Matrix Metalloproteinases-Modulating the Tumor Microenvironment

Marzenna Wiranowska1, Amyn M Rojiani2 and Mumtaz V Rojiani2-3

1Department of Pathology and Cell Biology, Morsani College of Medicine, University of South Florida, Tampa, Florida, USA
2Departments of Pathology, Medical College of Georgia-Georgia Regents University, Augusta Georgia, USA
3Department of Medicine, Medical College of Georgia-Georgia Regents University, Augusta Georgia, USA

*Corresponding author: Mumtaz V Rojiani, Departments of Pathology and Medicine, Medical College of Georgia, Georgia Regents University, Augusta GA 30912, USA, Tel: (706) 721-0295; E-mail: M-Rojiani@GRU.EDU

Received date: February 13, 2015; Accepted date: May 04, 2015; Published date: May 11, 2015

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Abstract

Observations on the collagenolytic activity of endopeptidases in tadpoles undergoing metamorphosis were the early steps in defining this family of matrix metalloproteinases (MMP). Extensive investigations into these enzymes in plants and animals have revealed the highly pleiotropic nature of these molecules, both in physiologic and pathologic conditions. The human MMP family is comprised of over 23 members, which are capable of degrading and processing almost all components of the extracellular matrix (ECM) such as proteins and proteoglycans including those of basement membrane. MMPs also can cleave a wide variety of non-matrix substrates such as cytokines, chemokines, growth factors and their receptors as well as adhesion molecules important in tumor microenvironment and at all stages of tumor progression.

Keywords: Matrix metalloproteinase; Tumor microenvironment; Extracellular matrix; Review

Introduction

Observations on the collagenolytic activity of endopeptidases in tadpoles undergoing metamorphosis were the early steps in defining this family of matrix metalloproteinases (MMP) [1]. Extensive investigations into these enzymes in plants and animals have revealed the highly pleiotropic nature of these molecules, both in physiologic and pathologic conditions. The human MMP family is comprised of over 23 members, which are capable of degrading and processing almost all components of the extracellular matrix (ECM) such as proteins and proteoglycans including those of basement membrane. MMPs also can cleave a wide variety of non-matrix substrates such as cytokines, chemokines, growth factors, and their receptors as well as adhesion molecules important in tumor microenvironment and at all stages of tumor progression [2-5].

MMPs are synthesized as zymogens and either secreted from the cell into ECM or anchored to the plasma membrane, or some are even found as intracellular proteins. Their expression is mainly regulated at the transcriptional level, but recent reports suggest that post-transcriptional events may play a role [6]. Most of MMPs contain four distinct functional domains such as: signal peptide, propeptide, catalytic domain, and hemopoexin-like domain [5]. They all share a highly conserved zinc binding site in their catalytic domain.

The classification of MMPs summarized below in Table 1 is based on their substrate specificity, domain organization and function [5,7]. MMPs that play an essential role in the tumor microenvironment can be found in each of these groups [8-10].

MMPs: Cellular Sources and Role in Inflammation

One of the hallmarks of cancer is inflammation. Various pro-inflammatory factors, including cytokines and MMPs are produced by the tumor as well as by the tumor surrounding stroma. The inflammatory cells of the stroma which contribute to the microenvironment of tumor include: mononuclear cells such as monocytes and macrophages; granulocytes such as neutrophils, eosinophils, and basophil/mast cells and T and B lymphocytes. Together, these cells can enhance turnover of ECM and tumor cell migration. Stromal cells such as tumor-infiltrating leukocytes including mononuclear cells (monocytes and macrophages), granulocytes (neutrophils, eosinophils, basophils/mast cells) and lymphocytes are known to be main producers of MMPs. A wide variety of MMPs can be produced by these cells including (MMP-1,2,3,7,9,10,12,13,14,19) capable of degrading ECM and inducing tumor angiogenesis. MMP-9 which is directly involved in angiogenesis is released mainly by macrophages at the tumor site. For example it was recently shown that glioma-associated microglial/macrophage MMP-9 expression promotes glioma infiltration into the normal brain parenchyma [11]. It had previously been shown that macrophages, mast cells and peripheral mononuclear cells amplify neoplastic cell proliferation and angiogenesis which was mostly attributed to the release of MMP-9 by these cells [12].

The release of MMPs from granulocytes in general, is based upon demand. MMPs released by neutrophils are MMP-8 and MMP-9 with latter shown to be highly potent proangiogenic enzyme. Tumor-infiltrating neutrophils localize predominantly in the tumor interior, in contrast to monocytes/macrophages which are found at the tumor periphery or tumor/stroma border. Mast cells produce MMP-9 and MMP-2, and like basophils, are able to release the vasoactive agents from their granules.

