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Breast cancer progression: insights into multifaceted matrix metalloproteinases

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Abstract: The restricted view of matrix metalloproteinases (MMPs) as simple destroyers of extracellular matrix components has largely ignored their substantial contribution in many aspects of cancer development and metastatic dissemination. Over the last few years, the relevance of MMPs in the processing of a large array of extracellular and cell surface-associated proteins has grown considerably. Our knowledge about the complex functions of MMPs and how their contribution may differ throughout cancer progression is rapidly expanding. These new findings provide several explanations for the lack of success of MMP inhibition in clinical trials. A complete understanding of MMP biology is needed before considering them, their substrates or their products as therapeutic targets. In this review, we explore the different faces of MMP implication in breast cancer progression by considering both clinical and fundamental aspects.

Keywords: Angiogenesis, Breast cancer, Cancer invasion, Degradome, Matrix metalloproteinases, Metastases; Stromal proteases

Introduction

Tumorigenesis and cancer progression rely on the acquisition by tumor cells of novel capacities which are shared by most if not all cancer types. According to Hanahan and Weinberg, six essential alterations in cellular physiology dictate malignant growth: (1) production of autocrine growth signals; (2) insensitivity to growth-inhibitory signals; (3) escape from apoptosis; (4) limitless replicative potential; (5) sustained angiogenesis and (6) tissue invasion and metastatic dissemination [1]. Initially, Matrix Metalloproteinases (MMPs) were claimed to be important in late stages of tumor progression by controlling tumor cell migration, invasion and metastasis through ECM degradation. However, due to the rapid development of innovative biochemical techniques [2-4] and the expanding use of transgenic and knockout mice [5, 6], it became obvious that the action of MMPs is not restricted to the massive destruction of physiological matrix barriers [7]. MMPs are now viewed as key regulators of the multiple cellular functions which dictate malignant growth. Although some MMPs are produced by tumor cells (e.g. MMP-7), most MMPs are rather produced by stromal cells and therefore might be considered as molecular determinants of the "seed and soil" concept proposed by Paget in 1889 [8]. Breast carcinomas are often characterized by a stromal reaction that consists of modifications in the composition of both cellular elements (infiltration of fibroblastic cells, endothelial cells and inflammatory cells) and the extracellular matrix (ECM) [9, 10]. An expansion of the tumor stroma and an increased deposition of ECM known as desmoplasia is often associated to invasive breast carcinomas [11]. Fibroblasts within the tumour stroma have acquired a modified phenotype similar to that of fibroblasts observed in wound healing [12]. Such "activated" fibroblasts named peritumoral fibroblasts, reactive stromal fibroblasts, carcinoma-associated fibroblasts (CAF) or tumor-associated fibroblasts [10, 13] actively control the malignant progression of breast cancers, at least through their capability to secrete MMPs. The present review aims at describing the emerging functions of MMPs which appear more and more as multifunctional enzymes tightly controlling proteolysis both at the cell surface and in the pericellular environment. Using examples of studies performed in animal models of breast cancers, we explore the mechanisms of MMP action with a special emphasis on the contribution of stromal MMPs. Although of great importance, the contribution of MMP in cancer-associated inflammation will not be addressed in this review and reader is referred to previous reviews [14-17].

The MMP family

MMPs are a family of 24 human zinc-binding endopeptidases that can degrade virtually all ECM components, release and activate/inactivate a growing number of modulators of cell functions [6, 7, 15, 16]. MMPs are multidomain proteins characterised by at least three conserved regions: (1) a zinc binding motif (HEXXHXXGXXH) required for proteolytic activity, (2) a propeptide cysteine site (PRCGXPD) whose cysteine residue interacts with the zinc ion in the zymogen form and (3) a "methionine turn" (XXMXP) which likely maintains the zinc-binding site integrity [15]. The activation of these proteases secreted as zymogens requires an amino-terminal cleavage of the pro-domain in the *trans* golgi network by furin-like convertases or extracellularly after their secretion (Fig. 1). The MMP production is precisely regulated at transcriptional and translational

