Matrix metalloproteinases in cancer

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Abstract

The extracellular matrix (ECM) holds cells together and maintains the three-dimensional structure of the body. It also plays critical roles in cell growth, differentiation, survival and motility. For a tumour cell to metastasize from the primary tumour to other organs, it must locally degrade ECM components that are the physical barriers for cell migration. The key enzymes responsible for ECM breakdown are matrix metalloproteinases (MMPs). To date, 23 MMP genes have been identified in humans and many are implicated in cancer. ECM degradation by MMPs not only enhances tumour invasion, but also affects tumour cell behaviour and leads to cancer progression. This review highlights recent developments with regard to the cellular and molecular mechanisms of MMPs that influence tumour cell growth, invasion and metastasis.

Introduction

Multicellular organisms consist of cells and a complex network of extracellular macromolecules such as collagens, proteoglycans, fibronectin, lamins and many other glycoproteins. This network, referred to as the extracellular matrix (ECM), holds cells together in an organized assembly, guides cell migration and creates correct cellular environments. The ECM also acts as a reservoir of growth factors and provides signals to the cell through ECM receptors on the

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cell surface [1]. The ECM thus plays essential roles in many biological processes, e.g. embryonic development, morphogenesis, tissue resorption and repair, cell differentiation, migration, growth and apoptosis. Degradation of the ECM modifies not only the structure of tissue but also cellular function and behaviour. The activities of ECM-degrading proteinases must therefore be precisely regulated. Although many proteinases are implicated in ECM degradation, a group of metalloproteinases called matrix metalloproteinases (MMPs), or matrixins, is considered to play a major role. ECM turnover associated with uncontrolled matrixin activities is involved in diseases such as arthritis, atherosclerosis, fibrosis and cancer. The involvement of MMPs in cancer metastasis has attracted particular attention, since it raises the possibility of developing MMP inhibitors as a new generation of cancer treatment. In addition to the involvement in metastasis, recent studies indicate that MMPs are also involved in vascularization and initial tumour development. In this review we discuss the current understanding of the role of MMPs in cancer metastasis and tumour progression.

What are the MMPs?

MMPs are structurally related zinc metalloproteinases (proteinases that contain a zinc atom at the catalytic site that is essential for hydrolysis of a peptide bond; see Chapter 1). They are secreted from the cell (soluble MMPs) or bound to the cell surface (membrane-type MMPs; TMT-MMPs) and degrade ECM and other proteins (Table 1) [2,3]. At present, 23 mammalian MMPs have been identified and they are classified according to their substrate specificity and structural similarity. All MMPs share common domain structures including a signal sequence, a propeptide, a catalytic domain, and a hemopexin-like (Hpx) domain (Figure 1). Propeptides contain a unique sequence signature called the ‘cysteine switch’ with a PRGPXD motif, whose cysteine residue (underlined) interacts with the catalytic zinc in the catalytic domain as a fourth ligand, thereby keeping the precursor zymogen (the inactive precursor form of an enzyme) proMMP inactive. Catalytic domains have a zinc-binding motif HEXGXGXXH, in which the three histidine residues are ligands of the catalytic zinc atom. The two gelatinases (MMP-2 and MMP-9) have three additional repeats of a fibronectin type II-like domain inserted in the catalytic domain, which enables them to bind to collagen. The Hpx domain often plays an important role in protein–protein interactions and in determining enzyme specificities. For collagenases to recognize and cleave triple-helical collagens, the Hpx domain is an absolute requirement. Two matrilysins (MMP-7 and MMP-26) lack the Hpx domain, and MMP-23 has a unique cysteine array and Ig-like domain instead of the Hpx domain.

MT-MMPs are further sub-divided into a transmembrane type and a glycosylphosphatidylinositol (GPI)-anchored type. Transmembrane type MT-MMPs
Table 1. Substrates of mammalian MMPs

