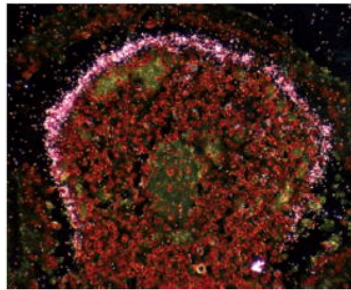


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Review

Matrix metalloproteinases at cancer tumor–host interface

Agnès Noël^{*}, Maud Jost, Erik Maquoi

Laboratory of Tumor and Development Biology, Centre de Recherche en Cancérologie Expérimentale (CRCE), Groupe Interdisciplinaire de Génoprotéomique Appliquée (GIGA-R), University of Liege, Tour de Pathologie (B23), Sart-Tilman, B-4000 Liège, Belgium

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Abstract

The increasing diversity in both substrates and functions of matrix metalloproteinases (MMPs) makes these enzymes central regulators in the complex tumor ecosystem composed of cancer cells and their microenvironment. In the majority of cancers, membrane-associated and extracellular proteases are mainly produced by host cells including inflammatory cells, endothelial cells, pericytes and fibroblasts. Recent data based on *in vitro* and *in vivo* studies have demonstrated the relevance of these enzymes in multiple processes controlling cancer growth, angiogenesis and metastatic dissemination. This review will present the emerging MMP-related features of cancer cells and host cells.

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Keywords: Stromal proteases; Cancer invasion; Angiogenesis; Inflammation

Contents

1. The tumor ecosystem	52
2. MMPs as key molecular determinants of Paget's "seed and soil" concept	53
3. MMPs and tumor cells	55
4. MMPs and host cells	56
4.1. Fibroblasts	56
4.2. Macrophages	56
4.3. Mast cells	56
4.4. Neutrophils	56
4.5. Vascular and perivascular cells	57
4.6. Adipocytes	57
5. Conclusions	57
Acknowledgements	58
References	58

1. The tumor ecosystem

Neoplastic cells have been the focus of interest in cancer research for many years. This approach has contributed to deciphering the molecular determinants of carcinogenesis, leading to the discovery that alterations in specific oncogenes and tumor suppressor genes have causal roles in the initia-

tion and progression of tumors. In this context, the traditionally prevailing explanation of metastasis is that during cancer progression, tumor cells acquire, through the accumulation of multiple genetic alterations, the ability to surmount a variety of obstacles including shedding from the primary tumor, intravasation into blood or lymphatic vessels, survival into circulation, extravasation and growth at a secondary site [1]. However, this tumor cell-centered view of cancer development has largely ignored the contribution of the tumor microenvironment to the malignant phenotype. Historically, the importance of tumor

^{*} Corresponding author. Tel.: +32 4 366 25 69; fax: +32 4 366 29 36.
 E-mail address: agnes.noel@ulg.ac.be (A. Noël).

microenvironment during cancer progression has already been recognized more than 100 years ago in the “seed and soil” hypothesis proposed by Paget in 1889 [2]. As important as tumor cells (“seeds”) are the diverse environments (“soils”) that tumor cells encounter as they progress throughout the body. A current definition of the “seed and soil” hypothesis is that primary and secondary tumor nodules consist of a complex ecosystem composed of cellular and non-cellular components. The cellular compartment includes not only tumor cells themselves, but also blood or lymphatic endothelial cells, pericytes, smooth muscle cells, (myo)fibroblasts, adipocytes, immune and inflammatory cells [3]. The non-cellular compartment consists of the various components of the extracellular matrix (ECM), whose composition directly and indirectly influences the phenotype of the cellular compartment. The ECM is not simply an extracellular scaffold; it also acts as a reservoir of biologically active molecules, such as growth factors and cytokines [4]. Some ECM components can express cryptic biological functions upon proteolysis. Hence, the important ECM remodelling associated to cancer progression influence cellular behaviour and phenotype.