levels [18, 19]. Once switched on, MMP proteolytic activity is under the control of various physiological inhibitors such as tissue inhibitors of metalloproteinases (TIMPs), the plasma inhibitor α2-macroglobulin and the reversion-inducing cysteine-rich protein with Kazal motifs (RECK) [20-22]. Most of the MMPs are secreted as soluble enzyme but six of them are membrane-type MMPs (MT-MMPs) which are associated with the cell membrane by either a COOH-terminal transmembrane domain (MT1-, MT2-, MT3-, MT5-MMPs) or a glycosylphosphatidyl-inositol (GPI) anchor (MT4-, MT6-MMPs) [23] (Fig. 1). MT1-MMP (MMP-14), one of the most studied MMPs displays pleiotropic functions during both physiological and pathological processes. Although most MMP-knockout mice generated up to now do not present any obvious phenotype without challenging, MT1-MMP-deficiency is associated with growth delay and leads to a lethal phenotype after birth [5, 24, 25]. MT1-MMP activates pro-MMP-2 [26] and pro-MMP-13 [27] and has a very wide range of matrix substrates [6, 23, 28]. Activation of pro-MMP-2 by MT1-MMP requires the tissue inhibitor of metalloproteinases-2 (TIMP-2) which acts as an adaptor molecule mediating pro-MMP-2 binding to MT1-MMP [29, 30].

An increasing number of in vitro studies, mouse models and human clinical studies demonstrate the implication of MMPs in all steps of cancer progression including tumor growth, angiogenesis and metastasis [7, 8, 18]. The increasing diversity in both substrates and functions of MMPs makes them central regulators in different steps of cancer progression and invasion. Now, some MMPs such as MMP-3, -8, -9, -11, -12, -19 and -26 are expected to have dual functions in tumor progression and even in some cases anti-tumor properties [17, 31]. Some of the known substrates of MMPs include ECM components, growth factors, chemokines, cytokines, cell surface proteins and adhesion molecules [6, 7, 17]. Thanks to the development of novel powerful proteomic techniques, a dedicated effort is currently underway to identify the key in vivo substrates of individual MMPs [2, 4, 32] (Fig. 2).

The multiple functions of MMPs in cancer

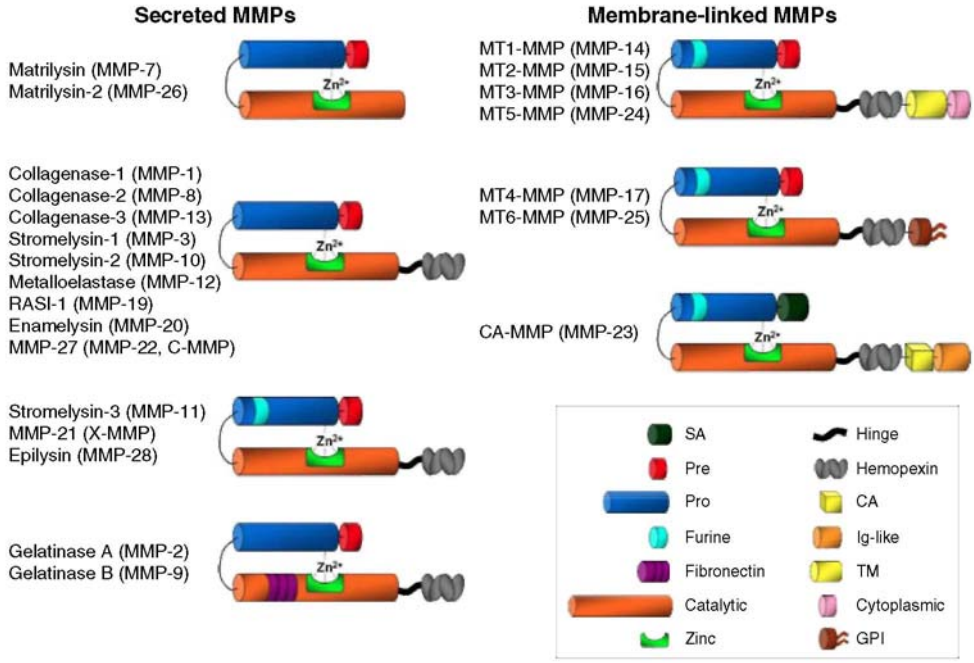
The recent identification of a large panel of matrix and non matrix substrates of MMPs revealed that aside their initial roles as ECM modulators, these proteases can regulate cellular physiology through several mechanisms. In early stages of cancer, the proteolytic processing of bioactive molecules contributes to the elaboration of a permissive microenvironment that promotes malignant transformation and tumor growth. MMP-3 can induce the expression of an alternative spliced form of Racl which causes an increase in cellular reactive oxygen species and genomic instability [33]. When bound, growth factors such as Transforming Growth Factor-β (TGFβ), insulin-like growth factor (IGF), Fibroblast Growth Factor (FGF) and Heparin Binding Epidermal Growth Factor-like growth factor (HB-EGF) are unable to interact with their receptor and to transduce a signal. Several MMPs control tumor cell proliferation by releasing growth factor bound to specific binding proteins or to matrix components. For instances, bioactive IGF is generated by the action of MMP-3 [34] or MMP-7 [35]. In addition, MMP-7 activates HB-EGF by cleaving its precursors anchored at the cell surface [36]. MT1-MMP confers a proliferative advantage to tumor cells when they are embedded in a 3D collagen-matrix [37]. Opposite effect on cell proliferation can be achieved by the shedding of growth factor receptors such as FGF receptor-1 (FGF-R1) [6, 38]. The cleavage of membrane bound Fas Ligand (mFasL) to soluble FasL (sFasL) by MMP-7 increases apoptosis in normal surrounding cells [39]. However, it permits tumor cells to escape from apoptosis [40, 41] since most cancer cells are relatively resistant to Fas-mediated apoptosis due to abnormalities in the signal transduction cascade [42]. Similarly, MMP-11 inhibits cancer cell death [43].

