Chapter 6

Matrix Metalloproteinases: Mediators of Tumour-Host Cell Interactions

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Abstract: Matrix metalloproteinases (MMPs) are a family of metalloendopeptidases that induce remodelling of extracellular matrix (ECM) and differentially cleave many soluble mediators that regulate cell physiology. Due to their matrix-degrading capabilities and elevated expression levels in both neoplastic and host cells in human cancer, MMPs have acquired considerable attention as targets for anti-cancer therapy. This chapter summarizes two decades of research examining MMP biochemistry and biology utilizing *in vitro* cell-based and biochemical analyses, more recent examination of their functional significance in *de novo* mouse models of human cancer development and results from human clinical trials where MMP inhibitors were evaluated for efficacy as anti-cancer therapeutics.

Key words: Matrix metalloproteinases, tumour-host cell, microenvironment, integrins, tumor, angiogenesis, metastasis, angiogenesis inhibitors, neoplastic cell progressison, TIMP, RECK, tumour-host interactions, "cysteine switch", ECM, TNFL, MMP, Chemokines, carcinogenesis, ECM, TGFβ, EGF, bFGF, E-cadherin, tumstatin, integrin, protease inhibitors

1. INTRODUCTION

Cancers develop in a multistep manner and evolve through distinct histopathological stages characterized by significant changes in cellular and acellular organization and phenotype. While it is clear that initiating events involving activation of oncogenes and inactivation of tumour suppressor genes are essential for cancer development (1-3), extrinsic changes involving the neoplastic microenvironment fundamentally contribute to and aid progression to the tumour state. Thus, cancer development can be viewed as a collaboration between initiated neoplastic cells and activated/responding "host" cells (fibroblasts, inflammatory cells and cells composing the vasculature) and the dynamic microenvironment in which they live (4-10).

Autocrine and paracrine interactions between cellular and acellular components within developing tumours enable enhanced proliferative capacity, activation and persistence of angiogenesis and lymphangiogenesis, evasion of cell death programs and ectopic tissue growth capabilities (4). Many of these cellular programs are modulated by the actions of a family of secreted and cell surface enzymes, e.g., matrix metalloproteinases (MMPs), a family of zinc-dependent proteinases originally identified for their ability to cleave extracellular matrix (ECM) components *in vitro* (11). Since their original identification as ECM-degrading enzymes, the known biological activities of MMPs has expanded and now encompasses liberation of ECM-sequestered growth factors (12), activation of inflammatory chemoattractants (13) and ligands regulating apoptosis (14), and inactivation of ligand-

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binding proteins modulating proliferation (15). Consistent with these multiple roles for MMPs during neoplastic progression, correlative studies on human cancers have revealed that elevated MMP mRNA levels are associated with higher tumour staging and worse clinical outcome (16, 17). Moreover, MMP loss-of-function and gain-of-function studies utilizing mouse models of human cancer development have revealed that MMPs are functionally significant potentiators of carcinogenesis (12, 18-21). This chapter focuses on the complexity of interactions during cancer development involving MMPs and reviews recent findings where the functional significance of MMPs during neoplastic progression has been addressed experimentally.

2. MMP STRUCTURE AND FUNCTION

MMPs belong to the super-family of metzincins metalloendopeptidases (11, 22, 23). To date, ~ 26 human secreted or transmembrane MMPs have been identified (Figure 1) (24-26). Vertebrate MMPs each have distinct, but often overlapping, substrate specificities and collectively possess enzymatic activity against virtually all ECM components (24, 26, 27). In addition to their dependence on zinc and calcium, MMPs share several other common features. Individual MMPs have been variously named, grouped and subdivided based on their substrate specificities and the presence or absence of specific functional protein domains (Figure 1).

2.1 MMP Structure

Like many other classes of proteolytic enzymes, MMPs are first synthesized as inactive proenzymes or zymogens. They are found as either secreted or cell surface enzymes sharing several highly conserved domains, including a pre- and pro-peptide domain, a catalytic domain containing a zinc atom binding site, as well as several other structural domains believed to facilitate specific interactions with substrates and/or other target molecules (11, 24, 25, 28).

With the exception of MMP-7, -26 and the type II transmembrane MMP, MMP-23, all MMP family members contain the carboxyl-terminal hemopexin/vitronectin-like domain. Several functions have been ascribed to this domain depending upon the specific MMP family member. The hemopexin domain in proMMP-2 and -9 is thought to mediate interactions with specific proteinase inhibitors (28), while in MMP-1 and -8 this domain is associated with inhibitor as well as substrate binding (28). With regards to substrate specificity, the hinge region that links the hemopexin and catalytic domains, may play a major role. Whereas the hinge region is variable in length and composition among family members, MMPs that are able to degrade fibrillar collagens (MMP -1, -8, -13, -14) contain a hinge region of distinct size and composition (25). Structure-function studies have confirmed the substrate specificity dictated by this region (29). The catalytic domain for all MMP family members contains three conserved histidines that coordinate the zinc ion in the active site (30). While MMP-2 and -9 contain these conserved histidine amino acid residues within their catalytic domains, they also contain a 182 amino acid insertion in this domain homologous to the collagen-binding region of fibronectin. This region is required for gelatinolytic activity as well as the collagen binding properties of MMP-2 (31, 32).

The seven different membrane type MMPs (MT-MMPs) are anchored to the cell membrane either by a transmembrane type I domain, a glycosylphosphatidylinositol (GPI) domain or a type II N-terminal signal domain containing a unique C-terminal cysteine array and an Ig-like domain (33). These distinct membrane-anchoring domains are thought to regulate location and activity of MT-MMPs (34). In addition, several MMPs contain small domain inserts that contribute to specific functions. For example, MMP-11, 14-17, 21-25 and –28 harbor furin-like inserts within propeptide domains that enable activation intracellularly by pro-protein convertases, Ca^{2+}-dependent serine proteases of the subtilisin group (furin/PACE) (35). In summary, although MMPs share functional domains, structural differences exist such that MMPs can be classified into eight categories (Figure 1). These differences are responsible in part for the variety of biological processes that MMPs are involved in.

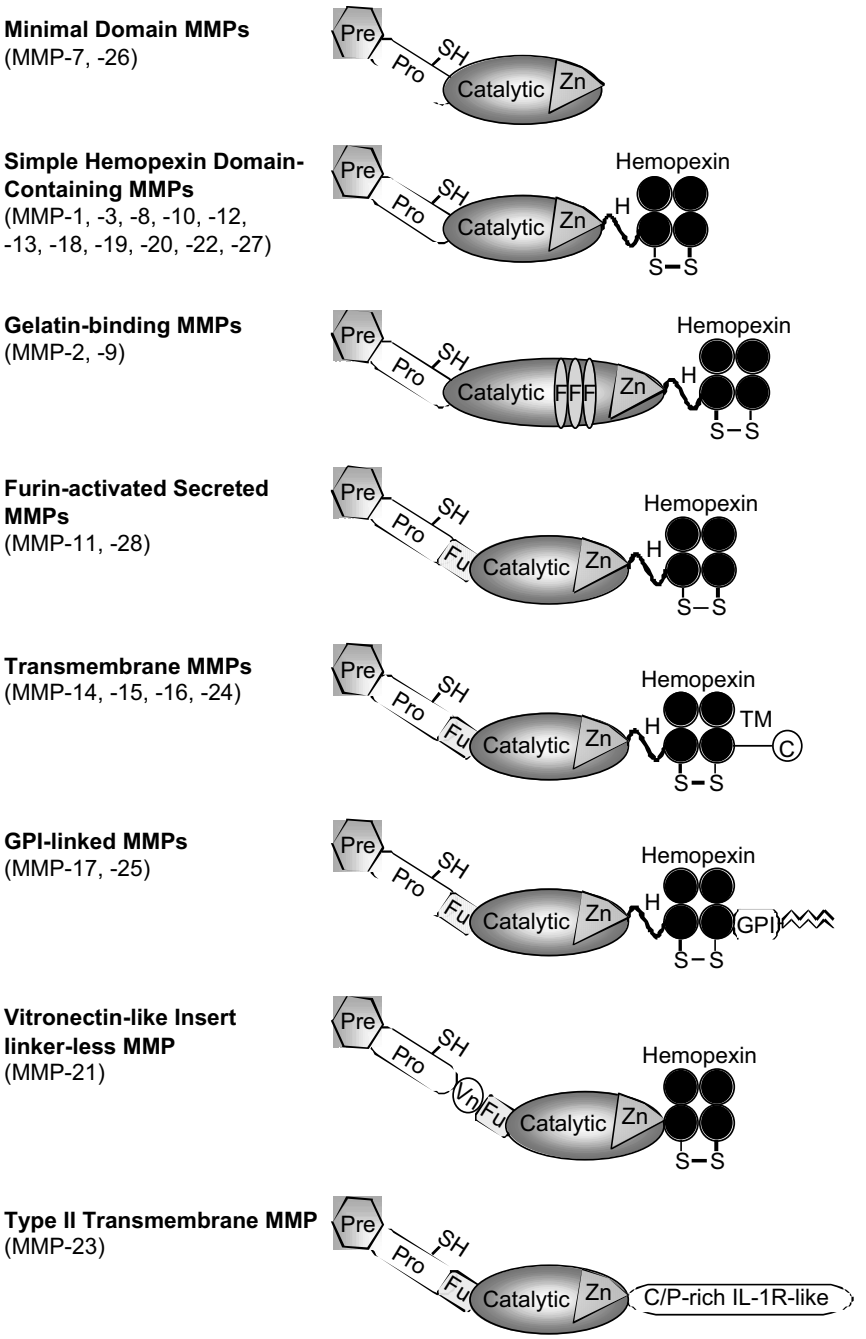

Figure 1. MMPs can be classified into eight groups based on their domain organization. Pre: signal sequence; Pro: zinc-interacting sulfydryl (SH) group containing propeptide; Fu: furin-susceptible site; Vn: virtonectin-like insert; zinc-binding site (Zn) containing catalytic domain; F: collagen binding fibronectin type II insert; H: hinge region; Hemopexin-like domain with the first and last repeat linked by a disulfide bond; TM: transmembrane domain; C: cytoplasmic tail; GPI: glycophosphatidyl inositol-anchoring domain; C/P-rich IL-1R-like: cysteine/proline-rich interleukin-1 receptor domain.

2.2 Regulation of MMP activity

The zymogen forms of MMPs are inactive. Crystallographic studies have confirmed that enzyme latency is due to coordinate bonding between the active site zinc atom with an unpaired cysteine thiol group located near the carboxyl end of MMP propeptides (36). Activation of zymogens is tightly controlled owing to cell-type specific expression characteristics, as well as post-translational regulation at the levels of zymogen activation, interaction with endogenous inhibitors and spatial constraints in pericellular microenvironments (25, 28, 37).

