it has become appreciated that a remote damage in the peripheral nervous system results in neuronal plasticity and changes in microglial and astrocyte activity, as well as infiltration of macrophages and T cells, which all contribute to central sensitization. Specifically, the release of pronociceptive factors such as cytokines and chemokines from neurons and non-neuronal cells can sensitize neurons of the first pain synapse. In this article we review the current evidence for the role of cytokines in mediating spinal neuron–non-neuronal cell communication in neuropathic pain mechanisms following peripheral nerve injury. Specific and selective control of cytokine-mediated neuronal–glia interactions results in attenuation of the hypersensitivity to both noxious and innocuous stimuli observed in neuropathic pain models, and may represent an avenue for future therapeutic intervention.

Keywords: anti-inflammatory cytokines, proinflammatory cytokines, microglia, astrocytes, first pain synapse

Introduction

Neuropathic pain is a chronic condition which arises following lesion or dysfunction of the somatosensory nervous system and may result in complex alterations in cognitive and emotional brain functions. Neuropathic pain commonly accompanies a variety of conditions, including peripheral nerve injury (postsurgical pain), central nervous system (CNS) injury (multiple sclerosis, spinal cord injury), viral infections (eg, postherpetic neuralgia), tumors, and metabolic disorders such as diabetes mellitus. In particular, chronic neuropathic pain resulting from peripheral nerve damage is a significant clinical problem which often proves refractory to current treatments, partially due to the fact that the mechanisms are insufficiently understood. Damage to a peripheral nerve results in amplification of responses to peripherally applied painful stimuli at the first synapse in the nociceptive pathway (first pain synapse), leading to excessive activity in the spinal cord. Traditionally, this phenomenon has been considered a purely neuronal response. However, extensive preclinical evidence now indicates a critical

Correspondence: Marzia Malcangio; Anna K Clark
Wolfson Centre for Age Related Diseases, King's College London, Guy's Campus, London Bridge, London, SE1 1UL, UK
Tel +44 207 848 6092
Fax +44 207 848 6165
Email marzia.malcangio@kcl.ac.uk; anna.clark@kcl.ac.uk

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Anti-inflammatory and immune-regulatory cytokines in rheumatoid arthritis

*Zhu Chen[1], Aline Bozec[2], Andreas Ramming[2] and Georg Schett[2]**

Abstract | Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by a failure of spontaneous resolution of inflammation. Although the pro-inflammatory cytokines and mediators that trigger RA have been the focus of intense investigations, the regulatory and anti-inflammatory cytokines responsible for the suppression and resolution of disease in a context-dependent manner have been less well characterized. However, knowledge of the pathways that control the suppression and resolution of inflammation in RA is clinically relevant and conceptually important for understanding the pathophysiology of the disease and for the development of treatments that enable long-term remission. Cytokine-mediated processes such as the activation of T helper 2 cells by IL-4 and IL-13, the resolution of inflammation by IL-9, IL-5-induced eosinophil expansion, IL-33-mediated macrophage polarization, the production of IL-10 by regulatory B cells and IL-27-mediated suppression of lymphoid follicle formation are all involved in governing the regulation and resolution of inflammation in RA. By better understanding these immune-regulatory signalling pathways, new therapeutic strategies for RA can be envisioned that aim to balance and resolve, rather than suppress, inflammation.

[1]*Department of Rheumatology and Immunology, The First Affiliated Hospital of the University of Science and Technology of China, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, China.*

[2]*Department of Internal Medicine 3, Friedrich Alexander University Erlangen-Nuremberg and Universitatsklinikum Erlangen, Erlangen, Germany.*

**e-mail: georg.schett@uk-erlangen.de*

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Rheumatoid arthritis (RA) is a severe inflammatory autoimmune disease that affects ~1% of the population worldwide and that is associated with substantial morbidity and mortality[1]. RA is a typical chronic disease, in which the failure of spontaneous resolution of inflammation causes the disease to persist in patients throughout their lives. Consequently, unravelling the pathways that underlie immune regulation and the resolution of inflammation are of major interest to better understand the pathophysiology of RA and to design new approaches to achieve a cure for this severe joint disease.

One of the hallmarks of RA is persistent synovitis that results from the sustained influx of immune cells into the joints. In this setting, effector T cells, together with B cells and other innate effector cells, form a complex network that promotes the production of pro-inflammatory cytokines, thereby triggering the activation of resident fibroblast-like synoviocytes and contributing to cartilage and bone damage[2,3]. Innate immune cells such as neutrophils[4] and mast cells[5] contribute to the development of synovitis, as do macrophages[6], which function through the release of pro-inflammatory cytokines (such as TNF, IL-1 and IL-6) and small-molecule mediators of inflammation (such as reactive oxygen species, nitrogen intermediates and prostanoids). For many years, the prevailing dogma was that macrophages polarize into a pro-inflammatory 'M1' phenotype in RA, leading to the production of pro-inflammatory mediators and to a reduction in regulatory and anti-inflammatory cytokines, such as transforming growth factor-β (TGFβ), IL-4, IL-13 and IL-10 (REF.[7]). However, the phenotypes of synovial macrophages in patients with RA are diverse and do not follow a strict M1 phenotype or an anti-inflammatory 'M2' phenotype[8].

Very few cytokines (if any) have exclusively pro-inflammatory or anti-inflammatory functions, but rather work in a highly context-dependent manner that varies between the disease processes and tissues involved. TNF and IL-6 are considered to be central hubs in the synovial cytokine network of RA. These cytokines stimulate osteoclast formation and the subsequent degradation of bone and cartilage, and also potently induce the release of other pro-inflammatory mediators, such as IL-1 and granulocyte-macrophage colony-stimulating factor (GM-CSF)[9–11]. Targeting TNF and IL-6 with neutralizing antibodies or, in the case of IL-6, with Janus kinase (JAK) inhibitors, is a strategy now widely used in the treatment of RA that can effectively suppress synovitis[12]. Furthermore, GM-CSF inhibition was effective in treating RA in early-phase clinical trials and is currently awaiting approval for clinical use[12]. Overall, current treatment strategies for RA tend to involve targeting pro-inflammatory

TSLP: An Epithelial Cell Cytokine that Regulates T Cell Differentiation by Conditioning Dendritic Cell Maturation

Yong-Jun Liu,[1] Vasilli Soumelis,[1] Norihiko Watanabe,[1] Tomoki Ito,[1] Yui-Hsi Wang,[1] Rene de Waal Malefyt,[2] Miyuki Omori,[3] Baohua Zhou,[3] and Steven F. Ziegler[3]

[1]Department of Immunology and Center of Cancer Immunology Research, University of Texas MD Anderson Cancer Center, Houston, Texas 77030; [2]Schering-Plough Biopharma, Palo Alto, California 94304-1104; [3]Immunology Program, Benaroya Research Institute, Seattle, Washington 98101; email: yjliu@mdanderson.org, sziegler@benaroyaresearch.org

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Key Words

inflammatory Th2, regulatory T cells, thymus, allergy, memory T cell

Abstract

Dendritic cells (DCs) are professional antigen-presenting cells that have the ability to sense infection and tissue stress, sample and present antigen to T lymphocytes, and induce different forms of immunity and tolerance. The functional versatility of DCs depends on their remarkable ability to translate collectively the information from both the invading microbes and their resident tissue microenvironments and then make an appropriate immune response. Recent progress in understanding TLR biology has illuminated the mechanisms by which DCs link innate and adaptive antimicrobial immune responses. However, how tissue microenvironments shape the function of DCs has remained elusive. Recent studies of TSLP (thymic stromal lymphopoietin), an epithelial cell–derived cytokine that strongly activates DCs, provide evidence at a molecular level that epithelial cells/tissue microenvironments directly communicate with DCs. We review recent progress on how TSLP expressed within thymus and peripheral lymphoid and nonlymphoid tissues regulates DC-mediated central tolerance, peripheral T cell homeostasis, and inflammatory Th2 responses.

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Review article

The interleukin (IL)-1 cytokine family – Balance between agonists and antagonists in inflammatory diseases

Jennifer Palomo, Damien Dietrich, Praxedis Martin, Gaby Palmer, Cem Gabay *

Division of Rheumatology, Departments of Internal Medicine Specialties and of Pathology-Immunology, University of Geneva School of Medicine, Switzerland

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ABSTRACT

The interleukin (IL)-1 family of cytokines comprises 11 members, including 7 pro-inflammatory agonists (IL-1α, IL-1β, IL-18, IL-33, IL-36α, IL-36β, IL-36γ) and 4 defined or putative antagonists (IL-1R antagonist (IL-1Ra), IL-36Ra, IL-37, and IL-38) exerting anti-inflammatory activities. Except for IL-1Ra, IL-1 cytokines do not possess a leader sequence and are secreted via an unconventional pathway. In addition, IL-1β and IL-18 are produced as biologically inert pro-peptides that require cleavage by caspase-1 in their N-terminal region to generate active proteins. N-terminal processing is also required for full activity of IL-36 cytokines. The IL-1 receptor (IL-1R) family comprises 10 members and includes cytokine-specific receptors, co-receptors and inhibitory receptors. The signaling IL-1Rs share a common structure with three extracellular immunoglobulin (Ig) domains and an intracellular Toll-like/IL-1R (TIR) domain. IL-1 cytokines bind to their specific receptor, which leads to the recruitment of a co-receptor and intracellular signaling. IL-1 cytokines induce potent inflammatory responses and their activity is tightly controlled at the level of production, protein processing and maturation, receptor binding and post-receptor signaling by naturally occurring inhibitors. Some of these inhibitors are IL-1 family antagonists, while others are IL-1R family members acting as membrane-bound or soluble decoy receptors. An imbalance between agonist and antagonist levels can lead to exaggerated inflammatory responses. Several genetic modifications or mutations associated with dysregulated IL-1 activity and autoinflammatory disorders were identified in mouse models and in patients. These findings paved the road to the successful use of IL-1 inhibitors in diseases that were previously considered as untreatable.

1. Introduction

Inflammation is a double-edged sword. On the one hand it is indispensable for host defense, but on the other hand the failure of the body to stop the inflammatory response will end in uncontrolled destruction of cells and tissue and can result in the development of chronic immune-mediated inflammatory diseases, allergies or cancer. The interleukin (IL)-1 family includes a set of cytokines, some of which have been demonstrated to play a critical role in host responses to pathogens and other noxious agents. Although detected at relatively low levels in the circulation, IL-1 cytokines induce potent inflammatory signals. The biological activity of IL-1 cytokines is controlled at the level of their production and maturation, of receptor binding, and of post-receptor signaling by naturally occurring inhibitors. Some of these inhibitors are members of the IL-1 family but exert receptor antagonist activities, while others belong to the IL-1 receptor (IL-1R) family and act as membrane-bound or soluble decoy receptors. The association of severe inflammatory syndromes with genetic deficiencies in some of these regulatory molecules has considerably increased our understanding regarding the biology of IL-1 cytokines. The objective of this article is to review the literature on natural IL-1 related cytokine inhibitors and on the clinical syndromes associated with a genetically dysregulated agonist–antagonist balance.

2. IL-1 cytokines, IL-1 receptors, and intracellular signaling

The IL-1 family of cytokines comprises 11 members, namely IL-1α, IL-1β, IL-1R antagonist (IL-1Ra), IL-18, IL-33, IL-36R antagonist (IL-36Ra), IL-36α, IL-36β, IL-36γ, IL-37, and IL-38. With the exception of IL-18 and IL-33, the genes encoding these cytokines map on chromosome 2 in both humans and mice. These cytokines share a common C-terminal three-dimensional structure with a typical β-trefoil fold consisting of 12-β-strands connected by 11 loops [1]. With the exception of IL-1Ra, IL-1 cytokines are synthesized without a hydrophobic leader sequence and are not secreted via the classical reticulum endoplasmic-Golgi pathway [2].

* Corresponding author at: Division of Rheumatology, University Hospitals of Geneva, Avenue de Beau-Séjour, 1211 Geneva 14, Switzerland.
E-mail address: cem.gabay@hcuge.ch (C. Gabay).

