TRABAJO FIN DE GRADO

ROLE OF MEMBRANE-TYPE MATRIX METALLOPROTEINASE IN ORAL CANCER

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FACULTAD DE CIENCIAS DE LA SALUD
UNIVERSIDAD EUROPEA DE MADRID

Abstract

Introduction: Matrix metalloproteinases are a family of endopeptidases that function to degrade the extracellular matrix and can be split into two groups depending on solubility or the presence of a membrane bound domain. The 6 membrane-bound matrix metalloproteinases utilize a transmembrane domain (MT-MMP 14,15,16 and 24) or a glycosylphosphatidylinositol anchor (MT-MMP 17 and 25). Oral cancer accounts for 3% of all cancers regularly diagnosed, and along with its common risk factors, the function of certain MT-MMP's has been shown to play a role in damaging the prognosis of oral cancer patients. **Objectives:** To acquire knowledge on both the function of membrane-type matrix metalloproteinases in oral cancer and its future applications regarding treatment. **Materials and methods:** Using relevant keywords, articles from 2010-2021 with the exception of 5 were selected for comparison and review. Keywords were used to narrow down the search in data bases like PubMed and Medline. **Results:** MT-MMP's 1, 2, 3 and 4 all showed involvement in oral cancer, be that as a prognostic exacerbator or as a biomarker. MT-MMP's 5 and 6 have not yet presented a link, however more research is needed. **Discussion and conclusion:** It's important to understand how and why certain MT-MMPs are involved in oral cancer, due to the treatment applications possible. Whether it's biomarkers for early diagnosis or preventing seemingly undamaging MT-MMPs from activating harmful pathways, the inner workings are complex and require more extensive research.

Resumen

Introducción: Las metaloproteinasas de matriz son una familia de endopeptidasas que funcionan para degradar la matriz extracelular y pueden dividirse en dos grupos dependiendo de la solubilidad o la presencia de un dominio unido a la membrana. Las 6 metaloproteinasas de matriz unidas a membrana utilizan un dominio transmembrana (MT-MMP 14, 15, 16 y 24) o un ancla de glicosilfosfatidilinositol (MT-MMP 17 y 25). El cáncer oral representa el 3% de todos los cánceres diagnosticados con regularidad y, junto con sus factores de riesgo comunes, se ha demostrado que la función de ciertas MT-MMP influye negativamente en el pronóstico de los pacientes con cáncer oral. **Objetivos**: Adquirir conocimientos tanto sobre la función de las metaloproteinasas de matriz de tipo membrana en el cáncer oral como sus futuras aplicaciones en el tratamiento. **Materiales y métodos:** Utilizando palabras clave relevantes, se seleccionaron artículos de 2010-2021 con la excepción de 5 para su comparación y revisión. Se utilizaron palabras clave para acotar la búsqueda en bases de datos como PubMed y Medline. Resultados: Los MT-MMP 1, 2, 3 y 4 mostraron implicación en el cáncer oral, ya sea como exacerbador pronóstico o como biomarcador. MT-MMP's 5 y 6 aún no han presentado un vínculo, sin embargo, es necesario investigar más. **Discusión y conclusión:** Es importante comprender cómo y por qué ciertas MT-MMP están involucradas en el cáncer oral, debido a las posibles aplicaciones de tratamiento. Ya sea que se trate de biomarcadores para el diagnóstico temprano o que impidan que las MT-MMP aparentemente no dañinas activen vías dañinas. El funcionamiento interno es complejo y requiere una investigación más extensa.

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1. Introduction

1.1. Definitions

1.1.1. Matrix metalloproteinase

Matrix Metalloproteinase or MMPs, are endopeptidases that are vital in the degradation of proteins in the extracellular matrix. These zinc-dependant proteinases play a role in tissue remodelling during various physiological processes such as angiogenesis, embryogenesis, morphogenesis and wound repair, as well as in pathological conditions such as myocardial infarction, fibrotic disorders, osteoarthritis, and cancer (1). Speaking specifically on the latter physiological process, this paper will be reviewing specific membrane associated MMP's and their relation to Oral Cancer. In vertebrates, the MMP family comprises 28 members, at least 23 are expressed in human tissues (2)**.**

Generally, the 23 members of the MMP family that are expressed in humans are arranged into 4 distinctive structural domains. The structural domains are as follows:

- **An amino terminal propeptide**

Usually consisting of around 80-90 amino acids, the propeptide incorporates a cysteine residue, which would interact with the zinc catalyst atom via a side chain thiol group. When this propeptide is removed via proteolysis, zymogen activation will occur (1).

- **A catalytic domain**

The catalytic domain contains one or more calcium ions that are attracted to various residues, as well as two zinc ions. One of these zinc ions is the active ion, which is present and involved in the catalytic activity of an MMP. The other zinc ion is known as the structural ion and is present with the calcium ions located around 12 atoms away from the previously

mentioned catalytic active zinc ion. It is the active zinc ion that has a fundamental role in the proteolytic activity of MMPs (2)

- **A hemopexin-like domain usually located at the carboxyl terminal of the molecule**

This domain of MMPs shows similarity to the plasma protein hemopexin in terms of its sequence and plays an important role in the function of substrate binding. It has also been shown to have interactions with other families of MMPs (3).

As mentioned previously, the MMP family consists of 28 members (1) and were observed for the first time in 1962 by two scientists named Jerome Gross and Charles Lapierre whilst studying tadpole tissue that presented collagenolytic activity. Human MMPs were isolated 6 years later, and can now be categorized based on the specificity of their substrates and homology into the following six groups: (4)

- Collagenases: MMP-1, 8 and 13
- Gelatinases: MMP-2 and 9
- Stromelysins
- Matrilysins
- Membrane-Type MMPs:
- Other MMPs

This major group of cell-matrix regulating enzymes have the ability to cleave one or several extra cellular matrix constituents as well as other proteins that are not present within the matrix. It is due to this cleavage function of Matrix Metalloproteinase that there is considerable interest in their association with cancer metastasis, and why there is ongoing research into the development of novel antimetastatic pharmaceuticals targeting the inhibition of MMP activity (3).

MMP's can also be characterized into two different groups, soluble MMP's (MMP-1, 2, 3, 7, 8, 9, 10, 11, 12, 13, 19, 20, 21, 22, 27 and 28) and MMP's that are membrane bound by either a transmembrane domain (MMP-14, 15, 16 and 24) or with a glycosylphosphatidylinositol anchor (GPI) (MMP-17 and 25) (1).

1.1.2. Membrane-Type MMPs

Membrane-Type MMPs or MT-MMPs, contain four transmembrane Membrane-Type MMPs (MMP 14, 15, 16 and 24) and also two MMPs that are glycosylphosphatidylinositol (GPI) anchored (MMP-17 and 25) (5). MT-MMPs have a furin-like pro-protein convertase recognition sequence at the C-terminus of the propeptide. They are intracellularly activated, and the activated enzymes are expressed on the cell surface. MT-MMPs have membrane anchoring domains and display protease activity at the cell surface, and therefore they are optimal pericellular proteolytic machines (1). As seen in figure one, MT1-MMP, MT2-MMP, MT3-MMP and MT5-MMP (also known as MMP 14, 15, 16 and 24 respectively) are anchored to the membrane by their usage of a transmembrane domain, whilst MT4-MMP and MT6-MMP (also known as MMP 17 and 25) are attached using GPI (4).

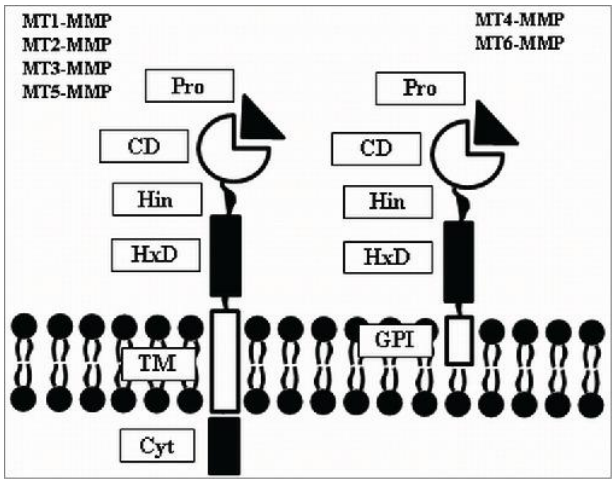

Figure 1. The binding of the two different kinds of membrane-type matrix metalloproteinase's, transmembrane domain and GPI (left and right respectively) (6).

1.1.3. Oral Cancer

Oral cancer refers to a broad category of locations for neoplasms of different etiologies and histological profiles. Although it generally refers to squamous cell carcinoma, the variability of anatomical location upon which oral cancer could be diagnosed does force a lack of scientific consensus on its definition (7). Oral cancer is the most common form of malignant carcinoma in the region of the head and neck. According to the journal of the American Dental Association (JODA) in 2015, around 3% of all cancers diagnosed where located in the mouth or in the back of the throat, making it a topic of much concern (8). The main risk factors of oral cancer include chronic usage of tobacco or alcohol (7), however (as will be discussed in further sections) there are overexpression's of certain intra-bodily molecules like the various MT-MMPs that could also be a potential risk factor. Another major risk factor for the development of oral cancer is infection with the human papilloma virus (HPV), which is a sexually transmitted uncurable infection. People with HPV tend to be linked with the development of Oropharyngeal cancer, which is oral cancer but involving oral tissues towards the back of the

mouth and throat (this also includes the tonsils and sublingual mucosa). Normally people who have oropharyngeal cancer related to HPV are 4 – 10 years younger than those with oral cancers not HPV related (9) Early detection/treatment are imperative in the reduction of mortality to oral cancer. Even though oral cancer occurs in regions with wide accessibility to dentists and their subsequent examinations, only 6.25% of lesions (according to the JODA) are diagnosed 'in situ' or stage 1, whilst stages 2, 3 and 4 correspond to 18%, 34.45% and 41.12% respectively (7).

Oral cancer can appear in a multitude of ways, often making its diagnosis all the more difficult for the clinical professional, or the patient in their day to day lives (8). The most common form of oral cancer is oral squamous cell carcinoma (OSCC), accounting for 90% of cancer in the oral cavity. OSCC is usually located on the lip, the anterior regions of the tongue, gingival mucosa, the mouth floor, the hard/soft palate and the retromolar trigone (10). The diagnosis of oral cancers such as OSCC usually depends on histological findings and how the tumour manifests clinically in the mouth, this makes it all the more difficult to diagnose as in its infant stages. OSCC (like almost all oral cancer) shows a painless and atypical mass with varying degrees of thickness. Some signs of the broader signs of oral cancer include unhealing ulcers or sores on the lips or mouth, white or red patches in the moth, pain or difficulty when swallowing, speaking or chewing, vocal changes or changes in the way the patient occludes (9).

Another problem with the diagnosis of oral cancers is when using visual inspection there may be difficulty detecting hidden or latent tumours, which could lead to very dangerous false negatives. The oral cavity is rich in lymph nodes and has highly vascularised tissues, due to this, regional migration and invasion of surrounding tissues are common. Currently the treatment methods of oral cancer normally involve surgery, chemotherapy or radiotherapy however due to the late diagnosis, the overall prognosis of most oral cancers is quite low with

a high rate of recurrence (8). When considering how we can improve the treatment outcome, gaining knowledge of potential biomarkers like MT-MMP's for an early screening or diagnosis is vital (10).

1.2. MMPs and MT-MMPs in their relation to Oral Cancer

The extra cellular matrix (ECM) is composed of a variety of things, including collagen, laminin and many types of connective tissue that acts as a natural barrier to prevent the invasion and metastasis of tumour cells. MMP's promote metastasis and soft tissue tumour invasion by essentially degrading the ECM, allowing tumour cells to seep into nearby blood vessels or tissue (11). Along with their metastatic invasion skills, MMPs also generally have the ability to initiate growth factors. This includes that of a vascular endothelial nature, fibroblastic growth factors and many others promoting dangerous cell proliferation and angiogenesis (12).

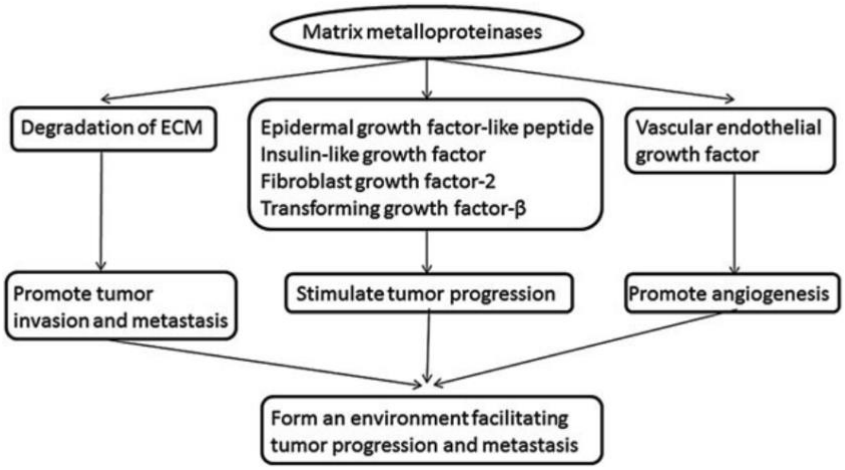

Figure 2. Matrix metalloproteinases and their possible pathways to stimulate tumour progression, angiogenesis and metastasis (12).

MT-MMPs appear on the surfaces of tumour cells and facilitate the capacity of the cancer to invade tissues. This depends on the specific glycosylphosphatidylinositol anchored transmembrane domain. MT-MMPs also have a high involvement in the activation of other MMPs. Members of the MT-MMP family can convert the proMMP-2 into proteolytic enzymes, each MT-MMP has specific attributes and activation ability (13).

1.2.1. MT1-MMP and Oral Cancer

MT1-MMP (also named MMP 14), has been studied to form a trimolecular complex, with inhibitors of metalloproteinase 2 and proMMP-2 on the surface of cells. ProMMP-2 is activated and unleashed with a low concentration of metalloproteinase 2, and subsequently mediated ECM degradation. Along with this, MT1-MMP has the capacity to act as a pericellular collagenase directly against ECM components. In the oral cavity, MT1-MMP acts on the surrounding mucosa by catalysing pericellular collagenolytic activity. By doing this it has been found to present advantageous circumstances for proliferating cells (14).

In oral squamous cell carcinoma (OSCC), MT-MMP over expression has been found in an enormous number of cases. For OSCC, MT1-MMP in the same study was found to be the only effective biomarker detected when looking for molecules that show the advancement of metastasis. They revealed that MT1-MMP can be used as a predictor of OSCC metastasis, and in cases that have lymph node affectation, MT1-MMP was almost always over expressed (10). MT1-MMP can be linked to causing carcinomas in the oral cavity due to its own proteolytic activity, but also due to its ability to activate other potentially harmful overexpressed MMP's. MT1-MMP has been observed to activate pro-MMP 2 (15) and pro-MMP 13 (16) through different cellular complexes. MMP2 and MMP13 have demonstrated to have dire consequences

regarding things such as increased level of lymph node invasion, prognostic determination, creation of an OSCC and the tumours resistance to cisplatin (10).