2.2.1 Transcriptional regulation of MMPs

In quiescent tissue, MMPs are typically expressed at low levels or more commonly transcriptionally silent. However, upon induction of tissue remodelling, MMP expression is rapidly induced by cytokines and polypeptide growth factors, e.g. interleukin (IL)-1, tumour necrosis factor (TNF)-α, vascular endothelial growth factor (VEGF), transforming growth factor (TGF)-β, epidermal growth factor (EGF), glucocorticoids, phorbol esters and collagen-induced signalling through receptor tyrosine kinases (discoidin domain receptors (DDR) 1 and 2) (38-42). A well-studied example of these processes is the induction of MMP-2 and -9 expression by TNF-α (43-46). Upon binding to its receptor, TNF-R55, TNF-α activates protein kinase R (PKR) to induce transcription of MMP-2 and -9 via phosphorylation of NF-κB, c-jun, c-fos and AP-1 (43-46). The importance of this pathway in regulating MMP expression is highlighted by the significant reduction in skin tumours induced by TPA (12-O-tetradecanoyolphorbol) in c-jun homozygous null (c-jun$^{-/-}$) mice (46). Alternatively, induction of MMP mRNA expression can be regulated as a result of varied interactions between ECM and pericellular collagens with plasma membrane spanning receptor tyrosine kinases, specifically discoidin domain receptor (DDR) 1 and 2 (47, 48). DDR1 is activated by types I, IV or V collagens, is expressed primarily in epithelial tissues and has been implicated in neoplasms such as breast cancer and glioblastomas (49). DDR1 regulates chemokine production in tissue infiltrating macrophages via p38 mitogen-activated protein kinase (50). In addition, studies using DDR1$^{-/-}$ transgenic mice indicate that DDR1 activation is required for MMP-2 mRNA expression in both invading macrophages and leukocytes (41, 51). DDR2 on the other hand is expressed in mesenchymal cells and in fibroblasts surrounding DDR1 positive tumour cells (52, 53). DDR2$^{-/-}$ transgenic mice and real time PCR studies have shown that DDR2 regulates MMP-1 and -2 expression in fibroblasts (42, 47). In summary, MMP mRNAs during neoplastic progression are regulated by diverse intracellular signalling pathways that reflect rapidly changing dynamic interactions between cells and their immediate microenvironments; thus, functionally linking MMP expression and tissue remodelling with the needs of expanding tumours.

Expression levels of MMP mRNAs can also be effected by single-nucleotide polymorphisms (SNPs) present within MMP promoter regions (54). These polymorphisms contribute to individual differences in MMP transcription and are associated with increased susceptibility to cancer (54). For instance, insertion of an additional guanine residue in the MMP-1 promoter results in significantly higher levels of MMP-1 mRNA (55). Clinical studies have shown that a significantly higher proportion of ovarian and colorectal cancer patients carry this polymorphism suggesting it as a risk factor for poor prognosis (56).

2.2.2 MMP activation by propeptide proteolysis

There are several distinct mechanisms by which MMP zymogens are activated. The first involves an inter-molecular proteolytic reaction known as the "cysteine switch" (57, 58). The consensus PRCGXPDV motif in MMP propeptide domains contains a cysteine-sulphydryl group that binds to Zn^{2+} ions in the active site of the N-terminal catalytic domain, thus preventing proteolytic activity (25). When interactions between the Zn^{2+} ion and the cysteine-suphydrl group are destabilized, either by chemical or physical means, proteolytic cleavage

occurs at the carboxy terminal side of the PRCGXPDV consensus motif (11, 59) resulting in irreversible loss of the cysteine residue allowing further intra/intermolecular proteolysis generating a fully active enzyme (60). In cell-free systems, the cysteine-zinc atom interaction can be interrupted by organomercurials and chaotropic agents. Alternatively, limited proteolysis of the propeptide destabilizes the cysteine-zinc bond. Interruption of the cysteine-zinc bond by any means, results in conformational changes rendering the "switch" open. Following opening, autocatalytic or proteolytic cleavage of the remainder of the propeptide yields a truncated and catalytically competent enzyme. In contrast to MMPs activated via the cysteine switch, MMP-23, a type II transmembrane MMP, is activated by a single cleavage site at Arg^{79} within the signal anchor domain (34, 61). Sharing only two common features with other MMP family members, a catalytic domain and the basic motif, MMP-23 is unique among the MMPs in that cleavage in the signal peptide at residue Arg^{79} is responsible for both secretion and activation (34, 61).

MMPs containing a furin-like recognition domain in their propeptides (MMP-11, -28 and MT-MMPs) are activated intracellularly by a group of calcium-dependent transmembrane serine proteinases of the subtilisin group termed furin/PACE/kex 2-like proteinases (Figure 1). MMPs without this recognition sequence are secreted in latent form (37). Proteolytic activation of latent secreted MMPs involves propeptide cleavage by other MMPs (62-64) or by serine proteases, such as those within the urokinase-type plasminogen activator (uPA)-plasminogen system (65-67) or serine proteases expressed by inflammatory cells such as mast cell chymase (68-70) and neutrophil elastase (71-74). Serine proteinase mediated cleavage of secreted MMP propeptide domains induces autocatalytic activation of MMP-1, -3 and –9, whereas proMMP-2 is resistant to activation by serine proteinases. Some activated MMPs can further activate other proMMPs. For example, MMP-3 activates proMMP-1 and proMMP-9; thus, serine and metalloproteinases also act as initiators for a complex array of proMMP activation cascades *in vivo*.

Cell-mediated activation mechanisms are also utilized as seen in the activation of proMMP-2 in complex with MMP-14 and TIMP-2. MMP-14 is associated with the plasma membrane where the N-terminal domain of TIMP-2 binds to active site residues in MMP-14 resulting in a dimeric complex that then serves as a receptor for proMMP-2 via the C-terminal domain of TIMP-2 interacting with the C-terminal domain of proMMP-2 (75). An adjacent free MMP-14 then cleaves proMMP-2 propeptides generating an intermediate MMP-2 species and the fully active MMP-2 is subsequently generated through an autocatalytic mechanism (67, 76). Recent data indicates that MMP-16 utilizes TIMP-2 and TIMP-3 to activate proMMP-2 by a similar process (77).

Several advantages for having proteolytic enzymes in a bound state at the cell surface have been proposed. First, bound proenzymes may be more readily activated, thus generating higher local levels of activity than what might be found in the soluble phase. Second, enzymes at the cell surface may be protected from activation by bound inhibitors. Third, the binding of an enzyme to the cell surface may provide a means of concentrating the components of a multistep pathway, thereby increasing the rate of reactions. Fourth, immobilizing enzymes on the surface of a cell or in the matrix may provide a means of restricting activity of the enzyme, so that only substrates in the vicinity of the cell or only adjacent matrix components are targeted. Hence, activation at the cell surface links MMP expression with proteolysis, and may actually provide the most significant control point in MMP activity.

2.2.3 Regulation of MMP activity by endogenous inhibitors

MMP activity is tightly regulated by several endogenous inhibitors including, tissue inhibitors of metalloproteinases (TIMPs), thrombospondins, α2-macroglobulin and RECK (Reversion Inducing Cysteine rich protein with Kazal motifs (Table 1 (78-82). The most thoroughly studied MMP inhibitors are the TIMPs. To date, four vertebrate TIMPS have been identified (TIMP-1 to -4). TIMPs are small proteins (21-28 kDa) that bind to MMPs in

a 1:1 stoichiometric ratio and reversibly block MMP activity (37). TIMP-1, -2 and –4 are secreted soluble proteins whereas TIMP-3 is matrix associated (83). TIMPs differ in both their expression patterns and affinities for MMPs. For example, TIMP-1 and TIMP-2 inhibit the activity of many MMPs. TIMP–3 on the other hand preferentially inhibits activity of MMP-1, -3, -7 and –13 (84), whereas TIMP-4 primarily inhibits MMP-2 and –7 and to a lesser extent MMP-1, -3 and –9 (85). Thrombospondin-2 binds MMP-2 and this complex results in scavenger receptor-mediated endocytosis and clearance of MMP-2 (86). Thrombospondin-1 on the other hand binds to proMMP-2 and –9 and thereby directly blocks their activation (79). The plasma protein α2-macroglobulin also regulates MMP activity by forming a complex resulting in scavenger receptor-mediated endocytosis (87); however, the inhibitory effect of α2-macroglobulin is more general in that it binds to the majority of MMPs (86). RECK is an endogenous inhibitor of MMP-2, -9 and -14 (82) and is abundant in adult tissues primarily found in vascular smooth muscle cells proximal to large blood vessels (82, 88). RECK is a secreted glycoprotein containing a serine-protease inhibitor-like domain, two epidermal growth factor-like repeats and a modified C-terminal GPI domain anchoring it to plasma membranes. RECK also inhibits secretion of proMMP-9 and the final processing step of proMMP-2 (82). The GPI anchor is thought to allow RECK access to regions of focal proteolysis along the cell surface thus enabling it to regulate proteolytic events during embryogenesis and angiogenesis (89).

Table 1. Characteristics of MMP inhibitors.
* Required for MMP-14 or MMP-16 mediated activation of MMP-2

MMP inhibitor	**MMP-2 activation***	**MMPs inhibited** (reference publication)
TIMP-1	No (365)	MMP-1 (366), -2 (367), -3 (366), -7 (368), -8 (369), -9 (367), -10 (366), -11 (370), -12 (118), -13 (371), -17 (372), -19 (373), -25 (374), -26 (375)
TIMP-2	Yes (67)	MMP-1 (376), -2 (376), -3 (366), -7 (377), -8 (378), -9 (376), -10 (366), -13 (371), -14 (379), -16 (380), -17 (372), -19 (373), -24 (381), -25 (374), -26 (375. 382)
TIMP-3	Yes (382)	MMP-1, (383), -2 (383), -9 (383), -13 (63), -14 (384), -16 (380, 382), -17 (372), -19 (373), -25 (374)
TIMP-4	No (385)	MMP-1 (386), -2 (374), -3 (374), -7 (374), -8 (385), -9 (374), -14 (374), -19 (373), -26 (375, 382)
RECK	No (82)	MMP-2 (82), -9 (88), -14 (82).
Thrombospondin-1	No (79)	MMP-2 (79), MMP-9 (79, 80)
Thrombospondin-2	No (86)	MMP-2 (86)
α-Macroglobulin	No (78)	Universally inhibits MMPs via receptor mediated endocytosis (86, 87)

2.2.4 MMP Localization

An increasing body of evidence suggests that cell surface localization of MMPs is critical for optimal MMP function (90). It has been shown that membrane bound MMPs and integrins are localized to invadopodia (91), whereas secreted MMPs transiently localize to cell surfaces by associating with cell surface proteoglycans, adhesion receptors or basement membrane components (92). Secreted MMPs like MMP-1 for example, associate with cell surfaces via integrin and EMMPRIN interactions (93-95). MMP-2 also associates with plasma membranes by interacting with αvβ3 integrin through its hemopexin-like domain (96), whereas MMP-7 binds to the hyaluronan receptor CD44 (97). MMP-9 associates with several plasma membrane spanning receptors (CD44, ICAM-1, integrins) as well as the basement membrane component type IV collagen (98-101).