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REVIEWS

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Pathways for Cytokine Secretion

Amanda C. Stanley[1] and Paige Lacy[2]

[1]Institute for Molecular Bioscience, University of Queensland, St. Lucia, Queensland, Australia; and [2]Pulmonary Research Group, Department of Medicine, University of Alberta, Edmonton, Alberta, Canada

paige.lacy@ualberta.ca

Cytokine secretion is a widely studied process, although little is known regarding the specific mechanisms that regulate cytokine release. Recent findings have shed light on some of the precise molecular pathways that regulate the packaging of newly synthesized cytokines from immune cells. These findings begin to elucidate pathways and mechanisms that underpin cytokine release in all cells. In this article, we review the highlights of some of these novel discoveries.

The secretion of cytokines and chemokines from cells is a fundamental response to injury and infection in the body. Cytokines profoundly alter the body's response to cellular damage or invasive pathogens and are secreted by a wide range of cell types. Among the first cells to secrete cytokines in response to pathogenic or harmful signals are epithelial and endothelial cells, which initiate potent immune and physiological responses (101, 121). These cells signal to a variety of innate immune cells and attract these to sites of injury or infection (5, 19). Epithelial cells work in concert with the innate immune system to mount appropriate inflammatory or adaptive immune responses (101). Innate immune cells generate a substantial range of cytokines and regulate the immune response to injury or infection, and these include macrophages/monocytes, dendritic cells (DCs), natural killer (NK) cells, mast cells, eosinophils, and neutrophils. These cells collectively fulfill an essential role in immunity by controlling the opportunistic invasion of a substantial range of viral, bacterial, and parasitic pathogens and can directly recognize pathogens, or their products, through a diverse array of receptors, including pattern-recognition receptors (PRRs), such as the Toll-like receptors (TLRs) (52). Innate immune cells can combat pathogens directly via the production of cytotoxic mediators, and in many cases this is combined with phagocytosis and intracellular killing of pathogens.

Epithelial and innate immune cells possess the ability to alert or disarm the rest of the immune system through the release of a large number of pro-inflammatory and immunoregulatory cytokines and chemokines. Some of the most potent pro-inflammatory cytokines and chemokines released by innate immune cells include tumor necrosis factor (TNF), interleukin (IL)-6, IL-1β, and CCL5, and collectively they have been reviewed previously (37, 47, 112). Cytokine secretion from these cells serves as a bridge for cross-communication with other innate immune cells and, with the adaptive immune system, to regulate the amplification of inflammation and the expansion of T cells and B cells with the associated production of antibodies and cytotoxic responses. The present understanding of cytokine secretion from lymphocytes has been reviewed elsewhere (51, 54).

Recently, more information has come to light from innate immune cells regarding the distal steps of cytokine secretion from the Golgi complex through membrane-bound organelles for classical secretion involving membrane fusion and exocytosis. Cytokines may also be released through alternative pathways, such as molecular transporters, in nonclassical secretion. Understanding these intracellular pathways is important for advancing our knowledge of cellular function in innate immunity and in disease. In this review, we focus on the latest advances describing mechanisms of cytokine and chemokine release.

The Release of Cytokines Through Diverse Trafficking Pathways

Multiple secretory pathways for cytokines have been characterized in individual innate immune cells. A key function for these distinct pathways is to confer selective control over the release of cytokines into the tissue microenvironment, both spatially and temporally, and therefore to enable the development of a controlled and appropriate immune or physiological response.

Until recently, very little was known about how cytokines are secreted. New findings have shown that most cytokines are released through classical secretion. In this form of secretion, cytokines may be packaged in the Golgi for storage in secretory vesicles or granules and then secreted only during receptor-mediated release in a form of "regulated exocytosis" (54, 79, 111), or they may be released rapidly upon their synthesis through recycling endosomes (REs) and small secretory vesicles through "constitutive exocytosis" (112, 113) (FIGURE 1). Constitutive exocytosis involves trafficking of newly synthesized protein cargo that may or may not be initiated by receptor stimulation of nuclear DNA transcription and RNA translation. A secretory granule is defined as a membrane-bound intracellular organelle, found

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IL-6 in Inflammation, Immunity, and Disease

Toshio Tanaka[1,2], Masashi Narazaki[3], and Tadamitsu Kishimoto[4]

[1]Department of Clinical Application of Biologics, Osaka University Graduate School of Medicine, Osaka University, Osaka 565-0871, Japan

[2]Department of Immunopathology, World Premier International Immunology Frontier Research Center, Osaka University, Osaka 565-0871, Japan

[3]Department of Respiratory Medicine, Allergy and Rheumatic Diseases, Osaka University Graduate School of Medicine, Osaka University, Osaka 565-0871, Japan

[4]Laboratory of Immune Regulation, World Premier International Immunology Frontier Research Center, Osaka University, Osaka 565-0871, Japan

Correspondence: kishimoto@ifrec.osaka-u.ac.jp

Interleukin 6 (IL-6), promptly and transiently produced in response to infections and tissue injuries, contributes to host defense through the stimulation of acute phase responses, hematopoiesis, and immune reactions. Although its expression is strictly controlled by transcriptional and posttranscriptional mechanisms, dysregulated continual synthesis of IL-6 plays a pathological effect on chronic inflammation and autoimmunity. For this reason, tocilizumab, a humanized anti-IL-6 receptor antibody was developed. Various clinical trials have since shown the exceptional efficacy of tocilizumab, which resulted in its approval for the treatment of rheumatoid arthritis and juvenile idiopathic arthritis. Moreover, tocilizumab is expected to be effective for other intractable immune-mediated diseases. In this context, the mechanism for the continual synthesis of IL-6 needs to be elucidated to facilitate the development of more specific therapeutic approaches and analysis of the pathogenesis of specific diseases.

IL-6 is a soluble mediator with a pleiotropic effect on inflammation, immune response, and hematopoiesis. At first, distinct functions of IL-6 were studied and given distinct names based on their biological activity. For example, the name B-cell stimulatory factor 2 (BSF-2) was based on the ability to induce differentiation of activated B cells into antibody (Ab)-producing cells (Kishimoto 1985), the name hepatocyte-stimulating factor (HSF) on the effect of acute phase protein synthesis on hepatocytes, the name hybridoma growth factor (HGF) on the enhancement of growth of fusion cells between plasma cells and myeloma cells, or the name interferon (IFN)-β2 owing to its IFN antiviral activity. When the BSF-2 cDNA was successfully cloned in 1986 (Hirano et al. 1986), however, it was found that the molecules with different names studied by various groups were in fact identical, resulting in the single name IL-6 (Kishimoto 1989). Human IL-6 is made up of 212 amino acids, including a 28-amino-acid

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IMMUNOLOGY REVIEW ARTICLE

Interleukin-17 and its target genes: mechanisms of interleukin-17 function in disease

Reiko M. Onishi[1,2] and Sarah L. Gaffen[1,2]

[1]*Department of Medicine, Division of Rheumatology & Clinical Immunology, University of Pittsburgh, Pittsburgh PA, and* [2]*Department of Oral Biology, University at Buffalo, State University of New York, Buffalo NY, USA*

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Correspondence: S. L. Gaffen, University of Pittsburgh, Division of Rheumatology & Clinical Immunology, S708 Biomedical Science Tower, 3500 Terrace Street, Pittsburgh PA 15261, USA. Email: sig65@pitt.edu
Senior author: Sarah L. Gaffen

Summary

Interleukin-17 (IL-17) has emerged as a central player in the mammalian immune system. Although this cytokine exerts a host-defensive role in many infectious diseases, it promotes inflammatory pathology in autoimmunity and other settings. A myriad of studies have focused on how IL-17-producing cells are generated. However, the means by which IL-17 achieves its effects, either for the benefit or the detriment of the host, are due in large part to the induction of new gene expression. Whereas many IL-17 target genes are common to different disease states, in some cases the effects of IL-17 differ depending on the target cell, infectious site or pathogen. Gene products induced by IL-17 include cytokines (IL-6, granulocyte-colony-stimulating factor, tumour necrosis factor-α), chemokines (CXCL1, CXCL2, CCL20, among many others), inflammatory effectors (acute-phase protesins, complement) and antimicrobial proteins (defensins, mucins). Different cell types appear to respond differently to IL-17 in terms of target gene expression, with notable differences seen in mesenchymal and epithelial cells compared with cells of haematopoietic origin. Here, we summarize the major IL-17 target genes that mediate this cytokine's activities in both autoimmune and chronic diseases as well as during various types of infections.

Keywords: cytokine; gene target; interleukin-17; inflammation; signal transduction

Introduction

The interleukin-17 (IL-17) family is the most recently described subclass of cytokines.[1] Since 2000, we have started to gain an understanding of IL-17 family members and their corresponding receptors, which has led to new insights into how immunity to infections and autoimmunity are governed. To date, there are six IL-17-family ligands [IL-17A, IL-17B, IL-17C, IL-17D, IL-17E (IL-25) and IL-17F], and five receptors (IL-17RA, IL-17RB/IL-25R, IL-17RC, IL-17RD/SEF and IL-17RE).[2] Interleukin-17A (hereafter referred to as IL-17) is the most intensively studied, but interest in the rest of the family is growing.

Originally IL-17 was thought to be produced exclusively by T cells,[3] but it is now known to be secreted by a variety of innate cells including macrophages, dendritic cells (DC), natural killer, natural killer T, lymphoid tissue inducer and γδ-T cells.[4] A major development in this field occurred with the recognition that IL-17-producing $CD4^+$ T cells arise as a population distinct from the classic T helper type 1 (Th1) and Th2 cells.[5–7] Whereas it was

Abbreviations: APC, antigen-presenting cell; BAFF, B-cell activating factor; BD, β-defensin; C/EBP, CCAAT/enhancer binding protein; DC, dendritic cell; DSS, dextran sulphate sodium; EAE, experimental autoimmune encephalomyelitis; GC, germinal centre; G-CSF, granulocyte colony-stimulating factor; GWAS, genome-wide association studies; IBD, inflammatory bowel disease; IFN, interferon; IL, interleukin; Lcn2, lipocalin 2/24p3; MMP, matrix metalloproteinase; NF-κB, nuclear factor-κB; NOD, nucleotide oligomerization domain; RA, rheumatoid arthritis; RANKL, receptor activator of nuclear factor-κB ligand; SEFIR, SEF/IL17R; SLE, systemic lupus erythematosus; STAT5, signal transducer and activator of transcription 5 ; TGF, transforming growth factor; Th, T helper; TLR, Toll-like receptor; TMEV, Theiler's murine encephalomyelitis virus; TNBS, trinitrobenzene sulphonic acid; TNF, tumour necrosis factor; VV, vaccinia virus.

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OSTEOARTHRITIS JOINT PAIN: THE CYTOKINE CONNECTION

Rachel E Miller[1], **Richard J Miller**[2], and **Anne-Marie Malfait**[1,*]

[1]Departments of Internal Medicine (Division of Rheumatology) and Biochemistry, Rush University Medical Center, Chicago, IL 60612

[2]Department of Molecular Pharmacology and Biological Chemistry, Northwestern University, 303 East Chicago Avenue, Chicago, IL 60611

Abstract

Osteoarthritis is a chronic and painful disease of synovial joints. Chondrocytes, synovial cells and other cells in the joint can express and respond to cytokines and chemokines, and all of these molecules can also be detected in synovial fluid of patients with osteoarthritis. The presence of inflammatory cytokines in the osteoarthritic joint raises the question whether they may directly participate in pain generation by acting on innervating joint nociceptors. Here, we first provide a systematic discussion of the known proalgesic effects of cytokines and chemokines that have been detected in osteoarthritic joints, including TNF-α, IL-1, IL-6, IL-15, IL-10, and the chemokines, MCP-1 and fractalkine. Subsequently, we discuss what is known about their contribution to joint pain based on studies in animal models. Finally, we briefly discuss limited data available from clinical studies in human osteoarthritis.

Keywords

osteoarthritis; pain; chemokines; cytokines; animal models

1. Osteoarthritis, a Painful Joint Disease

Osteoarthritis (OA), the most prevalent form of arthritis, is a chronic and painful disease of synovial joints, most commonly the knees, hips, and hands. The prevalence of OA increases with age. OA is a leading cause of disability among older adults in the US [1] and worldwide [2]. Obesity and joint injuries are other major risk factors [3]. The most prominent symptom of OA is pain. Since effective therapies for OA and the associated joint pain are not available, this disease represents an enormous unmet medical need [4, 5].

