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Matrix metalloproteinases in stem cell regulation and cancer

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Abstract

Since Gross and Lapiere firstly discovered matrix metalloproteinases (MMPs) as important collagenolytic enzymes during amphibian tadpole morphogenesis in 1962, this intriguing family of extracellular proteinases has been implicated in various processes of developmental biology. However, the pathogenic roles of MMPs in human diseases such as cancer have also garnered widespread attention. The most straightforward explanation for their role in cancer is that MMPs, through extracellular matrix degradation, pave the way for tumor cell invasion and metastasis. While this notion may be true for many circumstances, we now know that, depending on the context, MMPs may employ additional modes of functionality. Here, we will give an update on the function of MMPs in development and cancer, which may directly regulate signaling pathways that control tissue homeostasis and may even work in a non-proteolytic manner. These novel findings about the functionality of MMPs have important implications for MMP inhibitor design and may allow us to revisit MMPs as drug targets in the context of cancer and other diseases.

Keywords

Cancer; Stem cell niche; Cell differentiation; Invasion; Hemopexin domain

Introduction

Development of multi-cellular organisms is mediated by a tightly controlled program of cell fate decisions that determine whether a stem or progenitor cell will proliferate, differentiate or undergo apoptosis. Even in the adult organism, tissue resident stem cells are crucial to mediate tissue homeostasis and replenish the tissue on a daily basis. These cell fate decisions of stem cells within the parenchyma are strongly influenced by extrinsic signals provided by the surrounding microenvironment, or the niche, which consist of extracellular matrix (ECM), adjacent stromal cells as well as extracellular, soluble factors such as growth factors, cytokines and chemokines.

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Another group of extracellular factors that play important roles in stem cell niches during development are the matrix metalloproteinases (MMPs). MMPs are a family of zinc-dependent endopeptidases that were firstly described in amphibian tadpole morphogenesis about half a century ago [1]. MMPs have been found to play crucial roles in during tissue remodeling and organ development by rearrangement of the extracellular matrix as well as by specifically modulating signaling pathways through proteolytic interaction with multiple substrate molecules of very diverse nature [2]. However, there is a dark side to these proteinases, in particular when their function or expression goes awry, they can contribute to virtually all steps of tumor progression [3].

In this minireview we will concentrate on the emerging roles of MMPs as secreted factors within stem cell niches during development and how some of these functions may be hijacked during cancer.

MMPs in the stem cell niche

The microenvironment provides the context that dictates the behavior of adult stem cells in normal tissue homeostasis and in cancer. The stem cell niche consists of a microenvironment of adjacent cells and surrounding extracellular matrix, which provides localized signals and extrinsic factors that save the stem cells from depletion, while preventing uncontrolled self-renewal and proliferation [4].

Due to their ability to cleave, degrade and rearrange ECM molecules, MMPs can modulate a variety of stem cell niches. The hematopoietic stem cell system is one of the best studied examples of adult stem cells and several questions about the composition of their niche have already been solved [5]. MMPs take an active role in shaping the microenvironment of the niche in the bone marrow. MMP9 can cleave and mobilize Kit ligand, which enables bone marrow repopulating cells to translocate to a permissive niche that allows reconstitution after irradiation [6]. MMP14 (MT1-MMP) regulates HIF-mediated gene transcription of chemokines and cytokines within the hematopoietic stem cell niche [7]. These examples illustrate how MMP function can modify the microenvironment of the bone marrow stem cell niche by changing the bioavailability of cytokines and chemokines that affect stem cell function.

Many morphogens bind to components of the ECM, which limits the range of function of these growth factors within tissues. In Drosophila, MMP2 specifically cleaves the ECM component division abnormally delayed (dally)-like protein (Dlp), which renders it incapable of binding to the morphogen wingless (Wg). This could explain how Wg traverses long distances in the Drosophila ovary to promote follicular stem cell proliferation [8]. ECM cleavage by MMPs may also lead to the destruction niche related structures. In the case of human epidermal stem cells, long-term survival is maintained by inhibiting proteolysis through MMP2 and MMP14 in organotypic cultures [9], which otherwise would lead to proteolytic degradation of a stem cell promoting niche.