Loss of E-cadherin-mediated cell-cell adhesion is a prerequisite for tumor cell invasion and metastasis. Proteolytic degradation of E-cadherin by MMP-3 or MMP-7 is one of the mechanisms through which epithelial cell invasion is promoted by disrupting cell aggregation [44]. Proteolysis of E-cadherin and the release of free β catenin play a crucial role in epithelial to mesenchymal transition (EMT), a conversion of epithelial cells to an altered cellular phenotype which is associated with the acquisition of mesenchymal features and aggressive malignant behaviour [45, 46].

MMP-mediated degradation of ECM facilitates angiogenesis, tumor invasion and metastasis [7, 47]. Carcinoma cells were anticipated to produce by themselves proteolytic enzymes in order to degrade basement membrane for invading surrounding tissue. However, it is remarkable that individual tumor cells can cross ECM barriers through non proteolytic processes by exerting physical and mechanical forces that are capable of distorting matrix architecture [48]. Among several MMPs tested, only membrane-associated MMPs (MT1-MMP, MT2-MMP and MT3-MMP) can serve as direct-acting proteases that are able of dissolving BM during cell migration [49]. MT1-MMP is a key enzyme in fibrillar collagen processing and its deletion in mice leads to severe connective tissue defect [25, 50]. Of interest is the recent finding that collective migration of human breast cancer cells and multicellular strand formation is controlled by MT1-MMP through ECM remodelling [51]. Importantly membrane-associated MT-MMPs focus proteolytic activity on specific sites on the cell surface that