OA pathology is characterized by progressive cellular and molecular changes in all joint tissues, including articular cartilage, subchondral bone, synovium, ligaments, and peri-

*To whom correspondence should be addressed. anne-marie_malfait@rush.edu.

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Research Article

Euphorbia bicolor (*Euphorbiaceae*) Latex Extract Reduces Inflammatory Cytokines and Oxidative Stress in a Rat Model of Orofacial Pain

Paramita Basu, Rebecca S. Hornung, Dayna L. Averitt, and Camelia Maier

Department of Biology, Texas Woman's University, Denton, 76204 TX, USA

Correspondence should be addressed to Camelia Maier; cmaier@twu.edu

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Recent studies have reported that the transient receptor potential V1 ion channel (TRPV1), a pain generator on sensory neurons, is activated and potentiated by NADPH oxidase-generated reactive oxygen species (ROS). ROS are increased by advanced oxidation protein products (AOPPs), which activate NADPH oxidase by upregulating Nox4 expression. Our previous studies reported that *Euphorbia bicolor* (*Euphorbiaceae*) latex extract induced peripheral analgesia, partly *via* TRPV1, in hindpaw-inflamed male and female rats. The present study reports that *E. bicolor* latex extract also can evoke analgesia *via* reduction of oxidative stress biomarkers and proinflammatory cytokines/chemokines in a rat model of orofacial pain. Male and female rats were injected with complete Freund's adjuvant (CFA) into the left vibrissal pad to induce orofacial inflammation, and mechanical allodynia was measured by the von Frey method. Twenty-four hours later, rats received one injection of *E. bicolor* latex extract or vehicle into the inflamed vibrissal pad. Mechanical sensitivity was reassessed at 1, 6, 24, and/or 72 hours. Trigeminal ganglia and trunk blood were collected at each time point. In the trigeminal ganglia, ROS were quantified using 2′,7′-dichlorodihydrofluorescein diacetate dye, Nox4 protein was quantified by Western blots, and cytokines/chemokines were quantified using a cytokine array. AOPPs were quantified in trunk blood using a spectrophotometric assay. *E. bicolor* latex extract significantly reduced orofacial mechanical allodynia in male and female rats at 24 and 72 hours, respectively. ROS, Nox4, and proinflammatory cytokines/chemokines were significantly reduced in the trigeminal ganglia, and plasma AOPP was significantly reduced in the trunk blood of extract-treated compared to vehicle-treated rats. *In vitro* assays indicate that *E. bicolor* latex extract possessed antioxidant activities by scavenging free radicals. Together our data indicate that the phytochemicals in *E. bicolor* latex may serve as novel therapeutics for treating oxidative stress-induced pain conditions.

1. Introduction

Pain is a major submodality of the somatosensory system that serves as a warning to alert the organism to actual injury or the threat of injury. However, pain also can develop in the absence of injury or continue following the resolution of injury leading to a transition from acute to chronic pain. Acute and chronic pain manifest as the development and maintenance of hyperalgesia and/or allodynia. The International Association for the Study of Pain defines hyperalgesia as an increased sensitivity to noxious stimuli, while allodynia is defined as an increased sensitivity to nonnoxious stimuli. The transition mechanism from acute to chronic pain is not entirely understood, and once chronic pain has developed, it is hard to treat without the long-term use of addictive opioid-based narcotics. The identification of non-opioid pharmaceutical targets is needed to improve chronic pain management.

A potential target for chronic pain management may be managing the noxious effects of oxidative stress on peripheral sensory neurons. Patients with spinal cord injury and diabetic neuropathy [1, 2] suffer from hyperalgesia and allodynia arising, in part, from oxidative stress due to either excessive formation of reactive oxygen species (ROS) or a decrease in antioxidant capacity [3]. This is supported by preclinical studies reporting that superoxide (reactive

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Role of interleukin-1β during pain and inflammation

Ke Ren[a] and **Richard Torres**[b,*]

[a]Department of Neural and Pain Sciences, Dental School & Program in Neuroscience, University of Maryland, Baltimore, MD 21201-1586, USA

[b]Regeneron Pharmaceuticals, 777 Old Saw Mill River Road, Tarrytown, NY 10591-6707, USA

Abstract

The cytokine cascade in pain and inflammatory processes is a tremendously complex system, involving glial, immune, and neuronal cell interactions. IL-1β is a pro-inflammatory cytokine that has been implicated in pain, inflammation and autoimmune conditions. This review will focus on studies that shed light on the critical role of IL-1β in various pain states, including the role of the intracellular complex, the inflammasome, which regulates IL-1β production. Evidence will be presented demonstrating the importance of IL-1β in both the induction of pain and in the maintenance of pain in chronic states, such as after nerve injury. Additionally, the involvement of IL-1β as a key mediator in the interaction between glia and neurons in pain states will be discussed. Taken together, the evidence presented in the current review showing the importance of IL-1β in animal and human pain states, suggests that blockade of IL-1β be considered as a therapeutic opportunity.

1. Interleukin-1

Interleukin-1 α and β are prototypic proinflammatory cytokines that exert pleiotrophic effects on a variety of cells and play key roles in acute and chronic inflammatory and autoimmune disorders. There are two IL-1 receptors, IL-1 type 1 receptor (IL-1RI) and IL-1 type 2 receptor (IL-1 RII). IL-1α and IL-1β signal through IL-1RI. Binding to IL-1RII does not lead to cell signaling and it is therefore considered a decoy receptor. Upon binding of IL-1 to IL-1RI, a second receptor termed IL1 receptor accessory protein (IL-1RAcP) gets recruited at the cell membrane to form a high affinity binding receptor complex leading to intracellular signaling. A third IL-1 family member, IL-1 receptor antagonist (IL-1ra), binds to IL-1 receptors and prevents the interaction of IL-1 with its receptors, acting as a natural IL-1 inhibitor (reviewed in Dinarello, 1996 and Braddock and Quinn, 2004) This review will focus on the role of IL-1β in painful and inflammatory conditions.

IL-1β has important homeostatic functions in the normal organism, such as in the regulation of feeding, sleep, and temperature (reviewed in Dinarello, 1996). However, overproduction of IL-1β is implicated in the pathophysiological changes that occur during different disease states, such as rheumatoid arthritis, neuropathic pain, inflammatory bowel disease, osteoarthritis, vascular disease, multiple sclerosis, and Alzheimer's disease (reviewed in Dinarello, 1996; Braddock and Quinn, 2004, and Dinarello, 2004). IL-1β can be released from keratinocytes, fibroblasts, synoviocytes, endothelial, neuronal, immune cells such as macrophages and mast cells, and glial cells such as Schwann cells, microglia and astrocytes (Watkins et al., 1995; Copray et al., 2001; Shamash et al., 2002; Sommer and Kress, 2004;

*Corresponding author. richard.torres@regeneron.com (R. Torres)..

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Article

CGRP Induces Differential Regulation of Cytokines from Satellite Glial Cells in Trigeminal Ganglia and Orofacial Nociception

Shaista Afroz [1], Rieko Arakaki [2], Takuma Iwasa [1], Masamitsu Oshima [1], Maki Hosoki [1], Miho Inoue [1], Otto Baba [3], Yoshihiro Okayama [4] and Yoshizo Matsuka [1,*]

1 Department of Stomatognathic Function and Occlusal Reconstruction, Graduate School of Biomedical Sciences, Tokushima University, Tokushima 770-8504, Japan; shaista_afroz@yahoo.com (S.A.); c301551017@tokushima-u.ac.jp (T.I.); m-oshima@tokushima-u.ac.jp (M.O.); hosoki@tokushima-u.ac.jp (M.H.); inoue.miho@tokushima-u.ac.jp (M.I.)
2 Department of Oral Molecular Pathology, Graduate School of Biomedical Sciences, Tokushima University, Tokushima 770-8504, Japan; arakaki.r@tokushima-u.ac.jp
3 Department of Oral and Maxillofacial Anatomy, Graduate School of Biomedical Sciences, Tokushima University, Tokushima 770-8504, Japan; baba.otto@tokushima-u.ac.jp
4 Clinical Trial Center for Developmental Therapeutics, Tokushima University Hospital, Tokushima 770-8503, Japan; y-okayama@tokushima-u.ac.jp
* Correspondence: matsuka@tokushima-u.ac.jp; Tel.: +81-88-633-7350; Fax: +81-88-633-7391

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Abstract: Neuron-glia interactions contribute to pain initiation and sustainment. Intra-ganglionic (IG) secretion of calcitonin gene-related peptide (CGRP) in the trigeminal ganglion (TG) modulates pain transmission through neuron-glia signaling, contributing to various orofacial pain conditions. The present study aimed to investigate the role of satellite glial cells (SGC) in TG in causing cytokine-related orofacial nociception in response to IG administration of CGRP. For that purpose, CGRP alone (10 µL of 10^{-5} M), Minocycline (5 µL containing 10 µg) followed by CGRP with one hour gap (Min + CGRP) were administered directly inside the TG in independent experiments. Rats were evaluated for thermal hyperalgesia at 6 and 24 h post-injection using an operant orofacial pain assessment device (OPAD) at three temperatures (37, 45 and 10 °C). Quantitative real-time PCR was performed to evaluate the mRNA expression of IL-1β, IL-6, TNF-α, IL-1 receptor antagonist (IL-1RA), sodium channel 1.7 (NaV 1.7, for assessment of neuronal activation) and glial fibrillary acidic protein (GFAP, a marker of glial activation). The cytokines released in culture media from purified glial cells were evaluated using antibody cytokine array. IG CGRP caused heat hyperalgesia between 6–24 h (paired-*t* test, $p < 0.05$). Between 1 to 6 h the mRNA and protein expressions of GFAP was increased in parallel with an increase in the mRNA expression of pro-inflammatory cytokines IL-1β and anti-inflammatory cytokine IL-1RA and NaV1.7 (one-way ANOVA followed by Dunnett's post hoc test, $p < 0.05$). To investigate whether glial inhibition is useful to prevent nociception symptoms, Minocycline (glial inhibitor) was administered IG 1 h before CGRP injection. Minocycline reversed CGRP-induced thermal nociception, glial activity, and down-regulated IL-1β and IL-6 cytokines significantly at 6 h (*t*-test, $p < 0.05$). Purified glial cells in culture showed an increase in release of 20 cytokines after stimulation with CGRP. Our findings demonstrate that SGCs in the sensory ganglia contribute to the occurrence of pain via cytokine expression and that glial inhibition can effectively control the development of nociception.

Keywords: satellite glial cells; calcitonin gene related peptide; cytokine; trigeminal ganglion; thermal hyperalgesia

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Views and Perspectives

COVID-19 is a Real Headache!

Hayrunnisa Bolay, MD, PhD; Ahmet Gül, MD; Betül Baykan, MD

After the emergence of a novel coronavirus named SARS-CoV-2, coronavirus disease 2019 (COVID-19) was initially characterized by fever, sore throat, cough, and dyspnea, mainly manifestations of respiratory system. However, other manifestations such as headache, abdominal pain, diarrhea, loss of taste and smell were added to the clinical spectrum, during the course of the COVID-19 pandemic. The reports on the neurological findings are increasing rapidly and headache seems to be the leader on the symptom list. Headache was reported in 11%-34% of the hospitalized COVID-19 patients, but clinical features of these headaches were totally missing in available publications. According to our initial experience, significant features of headache presentation in the symptomatic COVID-19 patients were new-onset, moderate-severe, bilateral headache with pulsating or pressing quality in the temporoparietal, forehead or periorbital region. The most striking features of the headache were sudden to gradual onset and poor response to common analgesics, or high relapse rate, that was limited to the active phase of the COVID-19. Symptomatic COVID-19 patients, around 6%-10%, also reported headache as a presenting symptom. The possible pathophysiological mechanisms of headache include activation of peripheral trigeminal nerve endings by the SARS-CoV-2 directly or through the vasculopathy and/or increased circulating pro-inflammatory cytokines and hypoxia. We concluded that as a common non-respiratory symptom of COVID-19, headache should not be overlooked, and its characteristics should be recorded with scrutiny.