However, there is much more to the complexity of stem cell regulation by MMPs than simple degradation of the ECM. Our own work recently showed that MMP3 (also called Stromelysin-1) has an impact on the maintenance of adult epithelial stem cells in the

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mammary gland. These effects of MMP3 are based on its specific capacity to bind and inactivate the noncanonical Wnt ligand Wnt5b. Thereby, MMP3 acts as a regulator of Wnt signaling and may tip the balance towards the canonical side, which leads to increased signaling through β-catenin and expansion of the mammary stem cell pool (Fig. 1). Surprisingly, MMP3 may do so even in the absence of proteolytic activity, since overexpression of inactive mutants of MMP3 and the hemopexin domain alone was sufficient to cause hyperplastic growth in the mammary gland [10]. MMP3's next closest relative within the MMP family is MMP10 (also called Stromelysin-2). Similar to MMP3 in the mammary gland, MMP10 is involved in lung tumorigenesis based on bronchio-alveolar stem cell expansion in the context of Kras-driven lung cancer [11]. Even though a direct substrate or interaction partner for MMP10 was not identified in this study, the authors showed a causative role for MMP10, as Kras-induced lung tumors were significantly diminished in number as well as in size in MMP10-deficient mice. These studies provide interesting examples of how changes in the microenvironment—in this case overexpression or lack of an MMP—can alter the propensity of signaling pathways that promote stem cell expansion leading to increased neoplastic risk.

Regulation of cellular differentiation

The ability of cells to differentiate into cell types with more specialized function and more restricted fate is fundamental to the development of multi-cellular organisms, but also for regenerative processes as well as the daily maintenance of every tissue of the body. The decision of a precursor cell to differentiate is strongly context-dependent and may be influenced by changes in the surrounding microenvironment.

MMPs are potent proteolytic mediators of ECM remodeling, and thereby may provide the necessary changes of the microenvironment triggering cellular differentiation during developmental processes. In this context, MMP14 is required for adipocyte differentiation in vivo, since it may act as a pericellular collagenase that directs the dynamic adipocyte-ECM interactions during white adipose tissue development in a 3D context [12]. In a similar fashion, MMP14 also contributes to mesenchymal stem cell differentiation through promotion of the trafficking behavior of these cells into type I collagen-rich environments [13].

MMPs can also modulate signaling pathways that regulate differentiation. For example, transdifferentiation of pancreatic acinar cells is controlled by MMP7, which is required for activation of the Notch signaling pathway [14]. This process may be crucially involved in a cascade of events leading to acinar-to-ductal metaplasia, a precursor state of pancreatic ductal adenocarcinoma [15]. It remains to be determined whether MMP7 is required for the regulation of the Notch pathway in the differentiation of other cell types.

The abilities of MMPs to influence differentiation processes are sometimes hijacked in cancer. For example, MMP13 can stimulate osteoclast differentiation by activating proteolytic cascades involving cleavage of pre-MMP9 and galectin-3, a suppressor of osteoclastogenesis. This in turn allows MMP13 expressing MDA-231 breast cancer cells to promote a favorable microenvironment for bone metastasis [13].

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Regulation of proliferation

While stem cell proliferation and expansion are important during active phases of development or tissue regeneration, unregulated proliferation is a well-known feature of cancer cells. There are several ways by which MMPs may influence proliferation during development, but also in the tumor microenvironment, since they can alter the bioavailability or functionality of multiple important growth regulating factors.