A tumor is now viewed as a complex evolving ecosystem. One characteristic of all ecosystems is that minor alterations in one of the partners may cause dramatic reorganisation of the whole system. As a consequence, the tumoral stroma has a strong influence on many steps of tumor development and progression [5,6]. Morphological evidence of host participation in invasion and metastasis are as follows: (1) desmoplasia consisting of fibroblast-like cells and excessive deposit of ECM; (2) inflammation and immune response represented by infiltration of lymphocytes, macrophages, mast cells and dendritic cells; and (3) angiogenesis evidenced by newly formed blood and lymph vessels [7].

2. MMPs as key molecular determinants of Paget's “seed and soil” concept

Paget's concept of tumor cells being seeds that need appropriate soils (organ environment) to grow and disseminate [2] remains a valid concept that requires precise explorations at the molecular level. The communication between the different cellular (tumor islets and stroma) and non-cellular compartments of the tumor microenvironment is by large mediated by the so-called protease web [8]. In normal tissue homeostasis, the interacting network of proteases and their natural inhibitors maintain a proteolytic balance. During cancer progression, this balance is disturbed by overexpression of proteases including at least matrix metalloproteinases (MMPs) and related families of proteases, the ADAMs (a disintegrin and metalloproteinases) and ADAMTS (ADAM with thrombospondin repeats). This imbalance alters the non-cellular compartment, which in turn activates downstream molecular effectors leading to the establishment of a milieu permissive for tumor progression, invasion and dissemination.

The MMPs form a family of structurally and functionally related zinc endopeptidases which collectively are able of degrading virtually all ECM components [9–11]. The produc-

tion and activities of MMPs are precisely regulated at the level of transcription, activation of the precursor zymogens, interaction with specific ECM components, inhibition by endogenous inhibitors, and endocytosis [10,12]. Tissue inhibitors of metalloproteinases (TIMPs) control the local activities of MMPs in tissues [13–15]. MMPs display a large set of ECM and non-ECM substrates (Tables 1 and 2). They act as processing enzymes that perform highly selective and limited cleavage of specific substrates including growth factors and their receptors, cell adhesion molecules, cytokines, chemokines, apoptotic ligands and angiogenic factors [8,12].

Data supporting the role of proteases in cancer progression derive from *in vitro* and *in vivo* experiments demonstrating: (1) a correlation between protease expression and cell invasion and metastasis; (2) a modulation of the invasive properties by cell transfection with the cDNA of proteases and their inhibitors; (3) a reduction of tumor growth and/or metastatic potential by using natural or synthetic protease inhibitors, neutralizing antibodies or antisense oligonucleotides; and (4) a modulation of tumor growth and metastasis in MMP-deficient mice [4,8,9,11,12,16–18]. However, MMP functions are much more complex than initially anticipated; some MMPs playing a paradoxical protective role in tumor progression [19,20], and others displaying opposite functions depending upon the stage of cancer progression [8,11,21].

Recently, the emphasis has been to reveal the gene expression signatures of primary tumors, which have been associated with their metastatic potential [22,23]. Interestingly, these analyses have hinted at the importance of stroma-related genes and some MMPs have been identified in specific gene expression signature. MMP1 and MMP9 are among the 70 genes composing a gene signature able to predict distant metastasis in lymph node negative breast cancer patients [23]. Moreover, MMP1 and MMP2 have been described as genes that selectively mediate lung metastasis in a mouse model of breast cancer [24] and as members of a lung metastasis gene signature for human breast cancers [25].

In addition, emerging evidence suggests that MMPs also contribute to the elaboration of a so-called “pre-metastatic niche”. According to this novel concept, certain primary tumor cells can release soluble factors that induce a specific population of non-malignant haematopoietic cells to mobilize and engraft distant organ tissue, thereby establishing a “pre-metastatic niche” [26]. This process includes proteolytic matrix turnover and secretion of soluble growth factors and chemokines that create a permissive microenvironment for incoming circulating cancer cells [27]. Primary tumor cells release VEGF-A, TGF β and TNF α that in turn, induce the expression of chemoattractants by lung endothelium and myeloid cells, facilitating thereby the homing of tumor cells to the pre-metastatic niche within lung parenchyma [28]. MMP9 expressed in lung macrophages and endothelial cells promotes the invasion of lung tissues by tumor cells [29] (Fig. 1).