Key words: coronavirus disease 2019, headache symptoms, headache pathophysiology, angiotensin-converting enzyme 2, vasculopathy, inflammatory mediators

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After the emergence of a novel coronavirus named SARS-CoV-2, causing coronavirus disease 2019 (COVID-19) with a severe and deadly pneumonia in Wuhan, China, our known world has changed dramatically. COVID-19 is initially characterized by fever, sore throat, cough, and dyspnea, mainly manifestations of respiratory system.[1,2] However, other manifestations such as headache, abdominal pain, diarrhea, loss of taste and smell, and frost bite like skin lesions have been added to the clinical spectrum, during the follow-up of increased number of patients within 3 months. Neurologists are involved in many places together with all other physicians and health personnel in the war against the pandemic. Nowadays, the reports on the neurological findings are increasing rapidly and headache seems to be the leader on the symptom list.

The available reports related to headache symptom in patients with COVID-19 do not contain any details about headache characteristics (Table 1).[1-13] A recent meta-analysis (n = 3598 patients) and a handful of

From the Department of Neurology and Algology, Gazi University, Ankara, Turkey (H. Bolay); Istanbul Faculty of Medicine, Department of Rheumatology, Istanbul University, Istanbul, Turkey (A. Gül); Istanbul Faculty of Medicine, Department of Neurology, Headache Center, Istanbul University, Istanbul, Turkey (B. Baykan).

Address all correspondence to H. Bolay, Department of Neurology & Algology, Neuropsychiatry Center, Neuroscience and Neurotechnology Center (NÖROM), Gazi University Hospital, Besevler, 06510 Ankara, Turkey, email: hbolay@gazi.edu.tr

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REVIEW ARTICLE

Interleukin-6 in oral diseases: a review

L Nibali[1], S Fedele[2], F D'Aiuto[1], N Donos[1]

[1]*Periodontology Unit and Department of Clinical Research, UCL Eastman Dental Institute, University College London, London;*
[2]*Oral Medicine Unit and Department of Clinical Research, UCL Eastman Dental Institute, University College London, London, UK*

Interleukin-6 (IL-6) is a pleomorphic cytokine involved in a number of physiologic and pathologic processes including response to trauma and infection and development and progression of inflammation and malignancy. IL-6 is emerging as an important mediator and novel therapeutic target for chronic inflammatory diseases and cancer. The present study reviews the available evidence regarding the association between IL-6 and a range of oral diseases including infections (periodontal disease and endodontic infections), immunologically mediated disorders (oral lichen planus and Sjögren's syndrome) and malignancy (oral cancer and precancer). The role of common genetic variants of IL-6 in determining individual susceptibility to certain oral diseases, as well as novel therapeutic strategies based on IL-6 inhibition are also discussed.

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Keywords: interleukin-6; oral diseases; periodontitis; lichen planus; oral cancer; Sjögren's syndrome

Introduction

Cytokines are soluble proteins that play an important role in the initiation and maintenance of inflammatory and immune responses as well as intercellular cross-talking. Interleukin-6 (IL-6) is a multifunctional cytokine synthesized in response to stimuli such as infection and trauma (Kishimoto *et al*, 1995) by a variety of cells such as macrophages, neutrophils, keratinocytes, fibroblasts, and endothelial cells (Matsuki *et al*, 1992). IL-6 cell signals are transmitted through a receptor expressed in a wide range of target cell types. In addition to this, a soluble IL-6 receptor (sIL-6R) enables to widen the repertoire of cells responsive to IL-6 (Jones *et al*, 2001). IL-6 is able to stimulate a number of biologic processes including antibody (and autoantibody) production, activation of T cells, B cell differentiation, increase in acute-phase proteins, hematopoiesis, induction of angiogenesis, vascular permeability, and osteoclast differentiation (Hirano *et al*, 1988; Ridker *et al*, 1997). It is also a strong stimulator of hepcidin, a liver-produced hormone that regulates intestinal iron absorption (Hohaus *et al*, 2010), potentially contributing to sideropenic anemia in chronic inflammation. IL-6 activity in inflammation is considered double-edged, acting both as anti-inflammatory (e.g., downregulation of neutrophil recruitment and proinflammatory cytokine expression) (Schindler *et al*, 1990); Xing *et al*, 1998) but also as proinflammatory (e.g., induction of acute-phase reactants by the liver) in chronic diseases (Jones *et al*, 2001). IL-6 is also believed to have growth factor properties regarding the development and progression of many types of cancers (Barton, 2005; Nishimoto, 2010). Because of these multifaceted abilities, it is thought that individual variability in the ability to synthesize and release IL-6 may modulate the susceptibility, development, and progression of a number of autoimmune and inflammatory diseases (such as atherosclerosis, rheumatoid arthritis, systemic-onset juvenile idiopathic arthritis, and Castleman's disease) and malignancies (myeloma and mesothelioma) (Moreau *et al*, 2000; Park *et al*, 2007; Packard and Libby, 2008; Nishimoto, 2010). An association between low circulating IL-6 levels and longevity has recently been shown in a study on elderly individuals (Wassel *et al*, 2010). Furthermore, IL-6 inhibition therapy has been shown to give some promising beneficial effects in the treatment of rheumatoid arthritis (Patel and Moreland, 2010). A number of common oral diseases including oral cancer, lichen planus, and periodontal diseases have been recently reported to be associated with IL-6 deregulation. The aim of this study is to review the evidence regarding the expression of IL-6 in individuals with oral diseases and discuss potential diagnostic and therapeutic implications.

Correspondence: Luigi Nibali, Periodontology Unit and Department of Clinical Research, UCL Eastman Dental Institute, University College London, 256 Gray's Inn Road, London WC1X 8LD, UK. Tel: 0044 207 915 1086, Fax: 0044 207 915 1137, E-mail: l.nibali@ucl.ac.uk
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IL-6 in dental and periodontal disease

Periodontitis

The most common forms of periodontal diseases are gingivitis (plaque-induced inflammation of the marginal

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Research article

IL-10 and CXCL2 in trigeminal ganglia in neuropathic pain

Takuma Iwasa[a], Shaista Afroz[a], Miho Inoue[a], Rieko Arakaki[b], Masamitsu Oshima[a], Resmi Raju[a], Arief Waskitho[a], Masahisa Inoue[c], Otto Baba[d], Yoshizo Matsuka[a,*]

[a] Department of Stomatognathic Function and Occlusal Reconstruction, Graduate School of Biomedical Sciences, Tokushima University, Japan
[b] Department of Oral Molecular Pathology, Graduate School of Biomedical Sciences, Tokushima University, Japan
[c] Laboratories for Structure and Function Research, Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Japan
[d] Department of Oral and Maxillofacial Anatomy, Graduate School of Biomedical Sciences, Tokushima University, Japan

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ABSTRACT

Many trigeminal neuropathic pain patients suffer severe chronic pain. The neuropathic pain might be related with cross-excitation of the neighboring neurons and satellite glial cells (SGCs) in the sensory ganglia and increasing the pain signals from the peripheral tissue to the central nervous system. We induced trigeminal neuropathic pain by infraorbital nerve constriction injury (IONC) in Sprague-Dawley rats. We tested cytokine (CXCL2 and IL-10) levels in trigeminal ganglia (TGs) after trigeminal neuropathic pain induction, and the effect of direct injection of the anti-CXCL2 and recombinant IL-10 into TG. We found that IONC induced pain behavior. Additionally, IONC induced satellite glial cell activation in TG and cytokine levels of TGs were changed after IONC. CXCL2 levels increased on day 1 of neuropathic pain induction and decreased gradually, with IL-10 levels showing the opposite trend. Recombinant IL-10 or anti-CXCL2 injection into TG decreased pain behavior. Our results show that IL-10 or anti-CXCL2 are therapy options for neuropathic pain.

1. Introduction

Peripheral nerve injury induces neuropathic pain and neuronal hyperexcitation within sensory ganglia [1]. Although it has been reported that there are no synaptic contacts in sensory ganglia [2,3], depolarized sensory neuron somata can induce cross-excitation by activating neighboring neurons in the same ganglion [4], and this appears to be chemically mediated [5]. Some studies have reported that neurotransmitters such as substance P, calcitonin gene-related peptide (CGRP), and adenosine triphosphate are released from the somata of neurons in sensory ganglia [6–10], and go on to excite neurons [11,12]. The release of these neurotransmitters is reported to be increased in inflammatory and neuropathic pain conditions [7,13].

It has also been reported that cytokines are released from trigeminal ganglion (TG) glial-rich cultures [14,15]. The cytokines released may affect neighboring sensory neurons or the other satellite glial cells (SGCs) in the TGs. For instance, SGCs modulate the excitation of TG neurons through interleukin-1β (IL-1β) [16] and CGRP enhances communication between purinergic neurons and glial cells [17]. In some pain models, such as neuropathic pain and migraine, SGC activity increases cytokine release [18,19]. These reports showed that neuropathic pain might induce the cross-excitation of neighboring neurons and SGCs in the sensory ganglia, and increase pain signals from the peripheral tissue to the central nervous system.

One cytokine, chemokine (C-X-C motif) ligand 2 (CXCL2) also known as macrophage inflammatory protein 2-α belongs to the CXC chemokine family, along with growth-regulated protein β and Gro oncogene-2. CXCL2 is 90% identical in amino acid sequence to the related chemokine, CXCL1. This chemokine is reported to be secreted by monocytes and macrophages, and is chemotactic for polymorphonuclear leukocytes and hematopoietic stem cells [20–22]. It has been reported that CXCL2 and its receptor are up-regulated in neutrophils and macrophages that accumulate in injured sciatic nerves, and that this might elicit chronic neuroinflammation through neutrophil accumulation, leading to neuropathic pain [23].

IL-10 is a cytokine produced from type 2 helper T cells, activated B cells, monocytes, mast cells and keratinocytes. Its bioactivity varies widely, but it has a distinctly different feature from other cytokines of inhibitory activity. IL-10 mainly acts on monocyte line cells to suppress immune function, including the production of inflammatory cytokines

Abbreviations: GFAP, glial fibrillary acidic protein; CGRP, calcitonin gene-related peptide; CXCL2, chemokine (C-X-C motif) ligand 2; DRG, dorsal root ganglion; IONC, infraorbital nerve constriction; IL-1β, interleukin-1β; IL-10, Interleukin-10; SGCs, satellite glial cells; TG, trigeminal ganglion

* Corresponding author at: Department of Stomatognathic Function and Occlusal Reconstruction, Graduate School of Biomedical Sciences, Tokushima University, 3-18-15 Kuramoto-cho, Tokushima, 770-8504, Japan.
E-mail address: matsuka@tokushima-u.ac.jp (Y. Matsuka).

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ARTICLE

A correlative analysis between inflammatory cytokines and trigeminal neuralgia or hemifacial spasm

Ming-Xing Liu, Jun Zhong, Lei Xia, Ning-Ning Dou and Shi-Ting Li

Department of Neurosurgery, XinHua Hospital (The Cranial Nerve Disease Center of Shanghai), Shanghai JiaoTong University School of Medicine, Shanghai, China

ABSTRACT

Background: It is necessary to understand the mechanism of trigeminal neuralgia (TN) and hemifacial spasm (HFS) in order to seek for an effective noninvasive remedy. As previous studies implied that inflammatory cytokines induced by demyelination following the nerve injury may be the initiated factor causing neuropathic pain, we attempt to analyze the correlation between cytokines and these hyperactive cranial nerve disorders.

Method: The consecutive patients whose diagnosis were confirmed by microvascular decompression surgery as primary TN or HFS caused by vascular compression and healthy volunteers between March and May 2018 in XinHua Hospital Shanghai JiaoTong University School of Medicine were recruited. Preoperatively, venous blood was collected and the protein concentrations of IL-1β, IL-2, IL-6, IL-8, IL-10, TNF-α and IFN-γ were determined with ELISA. Each cytokine was compared between the patients and healthy volunteers.

Results: Ultimately, 28 healthy volunteers as well as 44 TN and 47 HFS patients were enrolled in this investigation. The serum levels of IL-1β, IL-6, IL-8 and TNF-α in either HFS or TN patients were significantly higher than that in healthy volunteers ($p < 0.05$), yet which were similar between TN and HFS patients ($p > 0.05$). Besides, there was a significantly correlation between IL-6 concentration and severity of HFS ($r = 0.933$, $p < 0.05$) or TN ($r = 0.943$, $p < 0.05$).

Discussion: Vascular compression of trigeminal or facial nerve roots may induce a rise in variety of cytokines, and IL-6 may play an important role in the signaling pathways to generate ectopic impulses from these cranial nerves.