The transforming growth factor-β (TGFβ) pathway mostly mediates tumor-suppressive effects by enforcing cytostasis and differentiation; however, in cancer, TGFβ may function differently due to mutations in the TGFβ receptor system, leading to tumor-promoting functions [16]. To add another layer of complexity, MMPs may be involved in the generation of active TGFβ from an inactive pro-form by proteolytic conversion [17]. Interestingly latent TGFβ is activated by MMP9, which is usually expressed by neutrophil granulocytes [18]. MMP9 is compartmentalized to the cell surface by docking to the surface receptor CD44 and then proteolytically activates TGFβ [17]. Similarly, MMP14 and MMP2 also activate TGFβ1 proteolytically [19]. While these effects of MMPs may halt cell proliferation during normal development, in cancer the circumstances are turned inside out, and the proteolytic activation of TGFβ by MMPs has tumor-promoting effects, for example by selectively driving stroma-mediated invasion and metastasis of the tumor.

Regulation of tissue invasion

Early developmental processes of pattern formation are commonly driven by invasive cell behavior. For example, the epithelial tissue of the mammary gland actively invades the fat pad during puberty in a process called branching morphogenesis, in which the proliferative front of the terminal end buds of the ductal epithelium paves its way through the stroma to form a network of ductal epithelium that fills the entire fat pad at the end of puberty [20]. While invasive cell behavior is essential for healthy development and organogenesis, it is hijacked by tumors when they become metastatic. The lethal outcome of the vast majority of all cancers is due to the dissemination of metastatic cells and the outgrowth of secondary tumors at distant sites. The process of metastasis is believed to occur in a sequence of events starting with the invasion of the tumor into the peripheral tissue leading to intravasation of cancer cells into blood or lymphatic vessels and their entry into the circulation. Some of these disseminated tumor cells will go on to extravasate from the circulation at distant sites to seed and colonize at distant organs to form secondary metastatic tumors.

MMPs are known to contribute to tissue invasion both during developmental processes as well as during tumor progression in a variety of ways. The most widely considered mechanism by which MMPs promote cellular migration and tissue invasion is based on their ability to cleave ECM and basement membrane components proteolytically, and thereby pave the way through the interstitium for invading tissues or cancer cells. In particular, MMP14 is well established in the context of pericellular proteolysis, which controls tumor cell traffic through the ECM [21], and facilitates single cell and collective tumor cell migration and invasion in a highly orchestrated manner [22]. Likewise, several other MMPs

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have been implicated in a similar manner (e.g. MMP1, -2, -13); however MMP14 appears to be the most important mediator of pericellular proteolysis [23,24].

Another possible mechanism of proteolytic induction of cell migratory behavior may be mediated through the proteinase-activated receptors (PARs), a set of G protein-coupled receptors that act during thrombosis and inflammation and that can affect tumor invasion by inducing cancer cell migration. These receptors are activated by proteolytic cleavage of their extracellular domain. In this context, MMP1 can cleave and thereby activate PAR-1 on breast carcinoma cells, which activates cancer cell migration and invasive behavior of the tumor [25,26]. The source of MMP1 in this case appears to be stromal, namely tumor-associated fibroblasts, which highlights the commonly found conspiracy between malignant tumor cells and their non-malignant stroma to promote tumor progression. MMP1 may also come from the tumor cells themselves and activate the same pathway through PAR-1 on endothelial cells to facilitate vascular intravasation and metastatic dissemination [27].

Genetic changes in MMP genes linked to cancer

MMPs are commonly overexpressed in various types of cancer. We have analyzed recent datasets [28–39] and present selected examples of MMPs that ranked highest regarding their fold overexpression in tumor compared to normal tissue and that are highly associated with certain cancers in Table 1. In recent years, several mutations and polymorphisms in genes encoding for MMPs have been linked to cancer. In lung cancer, several MMP2 and MMP13 polymorphisms appear to increase the risk for lung cancer and may be factors in an unfavorable prognosis [40]. A recent meta-analysis revealed an association of polymorphisms in the promoter regions of MMP1, -3, -7 and -9 with metastasis in some cancers [41]. A mutational analysis of the MMP family in melanoma identified somatic mutations in MMP8 in 23% of melanoma patients, which caused reduced enzymatic activity and therefore suggests that the wild type active form of MMP8 protects from melanoma progression [42]. Whole exome sequencing has shown that the rare autosomal recessive form of chondrodysplasia, metaphyseal anadysplasia, is caused by nonsense mutations in MMP13 [43]. Changes in MMP expression in cancer may involve regulation of the microRNA level. For example, microRNA-9 targets and MMP14 in neuroblastoma cells lead to decreased MMP14 expression, thus rendering these cells less invasive, metastatic and angiogenic [44].