Altogether these data identify MMPs as central regulators of cancer progression. An important issue is actually to identify the individual functions of MMPs and determine the cellular source of each MMP at specific steps of cancer progression.

Table 1
Selected extracellular matrix and cell surface-associated substrates of MMPs involved in cancer progression

Substrates	Impacts	Biological processes affected	Representative examples
Extracellular matrix components	ECM breakdown	Cell migration	MT1, MT2 and MT3-MMPs regulate basement membrane transmigration [42,16]
	Liberation of cryptic domain	Cell migration	MT1-MMP generates a fragment of laminin 5 promoting motility [111]
	Increase growth factors bioavailability	Angiogenesis (stimulation)	MMP9 mobilizes VEGF sequestered in ECM [81]
	Release of anti-angiogenic fragments	Angiogenesis (inhibition)	MMP9 cleaves type IV collagen and generates tumstatin [85]. MMP3, MMP9, MMP12, MMP13 and MMP20 generate endostatin by cleaving type XVIII collagen [86]
Cell surface molecules			
E-cadherin	Dissociation of epithelial cells	Cell–cell adhesion	MMP3 and MMP7 release E-cadherin fragment [33]
Tissue-transglutaminase (tTG)		Cell migration	MT1-MMP degrades tTG and promotes cell adhesion and locomotion [113]
Fas-L	Release of membrane-bound Fas ligand (mFasL)	Cell apoptosis	MMP7 cleaves Fas-L [34] MMP3 produced by stromal cells releases mFas-L and has pro-apoptotic effect on neighbouring epithelial cells [49]
Integrin CD44	Activation of $\alpha v \beta 3$	Angiogenesis Cell migration	MT1-MMP activates $\alpha v \beta 3$ [110] MT1-MMP cleaves cell membrane-associated CD44 [112]

Table 2
Selected soluble substrates of MMPs involved in cancer progression

Substrates	Impacts	Biological processes affected	Representative examples
Growth factors binding proteins			
IGF-BP	Increase IGF bioavailability	Cell proliferation	MMP3 degrades IGF-BP1 [101] - MMP7 generates bioactive IGF-II by degrading IGF-II/IGFBP-2 complex [103]
TGF β complex	Release of TGF β	Cell proliferation, angiogenesis	MMP2 and MMP9 release TGF β from an inactive complex consisting of TGF β , TGF β latency-associated protein and latent-binding protein [87]
Chemokines/cytokines			
LIX ENA-78 (CXCL5)	Activation of mouse LIX or human ENA-78	Chemoattraction inflammation	MMP8-deficiency in mice is associated with sustained inflammation [20,83]
IL8 (CXCL8) interleukin-8	Activation of IL8	Chemoattraction inflammation	MMP9 potentiates ten fold IL8 [88]
MCP-3 (monocyte chemo-attractant protein-3)		Chemoattraction inflammation	MMP2 cleaves (MCP-3), converting an agonist to a potent receptor antagonist [104]
SDF-1 (CXCL12)	Inactivation of SDF-1	Chemoattraction	MMP1, MMP2, MMP3, MMP13, MT1-MMP inactivate SDF-1 [89]
IL2-receptor	Cleavage of receptor	Immune response	MMP9 down-regulates T cell proliferation by cleaving IL2-receptor [102]
Proteases			
Pro-MMP	Activation of MMP	Proteolysis	Cascade of pro-MMP activation [10]
Plasminogen	Release of anti-angiogenic molecule	Angiogenesis (inhibition)	MMP12 generates angiostatin by plasminogen cleavage [71]
Protease inhibitor			
$\alpha 1$ proteinase inhibitor	Generation of bioactive fragment	Sensitivity to natural killer cells	MMP11 reduces the sensitivity of tumor cells to natural killer cells [21]