1.2.2. MT2-MMP and Oral Cancer

MT2-MMP can also have the ability to play a role in the progression and transmigration of cancers, however most of the research conducted so far seems to be around MT2-MMP's involvement in pancreatic cancer. Controlled by the action of a snail-related signal, MT2-MMP can be redirected to the cell surface of the tumour cells. Research has found that malignant tumour cells for example PANC-1 can activate MT2-MMP when under hypoxia. MT2-MMP is shown to be expressed in many different tumour types, for example bladder/renal cancer, and cancer of the urothelial tract (17).

In regard to cancer in the oral cavity, a clear correlation has been observed between MT2-MMP and angiogenesis and human oesophageal cancer (or ESCC).

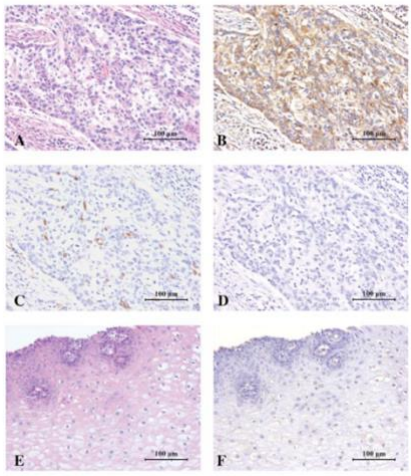

Figure 3. Immunochemical staining of MT2-MMP on a consecutive section of an ESCC specimen and intramural micro vessels. A: Haematoxylin and Eosin stain. B: MT2-MMP positive stain. C: Intramural micro vessels. D: Control (negative) E: Haematoxylin and Eosin stain: Negative MT2-MMP immunoreaction stain or normal oesophageal tissue (18).

In a study carried out in 2014, positive MT2-MMP staining's and immunoreactions were discovered in 85.4% of all ESCC tumour sections taken from 103 patients whereas none or very little was shown in healthy tissues. It was also shown that the patients overall survival rate was better with a low MT2-MMP protein level and patients had a higher death rate when there was a higher expression of MT2-MMP (18).

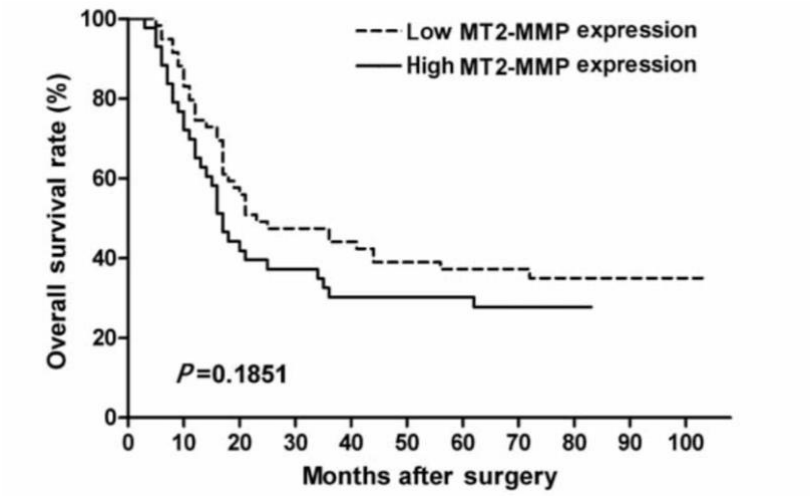

Figure 4. Association between MT2-MMP and the overall survival rate (%) post-surgery (18).

1.2.3. MT3-MMP and oral cancer

Like MT1-MMP, MT3-MMP seems to play a very important role in the progression and proliferation of cancers in and around oral cavity and the head and neck region. Speaking more specifically, it plays a very important role in oesophageal squamous cell carcinoma (ESCC). ESCC similarly to OSCC is a very common cancer type and one of the leading causes of cancer related deaths. Studies of cells from patients suffering from ESCC have confirmed through western bolt analysis (a process where the cells are sliced away from their tissue using an ultrasonic apparatus and are then incubated using a radio-immunoprecipitation buffer, electrophoresis is then used, and the cells are then transferred to a membrane where they are

further incubated and shot with antibodies) that during ESCC's advancement from tumour to its metastatic stage, MT3-MMP appears to be down-regulated.

The down regulation of MT3-MMP appears to lead to a poor prognosis of the disease. When a Kaplan-Meier analysis was used to check a relationship between MT3-MMP expression and the survival rate among 78 patients, those with down regulation of MT3-MMP had a median survival rate of 30.77 months, nearly 20 months lower than those without downregulation (median survival of 50.69 months) (19).

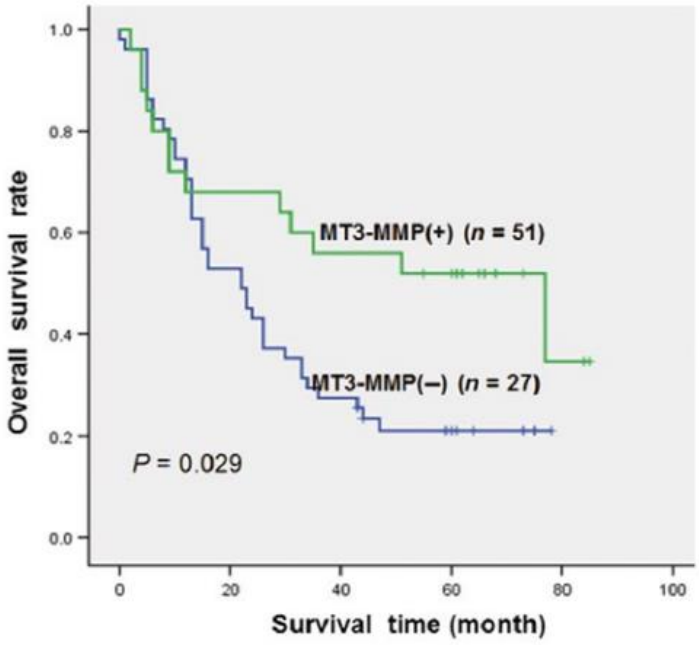

Figure 5. The difference in monthly survival time in months when comparing Mt3-MMP expression among patients in the sample (19).

1.2.4. MT4-MMP and oral cancer

MT-MMP's are physiologically linked together by their presence of a transmembrane domain, a GPI anchor or an amino-terminal link. When present in and around the ECM, MT-MMP's can directly smite all the surrounding components. The MT-MMP's that utilise the GPI anchor, more specifically, refer to the MT-MMP's that have an exclusive position in the lipid raft, giving them admission to a particular set of substrates. The two MT-MMP's that have this anchor are MT4-MMP and MT6-MMP (1). Being heavily linked to inflammation and angiogenesis, MT4-MMP is known to aggravate the two mainstays of cancer development and progression and its transcription has been detected in the following cancers: Prostate cancer, oral cancer, stomach cancer, leukaemia, lung cancer, cervical cancer, thyroid cancers and melanomas (20). MT4-MMP was first found to be transcribed in breast cancer, showing huge metastatic and angiogenic capabilities. It has also been demonstrated that MT4-MMP is a principal precursor and companion of the epidermal growth factor receptor (EGFR), augmenting its activation leading to the production of cancer cells by a non-proteolytic system of action (21).

Studies have shown a strong link between hypoxia and the expression of MT4-MMP in oral cancer and cancers of the head and neck. When experiments on pharyngeal squamous cell carcinoma (FADU) and squamous cell carcinoma of the tongue (SAS) were conducted, they presented large rises of MT4-MMP transcriptions in hypoxic conditions [a large expression of the hypoxia inducing factor alpha (HIF-1α)]. A retrospectively conducted clinical trial showed conclusively that out of the 68 patients with FADU and SAS, HIF-1α and MT4-MMP were colocalized and was heavily associated with a poor treatment prognosis (20). Unlike other members of the membrane associated metalloproteinase family, MT4-MMP does not present

the ability to activate pro-MMP 2 or pro-MMP 9 (21). This removes a lot of frames of concern when discussing its link to oral cancers.

1.2.5. MT5-MMP and Oral cancer

MT5-MMP, unlike the previously mentioned membrane-type matrix metalloproteinase, has very little impact on the progression and metastatic ability of cancers in and around the oral cavity. However, this does not mean that further research will not benefit us as a society, as overexpression and malfunction of MT5-MMP has been shown to be a factor in other diseases, such as Alzheimer's. Studies have shown that MT5-MMP's role (similarly to the other membrane-type metalloproteinases) in proteolytic pathways, can process the amyloid precursor protein (APP). The processing of APP has been shown to release a novel neurotoxic APP fragment which when trafficked and accompanied with other pro-inflammatory pathways will contribute to the pathogenesis of Alzheimer's disease (22).

1.2.6. MT6-MMP and oral cancer

Studies have shown that an augmented level of MT6-MMP mRNA expression has been shown in several human cancers, including brain, urothelial and most importantly colon cancer. The findings of the expression in colon cancers directly started the first studies of the overexpression of this protein clinically among patients, showing a strong link to overexpression of MT6-MMP mRNA and tumour invasions (20). However, unlike MT4-MMP (the other matrix metalloproteinase with a GPI anchor), little evidence has been provided to establish a direct link between overexpression of MT6-MMP and cancers of the oral cavity. MT6-MMP, like MT4-MMP, does not possess the ability to activate other potentially harmful MMP's such as MMP 2 or MMP 9 (21).

2. Objectives

Main Objective:

To gain knowledge on the characteristics and function of the membrane-type matrix metalloproteinases in the context of oral cancer.

Secondary Objective:

To gain knowledge on the future directions in oral cancer research regarding matrix metalloproteinases function.

3. Materials and Methods

The research methods used in this meta-analytic systematic review were precise and cross-sectional, using a variety of online resources to gather English language data to review and compare. Data regarding oral cancer, matrix metalloproteinase and the six membrane-type matrix metalloproteinases with their potential links to cancer were searched and only complete published scientific articles were used. The main data base used for research was Medline, however for ease of access PubMed was also used due to its improved user-friendly interface. Keywords were used when searching through the article databases, these keywords were as follows: Matrix Metalloproteinase, Oral Cancer, Oral Squamous Cell carcinoma, cancer, Membrane-Type Matrix Metalloproteinase, MMP, MT-MMP, MMP 14, MMP 15, MMP 16, MMP 17, MMP 24, MMP 25, MT1-MMP, MT2-MMP, MT3-MMP, MT4-MMP, MT5-MMP, MT6-MMP, GPI anchored, transmembrane proteinase.

When scanning and selecting articles to be reviewed, both inclusion and exclusion criteria were used. The exclusion criteria were set upon to exclude articles over ten years old (pre-2010) and exclude articles that have non-relevant or repeated information. Articles were included if they were between 2010-2021, with the exception of 5 articles due to the lack of

recent studies undertook. Only articles that contained relevant information were selected for review.

4. Results

When comparing and analysing the various papers on the 6 different membrane-type metalloproteinases and their different pathogenic applications towards cancer in the oral cavity, the results regarding which play a role in oral cancer and which didn't were not sincerely black or white. MT1, 2, 3, and 4-MMP's all showed key characteristics in the progression of oral cancer, be that as an assisting pathway to metastasis, or more simply as a biomarker. MT5, and 6-MMP's however involved in the pathogenesis of other cancers and diseases they may be, with the current experimental research completed and data available to analyse don't seem to have any tangible links to the progression or metastatic ability of cancers in the oral cavity.

5. Discussion

5.1. MT-MMP's and Oral Cancer

Changes in the bioenvironment are necessary for the survival of cells in both a pathological and physiological sense. Cancer or tumour cells, not unlike normal cells, depend on their influence of the surrounding ECM to present their malignant phenotype during advanced tumour stages and thus can complete their natural comportment. An important characteristic that tumour cells present is the capability to separate from the main tumour (primary tumour) and invade surrounding tissues. The protease family of zinc-dependent endopeptidases that are MMP's are one of the major protease family's when referring to the progression of malignant cancers, this is of course a complex process, involving both suppressive and stimulatory effects.

Matrix metalloproteinase's complex function of pathological and biological implications in cancer is compounded by their complex structure. Their structure complexity derives from MMP's containing multiple domains, discrepancies for tissue manifestation, interrelating proteins and the inhibition profile of certain cofactors. It was shown that MMP's appear to have the ability to target and cleave different substrates at extracellular sites. This is due to the ability to delete or add accessory enzyme domains, whose function is to create pathways for active proteases to cleave their substrate of choice. Consequently, the 6 members of the MMP family developed to be membrane anchored can cleave a huge differential of substrates of the ECM at many different locations, be that close or far.

MT-MMPs are seamlessly suited to for extracellular proteolysis. The fact that they are anchored to the membrane enables these 6 members of the MMP family to be able to reach vital membrane and outlying proteins and other components of the ECM and will thus play an essential role in the pathological process of changing the pericellular environment. The two types of anchoring domains (transmembrane and GPI) also enable diffusion and translocation of the functioning protease to the surface of the cell, enabling its action within the ECM (1).
Around 90% of cancers located in and around the oral cavity are defined as OSCC, and for the time being the most common treatment methods include surgery, radiotherapy and chemotherapy (10).

Migration and invasion are very common in OSCC, which can cause a huge problem when thinking about survival rate and treatment prognosis (23). As mentioned previously, the most common locations for OSCC to appear are the tongue, superior alveolus, buccal mucosa, the hard palate and the gingiva (10). This creates a problem for doctors and patients alike when trying to diagnose cancers in the oral cavity as they are in places that are either unnoticeable or very hard to see/self-diagnose. This combined with the fact that most malignant tumours in the

oral cavity have a painless presence (9) means that any patient with a OSCC or any other kind of oral cancer will have huge difficulty in noticing the tumour, at least not until it is in the more advanced stages. This leaves doctors and patients with little options other than regular screenings by the patient's dentist accompanied by their anamnesis (the presence of family history and risk factors) or symptom presentation (however, again the latter has a large risk of only coming into play during the tumours later stages).

5.2. MT1-MMP as a biomarker/prognosis exacerbator in oral cancer

In OSCC, due to the cancerous tumour being in the oral cavity, saliva and blood would serve to be an easy access sample that could be collected to be analysed to detect the levels of MMP's and other molecules to be used as biomarkers. This will be vital for the early detection, prognostic diagnosis, treatment response and threat assessment of the OSCC. Using methods like reverse transcriptase-polymerase chain reaction (RTPC), hybridization, and zymography, MMP's family members were discovered to be overexpressed in blood and saliva in patients with OSCC (10).

	MMP family members
Cancerization from oral preneoplastic lesion	MMP-7, MMP-9, MMP-11
OSCC identification	MMP-2, MMP-9
Advanced tumor stage	MMP-2, MMP-3, MMP-9
Lymph node metastasis	MMP-1, MMP-2, MMP-3, MMP-9
Aggressive invasion	MMP-1, MMP-3, MMP-7, MMP-13, MMP-14
Poor differentiation	MMP-1, MMP-2, MMP-3, MMP-7, MMP-9, MMP-26
Cisplatin resistance	MMP-13
Poor prognosis	MMP-2, MMP-8, MMP-9, MMP-14

Figure 6. Table showing the different members of the MMP family analysed from patients with OSCC and how they affected the disease at different stages, ranging from identification to the prognosis (10).