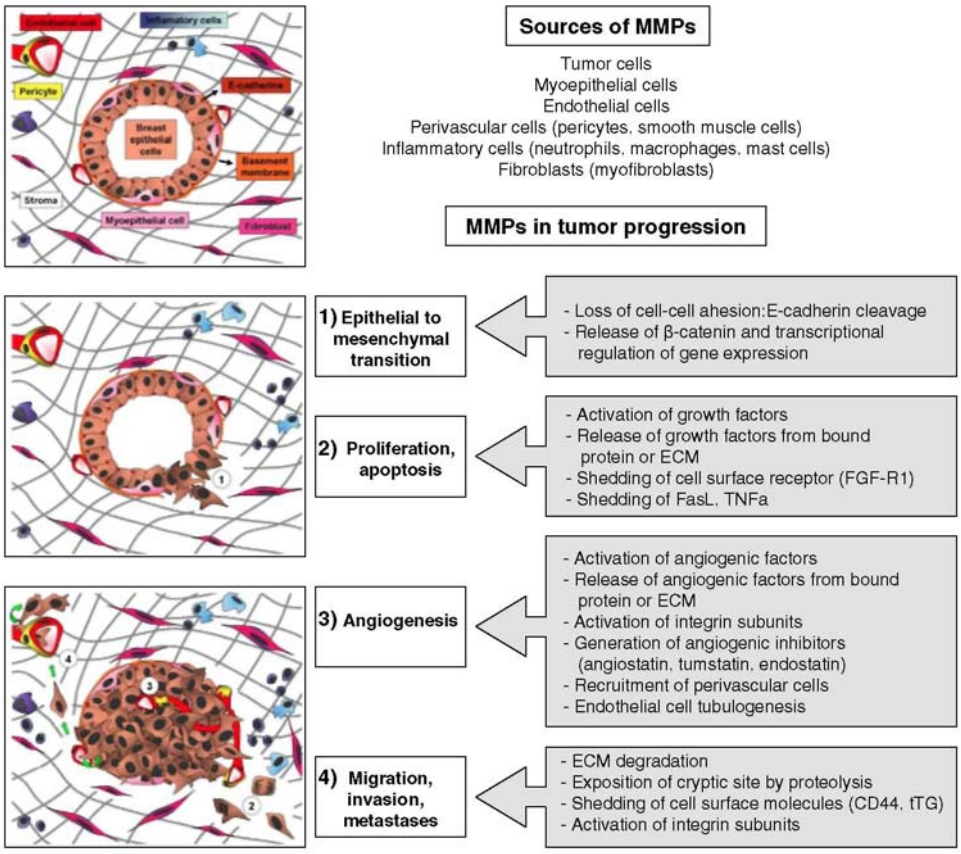
are involved in cell migration [23, 28]. In addition to its fibrinolytic and collagenolytic activities, MT1-MMP stimulates cell motility through the processing of cell adhesion molecules CD44 [52, 53], integrin subunits (pro αv-integrin, β3 subunit) [54, 55] and tissue transglutaminase (tTG) [56]. It is also worth noting that MMP cleavage of ECM components such as laminin 5 or type IV collagen can expose cryptic sites that promote cell migration [57-59].

Fig. 1: *Structure of MMPs. Matrilysins are the minimal-domain MMPs. They contain a signal peptide (Pre) for secretion and a propeptide (Pro) that maintains the enzyme in an inactive form by interacting with the Zinc binding site (Zinc) of the catalytic domain. Collagenases, stromelysins, metalloelastase, Enamelysin and MMP-27 are composed of these minimal domains and a hemopexin-like domain (hemopexin) connected to the catalytic domain with a hinge. The hemopexin domain allows the interaction with substrates and inhibitors. In addition of these domains, gelatinases display fibronec-tin type II modules (Fibronectin) improving collagen/gelatin degradation, and stromelysin-3, MMP-21, epilysin have a furin-like cleavage site allowing their intracellular activation. Membrane-Type MMPs (MT-MMPs) are linked to the cell membrane with either a transmembrane (TM) domain followed by a short cytoplasmic tail (Cytoplasmic) (MT1-, MT2-, MT3-, MT5-MMPs) or with a glyco-sylphosphatidyl-inositol (GPI) anchor (MT4- and MT6-MMPs). CA-MMP is a type II transmembrane MMP which is characterized by a N-terminal signal anchor (SA) targeting it to the membrane, a unique cysteine array (CA) and immunoglobulin-like (Ig-like) domains in C-terminal*