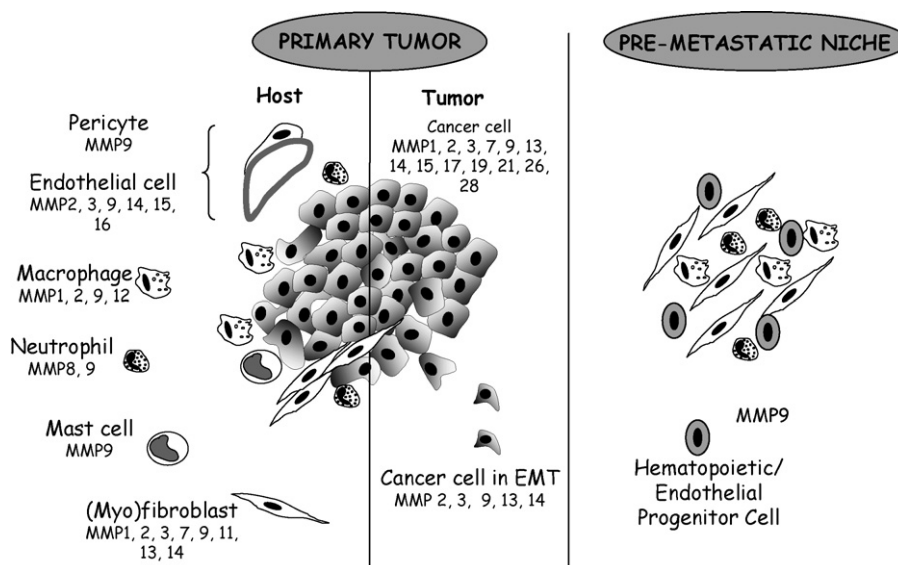


Fig. 1. MMP production in primary tumor and pre-metastatic niche. MMPs are produced by host cells and/or tumor cells. MMP9 is widely expressed in host and tumor compartments at both primary and secondary sites. The MMP9 production is induced in pre-metastatic lung endothelial cells and macrophages by VEGF secreted by primary tumors [21]. This MMP-9 induction precedes and promotes lung metastasis. EMT = Epithelial to Mesenchymal Transition.

3. MMPs and tumor cells

Only a few MMPs are exclusively expressed by tumor cells themselves and most MMPs secreted by tumor cells are also produced by host cells (Fig. 1). Two recently cloned epithelial MMPs (MMP21 and MMP26) are also expressed by macrophages and fibroblasts *in vivo* and in culture [30]. MMP7 (matrilysin) appears to be quite unique in its almost restricted expression in tumor cells. MMP7 is expressed in benign and malignant tumors that arise from the glandular epithelium and its secretion is regulated in a polarized system [31]. It influences early stages of tumorigenesis through an action on ECM and non-ECM substrates [18]. MMP7 regulates cell proliferation and apoptosis by cleaving the ectodomain of heparin binding-epidermal growth factor (HB-EGF) precursor [32], and affects cell–cell interaction and controls cell migration by releasing soluble E-cadherin [33]. By shedding the ectodomain of membrane-bound FasL (mFasL), MMP7 increases apoptosis in normal surrounding cells, cancer cells being themselves refractory to proapoptotic signal [34].

Among MMPs, MMP19 displays unique structural features and tissue distribution. MMP19 is expressed in normal human epidermis and downregulated during malignant transformation and dedifferentiation [35,36]. In a model of methylcholanthrene-induced chemical carcinogenesis, *MMP19*^{−/−} mice develop less fibrosarcomas and with a longer latency period than wild-type littermates [37]. In contrast, host MMP19-deficiency was associated with an acceleration of the angiogenic response after malignant keratinocyte transplantation [19]. These apparently paradoxical results may reflect different roles of MMP19 at different steps of cancer progression.

Overexpression of several MMPs (MMP2, MMP3, MMP9, MMP13, MT1-MMP) have been associated to the epithelial to

mesenchymal transition (EMT), a fundamental biological process where epithelial cells lose their polarity, cell–cell adhesion and adopt a mesenchymal morphology appropriate for migration [38]. In addition, both MMP1 and MMP7 contribute to EMT by degrading E-cadherin, a cell–cell adhesion molecule [33]. Epilysin (MMP28), the newest member of the MMP family is expressed in basal keratinocyte in the skin [39] and seems to contribute in EMT [40].