The significance of MMP localization in regulating their effects on cell function has been

examined by inhibiting cell surface localization of MMP-9 in a mouse mammary carcinoma cell line (102). This resulted in loss of both invasive and metastatic capacity, properties that were restored by constitutive cell surface expression of an MMP-9 fusion protein (102), suggesting that for at least some cell types, migration through basement membrane structures may rely upon these interactions. Furthermore, disruption of CD44-MMP-7 interactions in lactating mammary epithelia resulted in relocation of MMP-7 from apical to basal cell surfaces and was associated with increased epithelial cell death and tissue remodelling (97), suggesting that whereas cell surface localization of some MMPs may impart a migratory phenotype, similar association of other family members may regulate cell proliferation and/or cell death. Taken together, MMP activity is regulated at four levels, e.g. transcriptional, post-translational propeptide cleavage, inhibition by endogenous inhibitors and differential cell surface localization. These processes are tightly regulated in normal homeostatic conditions; however, as will be discussed below, during neoplastic progression, MMP expression and activation is enhanced, a property that can stimulate and/or promote various aspects of neoplastic cell growth.

2.3 MMP Function

MMPs are thought to functionally contribute to physiological and pathological tissue remodelling, especially during embryonic and tumour development (17). It is believed that ECM remodelling is essential for maintaining tissue integrity and involves a tightly regulated balance between ECM synthesis and ECM degradation (103). During wound healing, MMPs secreted by epithelial cells, fibroblasts and inflammatory cells remodel pericellular ECM in the immediate area of tissue damage (104). In turn, fibroblasts and vascular cells synthesize appropriate amounts and composition of ECM components (type I collagen, fibronectin etc.) important for tissue repair (104). In contrast, in fibrotic environments (i.e. liver cirrhosis, lung fibrosis and scleroderma), the balance between ECM synthesis, accumulation and degradation is shifted favouring synthesis and accumulation resulting in the fibrotic phenotype, a phenotype that can also be caused by increased synthesis of ECM components independent of the degradative enzymes that remodel it (105, 106). In contrast, a shift in favour of ECM degradation is seen in degenerative pathologies such as arthritis (107) and tumour development (17, 108). During tissue remodelling, ECM components such as type I collagen and basement membrane components such as types IV, XV and XVIII collagen and laminin can be cleaved by various MMPs (17, 37). Cleavage of these larger macromolecules into smaller fragments can result in release of cryptic embedded bioactive fragments that regulate cell physiology in context-dependent manners, e.g., proliferation, angiogenesis, cell adhesion and migration (90, 109). The realization that ECM remodelling not only alters the organization and composition of physical barriers between tissue compartments potentially enabling migration, but also provides novel products that affect cell physiology, adds an additional level of functionality to MMP family members (110).

Another major function of MMPs is thought to be in their ability to regulate presence of bioactive mediators such as other proteinases, proteinase inhibitors, clotting factors, chemokines, growth factors, growth factor binding proteins, cell surface receptors, and cell-cell and cell-matrix adhesion molecules (108, 111). These MMP substrate molecules are found sequestered in ECM or attached to cell surfaces, or represent ECM components themselves, e.g., type I, IV, XV and XVIII collagen and laminin (91, 110, 112-116). For example, MMP-9 is known to target the proangiogenic growth factor vascular endothelial growth factor (VEGF) (12); however, VEGF itself is not believed to be a direct cleavage target of MMP-9 suggesting that an ECM molecule sequestering VEGF is the target. Both MMP-2 and MMP-9 activate latent transforming grwoth factor beta (TGFβ) residing in the matrix (97) and numerous MMPs can activate components of the plasma clotting system such as fibrinogen and plasminogen (112, 117-119), while MMP-2, -3, -7, -9 and 12 can cleave plasminogen generating the angiogenic inhibitor angiostatin (112, 118, 120). It has also been shown that MMP-14 derived from macrophages regulates neovascularization in tumours by degrading fibrinogen networks that serve

as a temporary scaffold for endothelial cells (117). In addition, multiple MMPs can modulate immune responses by processing of chemokines (121, 122), a property important for resolution of acute inflammation and possibly also during tumour development.

MMPs are also thought to promote tumour cell survival by conferring protection against apoptotic cell death. For example, MMP-7 sheds membrane bound Fas ligand (FasL) resulting in production of soluble FasL that significantly lowers the ability to trigger apoptosis via the Fas receptor pathway (123). MMP-7 cleaves the heparin–binding EGF precursor (HB-EGF) from the cell surface resulting in generation of signals conferring protection from apoptosis by binding of mature active form of HB-EGF to both the ErbB1 and ErbB2 tyrosine kinase cell spanning receptors (97). MMPs, besides promoting tumour progression via these diverse mechanisms, also exhibit anti-tumour functions. For example, male homozygous null MMP-8 mice (MMP-$8^{-/-}$) exhibit a significant increase in skin tumour incidence upon chemically induced carcinogenesis (124). Tumour susceptibility is sex hormone dependent since removal of ovaries in MMP-$8^{-/-}$ females also results in a similar enhanced susceptibility to chemically induced skin carcinogenesis (124). Moreover, treatment of MMP-$8^{-/-}$ mice with tamoxifen, an estrogen receptor antagonist, also results in increased skin carcinogenesis in MMP-$8^{-/-}$ females (124), suggesting that loss of MMP-8 function, by either homozygous loss or MMP inhibition (natural or synthetic), enhances rather than reduces tumour susceptibility. Taken together, it is clear that MMP function extends well beyond ECM remodelling and, as a consequence of their diverse activities toward substrates, MMPs participate in many biological (e.g. embryogensis, angiogenesis, endometrial cycling and wound healing) and pathological (e.g. cancer, arthritis and cardiovascular disease) processes by both positive and negative mechanisms.

3. CELL-TYPE SPECIFIC MMP EXPRESSION

The association of MMP expression with neoplastic progression is well documented *in vivo* and *in vitro* (17). MMPs have been associated with the malignant phenotype in a wide variety of human tissues, including breast, colon, lung, ovary, pancreas, prostate, stomach and squamous cell carcinomas of the head, neck and skin (Table 2; reviewed in: (17, 125-128). MMP-2, -3, -7, -9, -10, -13, -14 and 17 were first cloned from tumour cells lines and MMP-11 was cloned as a metastasis-specific gene from metatstatic tumours (reviewed in (17)). In fact, whether constitutively expressed or induced by oncogenes, growth factors or cytokines, expression of all members of the MMP family has been documented in cultured neoplastic cells derived from diverse developmental lineages (125). Although this characteristic led investigators to speculate that expression of MMPs by epithelial tumour cells was a critical step in the transformation and/or invasive process, it is not representative of MMP expression observed in *in vivo* situations (17). *In situ* hybridization and immunodetection studies have revealed that whereas neoplastic cells express a limited repertoire of MMPs, MMP expression more frequently originates from tumour-associated stromal cells, i.e. activated fibroblasts, macrophages, neutrophils, mast cells, endothelial cells and pericytes (Table 2). These expression patterns are indicative of distinct processes at a particular stage in neoplastic progression that either neoplastic or stromal cells are involved in. For example, during mammary carcinogenesis, mammary epithelial cells express MMP-3, -7, -9 and -13 (129-136), whereas epithelial cells undergoing an epithelial to mesenchymal transition express MMP-11 (137). Differential expression of MMPs is also observed in stromal fibroblasts. An early step in neoplastic progression is marked by myofibroblast expression of MMP-13 (138). In contrast, at a later stage in neoplastic progression, myofibroblasts at the invasive front of a mammary carcinomas express MMP-1, -2, -11 and -14 (129, 130, 131).

Cells of the immune system recruited to tumour sites also express a variety of MMPs. Macrophages express MMP-9 and -12 (131, 139), neutrophils

express MMP-8 and -9 and lymphocytes express MMP-3 and -9 (129, 140). During angiogenesis, endothelial cells express MMP-2, -3 and -9 while pericytes express MMP-9 (131, 133). Additional evidence that MMP expression is stage and cell type-dependent comes from studies showing that MMP-3 expression in squamous cell carcinomas switches from stromal fibroblast to neoplastic cells during epithelial to mesenchymal transitions (141). In addition, transgenic mouse models of human cancer have proven useful tools to examine expression characteristics of MMP mRNAs in various organs as well as for determining the role of particular MMPs during neoplastic development (21). Excellent examples of this are represented by the Rip1-Tag2 model of pancreatic islet cell carcinogenesis and the K14-HPV16 model of squamous epithelial carcinogenesis (12, 20, 142). Data from both models have indicated that MMP-9 regulates activation of the angiogenic switch and that the sources of MMP-9 are predominantly inflammatory cells recruited to the neoplastic site (12, 20, 142). Taken together, these studies have several implications. MMP-expression during neoplastic progression is stage and cell type-dependent and the expression of MMPs observed in cultured cells may have to do with the fact that most culture environments fail to recapitulate the microenvironmental complexities present *in vivo*. Most notably, spatial restrictions of MMP mRNA expression are maintained where they are either expressed by neoplastic epithelial cells or stromal cells but not typically both, implying that mechanisms regulating cell-type specificity, across tumour types, are maintained during neoplastic transformation.

Table 2. Expression of MMPs in most common human cancers*
*Based on 2004 estimated US cancer cases (American Cancer Society). Adapted from (17, 125). ISH: detection of mRNA expression as demonstrated by in situ hybridization; RT-PCR: detection of mRNA expression by RT-PCR; IHC: detection of protein expression by immunohistochemistry.