The hemopexin domain as a non-proteolytic functional module

The hemopexin domain (HPX) is a distinct four-bladed β-propeller structure that is found at the C-terminus of most members of the MMP family excluding MMP7, -23 and -26. The HPX domain is believed to mostly contribute to protein–protein interactions and thereby mediate substrate specificity and the necessary guidance for the proteolytically active catalytic domain of MMPs to find their respective substrate molecule and subsequently cleave it. Besides this important function of the HPX domain, mounting evidence from recent studies indicate that some aspects of MMP function may be mediated solely through the HPX domain without involving proteolytic activity (reviewed recently in [3]).

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One example from our own research was already discussed above. We found that MMP3 may induce hyperplastic growth via its HPX domain even in the complete absence of the catalytic domain (Fig. 1C). This may be explained by a non-proteolytic interaction with Wnt5b that may be sufficient to interfere with receptor ligation of this non-canonical Wnt ligand [10]. This non-proteolytic function of the MMP3-HPX may also contribute to invasive behavior of breast cancer cells [45], suggesting that therapeutic interference with HPX domain function may be beneficial for breast cancer patients.

Interestingly, MMP3 may not be the only MMP that exhibits tumor-promoting activity non-proteolytically via the HPX domain. Recent reports show that MMP14 contributes to tumor growth in a mouse model for breast cancer solely through its HPX domain [46]. The authors of this study have used the Developmental Therapeutics Program (NCI/NIH) virtual ligand screening compound library to identify inhibitors that target the HPX domain of MMP14. These inhibitors potently blocked tumor growth and therefore provide the first pre-clinical proof of principle to therapeutically target the HPX domain instead of the catalytic domain.

These findings have important implications for the role of MMPs as drug targets and for strategies to interfere with MMP function in therapeutic applications. MMPs have been considered as drug targets for novel anti-cancer therapeutics tested in more than 50 clinical trials in the 1990s to early 2000s. These drug trials yielded disappointing efficacy and the reasons for these dismal results may be rooted in various aspects of the trial design [47]. However, the majority of MMP inhibitors used in these clinical trials were small compound inhibitors designed to interfere specifically with the catalytic domain of MMPs while leaving the HPX domain untouched (Fig. 2). In light of this novel functionality of MMPs independent of proteolytic cleavage, it stands to reason that these inhibitors were not capable of fully blocking all tumor-promoting functions of MMPs. Therefore, these results should encourage the community to revisit the potential of MMPs as drug targets and explore non-proteolytic aspects of MMP biology for example through the HPX domain in the context of development and cancer.

Conclusions

Taken together, recent work exploring the function of MMPs have added new facets to our whole understanding of this exciting family of extracellular proteases. The classic role of MMPs, namely cleavage and rearrangement of extracellular matrix, has been associated with novel functions such as the specific remodeling of stem cell niches. In addition, MMPs may directly regulate signaling pathways that control tissue homeostasis or invasion, which is crucial in developmental processes but may be hijacked in cancer. An important new aspect that has recently garnered more attention is that MMPs may work in a non-proteolytic manner, for example via the hemopexin domain. Future research should address whether previously described roles of MMPs in development and cancer may actually involve non-proteolytic functions rather than proteolytic cleavage of substrate molecules. This has important implications for MMP inhibitor design and may allow us to revisit MMPs as drug targets in the context of cancer and other diseases.