MT-MMP's (14,15,16,17,24 and 25), subsist on the surface of a dividing tumour cell, and bind either using the transmembrane domain or the GPI anchor (1). MT1-MMP has shown to have rich capabilities in worsening the prognosis of OSCC in a variety of ways. It has also been observed to have a role in activating the proMMP-2 mechanism (10), and as we can see from the table above, MMP-2 is heavily involved in the process of advancing tumour stages, lymph node metastasis, poor differentiation, and the overall worsening of prognosis. MT1-MMP does this by utilizing the TIMP-2/MT1-MMP complex, creating a molecule known as MSP-T2 (process shown in figure 4 below). MT1-MMP will not trigger the activation of pro-MMP2 alone, it requires TIMP-2 to facilitate this. When the two bind, the MSP-T2 serves as a receptor for the activation of pro-MMP2 (15).

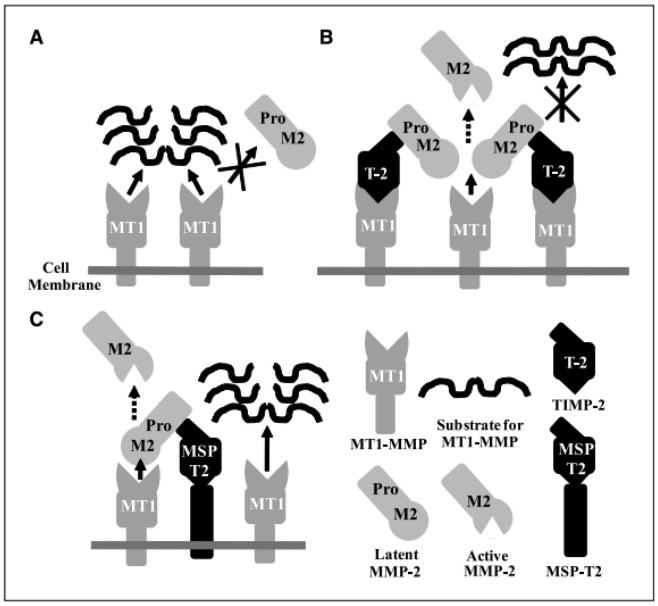

Figure 7. Diagram showing the MSP-T2 complex being created via binding of MT1-MMP and TIMP-2, and then going on to activate the pro-MMP2 molecule henceforth (15).

As we can see in figure 6, MMP 13 has involvement in a tumour's resistance to cisplatin and to an increase in aggressive invasion (10). Similarly to the activation of pro-MMP2, MT1-MMP possesses the ability to activate pro-MMP13, thus worsening the overall affliction of the patient in the previously mentioned means. This occurs utilizing some of the same mechanisms and molecules of the pro-MMP2 activation described previously (24). Pro-MMP-13 also has the capability to bind to the MSP-T2, due to its c-terminal being compatible to that of TIMP2, subsequently producing higher levels of MMP-13. Having different genotypes of MT1-MMP will also cause a difference in the pathogenicity of the molecule, as studies have shown. The +6767 and +7096 genotypes and the holotypes +6727 C: +6767 G: +7096 T: +8153 G have been shown to give the prediction of prognosis to OSCC (10).

5.3. MT2-MMP and ESCC.

When analysing research that has been conducted in regard to MT2-MMP and its relationship with oral cancer, the only concrete data seems to be the results of the aforementioned study. Evidently more research is needed as there is a clear correlation between expression of MT2-MMP and the angiogenesis of ESCC. The study previously mentioned (18) was very conclusive in its findings, as it can be seen in the results shown in figure 3 where there is a clear disparity in the staining between the normal oesophageal tissue and that of those with a carcinoma, and that there is also a clear change in death rate in the months post-surgery depending on the levels of MT2-MMP expression. However, it is important to consider the various factors that prevent the results from being extrapolated to the global population.

First of all, only one study was found, and this was carried out in China. Cultural factors must be taken into account when thinking of extrapolating data to a wider population. For example, number of patients that smoked, diet, oral hygiene, type of dental prosthetics and

amount of alcohol consumption to name a few. Sample size is also an important factor to consider. The study consisted to 103 patients which is not a large enough sample to be able to be able to generalize results to the population of China, let alone a global population.

When focusing on MT2-MMP and its links to pancreatic cancer, there is data to suggest that MT2-MMP when placed under hypoxic conditions increases the transcription rate (17). A study performed in 2011 showed that when pancreatic, cervical or lung cancer tumour cells were subjected to hypoxia, not only did the level of mRNA transcription increase but it also showed a decrease of hypoxia prompted apoptosis and an increased metastatic ability of the tumour cells (25). These experiments have yet to go into trial on cancers within the oral cavity, making it difficult to establish a link with it. Further research should be conducted to see how or if, when under the same hypoxic conditions, malignant tumour cells in either FADU, SAS, ESCC or OSCC would have the same increase in invasive potential as the cells in the studies already performed.

5.4. MT3-MMP and pro-MMP 2

When talking about MT3-MMP, more questions regarding its involvement with cancers are answered. Referring to the study cited earlier (19), a down regulation of MT3-MMP has an extreme effect on the prognostic diagnosis and survival rate of patients with ESCC, yet there isn't enough research to fully explain why. Most published papers, be it reviewing data or experimenting with biopsies and immunochemistry will state MT1-MMP overexpression as the key factor in worsening the prognostic diagnosis for patients with OSCC or ESCC, however there is small yet tangible evidence to support the data in figure 4. Like MT1-MMP, MT3-MMP does also appear to be involved in the activation of pro-MMP 2 (19), which like MT1-MMP, requires members of the TIMP family to do so.

Chromatography experimentations have proven that pro-MMP 2 can form trimolecular complexes with MT3-MMP and either TIMP-2 or TIMP-3, signifying that pro-MMP2 stimulation by MT3-MMP will involve a cell surface ternary complex (26). This could lead us to believe that MT3-MMP has more potential to activate pro-MMP 2 due to its ability to utilise both TIMP-2 or TIMP-3, however most data collected demonstrates that in most metastatic cancers in the oral cavity MT1-MMP has the most involvement in terms of activating the dangerous when overexpressed MMP 2.

5.5. GPI anchored MT4-MMP/MT3-MMP and oral cancer

Unlike other members of the MMP family, the 6 membrane-type MMP's find themselves in a unique position within the extracellular matrix. The MT-MMP's that find themselves associated with the membrane by the use of a GPI anchor are MT4-MMP and MT6-MMP. These GPI anchored matrix metalloproteinases, present unique characteristics that can be noteworthy when discussing their potential to aggravate the creation or the prognosis of oral cancer. Due to the fact that GPI MT-MMP's were discovered not much more than a decade ago, research is very limited when in comparison to the other 4 MT-MMP's. Nonetheless, within the limited research available we can see links to the progression of human cancers (including that of the human tongue).

In terms of their physical characteristics, the fact that MT4-MMP and MT6-MMP are presented right at the cell make them excellent pericellular proteolytic machines. However, the only link currently researched between direct ECM degradation ability and oral cancer appears to be with MT4-MMP when under hypoxic conditions (20). Granted there is little research in the topic, the links between MT4-MMP transcription and FADU/SAS seem very tangible. MT4-MMP transcription is increased when in the presence of HIF-1, and on the contrary,

supressing HIF-1 has been shown to decrease the expression and transcription of MT4-MMP. The interaction of MT4-MMP and HIF-1 will be something to consider when thinking about preventing over-transcription and its potential harmful effects. Evidence is available to state that both of the GPI anchored MT-MMP's (MT4-MMP and MT6-MMP) do not possess the ability to activate pro-MMP 2 or pro-MMP 9 (21). When referring back to figure 6, we see that this removes a lot of frames of concern when thinking about oral cancer such as advanced tumour stages, lymph node metastasis, bad differentiation and a poor prognostic diagnosis (10). Potentially the GPI MT-MMP's just didn't evolve in a way that means they could achieve pro-gelatinase instigation at the cell surface, however as they were discovered so recently, further research is required to establish and discuss this in more detail.

6. Future Applications and Responsibility

From the research that has been conducted and gathered, its fairly clear to see which MT-MMP's present the most risk when concerning oral cancer. The future applications involving these MT-MMPs could be immense, potentially reducing levels of metastasis, initial cancer development or even as a biomarker for early cancer screening and diagnosis. All of these things when put together would lower the overall prognostic diagnosis and hopefully reduce the incredibly high death rate of oral cancer.

When discussing the MT-MMP's that are worth targeting for future treatment options, although we have data to suggest which are involved and which aren't, more overall research is needed. For example, it's clear that MT2-MMP may have a grave impact on the prognosis of ESCCC, yet there is little to no research to show us how and why. We know from research the MT-MMP family can be used to identify cancers and predict the prognosis of the treatment. By understanding the function of how they operate, we can learn to inhibit overexpression and stop

the process of MT-MMP-harmful molecule activation. Some of the MT-MMP's have the ability to activate pro-MMP 2 and pro-MMP 9, these MT-MMP's are as follows: MT1-MMP and MT3-MMP. It is known that increasing levels of MMP 2 or 9 will have harmful effects on the initiation or the prognosis of oral cancer, and with an understanding on what causes the overexpression or activation of these two pro-MMP's we prevent this from occurring. As previously discussed, MT1-MMP and MT3-MMP need members of the TIMP family to able to form trimolecular complex's that serve to activate the pro-MMP's. In the past 10 years there hasn't been a lot of experimental studies conducted regarding potential ways to inhibit the MT-MMP/TIMP activation of the aforementioned pro-MMP's, however there is one study of note conducted in 2013 from which the results are very promising.

Within the study the murine 9E8 monoclonal antibody was used as a potential drug trial, with the results showing that it did not have harmful interactions with other members of the MMP family and that it also interrupted the MT1-MMP/pro-MMP 2 activation mechanism. It does this by identifying the loop structure of MT1-MMP and binding to it, thus taking the place and therefore inhibiting TIMP-2 from binding (18). Now as already stated other members of the MT-MMP family have the ability to activate other harmful pro-MMP's, and although in recent times there hasn't been a lot of research conducted regarding the use of other monoclonal antibodies for the same function, one would assume with the base data available the future is bright in that area.

The members of the MT-MMP family not only produces harmful effects activating pro-MMP's in the presence of TIMP, but also in the presence of hypoxic conditions. This does not only stand true for cancers of the oral cavity (MT4-MMP), but for other areas of the body for example the pancreas and bladder also (17). Regarding HIF-1α and MT4-MMP, it was shown when cancers such as FADU and SAS were metastasizing the levels of MT4-MMP

transcriptions were high, and that also the levels of MT4-MMP levels decreased when HIF-1α was silenced (20). Studies have shown that HIF-1α is a principal factor in tumour metastasis when combined with other molecules such as MT4-MMP etc, and upon its silencing have shown great results in improving the prognostic diagnosis (27). Effective HIF-1α can be a difficult task, but it is not impossible. One team of Chinese experimental scientists used a cationic mixed micellular nanoparticle (MNP) loaded with HIF-1α siRNA to silence HIF-1α in prostate cancer, showing promise for clinical applications in other areas of the body like the oral cavity.

7. Conclusion

Although the relationship between oral cancer and MT-MMP's is relatively unresearched, there are still links between the two which would support the data surrounding the poor prognosis of patients with high expressions of MT-MMP's. Not only this, but with further research carried out on the less known MT-MMP's such as 2, 4 and 5 we can extrapolate data from other cancers to better understand their effect on cancers of the oral cavity. With these not so studied MT-MMP's there is enough data available to say that they clearly have an effect of oral cancer, whether it be SAS, FADU, ESCC or OSCC, however there's not enough data to exactly well define the exact mechanism of action like the others.

Regarding the future applications of MT-MMPs in oral cancer, a lot must be said on the research that is already available however scarce it may be. Understanding the link between MT1-MMP and MT3-MMP the various pro-MMP's they activate will bring to light a huge number of treatment opportunities in the future, and maybe also help develop better preventative treatments in terms of screenings or early intervention. When looking at the association between MT2-MMP/MT3-MMP and HIF-1α there are already treatment methods

being put into place which could drastically improve the prognostic diagnosis of patients. However, it is left to be said that these specific treatment methods have only gone into trial with other kinds of cancer and have yet to be put into place to determine the effectiveness of treating oral cancer.

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Annexes

1.

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Biochemical and Biological Attributes of Matrix Metalloproteinases

Ning Cui, **Min Hu**, and **Raouf A. Khalil**
Vascular Surgery Research Laboratories, Division of Vascular and Endovascular Surgery, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA

Abstract

Matrix metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases that are involved in the degradation of various proteins in the extracellular matrix (ECM). Typically, MMPs have a propeptide sequence, a catalytic metalloproteinase domain with catalytic zinc, a hinge region or linker peptide, and a hemopexin domain. MMPs are commonly classified on the basis of their substrates and the organization of their structural domains into collagenases, gelatinases, stromelysins, matrilysins, membrane-type (MT)-MMPs, and other MMPs. MMPs are secreted by many cells including fibroblasts, vascular smooth muscle (VSM) and leukocytes. MMPs are regulated at the level of mRNA expression and by activation of their latent zymogen form. MMPs are often secreted as inactive proMMP form which is cleaved to the active form by various proteinases including other MMPs. MMPs cause degradation of ECM proteins such as collagen and elastin, but could influence endothelial cell function as well as VSM cell migration, proliferation, Ca^{2+} signaling and contraction. MMPs play a role in tissue remodeling during various physiological processes such as angiogenesis, embryogenesis, morphogenesis and wound repair, as well as in pathological conditions such as myocardial infarction, fibrotic disorders, osteoarthritis, and cancer. Increases in specific MMPs could play a role in arterial remodeling, aneurysm formation, venous dilation and lower extremity venous disorders. MMPs also play a major role in leukocyte infiltration and tissue inflammation. MMPs have been detected in cancer, and elevated MMP levels have been associated with tumor progression and invasiveness. MMPs can be regulated by endogenous tissue inhibitors of metalloproteinases (TIMPs), and the MMP/TIMP ratio often determines the extent of ECM protein degradation and tissue remodeling. MMPs have been proposed as biomarkers for numerous pathological conditions and are being examined as potential therapeutic targets in various cardiovascular and musculoskeletal disorders as well as cancer.

Keywords

Cell Signaling; Collagen; Extracellular Matrix; Proteinases; Protein Degradation; Remodeling

Correspondence and Reprints: Raouf A Khalil, MD, PhD, Harvard Medical School, Brigham and Women's Hospital, Division of Vascular Surgery, 75 Francis Street, Boston, MA 02115, Tel : (617) 525-8530, Fax : (617) 264-5124, raouf_khalil@hms.harvard.edu.

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2.