Other important cells in the tumor stroma are fibroblasts, endothelial cells and perivascular pericytes, which can also express MMPs [13,14]. The cross-talk between tumor cells and normal stromal cells can trigger fibroblasts to express MMPs, e.g., MMP-9. Other known fibroblast-derived MMPs includes MMP-1, 7 and 14. In addition, activated endothelial cells of the capillary network overexpress several MMPs (MMP-1, 9, and 14) during sprouting and
formation of lumina-containing tubules, although these cells are relatively deficient in MMP expression when in a quiescent state. Perivascular cells such as pericytes and smooth muscle cells have also been implicated in tumor angiogenesis, and pericytes have been shown to express MMP-9. Interestingly and as would be expected, it is believed that upon maturation of newly formed blood vessels, the interaction between pericytes and endothelial cells can lead to the silencing of MMPs [14,15].

| Family                  | MMPs                      | Key characteristics                                                                 |
|-------------------------|---------------------------|-------------------------------------------------------------------------------------|
| Collagenases            | MMP-1, -8, and -13        | These can cleave collagen and are able to process other ECM molecules                |
| Gelatinases             | MMP-2 and -9              | Play an important role in the remodeling of collagenous ECM, also targeting other ECM and non-ECM molecules |
| Stromelysins            | MMP-3, and -10            | Process many ECM components as well as some growth factors, cytokines and adhesion molecules, except for the native collagen |
| Stromelysin-like MMPs   | MMP-11, and -12           | MMP-11-induced in adipose tissue by cancer cells, and is responsible for tumor progression through the degradation of collage VI. |
| Matrilysins             | MMP-7, and -26            | Play important roles in degradation and processing of ECM and non-ECM proteins       |
| Transmembrane MMPs      | MMP-14, -15, 16, and -24  | Located on the cell surface and control the local environment of normal and tumor cells. Main activators of proMMP-2 and are involved in blood vessel formation. Also upregulated in tumors and in some cases associated with poor prognosis of several types of cancer. |
| Glycosyl-phosphatidylinositol (GPI)-type MMPs | MMP-17, and -25 | Produced by several carcinomas although their role is not yet well defined. MMP28 is believed to play a role in several diseases of the central nervous system (CNS) including multiple sclerosis. |
| MM-19-like MMPs         | MMP-19 and -28            | Produced by several carcinomas although their role is not yet well defined. MMP28 is believed to play a role in several diseases of the central nervous system (CNS) including multiple sclerosis. |
| Other MMPs              | MMP-18, -20, and -23      | MMP-23 produced by various normal tissues but their precise roles have not yet been elucidated |
| Disintegrin/Metalloproteinase | ADAMS (a disintegrin and metalloproteinase) and the ADAMTS (a disintegrin and metalloproteinase with thrombospondin motif) | An interaction between MMPs and ADAMTS was reported with MT4-MMP contributing to activation of ADAMTS-4 |

Table 1: The classification of MMPs.

The expression of MMPs is regulated by various inflammatory cytokines. For example, TNF-alpha secreted by macrophages in response to pro-inflammatory signals has stimulatory effect on MMPs produced by these cells. It was shown previously that a co-culture of tumor cells with macrophages resulted in enhanced MMP expression and invasiveness of tumor cells [16,17]. Recently, it was also reported that pro-inflammatory cytokines such as Interleukin (IL)-8 and –IL-17 enhance the activity of MMP-2 and MMP-9 which in turn increases cancer metastasis [18].

MMPs themselves can also regulate the inflammatory response [19]. For example, MMP-9 can enhance the activation of pro-inflammatory cytokines such as TNF, IL-1 beta, IL-6 and IL-8, but MMP-2 may dampen the inflammatory process [20]. On the other hand, some cytokines can have an inhibitory effect on the secretion of MMPs. For example, interferon (IFN) alpha/beta inhibited tumor cells secretion of active form of MMP-2 and chondroitin sulphate proteoglycan (CS), an ECM component, as well as tumor cell migration [21,22].

These interactions involving many cell types producing a range of MMPs within the tumor and the bordering stroma, as well as interaction of MMPs with their stimulators, inhibitors and substrates become even more complex at the cellular level. Thus, depending on the cellular source, the activity of a single MMP could have either inhibitory or stimulatory effect on tumor growth.