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Inflammatory cytokines; trigeminal neuralgia; hemifacial spasm; interleukin-6(IL-6); cranial nerves; vascular compression

Introduction

Both trigeminal neuralgia (TN) and hemifacial spasm (HFS) are common hyperactive cranial nerve disorders attributable to vascular loops compression [1–4]. This etiology has been clarified by the major pathological findings of axonal loss or demyelination in the compressed cranial nerve root and verified by successful microvascular decompression (MVD) surgery [2,5,6]. Although MVD has led to a very high postoperative cure today, this sort of open brain operation is invasive and sometimes may result in fatal complications [7,8]. Therefore, it is necessary to investigate the underlying pathogenesis of these cranial nerve hyperexcitability disorders in order to seek for an effective noninvasive remedy. Researches have demonstrated that the nature of the episode of pain or spasm is the ectopic action potential ignited by sodium channels emerged from the compressed nerve [3,9–11]. Based on these evidences we proposed a hypothesis on the pathogenesis:

> A certain degree of vascular compression give rise to demyelination of the suffered nerve root inducing emergence of transmembrane sodium channels upon the axons; with some trigger factors (e.g. transient fluctuations of blood pressure or pulse), these voltage-gated channels reach threshold and generate conductible action potentials from the damaged nerve eventually [6,12,13].

Accordingly, if we can block the signaling pathway from the demyelination to synthesis of sodium channels, we may cease the generation of ectopic action potentials and finally relieve the pain or spam for TN or HFS patients noninvasively.

When the nerve was injured, Schwann cells and macrophages phagocytize the degenerated myelin producing cytokines which further aggravate demyelination [14–17]. The role of cytokine-mediated neuroimmune interactions in the development and persistence of pain has been extensively studied [18–21]. For instance, intraneural application of inflammatory cytokines may induce behavioral signs associated with pain, and application of anti-inflammatory cytokines may induce analgesic action in animal models [22,23]. Through human nerve biopsies and serum analyses, studies showed that several inflammatory cytokines, *e.g.* IL-1, IL-2, IL-6, IL-8, TNF and IFN, were elevated in patients with painful neuropathies compared to non-painful neuropathies [19,24–26]. Consequently, it is possible that

CONTACT Jun Zhong ZhongJun@XinHuaMed.com.cn; Shi-Ting Li lishiting@XinHuaMed.com.cn Department of Neurosurgery, XinHua Hospital (The Cranial Nerve Disease Center of Shanghai), Shanghai JiaoTong University School of Medicine, 1665 KongJiang Rd, Shanghai 200092, China

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Review

PRO- *versus* ANTI-INFLAMMATORY CYTOKINES: MYTH OR REALITY

Jean-Marc CAVAILLON

Department of Physiopathology, Institut Pasteur, 28 rue Dr. Roux, 75015 Paris, France
Fax: +33 (0)1 40 61 31 60; E-mail: jmcavail@pasteur.fr

Received November 8, 2000; Accepted November 17, 2000

Abstract - Inflammation is characterized by an interplay between pro- and anti-inflammatory cytokines. Cytokines are commonly classified in one or the other category: interleukin-1 (IL-1), tumor necrosis factor (TNF), gamma-interferon (IFN-γ), IL-12, IL-18 and granulocyte-macrophage colony stimulating factor are well characterized as pro-inflammatory cytokines whereas IL-4, IL-10, IL-13, IFN-α and transforming growth factor-β are recognized as anti-inflammatory cytokines. In this review, we point out that this classification is far too simplistic and we provide numerous examples illustrating that a given cytokine may behave as a pro- as well as an anti-inflammatory cytokine. Indeed, the cytokine amount, the nature of the target cell, the nature of the activating signal, the nature of produced cytokines, the timing, the sequence of cytokine action and even the experimental model are parameters which greatly influence cytokine properties.

Key words: Inflammation, interleukin, chemokine, macrophages, neutrophils, endothelial cells

INTRODUCTION

Cytokines play an important role during the inflammatory process. Two cytokines, namely interleukin-1 (IL-1) and tumor necrosis factor (TNF) orchestrate the inflammatory response and initiate a cascade of mediators which are directly responsible for the various events associated with inflammation (e.g. increased vascular permeability, chemoattraction of circulating leukocytes, proteolysis…). Other cytokines such as IL-3 and granulocyte-macrophage colony stimulating factor (GM-CSF) amplify the release of IL-1 and TNF, thus favoring the inflammatory process. This is also the case for gamma-interferon (IFN-γ) the production of which is induced by IL-12 and IL-18. While the cytokines mentioned above are classified as "pro-inflammatory cytokines", IL-4, IL-10, IL-13, interferon-alpha (IFN-α) and transforming growth factor-β (TGF-β) are recognized as anti-inflammatory cytokines because of their ability to inhibit the release of pro-inflammatory cytokines, to induce the production of IL-1 receptor antagonist (IL-1ra) and the release of soluble TNF receptor (sTNFR) and to limit some of the pro-inflammatory activities of IL-1 and TNF. However, the events occurring during inflammation are not as simplistic as an interplay between pro- and anti-inflammatory actors. Indeed, they are far more complex ! In this short review we will provide some examples which illustrate the fact that each of these cytokines offers a "half angel - half devil" aspect and none can be simply labelled either "pro" or "anti".

A TOO SIMPLISTIC DICHOTOMY

René Magritte, the surrealistic Belgium artist, painted a pipe on a picture and wrote "Ceci n'est pas une pipe" (*This is not a pipe*). It is becoming more and more frequent to find reports reminiscent of this concept: e.g. "TNF is not a pro-inflammatory cytokine". For example, in their report entitled "TNF is a potent anti-inflammatory cytokine in autoimmune-mediated demyelination" Liu *et al.* (42) showed that in response to injection of myelin oligodendrocyte glycoprotein, TNF-deficient mice of different genetic backgrounds displayed a multiple sclerosis-like disease with a higher incidence, a higher mortality, a longer duration and a more severe auto-immune disease than their wild type counterparts. Similarly, in an experimental model of collagen-induced arthritis, it was found that blocking the activity of IFN-γ (either by anti-IFN-γ antiserum or by using IFN-γ receptor

ORIGINAL ARTICLE

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Pro-inflammatory cytokines in saliva of adolescents with dental caries disease

Agnieszka Gornowicz[1], Anna Bielawska[1], Krzysztof Bielawski[2], Stanisława Zyta Grabowska[3], Anna Wójcicka[3], Magdalena Zalewska[4], Elżbieta Maciorkowska[5]

[1] *Department of Biotechnology, Medical University, Bialystok, Poland*
[2] *Department of Synthesis and Technology of Drugs, Medical University, Bialystok, Poland*
[3] *Maxillofacial and Plastic Surgery Clinic, Bialystok, Poland*
[4] *Department of Public Health, University of Bialystok, Bialystok, Poland*
[5] *Department of Developmental Period Medicine and Paediatric Nursing, Medical University, Bialystok, Poland*

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Abstract

Introduction and Objective: Dental caries is an inflammatory disease with multifactorial etiology. The presented study was conducted to test the hypothesis that the elevation of salivary cytokines – interleukin-6 (IL-6), interleukin-8 (IL-8) and tumour necrosis factor (TNF-α) is changed in dental caries patients. IL-6, IL-8 and TNF-α are particularly relevant to inflammation, one of the very first responses of the host to a pathological insult.

Materials and Methods: Whole saliva from 26 patients with dental caries, as well as 10 healthy persons, was investigated for the presence of IL-6, IL-8 and TNF-α by enzyme immunoassay – ELISA.

Results: The results showed that an elevation of IL-6, IL-8 and TNF-α in unstimulated whole saliva in subjects with dental caries, compared with controls, increased and was statistically significant in all cases ($p < 0.05$). The study also show a positive correlation between TNF-α and IL-8.

Conclusions: These data suggest links between the production of tumour necrosis factor (TNF-α), interleukin-6 (IL-6), interleukin-8 (IL-8) in saliva and dental caries disease.

Key words

dental caries, saliva, interleukin-6, interleukin-8, tumour necrosis factor α, inflammation

INTRODUCTION

Dental caries is an infectious disease with multifactorial etiology [1]. A large number of research studies have been carried out to discover the cause of this disease. The process of dental caries is now well understood and is determined by a dynamic balance between pathological factors (acidogenic bacteria, reduced salivary function) and protective factors (proteins, fluoride, calcium, phosphate) [2]. It is also well known that saliva secretion and salivary components are important for dental health. Inorganic and organic components in saliva may influence the colonization and elimination of microorganisms from the oral cavity [3, 4]. Bacteria colonize the oral cavity and lead to the process of inflammation. These lesions induce both innate and adaptive immune responses by the host [2]. The predominant cell types within periapical lesions are neutrophils, macrophages, T- and B-lymphocytes, mast cells, osteoclasts, osteoblasts, and fibroblasts. These cells express a large number of proinflammatory cytokines, including interleukin IL-6, IL-4, IL-1-β, IL-1-α, tumour necrosis factor (TNF-α), and lymphotoxin-α [5, 6]. These cytokines are likely released into the systemic circulation, since animal models indicate that proinflammatory cytokine concentrations are higher within the serum of animals with periapical lesions. The concentrations of proinflammatory cytokines are also elevated within both the serum and gingival tissues of persons with periodontal inflammation, and may contribute to a systemic hyperinflammatory state, which is a risk factor for several types of systemic diseases [7].

The role of TNF-α in host defence and inflammatory responses is well documented [8, 9]. TNF-α is reported to promote the inflammatory cell infiltration by leukocyte adhesion molecules on endothelial cells and activate phagocyte killing mechanisms. TNF-α is a proinflammatory cytokine that was originally discovered as a protein with necrotizing effects in certain transplantable mouse tumors, and is now recognized as a cytokine with pleiotropic biological capacities. Besides its cytostatic and cytotoxic effects on certain tumour cells, TNF-α influences growth, differentiation, and/or the function of virtually every cell type investigated. Moreover, TNF-α is thought to be part of an integral network of interactive signals that orchestrate inflammatory and immunological events [8, 9].

IL-6 is a multifunctional cytokine playing a central role in inflammation and tissue injury [10]. Its levels positively correlate with higher all-cause mortality, unstable angina, propensity to diabetes and its complications, hypertension, and obesity. Moreover, proinflammatory cytokines were revealed to be sensitive systemic markers of tissue damage, and predictive of future adverse cardiac events among apparently healthy men. IL-6 and TNF-α levels have been shown in periapical lesions and in the liver of rats with induced periapical abscesses [10].

Address for correspondence: Anna Bielawska, Department of Biotechnology, Medical University, Kilinskiego 1, 15-089 Bialystok, Poland.
E-mail: aniabiel@umb.edu.pl

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Review Article

Dental Pulp Defence and Repair Mechanisms in Dental Caries

Jean-Christophe Farges,[1,2,3] Brigitte Alliot-Licht,[4] Emmanuelle Renard,[4] Maxime Ducret,[1,2,3] Alexis Gaudin,[4] Anthony J. Smith,[5] and Paul R. Cooper[5]

[1]*Institut de Biologie et Chimie des Protéines, Laboratoire de Biologie Tissulaire et Ingénierie Thérapeutique, UMR 5305 CNRS, Université Lyon 1, 69367 Lyon, France*
[2]*Faculté d'Odontologie, Université de Lyon, Université Lyon 1, 69372 Lyon, France*
[3]*Hospices Civils de Lyon, Service de Consultations et de Traitements Dentaires, 69008 Lyon, France*
[4]*INSERM UMR 1064, Centre de Recherche en Transplantation et Immunologie, Université de Nantes, Faculté d'Odontologie, 44042 Nantes, France*
[5]*Oral Biology, School of Dentistry, College of Medical and Dental Sciences, University of Birmingham, Birmingham B4 6NN, UK*

Correspondence should be addressed to Jean-Christophe Farges; jean-christophe.farges@univ-lyon1.fr

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Dental caries is a chronic infectious disease resulting from the penetration of oral bacteria into the enamel and dentin. Microorganisms subsequently trigger inflammatory responses in the dental pulp. These events can lead to pulp healing if the infection is not too severe following the removal of diseased enamel and dentin tissues and clinical restoration of the tooth. However, chronic inflammation often persists in the pulp despite treatment, inducing permanent loss of normal tissue and reducing innate repair capacities. For complete tooth healing the formation of a reactionary/reparative dentin barrier to distance and protect the pulp from infectious agents and restorative materials is required. Clinical and *in vitro* experimental data clearly indicate that dentin barrier formation only occurs when pulp inflammation and infection are minimised, thus enabling reestablishment of tissue homeostasis and health. Therefore, promoting the resolution of pulp inflammation may provide a valuable therapeutic opportunity to ensure the sustainability of dental treatments. This paper focusses on key cellular and molecular mechanisms involved in pulp responses to bacteria and in the pulpal transition between caries-induced inflammation and dentinogenic-based repair. We report, using selected examples, different strategies potentially used by odontoblasts and specialized immune cells to combat dentin-invading bacteria *in vivo*.