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Matrix Metalloproteinase Inhibitors in Cancer Therapy: Turning Past Failures into Future Successes

Arthur Winer[1], **Sylvia Adams**, and **Paolo Mignatti**

New York University School of Medicine, Department of Medicine and Perlmutter Cancer Center. 550 1 st Avenue, New York NY, 10016 USA

Abstract

The matrix metalloproteinases (MMPs) are a family of proteolytic enzymes that degrade multiple components of the extracellular matrix. A large body of experimental and clinical evidence has implicated MMPs in tumor invasion, neoangiogenesis and metastasis, and therefore they represent ideal pharmacological targets for cancer therapy. From the 1990's to early 2000's synthetic inhibitors of MMPs (MMPIs) were studied in various cancer types. Unexpectedly, despite strongly promising preclinical data, all trials were unsuccessful in reducing tumor burden or improving overall survival; in addition, MMPIs had unforeseen, severe side effects. Two main reasons can explain the failure of MMPIs in clinical trials. It has now become apparent that some MMPs have anti-tumor effects; therefore, the broad-spectrum MMPIs used in the initial trials might block these MMPs and result in tumor progression. In addition, although MMPs are involved in the early stages of tumor progression, MMPIs were tested in patients with advanced disease, beyond the stage when these compounds could be effective. As more specific MMPIs are now available, MMP-targeting could be reconsidered for cancer therapy; however, new trials should be designed to test their anti-metastatic properties in early-stage tumors, and endpoints should focus on parameters other than decreasing metastatic tumor burden.

Keywords

Cancer; Metastasis; Matrix Metalloproteinases; MMPs; MMP Inhibitors

Introduction

Cancer remains a leading cause of mortality worldwide, in some estimates accounting for more deaths than coronary artery disease or stroke. In the US, over 1.5 million new cases were diagnosed in 2016, leading to 595,000 deaths (1). Patients die of metastatic disease; therefore prevention of metastasis and treatment of micrometastatic disease is most important to improve cure rates. The mechanisms by which tumors metastasize are complex and involve numerous interactions between tumor cells and their microenvironment. A malignant cell invades into the surrounding tissue, enters the vasculature, and extravasates at

Corresponding Author, Present address: Arthur Winer, Fox Chase Cancer Center, 333 Cottman Avenue, Philadelphia PA, 19111 USA. Phone: 717-821-3169. Fax: 215-728-3639. Arthur.Winer@tuhs.temple.edu.

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3.

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Seesaw of matrix metalloproteinases (MMPs)

Charu Kapoor[1], Sharad Vaidya[2], Vijay Wadhwan[3], Hitesh[4], Geetpriya Kaur[5], Aparna Pathak[5]

[1] Department of Oral Pathology and Microbiology, Bhojia Dental College, Baddi, Solan, India

[2] Department of Prosthodontics and Implantology, Himachal Dental College, Sundernagar, Mandi, H.P, India

[3] Department of Oral Pathology and Microbiology, Subharti Dental College, Meerut, U.P, India

[4] Department of Oral Pathology and Microbiology, Manav Rachna Dental College, Faridabad, Haryana, India

[5] Paradise Diagnostics, Delhi, India

Date of Publication: Web 13-Apr-2016

Correspondence Address:
Charu Kapoor
Department of Oral Pathology and Microbiology, Bhojia Dental College, Budd, Baddi, Solan, Himachal Pradesh - 176 001
India
Login to access the email ID

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> Abstract

The family of human matrix metalloproteinases (MMPs) comprises several tightly regulated classes of proteases. These enzymes and their specific inhibitors play important roles in tumor progression and the metastatic process by facilitating extracellular matrix (ECM) degradation. As scientific understanding of the MMPs has advanced, therapeutic strategies focusing on blocking these enzymes by MMP inhibitors (MMPIs) have rapidly developed. This paper reviews MMPs in detail. Their perspectives in therapeutic intervention in cancer are also mentioned.

4.

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REVIEW

Matrix metalloproteinases in exercise and obesity

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Jonathan Jaoude[1]
Yunsuk Koh[2]

[1]Department of Biology, [2]Department of Health, Human Performance, and Recreation, Baylor University, Waco, TX, USA

Abstract: Matrix metalloproteinases (MMPs) are zinc- and calcium-dependent endoproteinases that have the ability to break down extracellular matrix. The large range of MMPs' functions widens their spectrum of potential role as activators or inhibitors in tissue remodeling, cardiovascular diseases, and obesity. In particular, MMP-1, -2, and -9 may be associated with exercise and obesity. Thus, the current study reviewed the effects of different types of exercise (resistance and aerobic) on MMP-1, -2, and -9. Previous studies report that the response of MMP-2 and -9 to resistance exercise is dependent upon the length of exercise training, since long-term resistance exercise training increased both MMP-2 and -9, whereas acute bout of resistance exercise decreased these MMPs. Aerobic exercise produces an inconsistent result on MMPs, although some studies showed a decrease in MMP-1. Obesity is related to a relatively lower level of MMP-9, indicating that an exercise-induced increase in MMP-9 may positively influence obesity. A comprehensive understanding of the relationship between exercise, obesity, and MMPs does not exist yet. Future studies examining the acute and chronic responses of these MMPs using different subject models may provide a better understanding of the molecular mechanisms that are associated with exercise, obesity, and cardiovascular disease.

Keywords: cardiovascular disease, gelatinases, collagenases, TIMP

Introduction

The property of matrix metalloproteinases

Matrix metalloproteinases (MMPs) were first observed in 1962 by Jerome Gross and Charles Lapiere in tadpole tissue that exhibited collagenolytic activity.[1] Eisen et al[2] were able to isolate human MMPs 6 years after its first discovery. MMPs are zinc- and calcium-dependent endoproteinases that play a crucial role in the remodeling of extracellular matrix (ECM) by breaking down its protein components.[3] MMPs can be categorized, on the basis of substrate specificity and homology, into the following six family groups: collagenases, gelatinases, stromelysins, matrilysins, membrane-type MMPs, and other MMPs (Figure 1; Table 1). All MMPs share common domain structures that degrade various ECM and nonmatrix.[4,5] Specific propeptide and catalytic domains exist (ie, MMP-7 and -26) along with a hemopexin-like, four-bladed, β-propeller domain located on the C-terminus, which is connected to a linker or hinge region (MMP-1, -3, -8, -11, -12, -13, -18, -19, -20, -21, -27, and -28).[6] These are the domains and regions that are involved in substrate recognition and inhibitor binding.[7–9] MMP-2 and -9 also have a fibronectin-like domain of three type II repeats.[6]

Correspondence: Yunsuk Koh
Department of Health, Human Performance, and Recreation, Baylor University, One Bear Place #97313, Waco, TX 76798, USA
Tel +1 254 710 4002
Fax +1 254 710 3527
Email yunsuk_koh@baylor.edu

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5.

cancers

MDPI

Article

Neoplastic Cells are the Major Source of MT-MMPs in *IDH1*-Mutant Glioma, Thus Enhancing Tumor-Cell Intrinsic Brain Infiltration

Ina Thome [1,†], Raphael Lacle [1,†], Andreas Voß [1], Ginette Bortolussi [1], Georgios Pantazis [1], Ansgar Schmidt [2], Catharina Conrad [1], Ralf Jacob [3], Nina Timmesfeld [4], Jörg W. Bartsch [5,6] and Axel Pagenstecher [1,6,*]

1 Departments of Neuropathology, Philipps University Marburg, 35043 Marburg, Germany; Ina.thome@staff.uni-marburg.de (I.T.); raphael.lacle@googlemail.com (R.L.); voss.andreas@klinikum-oldenburg.de (A.V.); bortolus@med.uni-marburg.de (G.B.); Georgios.Pantazis@ksgr.ch (G.P.); Catharina.Conrad@uth.tmc.edu (C.C.)
2 Departments of Pathology, Philipps University Marburg, 35043 Marburg, Germany; ansschmi@med.uni-marburg.de
3 Departments of Clinical Cytobiology and Cytopathology, Philipps University Marburg, 35037 Marburg, Germany; jacob@staff.uni-marburg.de
4 Department of Medical Informatics, Biometry and Epidemiology, Ruhr University Bochum, 44780 Bochum, Germany; Nina.Timmesfeld@rub.de
5 Departments of Neurosurgery, Philipps University Marburg, 35043 Marburg, Germany; jbartsch@med.uni-marburg.de
6 Centre for Mind, Brain, and Behaviour, 35032 Marburg, Germany
* Correspondence: pagenste@med.uni-marburg.de
† These authors contributed equally to this manuscript.

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Simple Summary: Most primary brain tumors infiltrate the surrounding brain even before the time of diagnosis and therefore cannot be removed completely. Matrix metalloproteases can degrade the extracellular proteins of the brain and thereby allow for the brain infiltration of glioma cells. Here, we demonstrate that tumor cells are the major source of several metalloproteases and as such responsible for the malignant behavior of gliomas. Our findings suggest that, controlling metalloproteases might be a promising therapeutic avenue in the treatment of glioma.

Abstract: Tumor-cell infiltration is a major obstacle to successful therapy for brain tumors. Membrane-type matrix metalloproteinases (MT-MMPs), a metzincin subfamily of six proteases, are important mediators of infiltration. The cellular source of MT-MMPs and their role in glioma biology, however, remain controversial. Thus, we comprehensively analyzed the expression of MT-MMPs in primary brain tumors. All MT-MMPs were differentially expressed in primary brain tumors. In diffuse gliomas, MT-MMP1, -3, and -4 were predominantly expressed by $IDH1^{mutated}$ tumor cells, while macrophages/microglia contributed significantly less to MT-MMP expression. For functional analyses, individual MT-MMPs were expressed in primary mouse $p53^{-/-}$ astrocytes. Invasion and migration potential of MT-MMP-transduced astrocytes was determined via scratch, matrigel invasion, and novel organotypic porcine spinal slice migration (OPoSSM) and invasion assays. Overall, MT-MMP-transduced astrocytes showed enhanced migration compared to controls. MMP14 was the strongest mediator of migration in scratch assays. However, in the OPoSSM assays, the glycosylphosphatidylinositol (GPI)-anchored MT-MMPs MMP17 and MMP25, not MMP14, mediated the highest infiltration rates of astrocytes. Our data unequivocally demonstrate for the first time that glioma cells, not microglia, are the predominant producers of MT-MMPs in glioma and can act as potent mediators of tumor-cell infiltration into CNS tissue. These proteases are therefore promising targets for therapeutic interventions.

6.

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REVIEW

Placental membrane-type metalloproteinases (MT-MMPs): Key players in pregnancy

Alejandro Majali-Martinez[a], Ursula Hiden[a], Nassim Ghaffari-Tabrizi-Wizsy[b], Uwe Lang[a], Gernot Desoye[a,#], and Martina Dieber-Rotheneder[a,c,#]

[a]Department of Obstetrics and Gynecology, Medical University of Graz, Graz, Austria; [b]Institute of Pathophysiology and Immunology, Medical University of Graz, Graz, Austria; [c]Institute of Pathology, Medical University of Graz, Graz, Austria

ABSTRACT

Membrane-type matrix metalloproteinases (MT-MMPs) are a sub-family of zinc-dependent endopeptidases involved in the degradation of the extracellular matrix. Although MT-MMPs have been mainly characterized in tumor biology, they also play a relevant role during pregnancy. Placental MT-MMPs are required for cytotrophoblast migration and invasion of the uterine wall and in the remodeling of the spiral arteries. They are involved in the fusion of cytotrophoblasts to form the syncytiotrophoblast as well as in angiogenesis. All these processes are crucial for establishing and maintaining a successful pregnancy and, thus, MT-MMP activity has to be tightly regulated in time and space. Indeed, a de-regulation of MT-MMP expression has been linked with pregnancy complications such as preeclampsia (PE), fetal growth restriction (FGR), gestational diabetes mellitus (GDM) and was also found in maternal obesity. Here we review what is currently known about MT-MMPs in the placenta, with a focus on their general features, their localization and their involvement in pregnancy disorders.

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extracellular matrix; fetal growth restriction, MT-MMP; preeclampsia; trophoblast

Introduction

The extracellular matrix (ECM) is a plastic matrix giving structure and grounding for the 3 dimensional organization of tissues. ECM is involved in multiple aspects of cell function including cell proliferation, differentiation, adhesion, migration and invasion.[1] Its degradation and remodeling is central for structural and developmental changes. Thus, the establishment of pregnancy as well as embryonic and fetal development requires ECM degradation to allow implantation, placental development, angiogenesis and parturition.[2] Vice versa, ECM composition modulates these processes. ECM degradation is tightly regulated since imbalances lead to pregnancy complications.[3]

Several proteases are involved in ECM degradation during pregnancy. These include serine proteases, cathepsins and matrix metalloproteinases (MMPs).[4] MMPs are a family of 24 zinc dependent endopeptidases capable of degrading virtually all ECM components. They have been classified into 5 groups: collagenases, gelatinases, stromelysins, membrane-type MMPs (MT-MMPs) and other MMPs.[5,6] This review will focus on MT-MMPs, a subgroup of 6 membrane anchored MMPs: MT1-MMP (MMP14), MT2-MMP (MMP15), MT3-MMP (MMP16), MT4-MMP (MMP17), MT5-MMP (MMP24) and MT6-MMP (MMP25).

Because of their key role in ECM degradation, various MMPs have been studied in depth regarding their function in pregnancy, but the majority of this work has focused on MMP2 and MMP9.[7-9] In contrast to secreted MMPs, MT-MMPs are membrane anchored and thus, allow a directed and spatially regulated mode of action. MT-MMPs have been shown to be required for tumor proliferation, invasion and angiogenesis,[10] processes that are also taking place in pregnancy, although tightly regulated. However, despite their function in ECM degradation, little is known about the role of MT-MMPs during pregnancy. This review summarizes the function of placental MT-MMPs, focusing on their localization, regulation and their involvement in the pathophysiology of pregnancy.

MT-MMPs: General features

MT-MMP structure

All members of the MMP family share a similar structure differing mainly in their domain organization. These

CONTACT Ursula Hiden ursula.hiden@medunigraz.at
#These authors contributed equally to this work.

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Policies for Prevention and Control of Oral Cancer in the light of Giddens' Structuration Theory

Fernando Lopes Tavares de Lima (https://orcid.org/0000-0002-8618-7608) [1]
Gisele O'Dwyer (https://orcid.org/0000-0003-0222-1205) [2]

Abstract *Challenges remain to ensure access to diagnosis and treatment ten years into continuous cancer prevention, control, and oral health policies. This study aims to analyze the oncology and oral health policies in force regarding the process of implanting oral cancer-related care components. Ten policies were analyzed under the lenses of the Structuration Theory, besides data on the supply of services between 2002 and 2017. Low coverage and inadequate regional distribution were highlighted in primary and secondary health care levels, despite increased funding and number of services. Unequal distribution of performed surgeries was identified in tertiary care. The limitation of home care services has hindered users' access to palliative care. A convergence was identified between the analyzed policies and concern with the regulation of authoritative resources and the increase of allocative resources, which stirred the expansion of services. Investments should be made in the expansion, regionalization, and universalization of services. A possible setback in these policies could aggravate the situation and contribute to the increase in health inequalities.*

Key words *Mouth Neoplasms, Health Policy, Oral Health*

[1] Instituto Nacional de Câncer José Alencar Gomes da Silva. Praça Cruz Vermelha 23, Centro. 20230-130 Rio de Janeiro RJ Brasil. flima@inca.gov.br
[2] Escola Nacional de Saúde Pública Sergio Arouca, Fundação Oswaldo Cruz. Rio de Janeiro RJ Brasil.

8.