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>MMP</th>
<th>Substrates</th>
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<tbody>
<tr>
<td><strong>Soluble types</strong></td>
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<tr>
<td><strong>Collagenases</strong></td>
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<tr>
<td>Interstitial collagenase (MMP-1)</td>
<td>MMP-1</td>
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<tr>
<td>Neutrophil collagenase (MMP-8)</td>
<td>MMP-8</td>
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</tr>
<tr>
<td>Collagenase 3 (MMP-13)</td>
<td>MMP-13</td>
<td>Collagens I, II, III, IV, IX, X, and XIV, gelatin, collagen telopeptides, Clq, fibronectin, SPARC, aggrecan, casein, α2M</td>
</tr>
<tr>
<td><strong>Gelatinases</strong></td>
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<tr>
<td>Gelatinase A (MMP-2)</td>
<td>MMP-2</td>
<td>Collagens I, II, III, IV, V, VII, and X, gelatin, fibronectin, laminin, aggrecan, link protein, elastin, vitronectin, tenascin, SPARC, decorin, myelin basic protein, α1PI, α1-ACT, IL-1β, IGFBP-3, substance P, α2M, proTNFα, MCP-3</td>
</tr>
<tr>
<td>Gelatinase B (MMP-9)</td>
<td>MMP-9</td>
<td>Collagens IV, V, XI, XIV, elastin, aggrecan, link protein, decorin, laminin, entactin, SPARC, myelin basic protein, α1PI, IL-1β, substance P, casein, α2M, proTNFα</td>
</tr>
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</table>

*Two identical genes are found in a head-to-head arrangement in chromosome 1. α1PI, α1-proteinase inhibitor; α2M, α2-macroglobulin; α1-ACT, α1-antichymotrypsin; TNFα, tumour necrosis factor α; IGFBP-3, insulin-like growth factor binding molecule 3; MCP-3, monocyte chemoattractant protein 3; SPARC, secreted protein acidic and rich in cysteine (osteonectin, BM40); COMP, cartilage oligomeric matrix protein; IL-1β, interleukin 1β; HSPG, heparan sulphate proteoglycan; DSPG, dermatan sulphate proteoglycan; Clq, complement protein 1q.
<table>
<thead>
<tr>
<th>Enzyme</th>
<th>MMP</th>
<th>Substrates</th>
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<tr>
<td><strong>Stromelysins</strong></td>
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<tr>
<td>Stromelysin 1</td>
<td>MMP-3</td>
<td>Collagens III, IV, V, IX, X, and XI, telopeptides (collagen I and II), gelatin, aggrecan, link protein, elastin, fibronectin, vitronectin, laminin, entactin, tenascin, SPARC, decorin, myelin basic protein, $\alpha_1$-PI, $\alpha_1$-ACT, IL-1$\beta$, IGFBP-3, substance P, T kininogen, casein, proMMP-1, proMMP-3, proMMP-8, proMMP-9, $\alpha_2$M</td>
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<td>Collagen III, IV, and V, gelatin, fibronectin, elastin, aggrecan, link protein, casein, proMMP-1, proMMP-7, proMMP-8, proMMP-9, $\alpha_2$M</td>
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<td>Matrilysin 1</td>
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<tr>
<td>Stromelysin 3</td>
<td>MMP-11</td>
<td>$\alpha_1$-PI, $\alpha_2$M, (for mouse enzyme: collagen IV, gelatin, fibronectin, laminin, aggrecan)</td>
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<td>Metalloelastase</td>
<td>MMP-12</td>
<td>Elastin, collagen IV, gelatin, fibronectin, vitronectin, laminin, entactin, aggrecan, myelin basic protein, $\alpha_2$M, $\alpha_1$-PI, proTNF$\alpha$</td>
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<tr>
<td>No name</td>
<td>MMP-19</td>
<td>Collagen type IV, laminin, nidogen, large tenascin-C isoform, fibronectin, gelatin, aggrecan, COMP</td>
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<tr>
<td>Enamelysin</td>
<td>MMP-20</td>
<td>Amerogenin, COMP</td>
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<tr>
<td>CA-MMP</td>
<td>MMP-23*</td>
<td>Gelatin</td>
</tr>
<tr>
<td>No name</td>
<td>MMP-27</td>
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<tr>
<td>Epilysin</td>
<td>MMP-28</td>
<td>Casein</td>
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**Membrane types**

**Transmembrane**

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<tr>
<th>MT1-MMP</th>
<th>MMP-14</th>
<th>ProMMP-2, proMMP-13, collagens I, II, and III, gelatin, fibronectin, vitronectin, laminins I and 5, entactin, aggrecan, fibrin, α2M, α1PI, decorin, proTNFα, CD44H</th>
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</thead>
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<td>MMP-15</td>
<td>ProMMP-2, laminin, fibronectin, tenascin, entactin, aggrecan, perlecan, proTNFα</td>
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<td>MT3-MMP</td>
<td>MMP-16</td>
<td>ProMMP-2, collagen III, fibronectin</td>
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<tr>
<td>MT5-MMP</td>
<td>MMP-24</td>
<td>ProMMP-2, HSPG, DSPG, gelatin</td>
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**GPI-anchored**

<table>
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<tr>
<th>MT4-MMP</th>
<th>MMP-17</th>
<th>Fibrinogen, fibrin, proTNFα</th>
</tr>
</thead>
<tbody>
<tr>
<td>MT6-MMP</td>
<td>MMP-25</td>
<td>Collagen IV, gelatin, fibrinogen, X-linked fibrin, fibronectin</td>
</tr>
</tbody>
</table>
have a transmembrane domain and a short cytoplasmic tail at the C-terminus.
GPI-anchored type MT-MMPs have a stretch of hydrophobic GPI-anchoring
signal sequence at the C-terminus [4].