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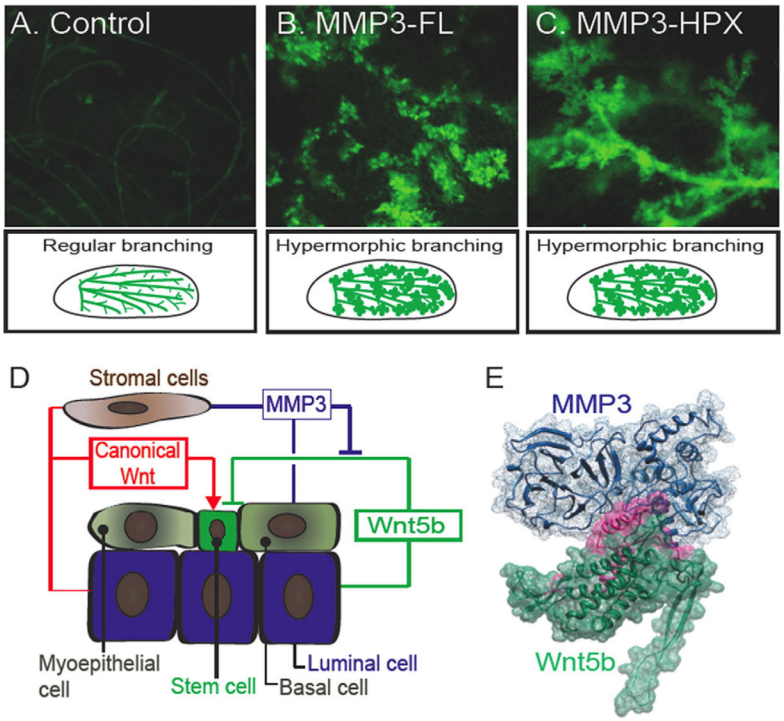

Fig. 1.

The role of MMP3 in the mammary stem cell niche. (A–C) MMP3 promotes hyperplastic growth in orthotopic transplants of lentivirally transduced mammary epithelial cells. Compared to control transplants (A), overexpression of proteolytically active full-length MMP3 (B) and MMP3-hemopexin domain (C) both promote a hyperplastic growth phenotype. (D.) This can be explained by the specific interaction of MMP3 with the non-canonical Wnt ligand Wnt5b, an inhibitor canonical Wnt signaling. Thereby, overexpression of MMP3 tips the balance towards canonical Wnt signaling, which promotes stem cell expansion and may disrupt epithelial homeostasis and lead to breast tumor formation. (E) Computational structural model of the complex formed by binding of MMP3 (blue) to Wnt5b (green) shown with minimal binding domain (pink). Modified from Kessenbrock et al., 2013.

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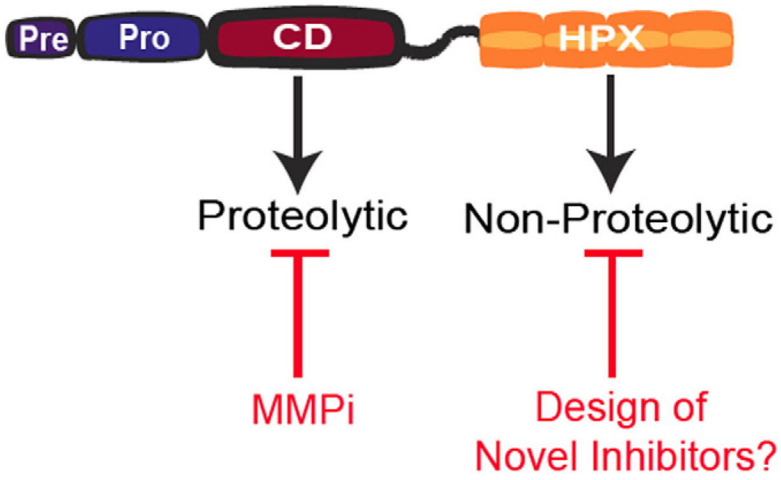

Fig. 2.