Several MMPs contribute to angiogenesis through different mechanisms [8, 28, 47, 60, 61]. They include at least the fibrinolytic activity [62], the collagenolytic activity [37], the morphogenesis of endothelial cell (tube formation or tubulogenesis) [63-65], the activation of αvβ3 integrin [66], the transcriptional regulation of Vascular Endothelial Growth Factor (VEGF) [67-69], the release of VEGF sequestered in the ECM [70] or bound to connective tissue growth factor (CTGF) [71], the post-translational processing of VEGF [72], the mural cell investment through a control of PDGF receptor function and the recruitment of perivascular cells contributing to vessel stabilization [8, 73, 74]. The role of MMPs in angiogenesis is dual and complex, some MMPs acting as positive regulators (MMP-1, MMP-2, MMP-9, MT-MMPs) [8, 47, 70, 75, 76] and other as negative regulators (MMP-19) [77] sometimes involved in vessel regression (MMP-10) [61]. Abrogation of angiogenesis can rely on the production of protein fragments endowed with anti-angiogenic activities. For instances, degradation of ECM components (collagen types IV, XVIII) or plasminogen can generate angiogenic inhibitors (tumstatin, endostatin, angiostatin) [78, 79].

Fig. 2: *Implication of MMPs in cancer progression. MMPs are implicated in all steps of cancer progression including tumor growth, angiogenesis and metastases via the degradation of extracellular matrix (ECM) components, the release and/or activation of growth factors sequestrated in the matrix or complexed to associated proteins, the cleavage of cell surface receptors and the shedding of adhesion molecules. Although not indicated in this schematic representation, MMPs are also key regulators of the inflammatory reaction associated to cancer progression*



MMPs in human breast cancers

With the aim of finding new powerful and earlier breast cancer prognostic bio-markers and new targets for cancer treatment, MMPs and MMP inhibitors (MMPIs), respectively, have been extensively investigated in human breast cancer clinical studies [80-82]. MMPs and TIMPs, are frequently overexpressed in human cancer tissues [15]. At least, MMP-1, -2, -9, -11, MT1-MMP, TIMP-1 and -2 levels have been largely investigated in breast cancer tissues by RT-PCR, immunohistochemistry, ELISA, in situ hybridization or zymography analyses (for a review see [80, 81, 83-88]). Despite some conflicting results regarding MMP-9 [89], in most of these studies, the tissue levels of MMPs and TIMPs have been correlated with poor outcome of breast cancer patients [81, 89, 90]. Additionally to their individual level of expression and activity, the ratio of MMP-2/TIMP-2 or MMP-9/TIMP-1, expected to reflect the proteolytic potential, has already been suggested as an early indicator of lymph-node metastases and prognosis [91, 92]. Regarding disease-free survival (DFS) and overall survival (OS) of breast cancer patients, MT1-MMP (MMP-14) mRNA [86, 93] but not protein levels [94, 95], stromal MMP-9 but not tumoral protein expression [95], MMP-2 protein [96] and MMP-7 mRNA expression [97] seem to have an unfavourable prognostic significance. In sharp contrast, MMP-26 has been proposed as a favorable prognostic factor [98]. MMP and TIMP levels in body fluids such as blood and urine of breast cancer patients have been extensively assessed in many pathological processes [99, 100] including breast cancer [80]. Up to now, MMP-2, -7, -9, TIMP-1, -2 concentrations and MMP-2, -9 activities have been analyzed by ELISA and gelatin zymography or immuno-capture assay, respectively, in blood and urine of breast cancers patients [80]. Despite some divergent data, many of these studies have linked circulating MMPs or TIMPs with breast cancer presence, disease status, lymph-node metastasis or other clinicopathological parameters of patients suggesting their potential use in breast cancer screening, follow-up and risk of metastasis establishment. MMP-2 and MMP-9 appear to have clinical value as diagnostic factors for breast cancer or predictive factors of metastases. In addition, proportions between the different forms or between MMPs and their tissue inhibitors (TIMPs), in term of concentration or activity could provide useful clinical information on breast cancer disease and classification [88, 101-104].