1. Odontoblasts in the Dental Pulp's Defence against Caries

The crowns of erupted human teeth are covered by symbiotic microbial communities, mainly composed of Gram-positive saprophytic bacteria which are normally harmless to the tooth. These communities adhere as biofilms to the highly mineralized enamel that constitutes a barrier which is impermeable to microorganisms and protects the underlying mineralized dentin and the loose connective tissue situated at the centre of the tooth, the dental pulp. However, when placed in a sugar-rich environment, specific bacterial populations from these communities release acids that progressively demineralize enamel [1, 2]. This leads to the appearance of a carious lesion characterized by a cavity within which "cariogenic" bacteria proliferate and release additional acids that progressively deepen the lesion. When the enamel barrier is disrupted, dentin becomes degraded by Gram-positive bacteria, including streptococci, lactobacilli, and actinomyces that largely dominate the dentin caries microflora [3]. The proliferation and metabolic activity of these microorganisms lead to the release of bacterial components into dentinal tubules and their diffusion towards the peripheral pulp. Dentin demineralization may also enable the release of bioactive molecules from the dentin matrix [4]. Recognition of bacterial components by host cells at the dentin-pulp interface triggers host protective events including antibacterial, immune, and inflammatory responses. These events may

Effect of dental caries on periodontal inflammatory status: A Split-mouth study

Runing title: Link between caries and periodontal inflammation

Ervin Taso[1], Vladimir Stefanovic[1], Alexis Gaudin[2,3], Jovan Grujic[4], Estela Maldonado[5], Aleksandra Petkovic-Curcin[6,7], Danilo Vojvodic[6,7], Anton Sculean[8], Mia Rakic[5,9]

[1] Clinic for Stomatology, Military Medical Academy, Belgrade, Serbia (Crnotravska 17, Belgrade, Serbia)
[2] Faculty of Dental Surgery, University of Nantes, Nantes, France;
[3]Inserm, U1229, Regenerative Medicine and Skeleton Research, RMeS, Nantes, France – CHU Nantes, PHU 4 OTONN, Nantes, France (1 Place Alexis-Ricordeau, Nantes, France)
[4] Faculty of Medicine, University of Belgrade, Belgrade, Serbia (Dr. Subotica 8, Belgrade, Serbia)
[5] ETEP (Etiology and Therapy of Periodontal Diseases) Research Group, Faculty of Dentistry, University Complutense of Madrid, Spain (Pza. Ramón y Cajal, s/n, Madrid)
[6] Institute for Medical Research, Military medical Academy, Belgrade, Serbia; (Crnotravska 17, Belgrade, Serbia)
[7] Medical Faculty, University of Defence, Belgrade, Serbia
M.D., Ph.D
[8] Faculty of Dental Medicine, University of Bern, Switzerland (Freiburgstrasse 7, Bern, Switzerland)
[9] Institute for Biological Research "Sinisa Stankovic", University of Belgrade, Belgrade, Serbia (Bulevar despota Stefana 142, Belgrade, Serbia)

Corresponding author:

Dr. Mia Rakic, D.D.S., Ph.D.
https://orcid.org/0000-0001-7093-7956
Faculty of Dentistry,
University Complutense of Madrid,
Plaza Ramón y Cajal s/n Ciudad Universitaria,
28040 Madrid, Spain
email: miarakic@ucm.es

Highlights

- Caries affected teeth exhibit significantly higher levels of IFNγ, IL1β, IL2, IL4 and IL6
- Post-treatment cytokines levels tended to increase particularly day 30
- Caries might provide additive inflammatory effects in periodontium in early-stage caries

Research Reports: Biological

Conditional TNF-α Overexpression in the Tooth and Alveolar Bone Results in Painful Pulpitis and Osteitis

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B.E. Hall[1], L. Zhang[2], Z.J. Sun[2], E. Utreras[3], M. Prochazkova[1], A. Cho[1], A. Terse[1], P. Arany[1], J.C. Dolan[4], B.L. Schmidt[4], and A.B. Kulkarni[1]

Abstract

Tumor necrosis factor–α (TNF-α) is a proalgesic cytokine that is commonly expressed following tissue injury. TNF-α expression not only promotes inflammation but can also lead to pain hypersensitivity in nociceptors. With the established link between TNF-α and inflammatory pain, we identified its increased expression in the teeth of patients affected with caries and pulpitis. We generated a transgenic mouse model (TNF-α^{flo}) that could be used to conditionally overexpress TNF-α. These mice were bred with a dentin matrix protein 1 (DMP1)–Cre line for overexpression of TNF-α in both the tooth pulp and bone to study oral pain that would result from subsequent development of pulpitis and bone loss. The resulting DMP1/TNF-α^{flo} mice show inflammation in the tooth pulp that resembles pulpitis while also displaying periodontal bone loss. Inflammatory infiltrates and enlarged blood vessels were observed in the tooth pulp. Pulpitis and osteitis affected the nociceptive neurons innervating the orofacial region by causing increased expression of inflammatory cytokines within the trigeminal ganglia. With this new mouse model morphologically mimicking pulpitis and osteitis, we tested it for signs of oral pain with an oral function assay (dolognawmeter). This assay/device records the time required by a mouse to complete a discrete gnawing task. The duration of gnawing required by the DMP1/TNF-α^{flo} mice to complete the task was greater than that for the controls; extended gnaw time in a dolognawmeter indicates reduced orofacial function. With the DMP1/TNF-α^{flo} mice, we have shown that TNF-α expression alone can produce inflammation similar to pulpitis and osteitis and that this mouse model can be used to study dental inflammatory pain.

Keywords: inflammation, facial pain, cytokine(s), toothache, animal model, Cdk5

Introduction

Tumor necrosis factor–α (TNF-α) is a pleiotropic cytokine that promotes inflammation by promoting recruitment of leukocytes, inducing vasodilation, and stimulating the production of pro-inflammatory cytokines (Bradley 2008). Elevated levels of TNF-α have often been detected in the serum and tissues of patients with severe infections or autoimmune disorders. For example, upregulation of TNF-α has been discovered in pulpal tissues from teeth with irreversible pulpitis (Pezelj-Ribaric et al. 2002; Kokkas et al. 2007) and in exudates of teeth with apical periodontitis (Safavi and Rossomando 1991). In addition to being proinflammatory, TNF-α may act directly on nociceptive neurons to increase pain sensitivity. The TNF-α receptors, TNFR1 and TNFR2, have been detected on nociceptive neurons that transmit peripheral pain to the central nervous system (Boettger et al. 2008; Schaible 2010). Subcutaneous injection of recombinant TNF-α promotes mechanical allodynia through sensitization of C-fiber nociceptors (Junger and Sorkin 2000), while application of TNF-α to cultured dorsal root ganglion neurons modulates ion channel activity (Czeschik et al. 2008).

Orofacial pain is a widespread public health problem that affects 20% of adults, with toothaches alone afflicting about 22 million Americans (Lipton et al. 1993). Animal models of dental pain often involve exposure of the tooth pulp and administration of lipopolysaccharide to induce an inflammatory immune response (Khan and Hargreaves 2010; Gibbs et al. 2013). We wanted to examine the effect of TNF-α on immune homeostasis within the tooth pulp and determine if overexpression of this inflammatory mediator alone could promote pulpitis. For this purpose, we decided to use a genetic approach to determine the cause of conditional overexpression of TNF-α in

[1]Functional Genomics Section, Laboratory of Cell and Developmental Biology, National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, MD, USA
[2]The State Key Laboratory Breeding Base of Basic Science of Stomatology & Key Laboratory of Oral Biomedicine, Ministry of Education, School and Hospital of Stomatology, Wuhan University, Wuhan, China
[3]Laboratory of Cellular and Molecular Mechanisms of Pain, Faculty of Sciences, University of Chile, Santiago, Chile
[4]NYU Bluestone Center for Clinical Research, Department of Oral and Maxillofacial Surgery, School of Dentistry New York University College of Dentistry, New York, NY, USA

Corresponding Author:
A.B. Kulkarni, Functional Genomics Section, Laboratory of Cell and Developmental Biology, National Institute of Dental and Craniofacial Research, National Institutes of Health, 30 Convent Drive, Room 130, MSC 4395, Bethesda, MD 20892, USA.
Email: ashok.kulkarni@nih.gov

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MINI-REVIEW

WILEY Journal of Cellular Physiology

Biological effects of interleukin-6 on Gingival Fibroblasts: Cytokine regulation in periodontitis

Koji Naruishi | **Toshihiko Nagata**

Department of Periodontology and Endodontology, Institute of Biomedical Sciences, Tokushima University Graduate School, Kuramoto, Tokushima, Japan

Correspondence
Koji Naruishi, DDS, PhD, Department of Periodontology and Endodontology, Institute of Biomedical Sciences, Tokushima University Graduate School, 3-18-15 Kuramoto, Tokushima 770-8504, Japan.
Email: naruishi@tokushima-u.ac.jp

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Periodontitis is a bacterial infectious disease, and many inflammatory cytokines regulate periodontitis pathophysiology through a crosstalk between tissue cells and immune cells. Interleukin (IL)-6 is an important cytokine involved in the regulation of host response to bacterial infection. Human Gingival Fibroblasts (HGFs) are the most abundant cells in gingival connective tissues. Various HGF responses to periodontal pathogens or inflammatory cytokines contribute to the development of periodontitis. Lipopolysaccharide derived from *Porphyromonas gingivalis* (Pg LPS) and IL-1β significantly increase IL-6 production in HGFs. However, IL-6 cannot function in HGFs without the soluble form of the IL-6 receptor (sIL-6R), because HGFs do not express sufficient cell surface IL-6R to bind appreciable levels of IL-6. Importantly, sIL-6R is essential for IL-6 signaling in HGFs, and the sIL-6R is produced by differentiated THP-1 cells treated with IL-6. Calprotectin, a heterodimer of S100A8 and S100A9, is released during inflammation and significantly induces IL-6 production in HGFs via toll-like receptor 4 (TLR4)/nuclear factor-kappa B (NF-κB) signals. Calprotectin also induces sIL-6R production in differentiated THP-1 cells. IL-6 induces vascular endothelial growth factor (VEGF), matrix-metalloproteinase-1 (MMP-1), and cathepsin L production in HGFs in the presence of sIL-6R. Taken together, calprotectin-induced IL-6 production in HGFs may cause periodontitis progression through a crosstalk of fibroblasts and macrophages. There are many reports that examine how cytokines are released from HGFs to cause beneficial or harmful effects in inflamed periodontal lesions. This review explores the pathophysiology of periodontitis by focusing IL-6-mediated crosstalk of HGFs and macrophages.

KEYWORDS
calprotectin, gingival fibroblasts, IL-6, macrophages, periodontitis

1 | INTRODUCTION

Periodontitis is a bacterial infectious disease, and many inflammatory cytokines regulate periodontitis pathophysiology through a crosstalk between tissue cells and immune cells (Graves & Cochran, 2003; Takashiba, Naruishi, & Murayama, 2003). Cytokine balance regulated by immune responses has an important role in the stability and progression of inflammation. Many researchers have explored the

Abbreviations: AGE, advanced glycation end products; AP-1, activated protein-1; bFGF, basic FGF; Cav-1, caveolin-1; C/EBPβ, CCAAT/enhancer binding protein β; ERK, extracellular-regulated kinases; GCF, gingival crevicular fluid; HGFs, Human gingival fibroblasts; IL, interleukin; IL-1RI, type I IL-1 receptor; IL-6R, IL-6 receptor; IRAK, IL-1 receptor-activated protein kinase; JNK, c-jun N-terminal kinase; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MMPs, matrix-metalloproteinases; MCP-1, monocyte chemotactic protein 1; MyD88, myeloid differentiation primary response gene 88; NK, natural killer; NF-κB, nuclear factor-kappa B; Pg, Porphyromonas gingivalis; RAGE, receptor for advanced glycation end-products; SAPK, stress-activated protein kinases; sIL-6R, soluble form of IL-6 receptor; STAT, signal transducer and activator of transcription; TIMPs, tissue inhibitors of MMPs; TACE/ADAM17, TNF-α-converting enzyme; TAPI, inhibitor of TNF-α-converting enzyme; TLR, Toll-like receptor; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor.