It has long been assumed that carcinoma cells would produce by themselves proteolytic enzymes or recruit them from host cells in an effort to degrade basement membrane for invading surrounding tissue. Surprisingly, tumor cells have been reported to cross ECM barriers through non-proteolytic process by exerting physical and mechanical forces that distort matrix architecture [41]. Originally characterized as type IV collagenases, MMP2 and MMP9 were viewed as essential proteases for BM-invasive events. However, transfection of COS cells with their cDNAs does not improve BM degradation and invasion [42]. Instead, MMP2 produced by mesenchymal cells and MMP9 secreted by inflammatory cells (macrophages and neutrophils) are now viewed as key regulators of pathological angiogenesis [43,44]. 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 [42]. Interestingly, MT4-MMP produced by breast carcinoma cells does not directly affect *in vitro* cell invasion [42,45], but promotes *in vivo* the formation of metastasis through a control of vessel architecture [45]. These observations emphasize the multiple functions of MMPs controlling various events related to cancer progression.

It is worth noting that the expression of the tumor cell-derived proteases is frequently modulated by stromal microenvironment and that important crosstalk are established between cancer cells

and host cells leading to a regulation of protease expression in both the tumor and host compartments [5].

4. MMPs and host cells

The tumor microenvironment contains several resident cell types (fibroblasts and vascular cells) and migratory cells derived from the bone marrow that play pivotal roles in the growth of primary tumor and the formation of metastasis.

4.1. Fibroblasts

Cancer cells might stimulate fibroblasts to synthesize MMPs in a paracrine manner through the secretion of interleukins, interferons, growth factors and EMMPRIN [4,10,46]. Fibroblasts constitute therefore an important source of MMPs including mainly MMP1 [47], MMP2 [48], MMP3 [49], MMP9, MMP11 [21,50], MMP13 [47] and MT1-MMP [17,51]. MMP2 produced by fibroblasts can bind the surface of tumor cells through interaction with for instance MT1-MMP and integrin $\alpha_v\beta_3$ [48,52,53]. The expression of MMP13 has been co-localized with that of MT1-MMP and MMP2 suggesting their contribution in a proteolytic cascade [47,54].

MMP11 has been clearly established as a stromal factor favouring the implantation of cancer cells in an aberrant environment [21]. An increased number of apoptotic cancer cells can be found in MMP11-deficient mice indicating that host MMP11 protects tumor cells towards apoptosis [55]. Surprisingly, MMP11 function differs throughout cancer history, it is an enhancer for primary tumor development, but a repressor for metastatic dissemination [21].

The role of fibroblasts-derived MMPs has been investigated in xenograft models in which tumorigenic and not tumorigenic cells are cotransplanted with fibroblasts [56], as well as in the matrix-inserted surface transplantation model [5,44]. The tumor promoting effect of fibroblasts in xenografts is reduced when their ability to produce activated MMPs is inhibited by TIMP2 or synthetic MMP inhibitor [57]. Interestingly, MMP11-null fibroblasts [58] or MT1-MMP-null fibroblasts [59] do not support *in vivo* growth of tumor cells whereas corresponding wild-type fibroblasts promoted tumor development. It is worth noting that upregulation of MMPs is one of the physiological changes that occur when fibroblasts undergo senescence, which may be an important component of the generation of a pro-oncogenic tissue environment that contributes to the increased incidence of cancers that occur with age [60,61]. Accordingly, fibroblasts that have been forced into senescence by DNA damage increased the growth of cancer cells in a MMP-dependent manner [61]. 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 MMP3 can cause sustained EMT and malignant transformation in cultured cells and genomically unstable mammary carcinomas in transgenic mice [49]. In this context, MMP3 has been reported to induce the expression of an alternative spliced form of Rac1 which causes an increase in cellular reactive oxygen species [62].