Neoplasia	MMP	Localization in tumour
Lung	MMP-1	Neoplastic cells (IHC)(387), Stromal cells (IHC) (387-390)
	MMP-2	Neoplastic cells (ISH) (387), Fibroblast (ISH) (391) (392-395), Endothelial cells (ISH: (393, 394)
	MMP-3	Neoplastic cells (IHC) (391, 393), Stromal cells (ISH) (393, 396), ECM near blood vessels (IHC) (396)
	MMP-7	Neoplastic cells (ISH) (396, 397), Endothelial cells (IHC) (397)
	MMP-9	Neoplastic cells (ISH) (391, 398-401), Stromal cells (ISH) (391, 393, 396, 402)
	MMP-10	Neoplastic cells (IHC) (403), ECM near blood vessels (IHC) (404)
	MMP-11	Neoplastic cells (IHC) (391, 398), Stromal cells (IHC) (391)
	MMP-13	Neoplastic cells (IHC) (391, 398), Stromal cells (IHC) (391)
	MMP-14	Neoplastic cells (ISH) (391, 393, 398), Fibroblast (ISH) (391, 393, 405), Endothelial cells (IHC) (393)
	MMP-26	Neoplastic cells (ISH) (406)
Breast	MMP-1	Neoplastic cells (ISH) (129, 130), Stromal cells (ISH) (129-131)
	MMP-2	Neoplastic cells (ISH) (129, 133, 134, 407), Stromal cells (ISH) (129-131), Endothelial cells (ISH) (133)
	MMP-3	Neoplastic cells (ISH) (130, 131, 133, 408), Stromal cells (ISH) (130, 131, 133, 408), Lymphocytes (IHC) (129), Endothelial cells (IHC) (133), ECM near blood vessels (IHC) (409)
	MMP-7	Neoplastic cells (ISH) (131)
	MMP-9	Neoplastic cells (ISH) (129, 133, 134, 408), Stromal cells (ISH) (129), Fibroblast (IHC) (133, 134, 136) , Macrophages (ISH) (139), Neutrophils (IHC) (139) Endothelial cells (ISH) (131, 133), Pericytes (ISH) (139)
	MMP-10	ECM near blood vessels (IHC) (409)
	MMP-11	Neoplastic cells (ISH) (137), Stromal cells (ISH) (131, 137, 410)
	MMP-12	Macrophages (IHC) (131)
	MMP-13	Neoplastic cells (IHC) (131), Myofibroblast (IHC) (138)
	MMP-14	Neoplastic cells (IHC) (134, 411), Myofibroblast (IHC) (412)
	MMP-19	Neoplastic cells (IHC) (413), Endothelial cells (IHC) (413)

Neoplasia	MMP	Localization in tumour
	MMP-26	Neoplastic cells (IHC) (382, 406)
Neoplasia	MMP	Localization in tumour
Prostate	MMP-2	Neoplastic cells (ISH) (414-417), Stromal cells (ISH) (417)
	MMP-7	Neoplastic cells (ISH) (414, 417)
	MMP-9	Macrophages (ISH) (417)
	MMP-10	ECM near blood vessels (IHC) (418)
	MMP-14	Neoplastic cells (IHC) (416)
	MMP-26	Neoplastic cells (IHC) (406, 419)
Colon	MMP-1	Neoplastic cells (ISH) (420), Stromal cells (ISH) (420, 421)
	MMP-2	Neoplastic cells (ISH) (422, 423), Fibroblast (ISH) (421-423), Endothelial cells (ISH) (424), Myofibroblast (ISH) (424), ECM (IHC) (425)
	MMP-3	ECM near blood vessels (IHC) (425)
	MMP-7	Neoplastic cells (ISH) (397, 426, 427), Endothelial cells (ISH) (397)
	MMP-9	Macrophages (ISH) (140, 175, 428), Neutrophils (ISH) (140), ECM (IHC) (425)
	MMP-10	ECM near blood vessels (IHC) (425)
	MMP-11	Fibroblast (ISH) (429)
	MMP-12	Neoplastic cells (ISH) (430)
	MMP-14	Neoplastic cells (ISH) (423, 431), Stromal cells (ISH) (423, 431), Macrophages (ISH) (431)
	MMP-21	Neoplastic cells (IHC) (432)
Ovary	MMP-1	Neoplastic cells (IHC) (433)
	MMP-2	Neoplastic cells (ISH) (433-436), Stromal cells (ISH) (433, 434, 436, 437), Fibroblast (ISH) (435)
	MMP-7	Neoplastic cells (IHC) (438)
	MMP-9	Neoplastic cells (ISH) (434, 436, 439), Stromal cells (ISH) (436, 439, 440), Macrophages (ISH) (434, 437), Neutrophils (IHC) (434)
	MMP-11	Fibroblast (ISH) (441)
	MMP-14	Neoplastic cells (ISH) (436, 441)
	MMP-21	Neoplastic cells (ISH) (432)
Squamous cell carcinoma of the skin	MMP-1	Neoplastic cells (ISH) (442) Stromal cells (IHC) (442)
	MMP-2	Fibroblast (ISH) (442-444)
	MMP-3	Neoplastic cells (ISH) (443), Stromal cells (ISH) (443, 445)
	MMP-7	Neoplastic cells (ISH) (446), Macrophages (ISH) (444), Neutrophils (ISH) (447) , Eosinophils (ISH) (447)
	MMP-10	Neoplastic cells (IHC) (448)
	MMP-11	Fibroblast (IHC) (449)
	MMP-12	Neoplastic cells (ISH) (450), Macrophages (ISH) (450)
	MMP-13	Neoplastic cells (ISH) (445), Stromal cells (ISH) (445)
	MMP-14	Neoplastic cells (IHC) (448), Fibroblast (IHC) (448)
	MMP-19	Neoplastic cells (RT-PCR) (451)
	MMP-21	Neoplastic cells (RT-PCR) (432)

4. MMPS AND NEOPLASTIC PROGRESSION: PRO AND ANTI-TUMOUR FUNCTIONS

Various members of the MMP family are present and active in tumour microenvironments where they are thought to participate in many aspects of neoplastic progression including inflammation, angiogenesis, neoplastic cell proliferation, migration, invasion into ectopic compartments and metastasis formation (Figure 2). Our understanding of the molecular and cellular mechanisms regulated by MMPs that influence these processes in different tumour types has expanded greatly in recent years, however many outstanding questions remain. Understanding these mechanisms and elucidating

how MMPs exert pro- and/or anti-tumour affects, may reveal novel drug targets for development of rational anti-cancer therapeutics.

4.1 Inflammation and MMPs during tumour development

Based on the characteristics of activation and the specificity of target recognition, the immune system can be divided into two subsets - innate and adaptive (143). The innate immune system, also called the first line of immune defence, comprises macrophages, neutrophils, granulocytes, mast cells, eosinophils, basophils and natural killer (NK) cells. The innate immune system is characterized by its ability to respond to foreign antigens in a non-specific manner and is not intrinsically affected by prior contact with pathogens. The adaptive immune system on the other hand is composed of T and B lymphocytes and antibodies, is very specific in its capacity to recognize antigens and is characterized by immunological memory (143). In order to provide sufficient protection against all kinds of infectious agents, the innate and adaptive immune systems are closely linked by influencing each others recruitment and activation pathways (144).

The immune system plays a dual role in tumour development and progression (145). Several studies have reported that the immune system, in particular the adaptive immune system, can suppress tumour development. Studies supporting this concept of immune-surveillance have shown that infiltration of tumours with T lymphocytes is beneficial for cancer patients (146-150). In addition, an increase in the incidence of spontaneous and chemically induced tumours has been observed in immune-deficient mouse models of tumour development (151). Based on the idea that a 'tumour' can be a recognizable target for the immune system, many groups have attempted to activate the immune system in order to obtain successful anti-tumour immune responses (152).

In contrast to the immune-surveillance theory, accumulating clinical and experimental data suggest that the other arm of the immune system, the innate immune system, plays a promoting role during neoplastic progression (6, 153). Extensive analysis of human tumour samples has revealed abundance of innate immune cells, in particular mast cells and macrophages, that correlates with angiogenesis and poor prognosis (154-160). Another indication that inflammatory cells play a promoting role in carcinogenesis is the observation that chronic inflammation often predisposes patients to the development of cancer (161, 162). Well-known examples are the association of inflammatory bowel syndrome with development of colon cancer (163) and the increased risk to develop gastric cancer in patients with chronic helicobacter pylori infection (164). Consistent with these clinical observations are experimental findings that development of colon cancer in TGFβ1-deficient mice is eliminated by maintaining mice in germ-free environments, thus reducing risk of inflammation (165). In addition, long-term use of aspirin and non-steroidal anti-inflammatory drugs has been shown to diminish cancers; colon cancer risk by ~ 50%, gastric and oesophageal cancer risk by ~ 40%, and breast cancer by ~ 20% (166-171). Thus, clinical data clearly suggest a promoting role of inflammatory cells during neoplastic progression; however, they do not provide any mechanisms by which inflammatory cells contribute to the tumour development process. Many investigators now believe that elucidating the mechanisms by which inflammatory cells participate in carcinogenesis will eventually facilitate development of novel therapeutic agents against human cancer (6, 153). As described above, inflammatory cells are important sources of MMPs in tissues engaged in either physiologic or pathologic remodelling. In the next paragraphs, we will focus on the role of inflammatory cell- and other host cell-derived MMPs in neoplastic progression.

Expression of MMPs in human cancer often correlates with poor prognosis (154-158), suggesting that MMPs promote carcinogenesis via either direct and/or indirect pathways. In human carcinomas, the majority of MMPs present are not expressed by neoplastic cells, although exceptions do exist, but instead are predominantly expressed by activated stromal cells, e.g., fibroblasts, vascular cells and a diverse assortment of inflammatory cells (Table 2) (6, 172-175). Since inflammatory cells are often strongly associated with cancer progression, several studies have investigated whether MMPs are

involved as mediators linking inflammation with malignancy.

Compelling evidence that inflammatory cells promote carcinogenesis via secretion of MMPs has been provided by experimental mouse models of *de novo* carcinogenesis harboring homozygous null mutations in various MMPs (12, 18-20). The role of MMP-9 during tumorigenesis was addressed in a transgenic mouse model of squamous carcinogenesis of the skin (176) by studying the phenotypic consequences of genetic deletion of MMP-9 (20, 177). In this tumour model, the appearance of activated MMP-9 in premalignant dysplastic lesions coincides with extensive mast cell infiltration of dermal stroma and when transgenic mice are rendered deficient for either mast cells (142) or MMP-9 (20), tumour-prone mice display significantly reduced epithelial proliferative indices, altered differentiation characteristics and attenuated angiogenesis. Importantly, MMP-9 deficiency results in 50% reduction in incidence of carcinomas as compared to MMP-9 proficient controls (20). Importantly, the characteristics of neoplastic progression in this model were restored by reconstitution with wild type MMP-9 sufficient bone marrow-derived cells (20), thus providing compelling data suggesting that inflammatory cells contribute to neoplastic progression, in part, by their production of MMP-9 in the neoplastic microenvironment. In a different *de novo* mouse tumour model, e.g., pancreatic islet cell carcinogenesis, MMP-9 is also only detected in infiltrating inflammatory cells, not in neoplastic cells (12). In this mouse model, genetic ablation of MMP-9 also results in suppression of angiogenesis and tumour growth (12). Likewise, growth and activation of angiogenesis in xenografted MMP-9-expressing human ovarian carcinomas is significantly attenuated in MMP-9-deficient/immune-deficient mice (178) that can be "rescued" by MMP-9 proficient splenocytes that induce MMP-9^{+} macrophage infiltration into the tumour microenvironment, resulting in increased vascularization and tumorigenicity (178). These data provide compelling support for the contention that inflammatory cell-derived MMP-9 contributes to tumorigenesis in multiple organ environments. Recently it has also become clear that inflammatory cell-derived MMPs also play a contributing role during metastasis formation (179, 180). Utilizing a mouse model system of experimental lung metastasis, MMP-9 expression in macrophages and endothelial cells of lungs of tumor-bearing hosts positively regulated metastasis formation to the pulmonary site (179). Correlating with this, human cancer patients with metastatic pulmonary disease similarly exhibit significantly elevated MMP-9 levels in diseased lung tissue as compared to those from tumour-free patients or disease-free lungs (179) suggesting that inflammatory cell-derived MMP-9 promotes metastatic tumour formation. What are the mechanisms by which activated stromal cells regulate MMP expression in neoplastic microenvironments and affect cancer development? MMPs are potent mediators with many different functional capacities and their biological activities greatly depend on the microenvironment in which they are deposited. Consequently, MMPs participate in many aspects of neoplastic progression, including proliferation of neoplastic cells, extracellular matrix remodelling, angiogenesis, lymphangiogenesis and metastasis formation.