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REVIEW ARTICLE

Periodontics and Periodontal Medicine

Relationship between levels of neuropeptide Substance P in periodontal disease and chronic pain: a literature review

Erica Dorigatti de Avila[1], Rafael Scaf de Molon[2], Daniela Aparecida de Godoi Gonçalves[1] & Cinara Maria Camparis[1]

1 Department of Dental Materials and Prosthodontics, School of Dentistry at Araraquara, University of Estadual Paulista — UNESP, Araraquara, Sao Paulo, Brazil

2 Department of Diagnosis and Surgery, School of Dentistry at Araraquara, University of Estadual Paulista — UNESP, Araraquara, Sao Paulo, Brazil

Keywords
chronic pain, neurogenic inflammation, periodontal disease, pro-inflammatory neuropeptide, Substance P.

Correspondence
Dr. Erica Dorigatti de Avila, Departamento de Materiais Odontológicos e Prótese, Faculdade de Odontologia de Araraquara, UNESP; Rua Humaitá, 1680, 14801–903 Araraquara, São Paulo, Brazil.
Tel: +55-16-3301-6424
Email: erica.fobusp@yahoo.com.br

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Abstract

The aim of the current review was to investigate the relationship between levels of neuropeptide Substance P in periodontal disease and chronic pain. Substance P is a neuropeptide that is directly related with pain. In periodontal disease, it is expressed during the inflammatory process, and is one of the factors responsible for bone resorption. Studies have shown that Substance P levels are highest in the gingival crevicular fluid from sites with active periodontal disease and bone loss. The persistence of these substances could be sufficient to stimulate neurogenic inflammation in susceptible tissues, and cause pain. The scientific literature shows that Substance P expressed during periodontal disease can be a risk factor for patients with systemic inflammatory pathologies, such as chronic arthritis or rheumatoid arthritis. Additional research is needed to confirm the participation of this substance in the origin of some types of chronic pain.

Introduction

Periodontal disease is a chronic bacterial inflammatory process mediating the destruction of periodontal tissues. Inflammatory responses in various organs have been reported to reveal a neurogenic component.[1] Recent evidence has indicated that patients with periodontitis exhibit increased systemic inflammation, demonstrated by raised plasma levels of various markers, when compared with controls.[2] Inflammation is typically defensive, but if the causative agent persists, it can become chronic with tissue damage. The magnitude of the inflammatory response is critical, because an insufficient response can lead to infection, whereas an excess can cause morbidity. Many studies have established a role for sensory neurons in vascular aspects of inflammation, and the term "neurogenic inflammation" has been created to define the contribution of the nervous system to local inflammatory responses.[3] Every neuron produces an electric impulse in reaction to a chemical or mechanical stimulus, conducts the impulse through its elongated cell structure at its terminal, and translates the electrical activity into a neurotransmitter. One of these electric impulses is Substance P (SP), a neuropeptide induced by cytokines and bacterial lipopolysaccharide (LPS).[4] SP causes vasodilation by acting directly on the smooth muscle cells and indirectly by stimulating histamine release from the mast cells. The fibers of periodontal tissues in humans are immunoreactive to this substance and to a number of neuropeptides, including calcitonin gene-related peptide (CGRP), vasoactive intestinal polypeptide (VIP), and neuropeptide Y (NPY).[5]

Substance P is a neuropeptide released from nerve endings in many tissues, and it plays an important role in inflammation. It is a mediator of tissue injury, as in asthma, arthritis, and allergy and autoimmune diseases. The scientific literature shows that SP-positive nerve fibers and mast

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CLINICAL FEATURE
REVIEW

Chronic periodontitis, inflammatory cytokines, and interrelationship with other chronic diseases

Elsa Maria Cardoso [a,b,c], Cátia Reis[d] and Maria Cristina Manzanares-Céspedes [e]

[a]CICS-UBI, Health Sciences Research Centre, Faculty of Health Sciences, University of Beira Interior, Covilhã, Portugal; [b]Faculty of Health Sciences (FCS-UBI), University of Beira Interior, Covilhã, Portugal; [c]Instituto Politécnico da Guarda, Guarda, Portugal; [d]Instituto de Investigação e Formação Avançada em Ciências e Tecnologias da Saúde, CESPU, Gandra PRD, Portugal; [e]Human Anatomy and Embryology Unit, Departament de Patologia i Terapèutica Experimental, Health University of Barcelona Campus (HUBc), University of Barcelona, Barcelona, Spain

ABSTRACT

Periodontal diseases, such as chronic periodontitis, share common inflammatory risk factors with other systemic and chronic inflammatory disorders. Mucosal tissues, such as oral epithelia, are exposed to environmental stressors, such as tobacco and oral bacteria, that might be involved in promoting a systemic inflammatory state. Conversely, chronic disorders can also affect oral health. This review will summarize recent evidence for the interrelationship between chronic periodontitis and other prevalent chronic diseases such as cardiovascular diseases, diabetes, cancer and chronic respiratory diseases. The association with pregnancy is also included due to possible obstetric complications. We will focus on inflammatory cytokines such as TNF-alpha, IL-1, and IL-6, because they have been shown to be increased in patients with chronic periodontitis, in patients with chronic systemic diseases, and in patients with both chronic periodontitis and other chronic diseases. Therefore, an imbalance towards a proinflammatory immune response could underline a bidirectional link between chronic periodontitis and other chronic diseases. Finally, we highlight that a close coordination between dental and other health professionals could promote oral health and prevent or ameliorate other chronic diseases.

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KEYWORDS
Inflammation; immune system; periodontium; chronic noncommunicable diseases; periodontal diseases

Introduction

Periodontal disease contributes significantly to the global burden of oral diseases and shares common risk factors with several chronic diseases. Recently, the World Health Organization (WHO) highlighted the importance of strengthening the control of periodontal disease worldwide [1,2]. According to the WHO, chronic noncommunicable diseases, including cardiovascular diseases, cancer, chronic respiratory diseases, and diabetes, remain the leading causes, about 70%, of death globally [3]. In addition, periodontal disease is one of the most important oral diseases contributing to the global burden of chronic diseases and therefore represents a major public health problem [4]. In the present review, we will first summarize the current classification of periodontal diseases, and lately, we will focus the discussion on chronic periodontitis and cytokines in the context of common systemic chronic inflammatory diseases.

Classification of periodontal diseases

Periodontal disease is a broad term for the spectrum of inflammatory diseases affecting the periodontium which comprises a set of structures that support the teeth: gingiva, cementum, periodontal ligament, and alveolar bone. In the 1999 classification system for periodontal diseases and conditions, over 40 different gingival diseases were listed, that were either dental-plaque induced or not associated with dental plaque [5]. In addition, other major categories of destructive periodontal diseases were listed and periodontitis can also be a manifestation of systemic diseases. An abbreviated version of the 1999 classification of periodontal diseases and conditions is shown in Table 1. Chronic periodontitis refers to the progression of the disease over time without treatment while aggressive periodontitis shows rapid attachment loss and bone destruction, and possible familial aggregation of disease. According to that consensus, both are subcategorized in local or generalized forms, depending on the percentage of tooth affected sites (above or below 30%) and regarding the severity of attachment loss (slight: 1 or 2 mm, moderate: 3 or 4 mm; severe ≥5 mm) [5,6]. The distinction between chronic and aggressive periodontitis is also based on several clinical features, namely age of onset, rates of progression, patterns of destruction, signs of inflammation, and relative amounts of plaque, and calculus [7]. However, the features of chronic periodontitis have been partially updated in 2014 by the American Academy of Periodontology (AAP) who have also announced that an update would commence in 2017 [8]. This AAP task force report addressed three specific areas of concern with the current classification: attachment level, chronic

CONTACT Elsa Maria Cardoso cardoso.elsamaria@fcsaude.ubi.pt CICS-UBI, Health Sciences Research Centre, Faculty of Health Sciences, University of Beira Interior, Av. Infante D. Henrique, Covilhã 6200-506, Portugal

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REVIEW ARTICLE OPEN

The cytokine network involved in the host immune response to periodontitis

Weiyi Pan[1], Qingxuan Wang[1] and Qianming Chen[1]

Periodontitis is an inflammatory disease involving the destruction of both soft and hard tissue in the periodontal region. Although dysbiosis of the local microbial community initiates local inflammation, over-activation of the host immune response directly activates osteoclastic activity and alveolar bone loss. Many studies have reported on the cytokine network involved in periodontitis and its crucial and pleiotropic effect on the recruitment of specific immunocytes, control of pathobionts and induction or suppression of osteoclastic activity. Nonetheless, particularities in the stimulation of pathogens in the oral cavity that lead to the specific and complex periodontal cytokine network are far from clarified. Thus, in this review, we begin with an up-to-date aetiological hypothesis of periodontal disease and summarize the roles of cytokines in the host immune response. In addition, we also summarize the latest cytokine-related therapeutic measures for periodontal disease.

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INTRODUCTION

Periodontitis is an inflammatory disease indicated by periodontal soft tissue inflammation and the progressive loss of periodontal ligament and alveolar bone.[1] Soft tissue inflammation, namely, gingivitis, is very common in populations. According to the results of the Fourth National Oral Epidemiological Investigation in China, bleeding on probing was detected in over 85% of adults within 35–64 years of age.[2] Through a long and slow process, uncontrolled inflammation in the gingiva may lead to the destruction of periodontal tissue and its attachment to teeth, which is defined as periodontitis.[3] The continuous loss of dentition to support tissue results in tooth looseness and the loss of teeth, which seriously affects patients' quality of life and causes a tremendous social and economic burden.[4] Severe periodontitis affects more than 700 million people (11% of the world's population), making it one of the most prevalent chronic inflammatory diseases worldwide.[4] In addition, an increasing amount of clinical and experimental evidence indicates the potential direct relationship between periodontitis and several systematic diseases including diabetes, rheumatoid arthritis, atherosclerosis, Alzheimer's disease and even cancers.[5–9]

The pathogenesis of periodontitis is a problem that plagues investigators. In the 20th century, one or a group of specific microorganisms[10] were identified as the pathogen of periodontitis by isolation and culture studies. Among these microorganisms, a pathogenic "red complex" that consists of *Porphyromonas gingivalis (P. gingivalis)*, *Treponema denticola* and *Tannerella forsythia* was suggested as the most representative theory of periodontitis pathogenesis in the late 1980s to 1990s.[11,12] However, with deeper immunological research, the important role of the local host immune response in the pathogenesis of periodontitis was revealed.[13] In addition, new data obtained from metagenomic and metatranscriptomic studies suggested that a more complicated microbial community is involved in the pathogenesis of periodontitis rather than one or several specific pathogenic bacteria.[14–18]

The initiation and progression of periodontitis are related to multiple aetiologic and risk factors, the most important of which are the local microbiota and host immune response.[19] Within the progression of periodontitis, the role of cytokines is extremely important. Cytokines are key modulators of both homeostasis and inflammatory processes that act in the first wave of responses against pathogens and stimuli at barrier sites and connect tissue cells with lymphocytes and accessory cell populations.[20] Many recent studies have found that single nucleoid polymorphisms in cytokines and associated receptor-encoding genes are related to the risk and severity of periodontitis,[21–24] which indicates that the disordered regulation of cytokines initiates or accelerates periodontitis. On the basis of human studies, studies in experimental animal periodontitis models also found that manipulating the expression of cytokines and their receptors affects the alveolar bone loss phenotype.[25,26] Research on the cytokine network in periodontal tissue has laid the foundation for the development of cytokine-targeting therapies for periodontal disease, some of which have shown positive effects in pre-clinical trials.[27] However, compared with the well-discussed site-specific immunocytes and cytokine network in other barrier sites, such as the skin and gastrointestinal and respiratory tracts, how the local immune system in periodontal tissue is trained and activated in healthy and pathological conditions remains to be further explored.[28] Thus, in this review, we have focused on an up-to-date mechanistic hypothesis of the pathogenesis of periodontal disease and the role of cytokines in periodontal disease. We have also summarized the latest cytokine-related therapeutic measures for periodontal disease.