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Diagnostic Pathology

RESEARCH Open Access

Clinical study on primary screening of oral cancer and precancerous lesions by oral cytology

Shintaro Sukegawa[1,2*], Sawako Ono[3,4], Keisuke Nakano[2], Kiyofumi Takabatake[2], Hotaka Kawai[2], Hitoshi Nagatsuka[2] and Yoshihiko Furuki[1]

Abstract

Background: This study was conducted to compare the histological diagnostic accuracy of conventional oral-based cytology and liquid-based cytology (LBC) methods.

Methods: Histological diagnoses of 251 cases were classified as negative (no malignancy lesion, inflammation, or mild/moderate dysplasia) and positive [severe dysplasia/carcinoma in situ (CIS) and squamous cell carcinoma (SCC)]. Cytological diagnoses were classified as negative for intraepithelial lesion or malignancy (NILM), oral low-grade squamous intraepithelial lesion (OLSIL), oral high-grade squamous intraepithelial lesion (OHSIL), or SCC. Cytological diagnostic results were compared with histology results.

Results: Of NILM cytology cases, the most frequent case was negative [LBC $n = 50$ (90.9%), conventional $n = 22$ (95.7%)]. Among OLSIL cytodiagnoses, the most common was negative (LBC $n = 34$; 75.6%, conventional $n = 14$; 70.0%). Among OHSIL cytodiagnoses (LBC $n = 51$, conventional $n = 23$), SCC was the most frequent (LBC $n = 31$; 60.8%, conventional $n = 7$; 30.4%). Negative cases were common (LBC $n = 13$; 25.5%, conventional $n = 14$; 60.9%). Among SCC cytodiagnoses SCC was the most common (LBC $n = 16$; 88.9%, conventional $n = 14$; 87.5%). Regarding the diagnostic results of cytology, assuming OHSIL and SCC as cytologically positive, the LBC method/conventional method showed a sensitivity of 79.4%/76.7%, specificity of 85.1%/69.2%, false-positive rate of 14.9%/30.7%, and false-negative rate of 20.6%/23.3%.

Conclusions: LBC method was superior to conventional cytodiagnosis methods. It was especially superior for OLSIL and OHSIL. Because of the false-positive and false-negative cytodiagnoses, it is necessary to make a comprehensive diagnosis considering the clinical findings.

Keywords: Cytology, Pathology, Liquid-based cytology, Screening, Inflammation

Background

Head and neck cancer is one of common malignancies in the world, and the most common histopathological type is squamous cell carcinoma (SCC). Several patients die every year because of advanced oral SCC [1]. Conversely, studies have reported that early detection and treatment of oral SCC can reduce mortality and morbidity and increase the likelihood of complete recovery [2, 3]. Therefore, it is important to use the simplest and the most accurate method that can to detect early-stage abnormalities in oral mucosal cells. An example of such method is exfoliated mucosal cytology, which involves

* Correspondence: gouwan19@gmail.com
[1]Department of Oral and Maxillofacial Surgery, Kagawa Prefectural Central Hospital, 1-2-1, Asahi-machi, Takamatsu, Kagawa 760-8557, Japan
[2]Department of Oral Pathology and Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan
Full list of author information is available at the end of the article

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What you should know about oral cancer

Detecting oral cancer early can nearly double your chance of survival.[1] Therefore, it is important that you know what factors put you at risk of developing the disease and what symptoms to watch for. Approximately 3% of all cancers diagnosed in 2015 involved the mouth or the back of the throat. When certain types of skin cancer were excluded, these oral cancers accounted for most head and neck cancers.[1]

RISK FACTORS

Some risk factors for developing oral cancer are beyond your control. Men tend to be at greater risk than women for oral cancer, which is diagnosed most often in adults between the ages of 55 and 64 years.[2] However, you can control other risk factors. For example, some behaviors that may put you at risk include

- using tobacco products;
- drinking alcohol heavily (more than 4 drinks a day)[3];
- using alcohol and tobacco products together (significantly increases the risk);
- using betel quid (paan)[4];
- eating a diet low in fruits and vegetables;
- spending long periods in the sun, which is associated with lip cancer.[5]

Another risk factor on the rise is infection with the human papilloma virus (HPV), which is sexually transmitted. Specifically, HPV is linked to cancers classified as *oropharyngeal*. Oropharyngeal cancer involves tissues near the back of the mouth and throat, including the back and base of the tongue, and the tonsils.[3] People who have HPV-related oropharyngeal cancer tend to be 4 to 10 years younger than people with oral cancers that are not related to HPV.[6]

ORAL CANCER SIGNS

Some signs you can watch for include

- a sore on the lips or in the mouth that will not heal;
- red or white patches in the mouth;
- pain, tenderness, or numbness on the lips or in the mouth;
- a lump, thickening, a rough spot, crusty area, or eroded area on the lips or in the mouth;
- difficulty chewing, swallowing, speaking, or moving the jaw or tongue;
- a change in the way your teeth fit together when you close your mouth;
- a lump or growth in your throat or neck;
- cough or sore throat that will not go away;
- earache;
- trouble swallowing;
- hoarseness or other changes in your voice.

WHAT CAN YOU DO?

Self-examinations, healthy lifestyle choices, and regular dental visits can go a long way toward catching oral cancer early, making the disease easier to treat. Commit to taking these steps in your life:

- Check your mouth and neck regularly for any of the above symptoms, and tell your dentist if you notice any of these or other changes;
- Avoid using tobacco or drinking heavily;
- Eat a healthy diet rich in fruits and vegetables;
- Avoid spending extended periods in the sun and use sunscreen;
- If you are sexually active, practice safe sex[7];
- See your dentist—as part of your dental visit, he or she will examine your mouth and neck for signs of oral cancer. ■

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"For the Patient" provides general information on dental treatments. It is designed to prompt discussion between dentist and patient about treatment options and does not substitute for the dentist's professional assessment based on the individual patient's needs and desires.

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10.

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Matrix Metalloproteinase Family as Molecular Biomarkers in Oral Squamous Cell Carcinoma

Authors | Authors and affiliations

Thian-Sze Wong ✉, Wei Gao, Zeng-Hong Li

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Abstract

Oral squamous cell carcinoma (OSCC) is one of the most common head and neck malignancies. Affected by the nonspecific symptoms, the OSCC patients are usually diagnosed in the advanced stages. To improve the treatment outcome and survival of OSCC, identification of the reliable biomarkers for early detection and prognosis prediction is necessary. Matrix metalloproteinases (MMPs) function in degradation of ECM, generation of active peptides, and activation of specific growth factors, resulting in forming an environment promoting tumor progression, invasion, and metastasis. MMPs can be applied as potential cancer biomarkers for early detection, risk assessment, prognostic analysis, and evaluation of response to treatment in OSCC. Moreover, the detection of MMPs in blood and saliva is a feasible mean to monitor OSCC in a noninvasive manner. Among all of the MMPs, MMP-9 probably appears to be the most promising biomarker with most of the documented cases. However, an updated meta-analysis is needed to confirm the advantages of MMP-9 over other MMPs in monitoring OSCC. Furthermore, an observation that MMP-11 in combination with Ets-1 or vascular endothelial growth factor (VEGF) leads to more accurate prediction in comparison with MMP-11 alone warrants further studies on the use of combined biomarkers in OSCC management.

Keywords

Oral squamous cell carcinoma | Matrix metalloproteinases | Biomarkers | Extracellular matrix | Lymph node metastasis | Invasion | Angiogenesis

List of Abbreviations

BL	Basal Lamina
ECM	Extracellular Matrix
EGF	Epidermal Growth Factor
ELISA	Enzyme-Linked Immunosorbant Assay
ER-a	Estrogen Receptor-a
ER-b	Estrogen Receptor-b
FGF-2	Fibroblast Growth Factor-2

11.

Metalloproteinases In Medicine

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REVIEW

Matrix metalloproteinases in head and neck cancer: current perspectives

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Ioannis Gkouveris[1]
Nikolaos G Nikitakis[2]
Jaya Aseervatham[1]
Nanditha Rao[1]
Kalu UE Ogbureke[1,2]

[1]Department of Oral Pathology, School of Dentistry, National and Kapodistrian University of Athens, Athens, Greece; [2]Department of Diagnostic and Biomedical Sciences, School of Dentistry, University of Texas Health Science Center at Houston, Houston, TX, USA

Abstract: Matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases encoded by 24 distinct genes. Their functions have been implicated in numerous normal and pathologic processes, including uterine involution and organogenesis, inflammation and wound healing, vascular and autoimmune disease progression. Pertinent to this review, the role of MMPs in cancer biology is fairly well researched and documented, and remains a subject of continuing intense investigation. Not only are several MMPs overexpressed in head and neck squamous cell carcinomas (HNSCCs), expression has been correlated with salient tumorigenic hallmarks, such as cell proliferation, angiogenesis, invasion, and metastasis. The utility of changes in the expression profile, as well as various MMP polymorphisms as potential prognostic markers in oral cancers and oral premalignant lesions, have been investigated. Furthermore, the potential therapeutic utility of targeting MMPs in cancer remains attractive, although outcomes in this respect appear so far to be less encouraging with respect to HNSCCs. Because of the disappointing results observed in clinical trials where MMP-targeting regimens for HNSCCs utilized broad-spectrum small MMP catalytic site inhibitors, investigators now envision new strategies for MMP-specific targeting based on the recognition of new noncatalytic MMP domains with distinct functions. This review provides an overview of MMP activities in general and in cancers, and an update of their activities in HNSCC. Specifically, their role in the development and progression of HNSCC and their function as signaling molecules is discussed. Finally, their role as potential prognostic biomarkers and therapeutic targets in HNSCC is revisited.

Keywords: MMPs, head and neck cancers, HNSCCs, oral squamous cell carcinoma, prognosis, therapy

Introduction

Head and neck squamous cell carcinoma (HNSCC) is the sixth-most common cancer worldwide, accounting for more than 550,000 cases and approximately 300,000 deaths annually.[1] HNSCCs are dominantly neoplasms arising from the squamous mucosae of the upper aerodigestive tract, accessory salivary glands, oropharynx, nasopharynx, and hypopharynx.[2] The 5-year survival rate for patients with HNSCC depends on the tumor stage at the time of diagnosis, but overall is approximately 50%, and has not improved significantly over the past five decades, despite advances in treatment techniques and modalities.[3] The molecular basis of HNSCC has been extensively studied, and several genetic and epigenetic alterations have been characterized and associated with cancer-cell proliferation, survival, differentiation, and invasion/metastasis, in an effort to identify novel diagnostic and prognostic markers and therapeutic targets.[2,4]

Correspondence: Kalu UE Ogbureke
School of Dentistry, University of Texas Health Science Center at Houston, 7500 Cambridge Street, Houston, TX 77054, USA
Tel +1 713 486 4406
Fax +1 713 486 4416
Email kalu.ogbureke@uth.tmc.edu

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Matrix Metalloproteinases

Changing Roles in Tumor Progression and Metastasis

Laurie A. Shuman Moss, Sandra Jensen-Taubman, and William G. Stetler-Stevenson

From the Radiation Oncology Branch, National Cancer Institute, NIH, Bethesda, Maryland

Articles on tumor invasion, metastasis, and angiogenesis in normal and disease states have been well represented among the pages of *The American Journal of Pathology*. In addition to exciting interest in a variety of disease processes, these studies have been central in defining the emerging field in cancer research known as the tumor microenvironment. Early studies in this field established the importance of the extracellular matrix on tumor cell growth and differentiation. With time, the role of the extracellular matrix and matrix metalloproteinases in the regulation of tumor invasion, metastasis, and angiogenesis was recognized, and *AJP* has published seminal articles in this field. Moreover, recent studies show evidence for a role of matrix metalloproteinases in the regulation of inflammation within tumor lesions, making the targeting of matrix metalloproteinases in cancer therapy even more complex. This review attempts to summarize the contribution of *AJP* to some of the key changes that have led to the evolution of this field. *(Am J Pathol 2012, 181:1895–1899; http://dx.doi.org/10.1016/j.ajpath.2012.08.044)*

It is now well established that the tumor microenvironment has a major influence on the development, invasion, and metastasis of cancer. Stephen Paget, who noted the propensity for some types of cancer to metastasize to specific organs, suggesting that the metastatic site is not simply a matter of chance, was probably the first to recognize the importance of the microenvironment. This concept of nonrandom metastasis is embodied in Paget's 1889 seed-soil hypothesis, which proposes that metastatic cancer cells (seeds) interact with specific organ microenvironments (soil) to result in metastasis formation.[1] We now know that the metastatic potential of a tumor cell is dependent on genetic alterations within cells of the primary tumor and also results from a dynamic series of interactions between structural, soluble, and changing cellular elements of the extracellular matrix and stromal tissue compartment. This commentary will briefly summarize *The American Journal of Pathology* contributions to the evolution of this field.

During the past 40 years, there has been increasing recognition that metastatic disease is responsible for the demise of most patients with cancer, resulting in a concurrent exponential increase in studies on the metastatic process. The seminal observations by Paget[1] challenged the prevailing viewpoint of his time that cancer metastasis was a random process. However, James Ewing,[2] who proposed that metastatic dissemination of cancer was purely dependent on the anatomical distribution of the vascular system, later challenged Paget's seed-soil hypothesis in 1928. This controversy was finally resolved with the work of Fidler and colleagues, who studied experimental metastasis in syngeneic mice to show that subsequent metastatic growth at a distant organ site was site specific, consistent with Paget's original hypothesis.[3] Critical to this work was the *in vivo* selection and characterization of invasive and metastatic mouse tumor models.[3] For example, tumors s.c. implanted in mice showed a different pattern of gene expression and metastasis formation than tumors implanted in the tissue of origin (orthotopic implantation), once again demonstrating the influence of the local microenvironment on tumor growth, selection, and metastasis.[4–6]

During the past 30 years, the scope of metastasis research has continued to expand, generating new roles for proteases and an increased understanding of the molecular mechanisms driving tumor angiogenesis. Moreover, transcriptome profiling of metastatic versus nonmetastatic tumors has revealed crucial information

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Address reprint requests to William G. Stetler-Stevenson, M.D., Ph.D., National Cancer Institute, NIH, Bldg 10, Room 2A33, 10 Center Dr, MSC 1500, Bethesda, MD 20892-1500. E-mail: sstevenw@mail.nih.gov.

13.

Matrix metalloproteinases and the development of cancer

Lisa M Coussens[1] and Zena Werb[2]

Proteolytic remodeling of the extracellular matrix is an important aspect of the creation and progression of cancer. Matrix metalloproteinases are important at several points during multistage neoplastic progression in tumor cells and responding blood vessels, inflammatory cells and stroma.

Addresses: [1]Department of Biochemistry and Biophysics and Hormone Research Institute, University of California, San Francisco, California, 94143-0534, USA and [2]Department of Anatomy, University of California, San Francisco, California, 94143-0750, USA.