**Targets and Substrates of MMP Action: Cellular or Extracellular**

Our understanding of MMP action has been greatly enhanced by the generation of mouse models. These have particularly facilitated the identification of many other *in vivo* substrates for MMPs, including many more non-ECM bioactive molecules. This includes growth factors receptors, adhesion molecules, cytokines, chemokines, angiogenic factors, apoptotic ligands, etc. [23,24].

**ECM substrates**

Proteolysis of the extracellular matrix leading to migration and invasion of tumor and endothelial cells is an important action mediated by MMP-14, which has been recognized as one of the most potent modifiers of the extracellular tumor microenvironment [25-27]. In addition, MMP-14 participates in the angiogenic process in growing tumors [15,25,28,29]. Remodeling of the basement membrane
matrix and in particular the basement membrane of endothelial cells, is a critical initial step in the angiogenesis process. The basement membrane, rich in laminins and collagen IV, undergoes degradation and re-assembly [30], with MMP-2, 9 and 14 playing a role in remodeling of the basement membrane in vivo [31]. The expression of MMP-2 by lung carcinoma metastatic to the brain has been correlated with increased angiogenic profiles at the metastatic tumor-host interface [32], likely modulated by these same mechanisms.

Non-ECM substrates

Various pro-angiogenic factors or inhibitors of angiogenesis are released secondary to modification of ECM or cell surface by MMPs [33]. An example of non-ECM substrates are cell surface adhesion molecules, e.g., CD44. The transmembrane proteoglycan CD44, which is found at the leading edge of the invasive tumor [34] was shown to bind through its extracellular domain to several MMPs including MMP-2. As a result of this interaction, the MMPs were localized at the migrating front of the tumor, leading to proteolytic degradation and promoting cell mobility [35]. In addition, it was also found that binding of MMP-9 to CD44 promotes MMP activation [23].

Impact of MMP on Tumor Microenvironment and Growth

Tissue remodeling, an important MMP function, is a result of interactions with and modulation by a network of cytokines and growth factors. Recall that both the ECM and basement membrane serve as storage points for cytokines and growth factors bound to proteoglycans. Enzymatic degradation of the ECM therefore results in the release and diffusion of cytokines and growth factors as well as activation of ECM molecules important in tissue pathology. Additionally, MMPs act as sheddases or convertases, as they transform membrane-bound cytokines, cytokine receptors, and adhesion molecules, into their soluble forms [36,37]. The proteolytic action of MMPs affects basic cellular events such as cell proliferation, migration, adhesion, and also physiological processes related to ECM remodeling such as angiogenesis. In the tumor microenvironment, the proteolytic modification of many complex fibrillar proteins by MMPs facilitates protease-dependent tumor cell migration and tumor angiogenesis. Therefore, the upregulation of MMPs has been associated with many pathological processes including inflammation and cancer.

MMPs in vitro show overlapping affinities for different ECM and non-ECM substrates and many MMPs can degrade and process several different classes of ECM proteins, e.g., MMP-2 and MMP-9 can degrade collagens I, IV, V, VII and X, gelatin, elastin, fibronectin, and proteoglycans.

Tumor cell proliferation and inhibition of apoptosis

Tumor progression from its earliest phase i.e. the growth of tumor cells at the primary site involves MMP activity. MMPs control cell division and proliferation through regulation of growth factor availability and activation or inactivation of growth factor receptors, e.g. their proteolytic activity contributes to the release and processing of factors such as fibroblast growth factor (FGF). MMPs can also inhibit apoptosis, as in the case of MMP-7, which can trigger an intracellular signaling pathway to promote cell survival [2,4].

Tumor migration, invasion, metastasis

MMP-2 and MMP-9, which are capable of degrading type IV collagen and disrupting the integrity of the basement membrane have long been recognized to play a role in tumor invasion. Studies of MMP-9 and MMP-2–null mice provided further evidence of the role of these MMPs in metastasis [2]. Recently, it was found that MMP-10 plays a significant role in cervical tumor growth and progression through regulation of angiogenic and apoptotic pathways [38]. In addition, MMP-1 was shown to play a major role in tumor growth and angiogenesis. Its suppression in vivo reduced growth and angiogenesis of lung tumors [39]. Similar findings were reported for MT2-MMP associated with lung tumor progression and angiogenesis [40].

Valuable insight into these molecules was gained from direct visualization of MMP activity in vitro and in vivo as well as localization of their proteolytic activity during migration and invasion of tumor cells [41,42]. In that respect, several studies evaluated MMP-14 in tumor cells [26,43,44], and found protease activity of MMP-14 to be localized at the polarized leading edge of the tumor cell [26] facilitating forward movement of the cell. However, controversy still exists as to extent of the role of MMPs in protease-dependent versus protease-independent amoeboid movement of tumor cells [27,43,44]. Using blocking antibodies against MMP-14 in a pancreatic cancer cell line, it was recently demonstrated that MMP-14 is an activator of several MMPs (MMP-2, MMP-9) and facilitates local ECM degradation and invasion [45].