The hemopexin (HPX) domain as a non-proteolytic functional unit of MMPs. MMPs typically consist of various domains including the Pre/Pro-domains, which need to be cleaved off to convert the zymogen into an active protease. Proteolytic activity is mediated through catalytic domain (CD). The C-terminal hemopexin (HPX) domain is present at the C-terminus of most members of the MMP family except for MMP7, -23 and -26, and is believed to mainly mediate substrate specificity via protein–protein interactions. Mounting evidence suggests that MMPs may function in a non-proteolytic manner, which is often exhibited through the HPX domain. These functions may be crucially implicated in MMP-mediated promotion of tumor progression. This has important implications for drug design and may explain why clinical trials using small compound inhibitors designed to target the CD of MMPs (MMPi) have yielded disappointing results. Future research should determine whether MMPs may be revisited as anti-cancer drug targets by specifically interfering with the non-proteolytic HPX-mediated function.

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Table 1

Cancer expression association analysis for selected members of the MMP family. The threshold used for this study (Cancer/Normal) was *p-value <0.001* and *fold change >10*. Gene rank *percentile < 1% (top 1%).* The differential expression analysis of MMP genes was calculated by Oncomine using a two-sided Student's *t*-test and multiple testing correction

Gene	Cancer	Subtype	*N* cases	*P*-value Cancer/normal	Fold Cancer/normal	% Gene ranking	Database reference
MMP1	Breast	Invasive ductal carcinoma	593	1.99E - 53	11.25	32 (top 1%)	TCGA
	Head–neck	Squamous cell carcinoma	79	5.71E - 44	86.33	1 (top 1%)	(Peng et al., 2011)
	Colon	Adenocarcinoma	36	4.61E - 09	12.81	6 (top 1%)	(Notterman et al., 2001)
	Skin	Squamous cell carcinoma	15	6.82E - 05	96.85	26 (top 1%)	(Nindl et al., 2006)
MMP3	Colorectal	Carcinoma	105	4.85E - 20	27.02	12 (top 1%)	(Skrzypczak et al., 2010)
	Head–neck	Squamous cell carcinoma	38	1.06E - 12	10.57	3 (top 1%)	(Ye et al., 2008)
	Skin	Basal cell carcinoma	87	6.45E - 07	17.96	166 (top 1%)	(Riker et al., 2008)
MMP7	Colorectal	Rectal adenocarcinoma	130	4.09E - 40	53.90	(top 1%)	(Skrzypczak et al., 2010)
MMP9	Lymphoma	Follicular	136	4.92E - 36	27.13	7 (top 1%)	(Compagno et al., 2009)
MMP10	Head-neck	Squamous cell carcinoma	15	5.40E - 04	19.10	109 (top 1%)	(Nindl et al., 2006)
MMP11	Breast	Invasive carcinoma	593	2.27E - 65	16.53	1 (top 1%)	TCGA
MMP12	Head–neck	Squamous cell carcinoma	54	5.50E - 24	15.60	2 (top 1%)	(Su et al., 2011)
	Lung	Lung adenocarcinoma	156	1.21E - 17	16.95	23 (top 1%)	(Hou et al., 2010)
	Esophagus	Squamous cell carcinoma	34	9.00E - 12	12.61	9 (top 1%)	(Hu et al., 2010)
	Pancreas	Adenocarcinoma	27	8.19E - 08	317.54	40 (top 1%)	(Hao et al., 2006)
	Lymphoma	Hodgkin's	67	3.29E - 07	19.94	176 (top 1%)	(Brune et al., 2008)
MMP13	Breast	Invasive ductal carcinoma	593	1.53E - 56	14.07	21 (top 1%)	TCGA
MMP14	Esophagus	Adenocarcinoma	48	1.58E - 14	14.19	1 (top 1%)	(Hao et al., 2006)