4.2. Macrophages

Tumor-associated macrophages (TAM) represent a major component of the lymphoreticular infiltrates of tumors [63,64]. High numbers of TAM have been observed in many tumors. The extent of the macrophage infiltrate correlates positively with angiogenesis and negatively with prognosis in some cancers [65,66]. In macrophage-deficient mice crossed with polyoma middle-T oncoprotein (PyMT mice), the incidence and initial rate of primary mammary tumors are not distinguishable to those of wild type mice, but the rate of tumor progression was slowed and their metastatic ability was almost completely abrogated [67]. Macrophages may have both pro- and anti-tumor activities. TAMs are educated by the tumor microenvironment, so that they adopt a trophic role that facilitates angiogenesis, matrix breakdown and tumor cell motility. They are able to produce a variety of MMPs including MMP1, 2, 7, 9 and 12 [68]. TAM-derived MMP9 appears to play a critical role in angiogenesis and progressive growth of human ovarian tumors in mice [69]. However, the production of the inhibitor of angiogenesis, angiostatin, has been correlated with TAM production of elastolytic metalloproteinases in a murine model of Lewis lung cell carcinoma [70]. Macrophage MMP12 is required for the generation of angiostatin [71]. MMP12-deficient mice develop more gross Lewis lung carcinoma pulmonary metastases than wild type counterparts, thus providing a role for MMP12 in suppressing the growth of lung metastases [72]. Although little is known about *in vivo* functions of MMP12, it is a candidate anti-target, but further experiments are required in MMP12-deficient mice to validate this concept [8].

4.3. Mast cells

Mast cells have been shown to accumulate within and around the tumors of different origins [73,74]. In experimental models, the injection of mast cell suspensions into rats leads to the acceleration of tumor growth [75]. In the same way, using a transgenic mouse model that expresses human papilloma virus (HPV)-16 genes in basal keratinocytes, Coussens et al. showed that carcinogenesis was accompanied by the infiltration of mast cells [76,77]. On the contrary, decreasing the number of mast cells leads to suppression of tumor growth [78] and pre-malignant angiogenesis was ablated in mast cell deficient HPV-16 transgenic mice [76]. The inhibition of degranulation suppresses tumor growth [75], suggesting that the tumor-promoting activity of mast cells is related with granule-associated mediators. Degranulating mast cells release different proteases including MMP2 and MMP9 [79], as well as serine proteases, such as tryptase and chymase which can activate latent MMP3 and MMP9 [79,80]. Interestingly, the release of MMP9 by inflammatory cells infiltrating normal pancreatic islets mobilizes sequestered vascular endothelial growth factor (VEGF) which triggers an angiogenic switch and promotes tumor growth [81].

4.4. Neutrophils

Polymorphonuclear neutrophils (PMN) are crucial inflammatory leukocytes in host protection from infection. Accumulating

evidence also indicates their important role during cancer progression. They represent an important source of MMP8 also called the neutrophil collagenase [82] and MMP9 [44]. MMP8 is produced primarily by PMNs and is released from the specific granules at sites of inflammation [82]. In contrast to other MMP-deficient mice, MMP8 null mice challenged with carcinogens showed a markedly increased susceptibility to tumorigenesis [20], but this only occurred in male mice. This was the first report of a MMP having a protective role in tumorigenesis, so validating MMP8 as an anti-target in cancer therapy [8]. In skin tumors chemically induced in MMP8-null mice, a prolonged chronic accumulation of PMN that did not dissipate was observed and associated to the reduction of bioactive molecule processing such as LIX, a neutrophil chemoattractant [20]. LIX bioactivity is increased in mouse upon N-terminal cleavage by MMP8 and comparable results were obtained with the human orthologues CXCL8/IL8 and CXCL5/ENA-78 [83]. Therefore, although MMP8 was long thought functionally restricted to ECM breakdown through collagenolysis, it is now viewed as a key regulator of chemokine activities.

4.5. Vascular and perivascular cells

It is widely recognized that tumors required angiogenesis to grow beyond a certain size. In addition to the sprouting of neighbouring pre-existing vessels, tumoral angiogenesis is supported by the mobilization of different cell types including haematopoietic cells, endothelial progenitor cells derived from the bone marrow leading to vasculogenesis, and mural cells (pericytes, smooth muscle cells) promoting vessel stabilization [84]. These processes involve a wide range of cell surface molecules (integrins, selectins, cell adhesion molecules, growth factor receptors) as well as soluble mediators including fibroblast growth factor (FGF), VEGF, angiopoietins, interleukins (IL1, IL8), tumor necrosis factor- α (TNF α), TGF- β . . . MMPs are perfectly designed to regulate their activation/inactivation, to control their biodisponibility by releasing them from ECM and to generate inhibitors of angiogenesis through the cleavage of molecules which do not display any angiogenic activity under native conformation (Tables 1 and 2) [85–89].