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Introduction

Invasion of cells from one tissue into a neighboring tissue occurs during many physiological processes, both normal and pathological. These include the invasion of blood vessels into sites of tissue growth and inflammation, cell migration during wound healing, embryo implantation, ovulation, involution of the mammary gland during lactation, and the dissemination of tumors. In all of these processes the invading cells must breach barriers opposing their movement. These barriers include basement membranes, the stromal matrix, and cell–cell junctions. A common mechanism is believed to facilitate breaching of all of these barriers during invasion, namely release of proteolytic enzymes from either the invading cells, the opposing and responding cells, or both. The types of proteinases involved, the types of cells expressing them, and their precise roles are likely to be different for different types of tissues and circumstances. Nevertheless, there are three classes of proteinases (matrix metalloproteinases, serine proteases and cysteine proteases) that have altered distribution, increased expression and/or increased activity, during these processes, and are therefore believed to be involved in the matrix remodeling that facilitates invasion.

The concept that tumorigenesis is a multistep process has been well documented and is widely accepted. Historically, this has been thought to be exclusively a process of the progressive acquisition of mutations in key growth control genes, (oncogenes or tumor suppressor genes). Such mutations bestow upon cells traits associated with malignancy, for example, enhanced proliferation, invasive capability and the ability to grow in ectopic tissue environments. During tumor development, changing relationships between the premalignant and malignant cells and their microenvironment characterize all stages of the tumorigenic process. Although intrinsic factors are necessary for cellular transformation, extrinsic factors affecting the distribution, composition, and function of the extracellular matrix (ECM) into which a tumor expands, clearly make just as important a contribution to neoplastic progression and malignant conversion. Proteolytic enzymes are some of these extrinsic factors. It is significant that expression of the genes encoding these extrinsic factors does not result directly from mutation. Instead, altered expression of the normal genes is part of the response of the tumor and host to the neoplastic process. Studies of proteolysis in tumorigenesis have previously focused on basement membrane destruction during tumor invasion and metastasis. However, recent evidence suggests that proteinases, specifically matrix metalloproteinases (MMPs), are also involved in the earlier stages of tumor progression.

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Single Nucleotide Polymorphisms and Haplotypes of *MMP-14* are Associated with the Risk and Pathological Development of Oral Cancer

Chia-Jui Weng PhD, Mu-Kuan Chen MD, Chiao-Wen Lin MS, Tsung-Te Chung MD & Shun-Fa Yang PhD

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Abstract

Background

Matrix metalloproteinase (MMP)-14 is one of the pericellular collagenases to degrade extracellular matrix (ECM), which is involved to the modulation of susceptibility or clinicopathological features of a cancer. The contributions of MMP-14 on the susceptibility or clinicopathological features of certain cancers have been well documented, and the expression of MMP-14 in oral squamous cell carcinoma (OSCC) also has been observed. This study was designed to examine the association of *MMP-14* gene polymorphisms with the susceptibility and clinicopathological development of OSCC.

Methods

A total of 363 patients with OSCC and 506 healthy control subjects were recruited. Six single nucleotide polymorphisms (SNPs) of *MMP-14* genes were analyzed by polymerase chain reaction-restriction fragment length polymorphism genotyping and haplotype-base analysis.

Results

MMP-14 +7096 TC/CC genotypes might lower the risk of OSCC, and *MMP-14* +6767 GA/AA genotypes cause a poor clinical status in OSCC patients. The +6727 C: +6767 G: +7096 T: +8153 G haplotype and diplotype increased the risk for OSCC by 1.706-fold (95% confidence interval (CI) 1.383–2.105) and 2.276-fold (95% CI = 1.531–3.384), respectively, compared with the reference. The diplotype with at least one CGTG exhibited a high risk (adjusted odds ratio, 1.639; 95% CI, 1.005–2.673) for developing a poor clinicopathological diagnosis of OSCC compared with the others/other diplotype.

Conclusions

The +7096 and +6767 polymorphic genotypes and haplotype +6727 C: +6767 G: +7096 T: +8153 G of *MMP-14* gene might contribute to the prediction of susceptibility and pathological development of OSCC.

15.

Research Article

Activation of Matrix Metalloproteinase-2 (MMP-2) by Membrane Type 1 Matrix Metalloproteinase through an Artificial Receptor for ProMMP-2 Generates Active MMP-2

Yuki Nishida,[1] Hisashi Miyamori,[1] Erik W. Thompson,[1,2] Takahisa Takino,[1] Yoshio Endo,[1] and Hiroshi Sato[1]

[1]Department of Molecular Virology and Oncology, Cancer Research Institute, Kanazawa University, Takara-machi, Kanazawa, Japan and [2]St. Vincent's Institute and University of Melbourne Department of Surgery, St. Vincent's Hospital, Fitzroy, Australia

Abstract

The suggested model for pro-matrix metalloproteinase-2 (proMMP-2) activation by membrane type 1 MMP (MT1-MMP) implicates the complex between MT1-MMP and tissue inhibitor of MMP-2 (TIMP-2) as a receptor for proMMP-2. To dissect this model and assess the pathologic significance of MMP-2 activation, an artificial receptor for proMMP-2 was created by replacing the signal sequence of TIMP-2 with cytoplasmic/transmembrane domain of type II transmembrane mosaic serine protease (MSP-T2). Unlike TIMP-2, MSP-T2 served as a receptor for proMMP-2 without inhibiting MT1-MMP, and generated TIMP-2–free active MMP-2 even at a low level of MT1-MMP. Thus, MSP-T2 did not affect direct cleavage of the substrate testican-1 by MT1-MMP, whereas TIMP-2 inhibited it even at the level that stimulates proMMP-2 processing. Expression of MSP-T2 in HT1080 cells enhanced MMP-2 activation by endogenous MT1-MMP and caused intensive hydrolysis of collagen gel. Expression of MSP-T2 in U87 glioma cells, which express a trace level of endogenous MT1-MMP, induced MMP-2 activation and enhanced cell-associated protease activity, activation of extracellular signal–regulated kinase, and metastatic ability into chick embryonic liver and lung. MT1-MMP can exert both maximum MMP-2 activation and direct cleavage of substrates with MSP-T2, which cannot be achieved with TIMP-2. These results suggest that MMP-2 activation by MT1-MMP potentially amplifies protease activity, and combination with direct cleavage of substrate causes effective tissue degradation and enhances tumor invasion and metastasis, which highlights the complex role of TIMP-2. MSP-T2 is a unique tool to analyze physiologic and pathologic roles of MMP-2 and MT1-MMP in comparison with TIMP-2. [Cancer Res 2008;68(21):9096–104]

Introduction

Recent studies have shown that members of the matrix metalloproteinase (MMP) gene family play a central role in the degradation of extracellular matrix (ECM) macromolecules under various physiologic and pathologic conditions (1–5). Membrane type 1 MMP (MT1-MMP, MMP-14) was the first member of the MT-MMP family to be discovered and was identified as the first physiologic activator of latent MMP-2 (proMMP-2; ref. 6). The role of MT1-MMP in pericellular proteolysis is not restricted to proMMP-2 activation because MT1-MMP is a functional enzyme that can also degrade a number of ECM components (7–10) and hence can play a direct role in ECM turnover. The MMP family is balanced by a family of tissue inhibitors of metalloproteinase (TIMP). TIMP-2 preferentially complexes with proMMP-2 (11) and plays a pivotal role in the MT1-MMP–mediated activation process (12–16). The suggested model implicates TIMP-2 as a bridging molecule, tethering proMMP-2 through binding between the COOH-terminal ends of proMMP-2 and TIMP-2 and binding between the NH_2-terminal ends of MT1-MMP and TIMP-2. The propeptide of proMMP-2 is cleaved by an adjacent TIMP-2–free MT1-MMP between Asn^{37} and Leu^{38}, generating an activated intermediate form that is further processed to the fully activated form by an intermolecular autocleavage when present at a sufficiently high concentration at the cell surface. ProMMP-2 activation was expected to occur only at low TIMP-2 concentrations relative to MT1-MMP, which would permit availability of active MT1-MMP to process the proMMP-2 bound in the ternary complex (12, 13, 17–19). Recent study showed that proMMP-2 is activated by MT1-MMP, which is mostly saturated with TIMP-2, and thus TIMP-2 inhibits cleavage of other direct MT1-MMP substrates even at the level that induces proMMP-2 activation (20). Furthermore, MT1-MMP generates TIMP-2–free active MMP-2 only in a narrow range of TIMP-2 concentration. Thus, TIMP-2 concentration dictates MT1-MMP substrate choice, proMMP-2 activation, or direct cleavage of substrates. The optimum TIMP-2 concentration to produce active MMP-2 is restricted to a narrow range, which has hampered the analysis of significance of MMP-2 activation in pathologic conditions.

In the present study, a TIMP-2 chimera protein with mosaic serine protease (MSP) was constructed (MSP-T2), which functions as a receptor for proMMP-2, but no longer inhibits MMP, and generates TIMP-2–free active MMP-2 even in cells expressing low level of MT1-MMP. MSP-T2 enables us for the first time to examine the true enzyme activities of MT1-MMP and MMP-2.

Materials and Methods

Cell culture. Human embryonic kidney 293T, HT1080 fibrosarcoma, and U87 glioma cells were obtained from American Type Culture Collection and cultured in DMEM (Sigma) supplemented with 5% FCS. 293T cells express negligible levels of MT1-MMP, MMP-2, and TIMP-2 and were used for transfection experiments (20). In contrast, HT1080 and U87 cells express a high and a low level of endogenous MT1-MMP, respectively. Three-dimensional collagen gel culture was done as described previously (21).

Antibodies and recombinant proteins. Polyclonal antibody against MSP was prepared by injecting recombinant protein expressed in *E. coli*

Requests for reprints: Hiroshi Sato, Department of Molecular Virology and Oncology, Cancer Research Institute, Kanazawa University, 13-1 Takara-machi, Kanazawa 920-0934, Japan. Phone: 81-76-265-2748; Fax: 81-76-234-4504; E-mail: vhsato@kenroku.kanazawa-u.ac.jp.

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16.

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Cellular activation of proMMP-13 by MT1-MMP depends on the C-terminal domain of MMP-13

Vera Knäuper[a,1,*], Louise Bailey[a,1], Joanna R. Worley[a], Paul Soloway[b], Margaret L. Patterson[a], Gillian Murphy[c]

[a] *School of Biological Sciences, University of East Anglia, Norwich NR4 7TJ, UK*
[b] *Roswell Park Cancer Institute, Department of Molecular and Cellular Biology, Buffalo, NY 16263, USA*
[c] *University of Cambridge, Department of Oncology, Cambridge Institute for Medical Research, Hills Road, Cambridge CB2 2XY, UK*

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Abstract Procollagenase-3 (proMMP-13) can be activated by soluble or cell associated membrane type matrix metalloproteinase 1 (MT1-MMP). In this study we show that the cell based activation of proMMP-13 by MT1-MMP was dependent on the C-terminal domain, as $\Delta_{249-451}$ proMMP-13, which lacks the haemopexin domain, and a chimaera from N-terminal MMP-13 and C-terminal MMP-19 (proMMP-13/19) were not processed by MT1-MMP expressing cells. Only the initial cleavage at Gly^{35}–Ile^{36} was dependent on MT1-MMP activity, as conversion to the active enzyme (Tyr^{85} N-terminus) required a functional MMP-13 active site. Unlike proMMP-2 activation, this process was independent of tissue inhibitor of metalloproteinase-2 (TIMP-2) as MT1-MMP expressing cells from the *TIMP-2−/−* mouse efficiently activated proMMP-13.

Key words: Activation; Procollagenase-3; Membrane type matrix metalloproteinase 1; TIMP-2 null mouse; Progelatinase A; Tissue inhibitor of metalloproteinase-2

1. Introduction

Human procollagenase-3 (proMMP-13) is a member of the collagenase subfamily of matrix metalloproteinases (MMPs) and is expressed in breast tumours, hypertrophic chondrocytes and skin fibroblasts in vivo [1–3]. One important mechanism for the regulation of the collagenolytic activity of MMP-13 in vivo is the activation of the respective proenzyme by extracellular events. MMP-13 is an inactive proenzyme [4,5], therefore the unravelling of physiologically relevant activation pathways represents an important topic of investigation. We have shown that active MMP-3, gelatinase A (MMP-2) and membrane type MMP (MT1-MMP) mediate proMMP-13 activation in vitro and in cell model systems [6]. It is, however, not clear to date which domains of proMMP-13 contribute to the MT1-MMP driven activation of the proenzyme at the cell surface and whether there is a contribution of tissue inhibitor of metalloproteinase-2 (TIMP-2) in this process. The activation of proMMP-2 by cell bound MT1-MMP involves the establishment of a complex between TIMP-2 and MT1-MMP that forms a 'receptor' which binds the C-terminal domain of proMMP-2 to the C-terminal domain of TIMP-2 [7]. In this study we assess the role of the C-terminal domain of proMMP-13 and of TIMP-2 in regulating MT1-MMP dependent activation of proMMP-13 at the cell surface. In conjunction with data evaluating the significance of autolytic proteolysis of proMMP-13 in this process we extend our knowledge of cellular activation of proMMP-13 by MT1-MMP.

2. Materials and methods

2.1. Expression and purification of recombinant MMPs and TIMPs

proMMP-13, the C-terminal deletion mutant of MMP-13 ($\Delta_{249-451}$ proMMP-13), proMMP-2, TIMP-1 and TIMP-2 were purified as published [4,8–10]. A chimaeric enzyme was constructed from N-terminal MMP-13 and C-terminal MMP-19 (proMMP-13/19) by ligating the *Xcm*I to *Eco*RI C-terminal domain fragment of MMP-19 into the pEE12 vector carrying the coding sequences of the N-terminal domain of proMMP-13. Stable NS0 cell lines were generated and proMMP-13/19 was purified using SP-Sepharose [4].

2.2. Generation of pEE12 E^{205}-A proMMP-13

A pEE12 expression vector for an inactive mutant of proMMP-13 (E^{205}-A) was generated by extension mutagenesis. Two PCR products were generated using the mutagenic primers: 5′-GTGGCCGAATGCATGCGCAGCAACAAGAAACAAG-3′ and 5′-CTGCGCATGCATTCGGCCACTCCTTAGGTCTTG-3′, in conjunction with two vector primers and proMMP-13 cDNA as the template. The PCR products were overlap extended using vector primers and the product was cleaved with *Hin*dIII and ligated into pEE12. The cDNA sequence was verified by dideoxy sequencing.

2.3. Cellular model systems to investigate the activation of proMMP-13 by MT1-MMP overexpressing cells

2.3.1. HT1080 cells constitutively overexpressing MT1-MMP. HT1080 cells transfected with MT1-MMP in the HCMV/gpt vector, pGWIH9, were from British Biotechnology [7]. They make 1.5 pmol MT1-MMP per mg of membrane protein or vector control cells (0.13 pmol MT1-MMP per mg membrane protein) and were cultured as described [7].

2.3.2. Inducible MT1-MMP overexpressing HTC75 fibrosarcoma cells. The HTC75 cell line, which carries the pTET off control element, was transfected with the human MT1-MMP cDNA in pTRE and the pSV2neo plasmid as a selective marker [11,12]. proMMP-13

*Corresponding author. Present address: Biomedical Tissue Research, University of York, York YO10 5YW, UK. Fax: (44)-1904-328659.
E-mail address: vk8@york.ac.uk (V. Knäuper).

[1] These authors contributed equally to the work presented.