Recently, the emphasis has been to reveal the gene expression signatures of primary tumors, which have been associated with their metastatic potential [105-107]. MMP-1 and MMP-9 are involved in the 70 genes identifying the "gene-expression signature" able to predict distant metastasis in lymph-node negative breast cancer patients [106]. Moreover, MMP-1 and MMP-2 have been described as genes that selectively mediate lung metastasis in a mouse model of breast cancer [107] and as members of a lung metastasis gene signature for human breast cancers [108]. Accordingly, MMP-1 has been identified as a useful marker to predict breast cancer development from ductal hyperplasia tissues by global gene expression analysis [109]. These data suggest that, in addition to their prognostic values, MMPs could be used as diagnostic factors to early predict breast lesions that may develop into cancer [80]. Interestingly, these global gene analyses have pinpointed the importance of stroma-derived genes [105, 108] and it is worth noting that peritumoral fibroblasts and inflammatory cells are mainly responsible for the production of tumor-associated MMPs, rather then tumor cells themselves. Peritumoral fibroblasts are the main producers of MMP-1 (interstitial collagenase), MMP-2, MMP-3 (stromelysin-1), MMP-11 (stromelysin-3), MMP-13, MMP-14 in breast cancers [83, 86, 87, 110-112]. The expression of MMP-13 has been co-localized with that of MT1-MMP and MMP-2 suggesting their contribution in a proteolytic cascade [87], [113]. MMP-2 produced by fibroblasts can bind the cell surface of tumor cells through interaction with for instance MT1-MMP and integrin $\alpha_v\beta_3$ [87, 114, 115]. In this context, it is worth noting that in patients with invasive breast carcinomas, mRNA [93, 116-118] and membranous—but not cytoplasmic—protein expression levels of MT1-MMP [95, 119] have been correlated with lymph-node metastasis.

MMPs in experimental models of breast cancer

Several genetically engineered mouse models have been developed to mimic tumor initiation and progression processes of different types of cancer. These models allow a better understanding of cellular and molecular mechanisms underlying cancer progression and can provide useful information for anti-cancer drug development [120]. In breast cancer, these models consist in targeting the expression of oncogenes such as ErbB-2, Ras, Wnt1 or the polyomavirus middle T antigen (PymT) in the mammary epithelium under the control of specific promoters including the mouse mammary tumor virus long terminal repeat (MMTV) and the whey acid protein (WAP) promoters [121]. The availability of these transgenic mice, together with others that are deficient for a specific MMP or that are overexpressing a MMP has been useful in attributing specific functions to individual MMPs in different steps of cancer progression [5, 6, 18]. Breast carcinogenesis can be achieved by crossing the transgenic mice lacking or over-expressing an MMP with mice expressing an oncogene in mammary glands, or by inducing mammary tumors chemically through the oral administration of 7,12-dim-ethylbenzanthracene (DMBA) [122].

Expression of MMP-3 and MT1-MMP in the mammary gland is sufficient to stimulate the development of invasive tumors [123, 124]. MMTV-MMP-3 and WAP-MMP-3 expressing mice display altered spontaneous or DMBA-induced tumor initiation [123, 125, 126]. Moreover, MMTV-MMP-7 expressing mice develop pre-malignant nodules and increased oncogene-induced (MMTV-ErbB-2) mammary tumors. In contrast, mice lacking MMP-7 expression with a mutated *Apc* allele show a transient reduction of mammary tumors [127, 128]. The transgenic deficiency in MMP-2 or MMP-9 expression, the transgenic expression of TIMP-1 or -2 (MMTV-TIMP) and the treatment with a MMPI are also reported to affect mammary tumorigenesis and lung metastases induced in MMTV-PymT or MMTV-Wntl models [122]. Altogether, these data implicate MMPs and their inhibitors in mammary tumor development. However, the situation is rendered even more complex by the fact that some MMPs appear to function as dual modulators of tumor progression. Indeed, MMP-11-deficient mice show a decreased DMBA-induced mammary carcinogenesis [129] and a decrease of tumor incidence/tumor growth [130]. However, MMP-11-/-/MMTV-ras mice develop more lung metastases than their wild type counterpart [130]. Therefore, MMP-11 function differs throughout cancer progression, it is an enhancer for primary tumor development, but a repressor for metastatic dissemination.