Angiogenesis and vasculogenesis

Angiogenesis, the formation of new blood vessels within the tumor, is initiated when the tumor has reached a critical size. It involves MMP’s degradation of ECM and non-ECM substrates and formation of new blood vessels from the pre-existing vascular network. In contrast, the de novo formation of blood vessels [14], which involves the development of endothelial cell networks by recruitment of circulating progenitors of the endothelial cells, is called vasculogenesis. During tumor progression the ‘angiogenic switch’ occurs when the balance between the proangiogenic and the antiangiogenic factors tilts towards a pro-angiogenic outcome. Some MMPs play an important role in the angiogenic process, MMP-9 is particularly known as a critical mediator of the angiogenic switch [2,46]. In addition Interleukin-32 (IL-32) has pro-angiogenic properties acting via regulation of MMP-9 and IL-8 and several other molecules [47]. We have previously shown correlation between increased angiogenesis and MMP-2 expression at the brain-tumor interface in CNS metastasis of lung carcinoma [32]. The gelatinases MMP-2 and MMP-9 are among the major MMPs affecting tumor angiogenesis [48].

Pleiotropic activities of MMPs in tumor microenvironment

Based on the observations that MMPs play an essential role in tumor cell proliferation, migration, invasion, metastasis and angiogenesis, it seemed very plausible that inhibiting MMPs at the tumor site would be a viable therapeutic target. The early transgenic mouse models overexpressing various MMPs supported the notion that MMPs contribute to tumor progression [49]. In addition, the observation that high levels of MMPs correlated with poor prognosis of cancer patients, paved the way for the clinical trials using inhibitors of MMPs. The outcomes of these trials were disappointing showing that indiscriminate targeting and broad spectrum inhibition of MMPs did not result in the anticipated inhibitory effect on the tumor growth.
On the contrary, in some studies inhibition of MMPs or MMP-induced molecules resulted in promoting tumor growth [50,51]. These unexpected findings led to the extensive studies using new mouse models of MMP knock-outs in which the generation of gain or loss-of function revealed the highly complex and pleiotropic nature of MMPs and their function [52]. Currently available MMP knock-out mouse models only encompass 17 out of 23 murine MMP genes. Additional MMP knock-out mouse models are necessary in order to better understand MMPs functions in human malignancies. In addition, generation of double or even triple knock-out mouse models may be necessary to minimize existing functional redundancy or compensatory mechanisms between various members of MMP family [6].

Suppressive and Stimulatory Effects of MMPs on Tumor Growth and Microenvironment

There are number of MMPs that can stimulate or suppress tumor growth, but some can exhibit both of these activities. In addition, remodeling of cell surface, basement membrane and ECM by MMPs, leads to the release of several membrane- or matrix-bound growth factors and cytokines. This includes for example positive and negative regulators of angiogenesis that impact tumor growth.

Stimulatory activities of MMPs

Several MMPs were shown to stimulate tumor growth, e.g., MMP-1. However, indirect stimulatory activities of MMPs on tumor progression are known as well. For example, one of the most studied positive regulators of angiogenesis released from ECM by MMP proteolysis is VEGF. In this regard, numerous studies have reported the effect of MMP-9 derived from inflammatory leukocytes such as macrophages and neutrophils [53] as well tumor cells [54] on VEGF release. Also, MMP-2 and MMP-14 were shown to be involved in mobilization and upregulation of VEGF [55,56]. In addition, MMP-3, 7 and 19 cleave matrix-bound isoforms of VEGF [57]. FGF-2, another molecule with stimulatory activity on angiogenesis is released from the ECM as result of proteolytic activity of MMPs [58,59]. Endothelial basement membrane-bound FGF-2 resides in ECM as an inactive form and needs to be proteolytically cleaved and released from ECM in order to be biologically active [60,61]. MMP-9 was shown to induce the release of FGF-2 [59]. In addition, new findings have shown that thyroid-hormone may be regulating adhesion, migration and MMP-9 activity in myeloma cells via integrin. This may lead to the development of new therapeutic targets for the treatment of myeloma by allowing a disruption of the thyroid-hormone-integrin-MMP-9 signaling cascade [62].