Abbreviations: MMPs, matrix metalloproteinases; TIMPs, tissue inhibitor of metalloproteinases; proMMP-13, procollagenase-3; E^{205}-A proMMP-13, inactive point mutant of proMMP-13; $\Delta_{249-451}$ proMMP-13, C-terminal deletion mutant of MMP-13; proMMP-13/19, chimaeric MMP-13 constructed from N-terminal proMMP-13 and C-terminal MMP-19; MMP-2, gelatinase A; MT1-MMP, membrane type matrix metalloproteinase 1

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17.

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Gene Section

Review

MMP15 (matrix metallopeptidase 15 (membrane-inserted))

Emiko Ito, Ikuo Yana, Nariaki Matsuura

Department of Molecular Pathology, Graduate School of Medicine and Health Sciences, Osaka University, Suita, Osaka 565-0871, Japan (EI, IY, NM)

Published in Atlas Database: October 2012

Online updated version : http://AtlasGeneticsOncology.org/Genes/MMP15ID41392ch16q21.html
DOI: 10.4267/2042/48760

Identity

Other names: MT2-MMP, MTMMP2, SMCP-2

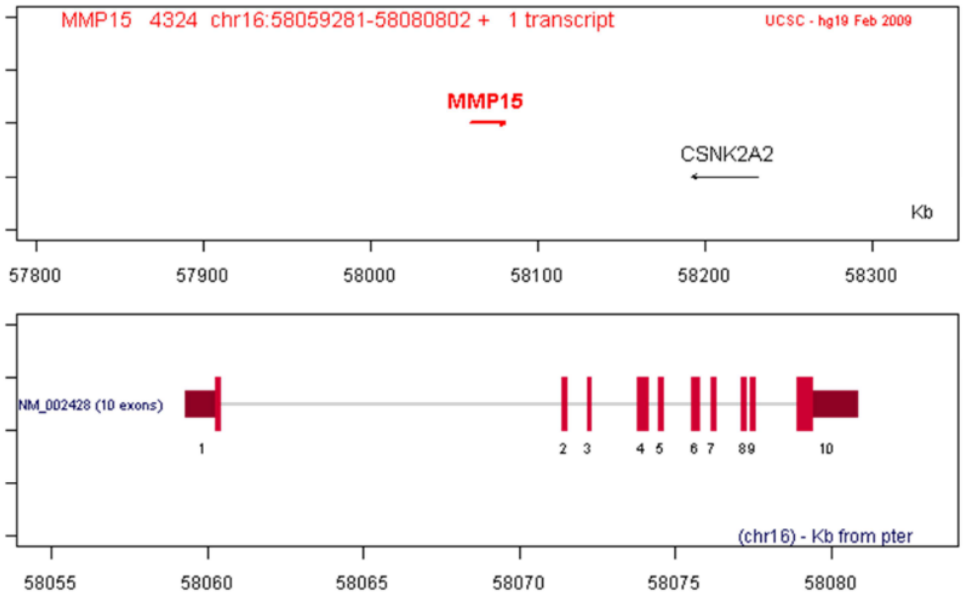
HGNC (Hugo): MMP15

Location: 16q21

DNA/RNA

Description

This gene can be found on chromosome16 at location: 58028573-58163296.



18.

ANTICANCER RESEARCH *30*: 4363-4368 (2010)

Immunochemical Staining of MT2-MMP Correlates Positively to Angiogenesis of Human Esophageal Cancer

LUJUN CHEN[1*], DONGMEI DI[2*], GUANGHUA LUO[1], LU ZHENG[1], YAN TAN[3], XIAOYING ZHANG[1,2] and NING XU[4]

[1]Comprehensive Laboratory, [2]Department of Thoracic Surgery and [3]Department of Pathology, the Third Affiliated Hospital of Suzhou University, Jiangsu, Changzhou 213003, P. R. China; [4]Section of Clinical Chemistry and Pharmacology, Department of Laboratory Medicine, Lund University, S-221 85 Lund, Sweden

Abstract. *Matrix metalloproteinases (MMPs) play an important role in the pathological processes of degradation of extracellular matrix and destruction of basement membrane, which leads to tumor invasion and metastasis. In the present study, we investigated membrane-type 2 MMP (MT2-MMP) expression pattern in esophageal cancer tissues collected from 103 patients, and explored MT2-MMP expression pattern in correlation to patients' clinicopathological features, intratumoral angiogenesis and postoperative prognoses. The intensity of immunochemical staining of MT2-MMP was significantly positively correlated to the intratumoral angiogenesis of esophageal cancer tissues. Positive MT2-MMP immunoreactions were found in 85.4% of total tumor sections, whereas none or very weak MT2-MMP staining occurred in normal esophageal tissues. In addition, MT2-MMP immunochemical intensities were significantly correlated to tumor size, but not to patient's gender, age, invasion depth, lymph node metastasis and distant metastasis. Moreover, MT2-MMP levels could not be applied for predicting patients' survival rate although the H-score cut-off value showed the overall survival rate of patients with low MT2-MMP protein level to be better than those with high MT2-MMP protein level.*

*These Authors contributed equally to this work.

Correspondence to: Xiaoying Zhang, MD, Comprehensive Laboratory, Third Affiliated Hospital of Suzhou University, Jiangsu Changzhou 213003, China. Tel: +86 51986181278, Fax: +86 51986621235, e-mail: xiaoyingzhang6689996@msn.com/Ning Xu, MD, Ph.D., Section of Clinical Chemistry and Pharmacology, Department of Laboratory Medicine, Lunds University, S-221 85 Lund, Sweden. Tel: +46 46173487, Fax: +46 46130064, e-mail: ning.xu@med.lu.se

Key Words: MT2-MMP, intratumoral angiogenesis, esophageal cancer.

Esophageal cancer is a quite aggressive malignancy of the upper gastrointestinal tract that ranks as the sixth cause of cancer deaths (1). Based on its distinct histopathological characteristics, esophageal cancer can be divided into two major types, namely adenocarcinoma and squamous cell carcinoma (SCC). The latter accounts for 90% of all esophageal cancer cases worldwide (2). Surgical resection of the tumor at the primary site is a standard treatment for esophageal cancer, and shows favorable trends for postoperative prognosis (3). Moreover, numerous alternative therapies have been available for the treatment of esophageal cancer, including chemotherapy, radiotherapy and immunotherapy, or a combination of these therapies. Due to the aggressive nature of this disease, patients suffering from esophageal cancer commonly undergo systemic and local recurrences even after curative operation, and the 5-year survival rate remains dismal (4).

It has been demonstrated that matrix metalloproteinases (MMPs) are related to tumor invasion and metastasis in most tumors (5). MMPs consist of more than 25 well-characterized members of secreted or transmembrane proteins that degrade the extracellular matrix (ECM) and basement membrane macromolecules (6). According to their structures and substrate specificities, MMPs are predominantly divided into five subgroups: collagenases, gelatinases, stromelysins, membrane-type MMPs (MT-MMPs) and other MMPs (7). MMPs regulate the tumor microenvironment, and their expression levels and/or activation might be altered in many human cancer tissues (5). Moreover, many studies have shown significant associations between MMP expression and the patient's clinicopathological features, as well as postoperative prognosis, which suggested that MMP levels might be used as biomarkers and therapeutic targets in human cancer (8). As yet, however, the expression patterns and physiopathological functions of MT-MMPs, a minority of the MMP family, have not been well documented in tumors. MT2-MMP was first characterized by Takino *et al.* (9) in 1995, and was

0250-7005/2010 $2.00+.40

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MT3-MMP down-regulation promotes tumorigenesis and correlates to poor prognosis in esophageal squamous cell carcinoma

Zengfu Xue, Xiumin Wu, Xiong Chen, Qi Luo

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Abstract

The membrane-type matrix metalloproteinases (MT-MMPs) play an important role in degrading the extracellular matrix (ECM) and facilitating protease-dependent tumor progression and invasion. Here, we report that unlike *MT1-MMP, MT3-MMP* was down-regulated in esophageal squamous cell carcinoma (ESCC) as detected by real-time PCR (qPCR), Western blot analysis, and immunohistochemistry (IHC). Down-regulation of *MT3-MMP* was observed at protein level in 66.3% of ESCC specimens (by IHC, n = 86) for routine pathologic diagnosis, as well as at mRNA level in 63.3% of surgically resected ESCC tumors paired with surrounding nontumor tissues (by qPCR, n = 30). Notably, *MT3-MMP* down-regulation significantly correlated with lymph node metastasis and poor overall survival of patients with ESCC (median 5-year survival = 50.69 vs. 30.77 months for patients with *MT3-MMP*-negative and -positive ESCC, respectively). Mechanistically, *MT3-MMP* negatively regulated proliferation, colony formation, and migration of ESCC cells, in association with cell cycle arrest at G1, due to up-regulation of $p21^{Cip1}$ and $p27^{Kip1}$. Together, as a tumor suppressor in ESCC, *MT3-MMP* down-regulation represents an unfavorable factor for prognosis of patients with ESCC.

20.

International Journal of
Molecular Sciences

MDPI

Review

MT4-MMP: The GPI-Anchored Membrane-Type Matrix Metalloprotease with Multiple Functions in Diseases

Cassandre Yip, Pierre Foidart, Agnès Noël and Nor Eddine Sounni *

Laboratory of Tumor and Development Biology, Groupe Interdisciplinaire de Génoprotéomique Appliqué-Cancer (GIGA-Cancer), University of Liège, Liège 4000, Belgium; cassandre.yip@uliege.be (C.Y.); pierre.foidart@chuliege.be (P.F.); agnes.noel@uliege.be (A.N.)
* Correspondence: nesounni@uliege.be; Tel.: +3243662570

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check for updates

Abstract: MT4-MMP (or MMP17) belongs to the Membrane-Type Matrix Metalloproteinase (MT-MMP) family. This family of proteases contributes to extracellular matrix remodeling during several physiological processes, including embryogenesis, organogenesis, tissue regeneration, angiogenesis, wound healing, and inflammation. MT4-MMP (MMP17) presents unique characteristics compared to other members of the family in terms of sequence homology, substrate specificity, and internalization mode, suggesting distinct physiological and pathological functions. While the physiological functions of MT4-MMP are poorly understood, it has been involved in different pathological processes such as arthritis, cardiovascular disease, and cancer progression. The *mt4-mmp* transcript has been detected in a large diversity of cancers. The contribution of MT4-MMP to tumor development has been further investigated in gastric cancer, colon cancer, head and neck cancer, and more deeply in breast cancer. Given its contribution to different pathologies, particularly cancers, MT4-MMP represents an interesting therapeutic target. In this review, we examine its biological and structural properties, and we propose an overview of its physiological and pathological functions.

Keywords: MT4-MMP; cancer; diseases

1. Introduction

The integrity of interstitial compartments is crucial for tissue homeostasis. The perturbation of the extracellular matrix and its related components destabilizes this balance, leading to pathogenesis. Matrix Metalloproteinases (MMPs) are the main remodeling enzymes of the extracellular matrix. This protease family counts more than 20 members, and most of them are secreted in the extracellular microenvironment. The membrane-type MMP (MT-MMPs) are associated to the membrane by a transmembrane domain, an amino-terminal link, or a glycosylphosphatidylinositol anchor (GPI). Together, secreted or attached to the membrane, MMPs can directly cleave almost all components of the extracellular matrix (ECM). However, the GPI anchor confers to MMPs a unique location in the lipid raft, giving access to a specific set of substrates. Only two MT-MMPs display this anchor: MT4-MMP (MMP-17) and MT6-MMP (MMP-25). In this review, we focus on MT4-MMP. Discovered more than 20 years ago, this protease aroused interest only a decade ago [1–4]. MT4-MMP exhibits unique characteristics, which distinguishes it from other MMPs. Unlike the others, it is unable to activate pro-MMP2 and cleaves only a few ECM components [5,6]. Its sensitivity to tissue inhibitors of metalloproteinases (TIMPs) is also different, with MT4-MMP being more sensitive to TIMP1 than TIMP2 [6,7]. These differences are probably due to the least degree of sequence identity [1]. MT4-MMP has been involved in inflammation and angiogenesis, contributing to associated pathologies such as

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MT4-(MMP17) and MT6-MMP (MMP25), A unique set of membrane-anchored matrix metalloproteinases: properties and expression in cancer

Anjum Sohail,
Department of Pathology, School of Medicine, and Proteases and Cancer Program, Barbara Ann Karmanos Cancer Institute, Wayne State University, 540 E. Canfield Ave., Detroit, MI 48201, USA

Qing Sun,
Department of Pathology, School of Medicine, and Proteases and Cancer Program, Barbara Ann Karmanos Cancer Institute, Wayne State University, 540 E. Canfield Ave., Detroit, MI 48201, USA

Huiren Zhao,
Department of Pathology, School of Medicine, and Proteases and Cancer Program, Barbara Ann Karmanos Cancer Institute, Wayne State University, 540 E. Canfield Ave., Detroit, MI 48201, USA

M. Margarida Bernardo,
Department of Pathology, School of Medicine, and Proteases and Cancer Program, Barbara Ann Karmanos Cancer Institute, Wayne State University, 540 E. Canfield Ave., Detroit, MI 48201, USA

Jin-Ah Cho, and
Department of Pathology, School of Medicine, and Proteases and Cancer Program, Barbara Ann Karmanos Cancer Institute, Wayne State University, 540 E. Canfield Ave., Detroit, MI 48201, USA

Rafael Fridman
Department of Pathology, School of Medicine, and Proteases and Cancer Program, Barbara Ann Karmanos Cancer Institute, Wayne State University, 540 E. Canfield Ave., Detroit, MI 48201, USA

Rafael Fridman: rfridman@med.wayne.edu

Abstract

The process of cancer progression involves the action of multiple proteolytic systems, among which the family of matrix metalloproteinases (MMPs) play a pivotal role. The MMPs evolved to accomplish their proteolytic tasks in multiple cellular and tissue microenvironments including lipid rafts by incorporation and deletions of specific structural domains. The membrane type-MMPs (MT-MMPs) incorporated membrane anchoring domains that display these proteases at the cell surface, and thus they are optimal pericellular proteolytic machines. Two members of the MT-MMP subfamily, MMP-17 (MT4-MMP) and MMP-25 (MT6-MMP), are anchored to the plasma membrane via a glycosyl-phosphatidyl inositol (GPI) anchor, which confers these enzymes a unique set of regulatory and functional mechanisms that separates them from the rest of the MMP

Correspondence to: Rafael Fridman, rfridman@med.wayne.edu.

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Journal of Neuroinflammation

HYPOTHESIS Open Access

MT5-MMP, just a new APP processing proteinase in Alzheimer's disease?

Kévin Baranger, Michel Khrestchatisky and Santiago Rivera*

Abstract

We have recently identified in a transgenic mouse model of Alzheimer's disease (AD) membrane-type 5-MMP (MT5-MMP) as a new player in Alzheimer's pathogenesis, which displays pro-amyloidogenic features and proteolytic processing of amyloid precursor protein (APP). Another group has reported that MT5-MMP processing of APP may release a novel neurotoxic APP fragment. Although MT5-MMP-mediated APP processing appears to be a key pathogenic step, we hypothesize that MT5-MMP may also contribute to AD pathogenesis through complementary mechanisms that involve the activation of pro-inflammatory pathways and/or APP trafficking.