Xenografts of human cancer cells transfected with one or other MMP cDNA is extensively used to investigate the behaviour of human cells in an in vivo environment. Indeed, different studies in which immunodeficient mice are injected with breast cancer cells over/down-expressing MMPs or TIMPs, demonstrate their implication in breast cancer progression and especially in development of metastases. Although most MMPs including for instance MMP-2 [131], MMP-11 [132, 133], MMP-3 [123], MT1-MMP [67, 134] and MT4-MMP [135] are generally positive regulators of cancer progression (tumor promoters), some of them such as MMP-8 [136] negatively regulate metastasis in breast cancer models. Similarly, as mentioned above, MMP-11 represses metastatic dissemination, while it enhances primary tumor development [130]. These opposite tumor/metastasis-promoting effects of different MMPs or of the same MMP at different stages of cancer progression is one of the explanations why clinical trials of broad spectrum MMP inhibitors have failed, underlining the importance to

develop more specific inhibitors of MMPs.

Since fibroblasts constitute the majority of stromal cells within a breast carcinoma and since they are a primary source of MMP, a co-implantation tumor xenograft model has been used to investigate the interplay between fibroblasts and breast carcinoma cells [10, 137]. The tumor promoting effect of fibroblasts in xenografts is blocked by TIMP2 or synthetic MMP inhibitor [137, 138]. Interestingly, MMP-11-null fibroblasts [129] or MT1-MMP-null fibroblasts [139] do not support in vivo growth of tumor cells whereas corresponding wild-type fibroblasts enhance tumor development. MMP-11 is a stromal factor which promotes the primary implantation of cancer cells in an aberrant environment [110]. In MMP-11-deficient mice, the number of apoptotic cancer cells is increased in primary tumors, indicating that host MMP-11 helps tumor cells in escaping apoptosis [43].

Cancer cells can stimulate fibroblasts to synthesize MMPs in a paracrine manner through the secretion of interleukins, interferons, growth factors and Extracellular Matrix Metalloproteinase Inducer (EMMPRΓN) [19, 140, 141]. The pathologic consequence of elevated EMMPRIN is supported by the accelerated growth and increased invasiveness exhibited by breast cancer cells overexpressing EMMPRIN [23, 142]. Interestingly, carcinoma-associated fibroblasts (CAF)s extracted from human breast carcinomas are better promoters of human breast adenocarcinoma cell growth in xenograft than normal primary fibroblasts derived from the same patient [143]. It is worth noting that the upregulation of MMPs is one of the physiological changes that occur when fibroblasts undergo senescence. This likely promotes the generation of a pro-oncogenic microenvironment that contributes to the increased incidence of cancers observed with age [144, 145]. Accordingly, fibroblasts that have been forced into senescence by DNA damage increased the growth of cancer cells in a MMP-dependent manner [145]. The tumor microenvironment can be a potent carcinogen, not only by facilitating cancer progression, but also by stimulating tumor formation. A stromal enzyme such as MMP-3 can cause sustained EMT and malignant transformation in cultured cells and genomically unstable mammary carcinomas in transgenic mice [33, 123].

Conclusions

Based on the fact that MMPs were initially viewed as invasion-associated proteases, preclinical studies of MMP inhibition were performed in different mouse cancer models. The success of these studies led to the rapid development of synthetic MMP inhibitors (MMPIs) and their assessment in clinical trials. However, the results obtained in phase III trials were disappointing with many adverse side effects [15, 18, 140, 146, 147]. The failure of MMP inhibition in cancer therapy is now better understood [146, 148]. One explanation, among others, is that clinical trials have been performed in advanced stages of cancers whereas MMPs are more expected to play crucial role in early steps of cancer progression. In addition, broad spectrum MMPI block the activity of all metalloproteases (including ADAMs and ADAMTS) and it is now well known that different MMPs can have opposite effects or different effects at different stage of cancer progression. Therefore, some MMPs are viewed as "drug targets", while others are considered as "anti-targets" for cancer therapy [17]. The initial concept of MMPs as simple modulators of ECM remodeling has been replaced by the consideration of MMPs as multifaceted proteases able to tightly control the biodisponibility and activity of a large panel of proteins. In addition, it is possible that substrates and products of MMPs could be preferred as targets for treating cancer rather than MMPs themselves. However, such strategies depend on better knowledge on how individual MMPs are contributing to tumor growth and metastatic dissemination. In this context, the complementarity between human clinical studies and mouse models is of great importance.

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