[1]State Key Laboratory of Oral Diseases & National Clinical Research Center for Oral Diseases & Chinese Academy of Medical Sciences Research Unit of Oral Carcinogenesis and Management, West China Hospital of Stomatology, Sichuan University, Chengdu, China
Correspondence: Qianming Chen (qmchen@scu.edu.cn)
These authors contributed equally: Weiyi Pan, Qingxuan Wang

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Effect of Anti-Infective Mechanical Therapy on Clinical Parameters and Cytokine Levels in Human Peri-Implant Diseases

Poliana Mendes Duarte,* Adriana Cutrim de Mendonça,* Maria Beatriz Braz Máximo,* Vanessa Renata Santos,* Marta Ferreira Bastos,* and Francisco Humberto Nociti Jr.†

Background: The objectives of this study were to clinically and immunologically assess the effects of mechanical anti-infective therapies for mucositis and peri-implantitis and to compare the levels of cytokines in untreated and treated peri-implant diseased sites to healthy ones.

Methods: Titanium dental implants were assigned to one of the following groups: healthy (n = 10) = control; mucositis (n = 10) = mechanical debridement using abrasive sodium carbonate air-powder and resin curets; and peri-implantitis (n = 20) = open surgical debridement using abrasive sodium carbonate air-powder and resin curets. Visible plaque accumulation, marginal bleeding, bleeding on probing, suppuration, and probing depth were assessed at baseline for all groups and at 3 months after therapies for diseased groups. At these times, the total amounts of interleukin (IL)-4, -10, and -12, tumor necrosis factor-alpha (TNF-α), receptor activator of nuclear factor-kappa B ligand (RANKL), and osteoprotegerin (OPG) in the peri-implant crevicular fluid (PICF) were measured by enzyme-linked immunosorbent assay.

Results: At 3 months, the anti-infective treatments resulted in a significant improvement in all clinical parameters for mucositis and peri-implantitis ($P < 0.05$). Moreover, the total amounts of TNF-α in PICF were significantly higher in untreated diseased implants compared to healthy ones, and the OPG/RANKL ratio was higher for healthy implants than for untreated peri-implantitis ($P < 0.05$). TNF-α levels were significantly reduced for both diseased groups ($P < 0.05$), achieving the same level as the healthy group at 3 months after therapies ($P > 0.05$).

Conclusion: The proposed anti-infective therapies may locally modulate the levels of TNF-α and the OPG/RANKL ratio and improve clinical parameters around peri-implant tissues. *J Periodontol 2009; 80:234-243.*

KEY WORDS

Cytokines; dental implants; mucositis; osteoprotegerin; receptor activator of nuclear factor-kappa B ligand; tumor necrosis factor.

* Department of Periodontics, Dental Research Division, Guarulhos University, Guarulhos, SP, Brazil.
† Department of Prosthodontics/Periodontics, Division of Periodontics, School of Dentistry at Piracicaba, University of Campinas, Piracicaba, SP, Brazil.

Dental implants are successful alternatives to conventional prostheses in partially or totally edentulous patients; however, the occasional failure has put the long-term outcome of implant rehabilitation at risk.[1,2] Evidence has shown that pathogenic bacterial infection plays the most important role in the late failure of dental implants.[3,4] Mucositis is an infectious disease that results in a reversible inflammatory process restricted to the soft tissues around osseointegrated implants, and peri-implantitis is an irreversible reaction that affects the soft tissues and the supporting bone around an implant in occlusal function.[1,2,5]

It has been recognized that pathogens and their products induce the host immune response in essentially different ways to affect the innate and adaptive immune systems.[6,7] The inflammatory process in response to bacterial infection is mediated by proinflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interferon-gamma, and interleukin (IL)-1β, -6, and -12, which, among other biologic

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ORIGINAL ARTICLE

WILEY

Relationship between self-rated pain and peri-implant clinical, radiographic and whole salivary inflammatory markers among patients with and without peri-implantitis

Tariq Abduljabbar DMSc[1] | Fahim Vohra MProRCS[1] | Anhar Ullah MSc[2] | Nawaf Alhamoudi MSD, ABOP[3] | Junad Khan BDS, MSD, MPH, PhD[4] | Fawad Javed DDS, PhD[5]

[1]Department of Prosthetic Dental Sciences, College of Dentistry, King Saud University, Riyadh, Saudi Arabia

[2]Department of Cardiac Sciences, King Fahad Cardiac Center, College of Medicine, King Saud University, Riyadh, Saudi Arabia

[3]Department of Periodontics and Community Dentistry, King Saud University, Riyadh, Saudi Arabia

[4]Orofacial Pain and TMJ Disorders, Eastman Institute for Oral Health, University of Rochester, New York, New York

[5]Department of Orthodontics, Eastman Institute for Oral Health, University of Rochester, New York, New York

Correspondence
Tariq Abduljabbar, Department of Prosthetic Dental Sciences, College of Dentistry, King Saud University, Box 60169, Riyadh 11545, Saudi Arabia.
Email: tajabbar@ksu.edu.sa

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Abstract

Background: There are no studies that have evaluated the correlation between self-rated pain, peri-implant clinical and radiographic parameters (plaque index [PI], bleeding on probing [BOP], probing depth [PD], and crestal bone loss [CBL]) and whole salivary interleukin (IL)-1β, IL-6, and tumor necrosis factor-alpha (TNF-α) levels among patients with and without peri-implantitis.

Purpose: The objective was to evaluate the correlation between self-evaluated pain, peri-implant clinical and radiographic parameters and whole salivary IL-1β, IL-6, and TNF-α levels among patients with and without peri-implantitis.

Materials and Methods: Included in this study were patients with and without peri-implantitis. Data regarding age, gender, duration of implants in function, and self-perceived pain were recorded using a question. Self-rated pain was assessed using the numeric pain rating scale. Peri-implant PD, PI, BOP, and CBL were recorded and samples of unstimulated whole saliva samples were obtained. Whole salivary IL-1β, IL-6, and TNF-α were measured. Sample-size was approximated and group comparisons were completed. *P*-values <.05 were regarded as statistically significant.

Results: Forty-six male individuals (21 with and 25 without peri-implantitis) were included. The mean age of individuals with and without PiD was 53.71 ± 5.45 and 50.92 ± 6.26 years, respectively. The mean self-rated pain score in patients with and without PiD was 3 ± 2 and zero, respectively. There was no significant difference in the SFR among patients with and without peri-implantitis. Levels of IL-1β ($P < .01$), IL-6 ($P < .01$), and TNF-α ($P < .01$) were significantly elevated in subjects with than without peri-implantitis. Regression analysis-based results reflected no significant association between increasing self-rated pain and whole salivary IL-1β, IL-6, and TNF-α levels.

Kiyomoto *et al. Mol Pain (2015) 11:48*
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MOLECULAR PAIN

RESEARCH Open Access

p38 phosphorylation in medullary microglia mediates ectopic orofacial inflammatory pain in rats

Masaaki Kiyomoto[1], Masamichi Shinoda[2*], Kuniya Honda[2], Yuka Nakaya[3], Ko Dezawa[3], Ayano Katagiri[2], Satoshi Kamakura[2], Tomio Inoue[1] and Koichi Iwata[2]

Abstract

Background: Orofacial inflammatory pain is likely to accompany referred pain in uninflamed orofacial structures. The ectopic pain precludes precise diagnosis and makes treatment problematic, because the underlying mechanism is not well understood. Using the established ectopic orofacial pain model induced by complete Freund's adjuvant (CFA) injection into trapezius muscle, we analyzed the possible role of p38 phosphorylation in activated microglia in ectopic orofacial pain.

Results: Mechanical allodynia in the lateral facial skin was induced following trapezius muscle inflammation, which accompanied microglial activation with p38 phosphorylation and hyperexcitability of wide dynamic range (WDR) neurons in the trigeminal spinal subnucleus caudalis (Vc). Intra-cisterna successive administration of a p38 mitogen-activated protein kinase selective inhibitor, SB203580, suppressed microglial activation and its phosphorylation of p38. Moreover, SB203580 administration completely suppressed mechanical allodynia in the lateral facial skin and enhanced WDR neuronal excitability in Vc. Microglial interleukin-1β over-expression in Vc was induced by trapezius muscle inflammation, which was significantly suppressed by SB203580 administration.

Conclusions: These findings indicate that microglia, activated via p38 phosphorylation, play a pivotal role in WDR neuronal hyperexcitability, which accounts for the mechanical hypersensitivity in the lateral facial skin associated with trapezius muscle inflammation.

Keywords: Microglia, Ectopic pain, Trigeminal spinal nucleus, Interleukin-1β, Trapezius muscle inflammation

Background

Referred pain originating from the trapezius muscle frequently produces orofacial pathological pain such as tension-type headaches or temporomandibular disorder (TMD) [1, 2]. Clinically, orofacial pain is likely to occur in areas far away from the trapezius muscle, which causes misdiagnosis and/or inappropriate treatment [3]. In animal experiments, it has been shown that masseter muscle injection of exogenous substances such as glutamate or nerve growth factor produces nociceptive disturbances in discrete areas similar to those reported in TMD patients [4–6]. Nevertheless, the mechanisms underlying nociceptive disturbances in discrete areas associated with such muscle inflammation are still poorly understood.

The mitogen-activated protein kinases (MAPKs), which belong to a highly conserved family of serine/threonine protein kinases, are involved in various cell signaling and gene expression in central nervous system (CNS) [7]. A variety of extracellular stimuli activate intracellular MAPKs by phosphorylation, which modulates intracellular responses driving different downstream signaling [8]. p38, which is a member of a MAPK family, is present constitutively in non-neuronal glial cells in the spinal cord, and is phosphorylated via proinflammatory cytokines released in the spinal cord associated with peripheral inflammation, and is thought to play an

*Correspondence: shinoda.masamichi@nihon-u.ac.jp
[2] Department of Physiology, Nihon University School of Dentistry, 1-8-13 Kandasurugadai, Chiyoda-ku, Tokyo 101-8310, Japan
Full list of author information is available at the end of the article

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Targeting cytokines for treatment of neuropathic pain

Alice L. Hung[a], **Michael Lim**[a], and **Tina L. Doshi**[b,*]

[a]Department of Neurosurgery, Johns Hopkins University School of Medicine, Baltimore, MD, USA

[b]Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Abstract

Background—Neuropathic pain is a challenging condition often refractory to existing therapies. An increasing number of studies have indicated that the immune system plays a crucial role in the mediation of neuropathic pain. Exploration of the various functions of individual cytokines in neuropathic pain will provide greater insight into the mechanisms of neuropathic pain and suggest potential opportunities to expand the repertoire of treatment options.

Methods—A literature review was performed to assess the role of pro-inflammatory and anti-inflammatory cytokines in the development of neuropathic pain. Both direct and indirect therapeutic approaches that target various cytokines for pain were reviewed. The current understanding based on preclinical and clinical studies is summarized.

Results and conclusions—In both human and animal studies, neuropathic pain has been associated with a pro-inflammatory state. Analgesic therapies involving direct manipulation of various cytokines and indirect methods to alter the balance of the immune system have been explored, although there have been few large-scale clinical trials evaluating the efficacy of immune modulators in the treatment of neuropathic pain. TNF-α is perhaps the widely studied pro-inflammatory cytokine in the context of neuropathic pain, but other pro-inflammatory (IL-1β, IL-6, and IL-17) and anti-inflammatory (IL-4, IL-10, TGF-β) signaling molecules are garnering increased interest. With better appreciation and understanding of the interaction between the immune system and neuropathic pain, novel therapies may be developed to target this condition.

Keywords

Neuropathic pain; Immune modulation; Cytokines; Pro-inflammatory; Anti-inflammatory

*Corresponding author at: 550 N. Broadway, Suite 301, Baltimore, MD 21287, USA. tina.doshi@jhmi.edu (T.L. Doshi).

Ethical issues
None.

Conflict of interest
The authors declare that there is no conflict of interest.

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