Keywords: Matrix metalloproteinases, Neurodegenerative disease, Trafficking, Neuroinflammation, IL-1β, Amyloidogenesis, Amyloid precursor protein

Background

MT5-MMP belongs to the multigenic family of Zn^{2+} MMPs, which have been extensively associated with different physiological and pathological settings [1, 2]. MT5-MMP was first isolated from mouse brain tissue and from glioblastoma by two laboratories in 1999 [3, 4]. MT5-MMP is predominantly expressed in the nervous system [5], mainly in neurons, and to a lesser extent also in astrocytes and microglial and endothelial cells [6–8]. MT5-MMP is a 645 amino acid transmembrane glycosylated proteinase that is intracellularly activated by the Ca^{2+}-dependent proprotein convertase furin. The latter can also cleave MT5-MMP above its transmembrane domain before it reaches the plasma membrane, thus leading to the release of a truncated active soluble form of MT5-MMP [9]. MT5-MMP harbors nuclear localization sequences that may tag the proteinase for import into the nucleus [10]. The proteolytic activity of MT5-MMP is mainly under the control of the endogenous tissue inhibitor of MMP-2 (TIMP-2). Alternatively, adaptor proteins such as Mint-3 regulate MT5-MMP activity by controling its recycling from the trans-golgi network to the cell membrane and its localization in cells [11]. Moreover, MT5-MMP can be targeted to synapses through interaction with proteins containing PDZ domains such as the AMPA receptor binding protein (ABP) and the glutamate receptor interacting protein (GRIP) [12]. Overall, MT5-MMP appears as a functionally versatile molecule by virtue of its multiple interactions and localizations in the intracellular and pericellular compartments. An open question is whether MT5-MMP may in turn influence the subcellular localization and activity of its interacting proteins, and should be considered as a "moonlighting protein." One recent example among MMPs concerns MMP-12, which besides its well-known proteolytic activity has also transcription factor properties [13].

We are just starting to understand the functional diversity of MT5-MMP in pathology. Early studies showed the ability of MT5-MMP to proteolytically activate MMP-2 [3] and to process KiSS-1 protein and KISS-1-derived decapeptide metastin [14], which overall promotes cancer progression. MT5-MMP has been also reported to stimulate neuropathic pain by promoting aberrant axonal sprouting in the spinal cord after sciatic nerve injury in mice [15]. Moreover, it has been suggested that MT5-MMP is necessary for the inflammatory response to interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) in the peripheral nervous system [16]. It is noteworthy that no overt developmental abnormalities have been detected in MT5-MMP$^{-/-}$ mice, in contrast with the clearly marked phenotypes they display in pathological conditions [15–17], and also in

* Correspondence: santiago.rivera@univ-amu.fr
Aix Marseille Univ, CNRS, NICN, Marseille, France

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Review Article

Essentials of oral cancer

César Rivera

Department of Basic Biomedical Sciences, University of Talca (UTALCA) Talca, Maule Region, Chile; Department of Oral Diagnosis, School of Dentistry, State University of Campinas (UNICAMP) Piracicaba, São Paulo, Brazil; Mass Spectrometry Laboratory, Brazilian Biosciences National Laboratory (LNBio), National Center for Research in Energy and Materials (CNPEM) Campinas, São Paulo, Brazil

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Abstract: Oral cancer is one of the 10 most common cancers in the world, with a delayed clinical detection, poor prognosis, without specific biomarkers for the disease and expensive therapeutic alternatives. This review aims to present the fundamental aspects of this cancer, focused on squamous cell carcinoma of the oral cavity (OSCC), moving from its definition and epidemiological aspects, addressing the oral carcinogenesis, oral potentially malignant disorders, epithelial precursor lesions and experimental methods for its study, therapies and future challenges. Oral cancer is a preventable disease, risk factors and natural history is already being known, where biomedical sciences and dentistry in particular are likely to improve their poor clinical indicators.

Keywords: Mouth neoplasms, oral cancer, oral squamous cell carcinoma, carcinogenesis, neoplasm staging, tumor microenvironment

Introduction

Oral cancer is a highly relevant problem of global public health, especially for dental surgeons. It is located within the top 10 ranking incidence of cancers and despite the progress in research and therapy, survival has not improved significantly in the last years, representing a continuing challenge for biomedical science. This paper aimed to report key aspects of this cancer, integrating clinical, histological and molecular concepts for a better understanding of their biological pathways, allowing the reader and researcher construct a map which could serve to place and integrate this growing information.

Definition

Oral cancer is a malignant neoplasia which arises on the lip or oral cavity. Is traditionally defined as a squamous cell carcinoma (OSCC), because in the dental area, 90% of cancers are histologically originated in the squamous cells [1]. It has different levels of differentiation and a propensity for lymph node metastasis [2].

Epidemiology

Oral cancer is two to three times more prevalent in men than women in most ethnic groups [http://seer.cancer.gov/statfacts/html/oralcav.html]. In worldwide reports, cancers of all regions of the oral cavity and pharynx are grouped and collectively represent the sixth most common cancer in the world [3]. According to the latest reports of the International Agency for Research on Cancer (IARC) for oral cancer (ICD-10 code C00-08: Lip, Oral Cavity) which includes lips, tongue, gingiva, mouth floor, parotid and salival glands, annual incidence is higher around the world, which is over 300.000 diagnosed cases, and the annual mortality is about 145,000 death [http://globocan.iarc.fr/Pages/summary_table_pop_sel.aspx]. **Table 1** shows the incidence and mortality for oral cancer according to the regions of the World Health Organization (WHO), and those that present the most critical numbers are WHO South-East Asia region (SEARO) and WHO Europe region (EURO). Specifically by area, those that are characterized by a high incidence of oral cancer are found in South and Southeast Asia (Sri Lanka, India,

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Arthritis Research & Therapy

REVIEW Open Access

New insights on the MMP-13 regulatory network in the pathogenesis of early osteoarthritis

Heng Li[1], Dan Wang[1], Yongjian Yuan[1] and Jikang Min[1,2*]

Abstract

Osteoarthritis (OA) is the most common joint disorder and affects approximately half of the aged population. Current treatments for OA are largely palliative until the articular cartilage has been deeply damaged and irreversible morphological changes appear. Thus, effective methods are needed for diagnosing and monitoring the progression of OA during its early stages when therapeutic drugs or biological agents are most likely to be effective. Various proteinases involved in articular cartilage degeneration in pre-OA conditions, which may represent the earliest reversible measurable changes, are considered diagnostic and therapeutic targets for early OA. Of these proteinases, matrix metalloproteinase 13 (MMP-13) has received the most attention, because it is a central node in the cartilage degradation network. In this review, we highlight the main MMP-13-related changes in OA chondrocytes, including alterations in the activity and expression level of MMP-13 by upstream regulatory factors, DNA methylation, various non-coding RNAs (ncRNAs), and autophagy. Because MMP-13 and its regulatory networks are suitable targets for the development of effective early treatment strategies for OA, we discuss the specific targets of MMP-13, including upstream regulatory proteins, DNA methylation, non-coding RNAs, and autophagy-related proteins of MMP-13, and their therapeutic potential to inhibit the development of OA. Moreover, the various entities mentioned in this review might be useful as early biomarkers and for personalized approaches to disease prevention and treatment by improving the phenotyping of early OA patients.

Keywords: Matrix metalloproteinases, MMP-13, Osteoarthritis, Non-coding RNA, DNA methylation, Autophagy

Background

Osteoarthritis (OA) is the most common joint disorder, affecting approximately half of the aged population (>65 years) and is characterized by the progressive degeneration of articular cartilage. The major clinical manifestation includes symptoms of knee pain, knee swelling, ankylosis, and limited activity [1]. OA results in mobility problems and severe pain during the intermediate or advanced stages and represents a leading socio-economic burden in the developed world [2].

Currently, clinical diagnosis and monitoring of OA mainly rely on symptomatic and radiographic assessments and certain traditional laboratory tests [3–5]. Although their sensitivity and accuracy are relatively high, these methods fail to distinctively identify the developmental stages of OA. Similarly, the current treatments for OA are largely palliative until the articular cartilage has been deeply damaged and irreversible morphological changes have occurred; during the progression of OA the joints become completely dysfunctional and prosthetic replacement becomes necessary [6]. Thus, effective methods for diagnosing OA during its early stages are imperative and OA-related changes can likely be reversed by effective therapeutic drugs.

However, the development of disease-modifying drugs and the verification of their effectiveness in clinical trials are difficult to achieve due to the lack of a biomarker for the identification of patients with early OA-related changes. Articular cartilage damage is one of the most significant hallmarks of the early stages of OA [7]. Recently, studies have focused on the identification of biomarkers involved in articular cartilage degeneration in very early OA, which may represent the earliest reversible measurable changes.

* Correspondence: mjk@medmail.com.cn
[1]The First Affiliated Hospital of Huzhou Teachers College, Zhejiang Province 313000, China
[2]Department of Orthopaedics, The First Affiliated Hospital of Huzhou Teachers College, The First People's Hospital of Huzhou, Zhejiang Province 313000, China

25.

Transcriptional upregulation of MT2-MMP in response to hypoxia is promoted by HIF-1α in cancer cells

Shikai Zhu, Yu Zhou, Lin Wang, Jianjun Zhang, Hanqing Wu, Jiongxin Xiong, Jinghui Zhang, Yuan Tian, Chunyou Wang, Heshui Wu

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Abstract

Hypoxia is a critical event in solid tumor development, invasion, and metastasis. Cellular adaptation to hypoxic microenvironment is essential for tumor progression and is largely mediated by hypoxia-inducible factor-1α (HIF-1α) through coordinated regulation of hypoxia-responsive genes. In this study, we found that membrane type-2 matrix metalloproteinase (MT2-MMP), one of the matrix metalloproteinase (MMP) family members, was a novel hypoxia-responsive gene and was upregulated by HIF-1α under hypoxia. When cancer cells were subjected to hypoxia (1% O_2) treatment, the mRNA and protein levels of MT2-MMP were significantly increased in a time-dependent manner in all three tested cancer cell lines including pancreatic cancer cells (PANC-1), nonsmall cell lung cancer cells (A-549), and cervix cancer cells (HeLa). Further analyses indicated that there were two hypoxia-responsive elements (HREs) in the MT2-MMP promoter, and HRE1 but not HRE2 was essential for MT2-MMP transcriptional activation under hypoxia. HIF-1α specifically and directly bound to MT2-MMP promoter was analyzed by HIF-1α binding/competition and chromatin immunoprecipitation (ChIP) assays. Furthermore, we found that upregulation of MT2-MMP under hypoxia could confer resistance to hypoxia-induced apoptosis and increase invasiveness of cancer cells. These findings provided a new insight into how cancer cells overcome hypoxic stress and trend to survive and invade, demonstrated a new regulatory mechanism of MT2-MMP expression in caner cells, and also revealed that MT2-MMP was a novel hypoxia-responsive gene and was upregulated by HIF-1α under hypoxia. © 2011 Wiley-Liss, Inc.

26.

Differential inhibition of membrane type 3 (MT3)-matrix metalloproteinase (MMP) and MT1-MMP by tissue inhibitor of metalloproteinase (TIMP)-2 and TIMP-3 rgulates pro-MMP-2 activation

Huiren Zhao [1], M Margarida Bernardo, Pamela Osenkowski, Anjum Sohail, Duanqing Pei, Hideaki Nagase, Masahide Kashiwagi, Paul D Soloway, Yves A DeClerck, Rafael Fridman

Affiliations + expand

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Free article

Abstract

The membrane type (MT)-matrix metalloproteinases (MMPs) constitute a subgroup of membrane-anchored MMPs that are major mediators of pericellular proteolysis and physiological activators of pro-MMP-2. The MT-MMPs also exhibit differential inhibition by members of the tissue inhibitor of metalloproteinase (TIMP) family. Here we investigated the processing, catalytic activity, and TIMP inhibition of MT3-MMP (MMP-16). Inhibitor profile and mutant enzyme studies indicated that MT3-MMP is regulated on the cell surface by autocatalytic processing and ectodomain shedding. Inhibition kinetic studies showed that TIMP-3 is a high affinity inhibitor of MT3-MMP when compared with MT1-MMP (K(i) = 0.008 nm for MT3-MMP versus K(i) = 0.16 nm for MT1-MMP). In contrast, TIMP-2 is a better inhibitor of MT1-MMP. MT3-MMP requires TIMP-2 to accomplish full pro-MMP-2 activation and this process is enhanced in marimastatpretreated cells, consistent with regulation of active enzyme turnover by synthetic MMP inhibitors. TIMP-3 also enhances the activation of pro-MMP-2 by MT3-MMP but not by MT1-MMP. TIMP-4, in contrast, cannot support pro-MMP-2 activation with either enzyme. Affinity chromatography experiments demonstrated that pro-MMP-2 can assemble trimolecular complexes with a catalytic domain of MT3-MMP and TIMP-2 or TIMP-3 suggesting that pro-MMP-2 activation by MT3-MMP involves ternary complex formation on the cell surface. These results demonstrate that TIMP-3 is a major regulator of MT3-MMP activity and further underscores the unique interactions of TIMPs with MT-MMPs in the control of pericellular proteolysis.

27.

Therapeutic delivery of siRNA silencing HIF-1 alpha with micellar nanoparticles inhibits hypoxic tumor growth

Xi-Qiu Liu [1], Meng-Hua Xiong, Xiao-Ting Shu, Rui-Zhi Tang, Jun Wang

Affiliations + expand

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Abstract

The particular characteristics of the tumor microenvironment have the potential to strongly promote tumor growth, metastasis and angiogenesis and induce drug resistance. Therefore, the development of effective, systemic therapeutic approaches specifically based on the tumor microenvironment is highly desirable. Hypoxia-inducible factor-1α (HIF-1α) is an attractive therapeutic target because it is a key transcription factor in tumor development and only accumulates in hypoxic tumors. We report here that a cationic mixed micellar nanoparticle (MNP) consisting of amphiphilic block copolymers poly(ε-caprolactone)-block-poly(2-aminoethylethylene phosphate) (PCL(29)-b-PPEEA(21)) and poly(ε-caprolactone)-block-poly(ethylene glycol) (PCL(40)-b-PEG(45)) was a suitable carrier for HIF-1α siRNA to treat hypoxic tumors, which showed an average diameter of 58.0 ± 3.4 nm. The complex MNP(siRNA), formed by the interaction of MNP and siRNA, was transfected into PC3 prostate cancer cells efficiently, while the inhibition of HIF-1α expression by MNP loaded with HIF-1α siRNA (MNP(siHIF)) blocked PC3 cell proliferation, suppressed cell migration and disturbed angiogenesis under in vitro hypoxic mimicking conditions. It was further demonstrated that systemic delivery of MNP(siHIF) effectively inhibited tumor growth in a PC3 prostate cancer xenograft murine model without activating innate immune responses. Moreover, delivery of MNP(siHIF) sensitized PC3 tumor cells to doxorubicin chemotherapy in vitro and in vivo by downregulating MDR1 gene expression which was induced by hypoxia. The underlying concept of use of MNP(siHIF) to block HIF-1α holds promise as an example of a clinical approach using specific siRNA therapy for cancer treatment aimed at the hypoxic tumor microenvironment.