Therefore, the roles of MMPs in angiogenesis are dual and complex. Positive regulators of angiogenesis include at least MMP1, MMP2, MMP9, MMP10 and MT-MMPs. MMP2 and MMP9 have been shown to be critical for the “angiogenic switch” when tumors become vascularized [90]. The importance of MMP2 and MT1-MMP in vessel formation is reflected by embryonic lethality of double KO mice [91] and post-natal lethality in MT1-MMP-deficient mice [92,93]. MT1-MMP control tumoral angiogenesis through diverse mechanisms reported in previous reviews [17,51,94]. Whereas considerable data suggest that MT-MMPs control endothelial cell tube morphogenesis in 3D ECM [95–97], MMP1 and MMP10 (stromelysin-2) appear to control the process of regression rather than morphogenesis [98]. MT1-MMP deficiency [95], but not that of MMP2 and/or MMP9 deficiency [44] directly affected the migration and sprouting of endothelial cells from aortic rings. However, double mutant MMP2 $-/-$; MMP9 $-/-$ mice showed reduced angio-

genesis after transplantation of malignant keratinocytes [44]. This demonstrates the implication of different host cells during angiogenesis, MMP2 being produced by mesenchymal cells and MMP9 by neutrophils in this experimental model [44]. Interestingly, MMP9 plays a key role in vasculogenesis through the release of soluble ckit ligand allowing the transfer of hematopoietic and endothelial stem cells from a quiescent to a proliferative compartment in the bone marrow [99]. Furthermore, MMP9 regulates vessel stabilization by controlling pericyte recruitment [100].

By their capacity to generate angiogenic inhibitors through the cleavage of plasminogen, type IV or type XVIII collagens, MMP3, MMP7, MMP9, MMP12, MMP13 and MMP20 are expected to be negative regulators of tumor angiogenesis [85,86]. Similarly, MMP19 could be considered as an anti-tumor target since its deficiency in mice has been associated to accelerated angiogenesis [19].

4.6. Adipocytes

The adipocytes represent one of the most abundant cell type surrounding breast cancer cells and may prove to be a key player in the stromal-ductal epithelial cell–cell interactions within the mammary microenvironment. Indeed, many tumors break through the basement membrane and infiltrate fibrous tissue barriers, resulting in immediate proximity to adipocytes. Preadipocytes and adipocytes emerge as cells with the potential to affect growth and development of malignant breast cells [105,106]. Adipocytes are highly active endocrine cells that secrete numerous factors including growth factors, cytokines, ECM proteins and MMPs [107,108]. Interestingly, adipocytes appear to be involved in initial cancer cell survival in connective tissue and this effect is mediated, at least partly by MMP11 [109].

5. Conclusions

MMPs regulate a multitude of cell functions and are key regulators in a complex molecular network controlling both tumor cell and host cell features. MMPs are implicated in virtually all aspects of cancer progression and dissemination. Despite structure and sequence homologies and substrates overlapping between MMPs, different cell types express various MMPs at specific steps of cancer progression. MMPs display diverse and some time opposite effects depending upon the cellular source, tissue location and step of cancer evolution considered. The failure of clinical trials employing synthetic MMP inhibitors in cancer chemotherapy has led to disappointing results [10], but in the meantime led to the interesting concept that some MMPs may actually serve the host in its defence against tumor growth and evolution. This concept has been and is currently being validated in human cancers and in different *in vivo* murine models thanks to the recent generation of MMP-deficient mice. Future efforts to identify which, where and when MMPs are friends or foes will be essential to identify the specific targets and anti-targets among the MMP family. Elucidation of their *in vivo* substrates is also mandatory to determine their mecha-

nisms of action and pave the way for appropriate drug design for anti-cancer therapies [110–113].

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