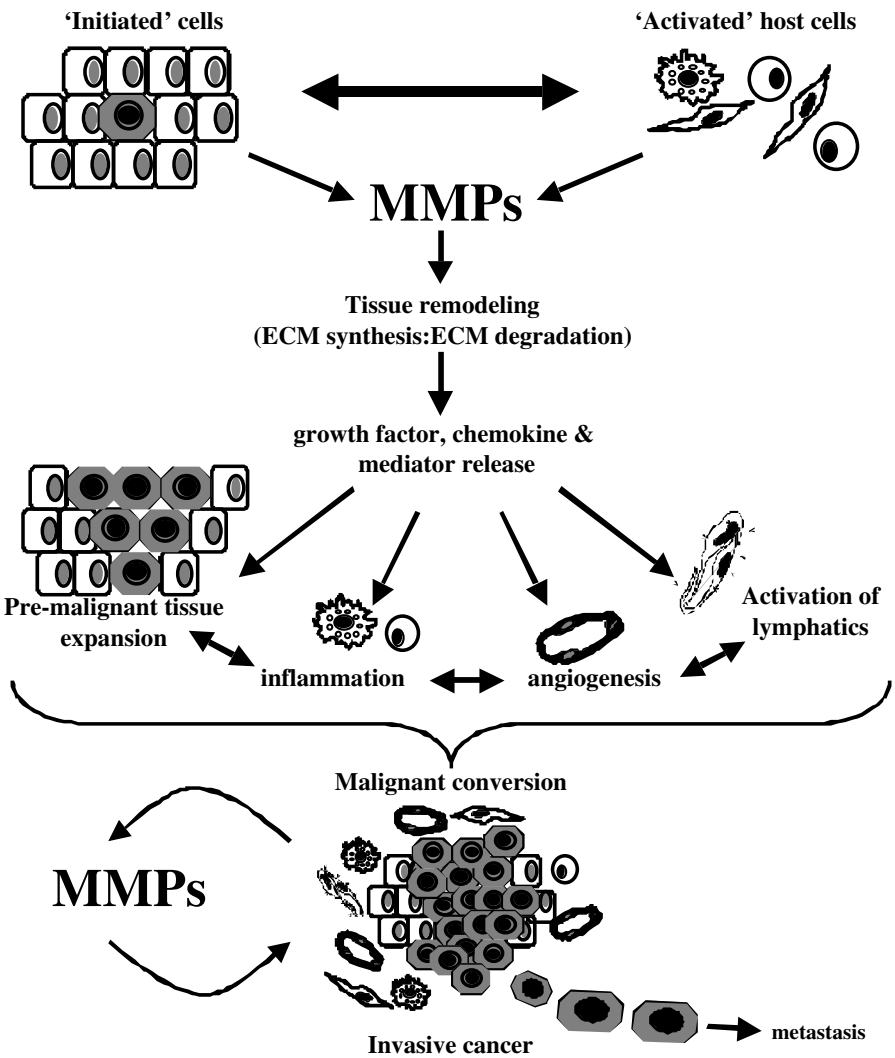

Figure 2. MMPs and tumor-host cell interactions: Cancer development results from the interplay of genetically altered neoplastic cells with activated stromal cells and the dynamic microenvironment in which they live. The presence of genetically altered cells in otherwise healthy tissue activates a "host response", in particular activation of fibroblasts and immune cells. Both genetically altered cells and activated host cells present in early pre-malignant lesions secrete diverse factors, including MMPs. MMPs can initiate remodeling of virtually all ECM components, resulting in release of mediators sequestered in the ECM and activation of latent growth factors. Altered bioavailability of these mediators triggers proliferation of neoplastic cells and angiogenesis. In addition, MMPs, produced by neoplastic and activated host cells, regulate various aspects of tumour development and facilitate many collaborative interactions between diverse cells types present in the neoplastic microenvironment. Known regulatory mechanisms involving MMPs include: stimulating neoplastic cell hyperproliferation, activation of angiogenesis, stimulating inflammatory cell recruitment and function via modulation of chemotactic mediators, as well as inducing tissue remodelling resulting in both the synthesis as well as degradation of matrix components. Following malignant conversion and development of bona fide invasive cancers, MMP activity can further influence the malignant phenotype of emerging tumours as well as the viability of metastatic cells in distant tissue compartments.

4.2 MMPs and neoplastic cell proliferation

The balance between neoplastic cell proliferation and cell death is a critical determinant of tumour outgrowth. Multiple paracrine and autocrine growth factors have been identified that modulate the mitogenic activity and/or survival capacity of various cell types within tumours. Since inhibition of growth factor-induced signalling cascades can block expansion of neoplastic cells in some contexts, and delay or inhibit growth in others, (181-187), there has been great interest in characterizing the mechanisms regulating growth factor bioavailability in neoplastic microenvironments.

It has become clear that ECM remodelling by stromal- and/or neoplastic cell-derived MMPs results in release of a variety of growth factors sequestered in the ECM and in proteolytic shedding and activation of multiple latent ECM and membrane-anchored growth factors (108, 188-190). The increase in bio-available growth factors regulated by MMP-mediated proteolytic cleavage directly impacts proliferative capacity of diverse cell populations, including neoplastic cells (108). The role of MMPs in modulating the proliferative activity of neoplastic cells has been underscored by the observation that neoplastic keratinocytes in MMP-9 deficient/HPV16 transgenic mice exhibit a suppressed proliferative index (20). Likewise, collagenase expression in transgenic mouse skin promotes hyperproliferative changes in the epidermis (191) and transgenic overexpression of TIMP-1 inhibits SV40 T antigen-induced hepatocyte proliferation (192, 193).

Several growth factors are produced as membrane anchored precursors requiring conversion to soluble forms for biological activity (97, 194-196). Great effort has been placed in identification of enzymes responsible for proteolytic conversion of insoluble mitogenic precursors into diffusible active growth factors, as this is an important post-translational event regulating growth location, activity and bioavailability. MMPs play a crucial role in proteolytic release of mitogenic precursors from the cell surface membrane, a process frequently referred to as ‘ectodomain shedding’ (197, 198). For example, EGF family members, including EGF, heparin binding EGF-like growth factor (HB-EGF) and TGFα, are synthesized as latent membrane spanning proteins requiring cleavage and release by MMPs in order to obtain a conformation suitable for binding to their plasma membrane receptors (194-196). Soluble EGF family ligands stimulate many biological responses, in particular proliferation and migration in cells expressing EGF receptors, altered expression of which has been reported in various human cancers. MMP-3 releases HB-EGF from the cell surface whereas an MMP related proteinase ADAM17, releases soluble TGFα (195). HB-EGF and MMP-7 form a complex with CD44, a heparin sulphate proteoglycan found on the surface of normal and neoplastic cells (97, 199). Formation of this complex allows cleavage of HB-EGF by MMP-7, thus generating mature HB-EGF, which in turn enhances cell proliferation and cell survival (97). The importance of CD44 in neoplastic cell proliferation has been underscored by the observation that transgenic mice expressing antisense CD44 cDNA in skin keratinocytes display impaired keratinocyte proliferation and fail to undergo hyperproliferative growth in response to carcinogen exposure (200).

Proteolytic release of membrane-anchored growth factor precursors can be inhibited by TIMPs (84, 196, 201) and by synthetic metalloprotease inhibitors (MPIs) (194, 202). For example, blocking proteolytic shedding of membrane-anchored EGF family member precursors by treatment with MPIs almost completely abolished proliferation of human mammary epithelial cells and colon cancer cell lines (194). Thus, proliferation of neoplastic cells can be manipulated by MMP-mediated regulation of ectodomain shedding suggesting that MPIs might be applied therapeutically to regulate bioavailability of growth factors in proliferating tissues.

Other growth factors are maintained in a latent form by complex formation with soluble or cell-surface bound proteins. For example, activity of insulin-like growth factors IGF-I and IGF-II is controlled by binding to various soluble IGF-binding proteins (IGF-BP) (203-205). Proteolytic cleavage of IGF-BP by several MPs, including MMP-1, -2, -3, -9 and -11, releases IGF that subsequently exerts mitogenic effects (206-211). Expression of IGFs is often upregulated in hyperproliferative tissues, including cancer tissues where they correlate with

poor prognosis (204, 212-215). The importance of MMPs in promoting neoplastic cell proliferation via increasing bioavailability of IGF has been demonstrated in a transgenic mouse model of hepatic carcinogenesis (211). Transgenic overexpression of TIMP-1 in SV40 T antigen-induced hepatocytes inhibited proliferation (211) due to inhibition of MMP-mediated proteolysis of IGF-BP-3 resulting in reduced levels of bioavailable IGF-II (211). Similar to IGF, basic FGF (bFGF), a mitogenic growth factor linked to angiogenesis and fibroblast activation is sequestered in the ECM by specific binding to various proteins (216). Several heparin sulfates, including perlecan, regulate bioavailability of FGF by sequestering latent FGF at cell surfaces and within basement membranes (217). MMP-1 and -3 have been reported to degrade perlecan resulting in FGF release (216). However, MMP activity does not always result in enhancement of proliferation. MMP-2 has been reported to cleave FGF receptor 1, which in turn prevents mitogenic signalling (218). Another protein regulating FGF activity is FGF-BP. In contrast to perlecan, FGF-BP does not limit bioavailability of FGF, but instead mobilizes and activates FGF (219). Whether MMPs also degrade FGF-BP and thus negatively modulate FGF bioavailability remains to be established. Likewise, bioavailability of TGFβ, a multi-potent polypeptide growth factor, is regulated by MMPs (220). The role of TGFβ during tumor progression and development is very complex and depends on the type and progression stage of neoplastic cells (221-224). In general, activated stromal and neoplastic cells in early tumour stages are sensitive to TGFβ-mediated growth inhibition (225, 226), whereas neoplastic cells in later stages often escape TGFβ-mediated growth inhibition (222, 223). TGFβ is produced as a latent protein activated in part by proteolytic mechanisms (220, 227). The TGFβ prodomain, also referred to as β-latency associated peptide (β-LAP), binds non-covalently to mature TGFβ thus forming an inactive latent complex (220). Latent TGFβ-binding proteins link to this complex stabilizing and maintaining TGFβ sequestered within ECM in an inactive state (227-230). TGFβ can be activated by proteolytic degradation of LAP by MMP-9 and MMP-2, resulting in release of active TGFβ (102). Likewise, several TGFβ binding proteins that sequester active TGFβ in ECM, including membrane-anchored proteoglycan betaglycan and the ECM proteoglycan decorin, are cleaved by various MMPs (231-234), where upon release from latent complexes, TGFβ exerts its tumor suppressive and/or promoting functions (222).