Suppressive activities of MMPs

Although many MMPs stimulate tumor growth, there are some MMPs that can suppress tumorigenesis. The generation of new genetically modified animal models demonstrated that several MMPs, such as MMP-8 and MMP-12 have inhibitory activities on tumor growth. MMP-8 plays a protective role in cancer because of its capability to regulate the inflammatory response. The expression of MMP-8 derived from neutrophils was shown to be elevated in non-metastatic cell line and correlated with its protective effect on tumor cell invasion and metastasis [2,63,64]. MMP-12 overexpression in colon cancer cells was shown to be associated with increased survival [65]. In addition, it was reported that MMP-12 overexpression in myeloid lineage cells affected modulation of myelopoiesis and resulted in immune suppression. This study was done both in in vitro and in vivo using immature cells from MMP12-overexpressing bitransgenic mice showing immunosuppressive function of these immature cells on T-cell proliferation and function [66]. Similarly, it was shown in mice deficient for MMP inhibitor–TIMP-2, that there was an elevated MMP activation associated with an increase in myeloid-derived suppressor cells coexpressing VEGF [67]. Recently, tumor-suppressive functions of MMP-9 were shown in colitis-associated cancer [68] and in colorectal cancer [69].

In addition, inhibitors of angiogenesis are also released indirectly during ECM remodeling by MMPs [33]. These inhibitors include angiotatin, endostatin, and tumstatin [70]. The MMPs capable of contributing to the production of angiotatin include MMP-2,7,9, and 12 with MMP-12 being the most efficient inducer of angiotatin resulting in inhibition of angiogenesis [71,72]. Endostatin, another inhibitor of angiogenesis was reported to be produced by cleavage from collagen type XVIII of basement membrane by MMP-3, -7, -9, -12 and -20. Also some select MMPs, e.g., MMP-9 were implicated in production of tumstatin, another inhibitor of angiogenesis, from collagen type IV [71].

MMPs and MMPs-induced molecules as targets for cancer therapy

Clinical studies using inhibitors of MMPs failed to show desired, expected anti-tumor effect [50,51]. The original premise for targeting MMPs was an understanding that MMPs are primarily involved in degradation of ECM proteins that play a key role in metastasis and angiogenesis [73]. It is now known that several MMPs can play dual roles as tumor stimulators or inhibitors depending on the type of tissue and progression of the disease. There are several MMPs that have this dual role, e.g MMP-3, 9 and 11 [2, 6,74,75]. In addition, depending on the cellular source of the same MMP, e.g. MMP-12, could be pro-tumorogenic when derived from tumor cells. However, when derived from tumor-associated macrophages, MMP-12 has a protective effect leading to differentiation of tumor cells followed by better outcome of the disease [76].

A similar finding related to MMP-induced molecules such as VEGF involved in tumor angiogenesis and known to be sequestered in the ECM. Targeting and inhibition of the VEGF pathway in vivo in pancreatic carcinoma and glioblastoma mouse models resulted in worsening of the disease process by increasing tumor cell invasiveness and metastasis [77]. Similarly it was shown that deletion of VEGF in myeloid cells accelerated tumorigenesis [78]. Yet, another paradox was reported relating to MMP-9, which is known to be associated with the production of tumstatin, an inhibitor of angiogenesis. It is known that MMP-9 activity is associated either with promoting or decreasing angiogenesis.

The first anticancer broad-spectrum MMP inhibitors used in clinical trials were tested alone or in combination with standard chemotherapeutics in patients with advanced pancreatic, brain, lung prostate and gastrointestinal cancers. However, after Phase III clinical trials, failed to show efficacy, but often significant side effects, further clinical studies were conducted [73]. There is also a large body of literature covering various dietary antioxidants and cannabinoids on MMPs’ role in cancer growth [79-81].

Some recently developed modalities of nanodelivery of therapeutics which target tumors more efficiently, resulted in tumor cell growth.
arrest, apoptosis, and prolonged survival in vivo. This was associated with reduction of VEGF secretion, reduction of blood vessel density and decreased MMP levels. An example of this methodology was the selective therapeutic targeting via nanodelivery of anaplastic lymphoma kinase (ALK)-specific siRNA for the treatment of neuroblastoma [82]. In another study investigators used nanoparticles based delivery of tetrandrine to lung cancer cells [83]. They showed that nanoparticle delivered tetrandrine inhibited migration and invasion of lung cancer cells more efficiently than free tetrandrine by down-regulating MMP-2 and MMP-9.

The implication of MMPs in cancer development and progression continue to be of great significance. Current research efforts are focusing on learning more about the mechanism of action of MMPs as well as the discovery of new, selective therapeutic targets for MMP activity. MMP inhibitors thus remain strong considerations for the development of anticancer therapies.

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