In conclusion, the function of stromal cell- and neoplastic cell- derived MMPs is not limited to degradation and remodelling of ECM. An additional function, one that has implications for therapeutic anti-cancer strategies, is the shedding of various potent growth factors from cell surfaces and release of mitogens sequestered by ECM; thus, by regulating bioavailability of growth factors, MMPs deposited in tumor microenvironments can drive neoplastic progression and cancer development.

4.3 MMP regulation of neoplastic cell adhesion, migration and invasion

Tumours are characterized by their phenotype, cell of origin and whether they exhibit either benign or malignant characteristics, with malignancy directly inferring neoplastic cell invasion across basement membranes and ectopic tissue growth. In order for neoplastic cells to invade surrounding tissue, they must exit the primary tumour site, cross tissue boundaries and migrate into ectopic tissue. Based upon their collective ability to degrade structural components of basement membranes and ECM *in vitro*, MMPs have long been viewed as key regulators of neoplastic cell migration and invasion (17). However, examination of MMP functions in *de novo* mouse models of tumour development have challenged these viewpoints and revealed new mechanisms for MMP action that functionally contribute to tumour development.

Substrate targets for MMPs have been extensively studied *in vitro* (reviewed in (17, 111) which has generated a large body of literature describing ECM as well as non-ECM substrates for MMP family members, suggesting a role for MMPs in tissue remodelling and other physiological and pathological processes, including cancer. These studies have revealed tremendous overlap and functional redundancy among MMP family members (Table 3).

Table 3. MMP Substrates. Adapted from (17, 125). *Only few MMP substrates have been verified as in vivo substrates. ADAMTS, A disintegrin and metalloproteinase with thromobospondin type 1 motifs; C1q, complement component 1q; FGFR, fibroblast growth factor receptor; HB-EGF, heparin-binding epidermal growth factor; IGF-BP, insulin-like growth-factor-binding-protein; IL-1β interleukin-1β; IL-2Rα, interleukin-2 receptor α; MMP, matrix metalloproteinase; NC1, non-collagenous 1 region; PA1, plasminogen activator inhibitor; TGF-β transforming growth factor-β; TNF-α, tumour necrosis factor-α; uPA, urokinase-type plasminogen activator.

MMP	ECM Substrates		Non ECM substrates			
	Collagen	**Other ECM components**	**Chemokines and Cytokines**	**Growth Factors**	**MMPs**	**Other**
MMP-1	Type, I, II, III, VII, X (24), XI (59) collagen	Gelatins (24), aggrecan (24), brevican (452) entatctin/nidogen (24), fibronectin (59) laminin (59), tenascin (24), vitronectin (59)	CXCL12 (4), IL-1β (59) proTNF-α (59)	TGFβ (59)	ProMMP-2 (24)	IGFBP-2, -3, link protein (24), α1-antichymotypsin (59), α2-macroglobulin (59), α1-proteinase inhibitor (59), C1q (59), casein (59), myelin basic protein (59), L-selectin (5), fibrin (59) link protein link protein (24), link protein (24)
MMP-2	Type, I (24), III (59), IV (24), V (24), VII (24), X (24) XI (24) collagen	Gelatins (24), aggrecan (24), brevican (452), decorin (59), elastin (24), entactin/nidogen (59), fibronectin (24), fibulins (453), laminin (24), osteonecin (59), tenascin (59), vitronectin (59), ADAMTS-1 (454)	CXCL12 (4), IL-1β(59) TNF-α (59)	Pro-HB-EGF (195)	ProMMP-9 (24), -13 (63)	IGF-BP (24), link protein (59), C1q (59), α1-antichymotypsin (59), α1-proteinase inhibitor (59) FGFR1 (218), substance P (59) plasminogen (59), myelin basic protein (59)
MMP-3	Type III (59), IV (24), V (24), VII (24), IX (24), X (24), X1 (24) collagen	Gelatins (24), aggrecan (452), decorin (59), elastin (59), brevican (59), decorin (59), elastin (59), entactin. nidogen (24), fibronectin (59), laminin (24), osteonectin (59), osteopontin (455), perlecan (216), tenascin (24), vitronectin (24), NC1 fragment of collagen XVIII (289)	CXCL12 (121), pro-TNF-α (59)	Pro-HB-EGF (97)	ProMMP-1 (24), -7 (195), -8 (369), -9 (456), -13 (24)	PAI-1 (457), plasminogen (59), substance P (59), T kininogen(59), α1-antichymotrypsin (24), α2-macroglobulin (24), α1-proteinse inhibitor (24), uPA (458), link protein (24), myelin basic protein (59) C1q (59), casein (59), E-cadherin (24), fibrin (24), fibrinogen (59), L-selectin (459), fibrillin (59)

MMP	ECM Substrates		Non ECM substrates			
	Collagen	**Other ECM components**	**Chemokines and Cytokines**	**Growth Factors**	**MMPs**	**Other**
MMP-7	Type I (59), IV (59) collagen	Gelatins (24), aggrecan (59), brevican (452) decorin (59) elastin (24), entactin/nidogen (24), fibronectin (24), fibulins (24), laminin (24), vitronectin (24), osteonectin (59), tenascin, (24),β4 integrin (246)	Pro-TNF-α (59)		ProMMP-1 (460), -2 (24), -9 (460)	Link protein (24), myelinbasic protein (59), osteopontin (461), α1-proteinase inhibitor (24), casein (59), E-cadherin, (59), FAS ligand (14), fibrinogen (59), plasminogen (59),
MMP-8	Type I (24), II (24), III (24) collagen	Aggrecan (24), brevican (452), ADAMTS-1 (454)		Latent TGF-β (102)		α2-macroglobulin (fibrillin (59), C1q (59), fibrinogen (59), substance P (59)
MMP-9	Type IV (24), V (24), XI (24), XIV (24) collagen	Gelatins (24), aggrecan (24), decorin (59), elastin (24), laminin (59), NC1 fragment of collagen XVIII (289), osteonectin (59), vitronectin (24)	CXCL1 (322), CXCL4 (322), CXCL7-precursor (322), CXCL12 (121), IL-1β (59), IL-1β (59), IL-8/CXCL8 (322), IL-2Rα (123), pro-TNF-α (59)		ProMMP-2 (24)	Link protein (24), myelin basic protein (24), α2-macroglobulin (59), α1-proteinase inhibitor (59), casein (59), C1q (59), endothelin (462), fibrin (59), fibrillin (59), fibrinogen (59), galectin-3 (463), plasminogen (59), substance P (59), IGF-BP3 (r29), fibrillin (59)
MMP-10	Type III (464), IV (464), V (464), collagen	Gelatins (24), aggrecan (59), brevican (452), elastin (24), fibronectin (464)			ProMMP-1 (24), -7 (465), -8 (466), -9 (465)	Link protein (24), casein (59), fibrinogen (59)
MMP-11						IGF-BP (2), α2-macroglobulin (24), α1-proteinase inhibitor (24)

MMP	ECM Substrates		Non ECM substrates			
	Collagen	**Other ECM components**	**Chemokines and Cytokines**	**Growth Factors**	**MMPs**	**Other**
MMP-12	Type I, (2), IV (24) collagen	Gelatins (24), aggrecan (59), elastin (24), fibronectin (24), entactin/ nidogen (24), fibrillin (59), laminin (24), vitronectin (59), NC1 fragment of collagen XVIII (289)	Pro-TNF-α (59)			Myelin basic protein (24), α2-macroglobulin (59), α1-proteinase inhibitor (24), factor X11 (59), fibrinogen (24), IgG (467), plasminogen (24)
MMP-13	Type I (24)II (24), III (24), IV (468), VI (59), IX (468), X (468), XIV (468)	Gelatins (59), aggrecan (59), brevican (452), fibronectin (468), osteonectin (468), tenascin (468)				Fibrillin., α2-macroglobulin (59)
MMP-14	Type I (469), II, (469), III (469) collagen	Gelatins (24), aggrecan (469), entactin/nidogen (469), fibrillin (59), fibronectin (469), perlecan (469), vitronectin (24), tenascin (469),	CXCL12 (59), pro-TNF-α (469)		ProMMP-2 (59), -13 (63)	α2-macroglobulin (1), α1-proteinase inhibitor (24), CD44 (237), factor XII (59), fibrin (59), fibrinogen (59), αv integrin (470) tissue transglutaminase (248)
MMP-15		Aggrecan (471), entactin/nidogen (471), fibronectin (471), perlecan (471), laminin (471), tenascin (471), tissue, transglutaminase (248), ADAMTS-1 (472)			ProMMP-2 (471)	
MMP-16	Type III (59) collagen	Gelatin (473), fibronectin (59)			ProMMP-2 (382)	Casein (473), tissue transglutaminase (248)
MMP-17		Gelatin (474)	TNF -α (471)		ProMMP-2 (474)	Fibrin (372), fibrinogen (372)

MMP	ECM Substrates		Non ECM substrates			
	Collagen	**Other ECM components**	**Chemokines and Cytokines**	**Growth Factors**	**MMPs**	**Other**
MMP-19	Type I, (59), IV (373) collagen	Gelatins (373), aggrecan (475), entactin/nidogen (373), fibronectin (373), laminin (373), tenascin (373), Cartilage oligomeric matrix protein (475)				Casein (59)
MMP-20		Aggrecan (475), cartilage oligomeric matrix protein (475) NC1 fragment of collagen XVIII (289)				Amelogenin (19)
MMP-22		Gelatin (476)				Casein (476)
MMP-24		Gelatin (474), fibronectin (474),			ProMMP-2 (381)	
MMP-25	Type IV (374) collagen	Gelatin (374), fibronectin (477)			ProMMP-2 (375)	Fibrinogen (374), fibrin (374).
MMP-26	Type IV (375) collagen	Gelatin (478), fibronectin (375), vitronectin (406)			ProMMP-9 (375)	α1-proteinase inhibitor (59), casein (478), fibrinogen (406)
MMP-28						Casein (479)
Mcol-A	Type I (480), II (480) collagen					
75-kDa chicken gelatinase	Gelatins (481), fibronectin (481)					

To date however, only a few MMP substrates have been verified as bone fide *in vivo* substrates (17), validation of which in appropriate *in vivo* contexts is necessary to fully understand the multitude of molecular and cellular events regulated by MMPs.

Cell surface expression of cell-cell and cell-ECM adhesion molecules are tightly regulated (235) with expression varying to accommodate changes in pericellular microenvironments and differential regulation of stationary versus migratory growth characteristics. Besides impacting migration and invasive capacities of neoplastic cells by remodelling key ECM molecules, MMPs also act in concert with diverse cell surface molecules implicated in adhesion (236-238). One family of cell surface adhesion molecules differentially affected by MMPs are integrins. These consist of dimeric membrane spanning cell-ECM adhesion molecules containing one α and β subunits (239). Integrins are important mediators of cell migration in part due to the diversity of complexes formed by α and β subunits forming ~ 24 different cell-ECM receptors in humans (240). Integrins engage ECM molecules pericellularly, whereas intracellulary they interact with signalling molecules and cytoskeletal components and regulate cell shape, polarity, differentiation and various aspects of intracellular signal transduction (240). When cells are at rest and tissues are homeostatic, integrin expression reflects cell-ECM interaction favouring structural integrity and polarized cell growth (241). In contrast, when tissues are engaged in either physiological or pathological remodelling, integrin expression and repertoires change in a manner consistent with a cells need to 'move' within the microenvironment (242). While MMPs are known to target components of ECM to facilitate migration, they also are known to associate with various integrin receptors on cell surfaces where pericellular proteolysis is concentrated (111, 189). Several MMPs have been reported to co-localize with integrins at attachment and detachment sites on migrating cells, specifically MMP-2 and MMP-14 co-localize with αvβ3 integrins on migrating epithelial cells (243, 244). Co-localization of MMP-2 with αvβ3 integrin, in combination with the observation that MMP-2 triggers cell migration by cleaving laminin 5, a component of basement membranes, suggests a mechanism by which MMPs promote cell migration and invasion (91). Moreover, it has been reported that type I collagen binding to integrin α2β1 results in increased expression of MMP-1, suggesting that interaction of integrins with ECM ligands regulates MMP expression (245). However, all MMP-integrin interactions are not merely mechanisms favouring membrane co-localization. This fact is highlighted by the observation that MMP-7 cleaves (or sheds) the extracellular domain of β4 integrins on prostatic carcinoma cells resulting in downregulation of β4 integrin-ECM adhesion – a scenario that favours a more migratory phenotype (246). Taken together, these observations articulate the diversity of interactions MMPs are involved in that can either favour a migratory phenotype or differentially regulate cellular response by inducing gene expression of proteins that themselves regulate stationary versus migratory cell growth.

Tissue transglutaminase (tTG) is a ubiquitous cell surface receptor that promotes attachment of fibronectin via its association with β1 and β2 integrins and thereby impacts cell migration (247). Membrane-bound MT-MMPs have been shown to cleave and inactivate tTG resulting in decreased adhesion and migration of cells on fibronectin *in vitro* suggesting that tumour cells can adjust their adhesion and locomotion dependening upon matrix substrates (248).

The transmembrane cell adhesion molecule E-cadherin regulates homotypic interactions between epithelial cells via pericellular ectodomain engagement on opposing cells and intracellular engagement with catenins and components of cytoskeleton (249). It is thought that homotypic E-cadherin-mediated interactions are significant for epithelial cell migration based on the observation that E-cadherin expression is downregulated or lost in many carcinomas (249-253), suggesting that E-cadherin acts, in part, as a tumour suppressor (254). Based on these observations, Christofori and colleagues tested this hypothesis using a mouse model of pancreatic islet cell carcinogenesis, e.g., Rip1-Tag2 mice (254-256). To test whether loss of E-cadherin-mediated cell adhesion is a cause or a consequence of tumour cell migration, either full length E-cadherin or a dominant-negative E-

cadherin mutant was overexpressed in Rip1-Tag2 pancreatic β cells. Expression of E-cadherin arrested tumour development at an early stage, while expression of the dominant negative E-cadherin mutant induced early invasion and metastasis (254-256). These results suggest that loss of E-cadherin mediated cell-cell adhesion is a rate-limiting step during carcinogenic progression. Ectodomain shedding of E-cadherin has been demonstrated downstream of MMP-3 and -7 *in vitro*, cleavage of which parallels onset of migration in some cell types (236, 257). In human carcinomas, elevated MMP-3 expression correlates with late-stage tumour development and overall prognosis (141, 258), suggesting a possible cell-cell regulatory mechanism important for invasive growth capacity. The significance of MMP-3 in regulating cell-cell and cell-ECM interactions is underscored by the observation that transgenic mice expressing an autoactivated form of MMP-3 in mammary epithelial cells develop reactive stroma and mammary tumours independent of carcinogenic initiation (259-261), suggesting that active MMP-3 exhibits strong tumor promoting effects. The overexpression of MMP-7 in the mouse mammary gland promotes mammary hyperplasia and accelerates the onset of mammary tumours (262), which is thought to be mediated by the selection for apoptosis resistant cells during this chronic exposure to MMP-7 (263) as well as by the shedding of FasL by MMP-7 (123). In contrast, deletion of MMP-7 in the *Min* mouse model of colorectal cancer resulted in suppression of intestinal tumourigenesis (18). MMP-7 also mediates E-cadherin shedding in injured lung epithelium (264) suggesting that MMP-7 regulates cell migration and invasion via differential regulation of E-cadherin.

The hyaluronan receptor CD44 is a broadly distributed transmembrane glycoprotein expressed by many cell types and is involved in a variety of physiological cell functions such as adhesion, migration, invasion and survival (237, 265-267). CD44 mediates cell-cell and cell-matrix interactions mainly via its affinity for hyaluronan, a glycosaminoglycan constituent of the ECM, but also to a lesser extend via its affinity for other ligands such as osteopontin (268). Histochemical evaluations of human carcinomas suggest that expression levels of CD44 positively correlate with poor prognosis implying a role for CD44 in tumour progression (269). Stamenkovic and colleagues have shown that CD44 serves as a docking molecule for MMP-9, retaining MMP-9 proteolytic activity at the cell surface (98). In addition, CD44 was reported to complex MMP-7 as well as MMP-14 at the cell surface of neoplastic cells and localize them to lamellipodia where they might be involved in migratory processes (97, 270). Taken together, these data suggest that CD44 mediated tumor cell migration and invasion is mediated by the targeted retention of MMPs at the tumor cell surface, thus directing ECM degradation to facilitate tumour cell migration through ECM.

Taken together, there is an overwhelming body of experimental evidence supporting the concept that MMPs play a critical role in the invasion and metastatic potential of neoplastic cells. However, transgenic mouse models of *de novo* tumour formation harbouring homozygous null mutations in individual MMP genes, while generally demonstrating a decreased incidence of malignant tumours, have not revealed a significant role for any one MMP in regulating cellular invasion *in vivo* (12, 20, 262). Why this disparity? One possible explanation is that although the two- and three-dimensional *in vitro* culture conditions mimic microenvironmental conditions *in vivo*, they are not an exact recapitulation and do not include the alterations seen *in vivo*; thus, *in vitro* experiments can only provide clues about MMP-mediated events such as invasion and metastasis of tumour cells.

4.4 MMPs and Tumour-associated Angiogenesis

When any tissue expands or a primary tumour develops, in order to grow beyond ~2-4 mm^3, influx of oxygen and nutrition and efflux of waste products must be ensured (272). In order to meet these metabolic needs of a rapidly growing tumour mass, development of a new blood vasculature is required and accomplished by activation of pre-existing vascular beds, e.g., angiogenesis (273-277). During angiogenesis, a well-orchestrated series of events encompassing initiation of endothelial cell proliferation and directional migration of endothelial

cells through remodelled basement membrane and perivascular stroma towards angiogenic stimuli (developing neoplasms) occurs (8, 278, 279). Once endothelial cells are enticed into a proliferative and migratory state, recruitment of perivascular support cells enables stabilization of nascent vessels, functional lumen formation and appropriate blood flow; however, while all these regulatory programs (cellular and molecular) are common to physiologic angiogenesis, tumour-associated angiogenesis possess a distinctly tortuous and chaotic organization that is inherently leaky (reviewed in (37, 280-283). Activation of pro-angiogenic molecular and cellular programs in a neoplastic context are regulated at many levels and controlled by a diverse assortment of positive and negative-acting soluble and insoluble mediators whose balanced equilibrium is kept tightly in check under homeostatic conditions; however, under conditions of tissue stress, such as occurs during premalignancy, their balance is rapidly upset favouring the pro-angiogenic phenotype (4, 8, 278, 284).

MMPs have been functionally implicated as mediators of tumour angiogenesis at several discrete steps, based upon bioactivity of their effector substrates that regulate angiogenesis by both positive and negative mechanisms. For example, using a modified chick chorioallantoic angiogenesis assay (CAM) that quantifies new blood vessel development into fibrillar collagen implants, it was revealed that helical domain cleavage of fibrillar type I collagen is required for growth factor stimulated angiogenesis (285). New vessel growth was significantly reduced by TIMP-1, a synthetic MPI BB3103 or when collagen implants were composed of collagenase-resistant type I collagen (286) suggesting that MMP mediated cleavage of type I collagen is a rate limiting step in growth factor-stimulated angiogenesis *in vivo*. In addition to cleavage products of type I collagen, a cleavage product of type IV collagen has been shown to promote angiogenesis *in vivo* (287). Proteolytic cleavage of type IV collagen by MMP-2 results in exposure of a cryptic epitope, designated HUIV26, within the triple helical domain that is required for angiogenesis and tumour growth (287). Inhibition of interactions between endothelial cells and the HUIV26 site by a monoclonal antibody directed to this site (Mab HUVI 26) decreased basic fibroblast growth factor (bFGF) and/or VEGF-induced angiogenesis by 70% compared to controls in both a rat corneal micropocket assay (288) and chick CAM angiogenic assay (287). Furthermore, Mab HUVI26 inhibited tumour growth in nude mice injected with M21 human melanoma cells and chick embryos injected with HT1080 human fibrosarcoma cells by 80% - 90% when compared to controls (287). Interestingly, the exposure of the HUVI26 epitope was associated with a loss of endothelial cell $\alpha1\beta1$ integrin binding and a gain in $\alpha v\beta3$ binding suggesting that this shift in endothelial cell-integrin binding initiates a signaling cascade required for angiogenesis *in vivo* (287).

In contrast to the angiogenic promoting activity of ECM cleavage products, the C-terminal globular non-collagenous (NC1) domains of the basement membrane collagens types IV, XV and XVIII have been shown to be potent inhibitors of angiogenesis. One of the first angiogenic inhibitors discovered was endostatin, a 20-kDa NC1 fragment from type XVIII collagen (112). Endostatin can be produced by cleavage of collagen type XVIII by MMP-3, -7, -9, -12, -13 and –20 (289) and acts by reducing endothelial cell proliferation (112, 290). In addition, restin, a 22-kDa NC1 fragment from type XV collagen inhibits migration, but not proliferation, of endothelial cells *in vitro* and suppresses tumour induced angiogenesis in a renal xenograft carcinoma model (116). All three chains of type IV collagen ($\alpha1$, $\alpha2$ and $\alpha3$) are potent inhibitors of angiogenesis and tumour growth (110, 113, 114, 291). For instance, the 24-kDa NC1 fragment of the $\alpha1$ chain of type IV collagen, termed arrestin, inhibits the growth of human xenograft tumours in nude mice by significantly inhibiting growth factor mediated angiogenesis (110). Furthermore, its anti-angiogenic activity is mediated by binding to endothelial $\alpha1\beta1$ integrins (110). Likewise, canstatin, the 24-kDa NC1 fragment of the $\alpha2$ chain of type IV collagen, suppressed growth of human xenograft tumours in nude mice by inhibiting angiogenesis (113). *In vitro* studies indicate that canstatin specifically inhibits proliferation, migration and tube formation of endothelial cells (113). Lastly, the 24-kDa NC1 fragment of the $\alpha3$

chain of type IV collagen, termed tumstatin, acts as an angiogenesis inhibitor, inhibiting both endothelial cell proliferation and blood vessel formation (114, 115, 291, 292) Studies using transgenic mouse models indicate that tumstatin is generated by MMP-9 and suppresses angiogenesis via αvβ3 integrin interactions (293). Other MMP substrates identified as possessing anti-angiogenic activities include angiostatin, a cleavage product of plasminogen, that is a potent inhibitor of endothelial cell proliferation (118, 294). Pozzi et al. demonstrated that treatment of mice with doxycycline, which preferentially inhibits MMP-9 activity (295) results in reduced MMP-9 plasma levels and consequently in reduced angiostatin generation, that in turn results in decreased angiogenesis (296). Taken together these studies indicate that MMP-generated cleavage products of ECM, basement membrane proteins and other soluble molecules act as suppressors or activators of pathological angiogenesis in tissue-dependent and stage-dependent manners and implicate MMPs as important mediators of tumour-associated angiogenesis by pro-tumour and anti-tumour mechanisms.

4.5 MMPs and metastasis

Metastases arise upon the spread of malignant cells from primary tumour sites to distant organs and are commonly found in the first capillary bed encountered by metastasizing malignant cells (10, 297, 298). Tumour cells spread via three routes, e.g., hematogenous spread, dissemination via lymphatic vessels and direct migration along facial planes (10, 299-305). To spread via a hematogenous route, malignant cells must leave the primary tumour, intravasate into blood vasculature, survive and extravasate at a distal site where once present, reinitiate proliferation, induce local angiogenesis, resist local cell death programs and grow to form a secondary tumour – a multi-step process where tissue remodelling is a prerequisite and thus implicating MMPs.

MMPs were first implicated in hematogenous spread of tumour metastasis based on clinical observations correlating increased MMP expression in primary tumours with metastasis at distant sites (17, 127). For example, MMP-1 expression in primary cervical carcinomas is associated with lymph node (306) and peritoneal gastric metastases (307), while increased expression of MMP-7 in gastric carcinomas correlates with liver and lymph node metastases (308). It has also been observed that expression levels of MMP-2 and -9 are especially high in metastatic lung carcinomas and melanomas (309). In the case of MMP-2, high serum levels were reported to correlate with the presence of metastases in lung cancer patients (310). To address the significance of these clinical correlates, several groups variably altered MMP expression/activity in experimental immune-deficient models of metastasis (311-317). While results from these studies were compelling, and in part fuelled by use of MPIs in human clinical trials (128, 318-321), to date experimental evidence definitively demonstrating that MMPs regulate *de novo* metastasis formation *in vivo* is minimal. One study has however provided a functional role for MMP-9 as a regulator of metastatic growth (179). In this study, 3LL-LLC cells spontaneously metastasize to lung in a VEGF receptor 1 (VEGFR1)-dependent manner. Increased MMP-9 expression in lungs of tumour-bearing animals was demonstrated to be essential for distal tumour formation, suggesting that MMP-9 was not utilized for travel to the secondary site, but instead was essential for establishing vascular support and/or tissue remodelling in the metastatic microenvironment (179, 180). Taken together, these studies suggest that MMPs are involved in metastasis formation; however, it is not clear, which MMPs promote or prevent metastasis development and what the underlying mechanisms they regulate are.

Chemokines have also been identified as important protein substrates of MMPs *in vivo* and as a consequence variably regulate infiltration and migration of leukocytes into or out of tissue compartments (13, 322) and by similar mechanisms, variably regulate neoplastic cell movements. For example, MMP-1, -3, -9, –13 and –14 target and inactivate CXCL12, the ligand for CXCR4 on leukocytes (121). The observation that expression of CXCR4 on breast carcinoma cells and its binding to CXCL12 is implicated in metastasis development (323), in combination with CXCL12 being reported to be a MMP target, suggest that MMPs might be

involved in regulating CXCR4/CXCL12 mediated metastasis development. A study by van den Steen *et al.* suggested that MMP-9-targetted CXCL8 increased chemokine activity tenfold (324). Since signalling via the two CXCL8 receptors CXCR1 and CXCR2 is required for the invasive potential of melanoma cells *in vitro* (325, 326), MMP-9 might be involved in metastasis of melanoma by regulating the binding activity of CXCL8 to its receptors. These studies suggest that MMPs directly impact chemokines by cleavage resulting in either inactivation or activation of the respective chemokine. These modifications change the binding capacities of chemokines to their receptors and thus impact metastasis of tumour cells.

5. CLINICAL IMPLICATIONS

The studies discussed above indicate that complex interactions between neoplastic cells and their surrounding microenvironment regulate MMP expression, localization, activation and biological effect. Furthermore, these studies indicate that MMPs play diverse roles in tissue remodelling essential for tumour growth and maintenance. Based on compelling data supporting a pro-tumour role for MMPs in cancer development, in combination with data suggesting anti-cancer roles for TIMPs (192, 211, 327-339), synthetic MPIs were developed (340) and evaluated in both *in vitro* and *in vivo* cancer models (318-321, 341-345). To date, over 150 US patents have been issued for MPIs (16, 346) that can be categorized into five groups, e.g., collagen peptidomimetics, collagen non-peptidomimetics, tetracycline derivatives, small peptides and unconventional MPIs (16, 17, 344). Peptidomimetic MPIs were designed to mimic cleavage sites of MMP substrates where the zinc binding group is positioned at the cleavage site, resulting in blockage of the active site zinc upon binding to the target MMP and are exemplified by Batimastat and Marimastat (16, 17, 344). Collagen non-peptidomimetics, also known as deep pocket MPIs, were designed based on the crystal structure of MMP catalytic sites (16, 17, 344) and includes Prinomastat/AG3340 and tanomastat/BAY 12-9566 (344) among others. Tetracycline derivatives, such as Metastat, act by inhibiting both the synthesis and activity of MMPs (342). Finally, the small peptide class was generated by screening phage display peptide libraries where peptides demonstrating high specificity for individual MMPs were amplified (347). For example, a class of cyclin peptides containing a HWGF motif specifically inhibits MMP-2 and -9 activity and inhibits tumour growth in mouse models (347). Finally, unconventional MPIs include an extract from shark cartilage (Neovastat/AE-941) and a component of green tea (348, 349).

Initial efficacy of a broad spectrum MPI (SC-44463) was first reported in an experimental mouse model of metastasis formation (350). Many studies followed testing individual MPIs in more complex and clinically relevant models (16, 321, 351-355). For example, treatment of immune-deficient mice with batimastat, a broad-spectrum hydroxamate inhibitor, following resection of human breast cancer xenografts reduced metastasis and inhibited local re-growth of tumours (356). In addition, in the *Min* mouse model of intestinal tumorigenesis, batimastat reduced tumour multiplicity by 48% when administered between 6 and 14 weeks of age (354) and A-177430, a broadspectrum MPI, reduced tumour multiplicity by 69% when administered between 5 and 12 weeks of age (357). Furthermore, MMI-166, a selective MPI for MMP-2, -3 and -9, significantly decreased the number of metastases of TK-4 human colon cancer cells injected in nude mice (358). Similar results were observed when CT1746, a selective inhibitor for MMP-2, -3, -7 and -9 was administered to nude mice injected with the human colon cancer cell line CO-3 (359). Taken together, MPI studies in tumour xenograft mouse models strongly supported MPIs as promising anticancer therapeutics. More compelling and biologically relevant studies with MPIs involved efficacy testing in mouse models of *de novo* tumour formation (354, 355). MPI treatment in these models indicated that efficacy was best achieved if the MPI was administered during premalignant progression and prior to overt tumour development (354, 355) suggesting that tumor stage is a critical determinant of MPI efficacy.

In spite of encouraging results with MPI in numerous mouse models of cancer development,

human clinical trials with MPIs were discouraging (128, 318-321, 346, 360, 361). While some MPIs elicited adverse patient effects in early trials, others entered Phase III clinical trials either alone or in combination with conventional chemotherapy (gemcitabine) as compared to chemotherapy alone where no significant survival advantage was found (128, 321, 360, 362). In advanced gastric cancer, advanced glioblastoma, small lung cell carcinoma (SCLC), non-small cell carcinoma (NSCLC) and ovarian cancer Phase III trials, no significant increase in survival was observed in Marimastat treated cohorts when compared to patients receiving placebo (128, 362). However, a significant improvement in survival was observed in patients that either received chemotherapy prior to entering trial or did not have metastases at time of diagnosis when compared to placebo treated patients (128, 362) implying that Marimastat, if administered at earlier stages of cancer development represented an efficacious therapy (128, 321). In trials evaluating Prinomastat in advanced SCLC, no significant survival benefits were observed in patients treated with conventional chemotherapy (either cisplatin + gemcitabine or cisplatin + paclitaxel) plus Prinomastat and similar results were observed in patients with metastatic hormone refractory prostate cancer treated with chemotherapy (mitoxantrone + prednisone) plus Prinomastat (128). The studies involving Tanomastat were even more disappointing and were terminated prematurely when patients demonstrated significantly poorer survival rates than patients receiving placebo (363).

Given our current knowledge of MMP biology and retrospective analysis of their mechanisms of action in developing tumours, the failure of MPIs in human clinical trials was not surprising. While human clinical trials were conducted according to currently accepted criteria, they failed to consider many facets of MMP biology and largely did not consider MMP expression differences between tumour types. Trials were conducted in patients harbouring large tumour burdens where efficacy would only have been possible if tumour regression or enhanced survival was achieved - unlikely endpoints for non-cytotoxic agents and improbable given results obtained with *de novo* models of tumour development where best efficacy was achieved when MPIs were administered during early tumour development. Failure of MPIs in clinical trials was in part attributed to limited understanding and appreciation for the diversity of cellular and mechanisms regulated by MMPs *in vivo* as exemplified by the fact that spatial and temporal expression and activity differences between MMPs during neoplastic progression of diverse cancer types was not taken into consideration. Use of broad spectrum MPIs that, amongst other MMPs, inhibit MMP-8 activity, results in a significant increase rather than a decrease in tumour incidence (124). Given the observation that MMP-8 homozygous null mice exhibit an increased tumour incidence following carcinogen exposure (124) suggest that a sophisticated understanding of MMP biology is crucial for effective targeting of MMPs during carcinogenesis.

6. CONCLUDING REMARKS

MMPs have been found to promote or inhibit neoplastic progression by a multitude of mechanisms that not only include remodelling of ECM components, but also by regulating bioavailability and/or activity of cell adhesion molecules, growth factors, other proteases, chemokines, cytokines and proteins involved in the clotting cascade. A more thorough understanding of the underlying mechanisms of MMP mediated molecular and cellular pathways important during carcinogenesis, as well as elucidating what MMPs are active at which tumour stage and type, will be crucial to insure that future MPI anti-cancer therapies will be effective.

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