Most of the soluble MMPs are activated extracellularly by proteinases.
Exceptions, however, are MMP-11, MMP-23 and MMP-28, which are thought
to be activated intracellularly and secreted in an active form. These MMPs have
the basic amino acid motif [RX(R/K)R] at the end of the propeptide, facilitating
recognition by proprotein convertases, such as furin, in the Golgi apparatus (see
Chapter 7). MMP-23 has a type II transmembrane domain in the N-terminal
propeptide, so it becomes a soluble enzyme upon activation. MT-MMPs also
harbour the RX(R/K)R motif at the end of propeptide, so that they are also
likely to be processed by a proprotein convertase and appear on the cell surface
as the active form.

Table 1 lists the protein substrates degraded by MMPs that have been charac-
terized mostly *in vitro*. Some MMPs, such as MMP-11 and MT4-MMP (MMP-
17), have only a weak proteolytic activity against ECM proteins. The activities of
the more recently discovered MMP-27 and MMP-28 have not been well charac-

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**Figure 1. Domain structures of MMPs**

Schematic representations of the domain structures of MMPs are shown. FN type II, fibronectin
type II-like domain; PC, pro-hormone convertase; Cys array, cysteine array domain; TM/CP, transmembrane and cytoplasmic domains.
terized. Recent studies have indicated that the functions of MMPs are not simply
to destroy the ECM, but to expose cryptic functions of ECM molecules through
proteolysis, e.g. specific cleavage of γ2 chain of laminin 5 by MMP-2 or MT1-
MMP stimulates epithelial cell migration (see below). MMPs can also process
soluble non-ECM proteins that exhibit biological activities, e.g. inactivation of
interleukin 1β, monocyte chemoattractant protein 3 and insulin-like growth
factor binding proteins, and the activation of tumour necrosis factor α.

The activities of MMPs are regulated by endogenous inhibitors, plasma
inhibitor α2-macroglobulin and tissue inhibitors of metalloproteinases
(TIMPs) [5]. α2-Macroglobulin inhibits most endopeptidases (proteolytic
enzymes that hydrolyse the internal peptide bond of a polypeptide chain; see
Chapter 1, Figure 3) and it is also an effective inhibitor of MMPs. TIMPs are
the main inhibitors in tissues. Four TIMPs (TIMP-1, -2, -3 and -4) have been
identified in mammals. They are 21–29 kDa proteins with six conserved disul-
phide bonds and are composed of N-terminal and the C-terminal domains
(Figure 2). The MMP inhibitory site is located in the N-terminal domain, with
residues 1–4 and 68–70 being the critical regions. Cys1 and Cys70 are linked by
a disulphide bond, and form a wedge-like ridge that slots into the active site
cleft of MMPs. The catalytic zinc is bound by the α-amino group and the car-
bonyl oxygen of the N-terminal cysteine (Figure 2). TIMPs are specific
inhibitors of MMPs and they do not inhibit other metalloproteinases. The
exception is TIMP-3 which inhibits some members of the ADAM (a disinte-
grin and metalloproteinase) family, e.g. ADAM-10, -12, -17, and ADAMTS-4
and -5 (ADAM with thrombospondin motifs) (see Chapter 11).

Many synthetic MMP inhibitors have been generated in the hope that they
can be used for treatments of MMP-related diseases, including cancer. They
bind to the active site of the enzyme like a substrate and inhibit it by chelating
the catalytic zinc atom with a moiety such as a hydroxamic acid, a thiol, a car-
boxyl, or a phosphorous group.

**MMPs and tumour cell invasion**

Metastasis is the spread of cancer cells from the primary tumour to distant sites in
the body. It is the leading cause of death in cancer patients. For a tumour cell to
metastasize it must accomplish the following four events: (i) detachment from the
primary tumour and subsequent invasion into the connective tissue stroma; (ii)
entrance to the blood vessel or lymphatic system (intravasation) to traverse to
distant sites in the body; (iii) exudation from the circulation (extavasation); and
(iv) formation of metastatic colonies (Figure 3). For migratory cells to achieve
these tasks, ECM components are major physical barriers. Liotta et al. [6] have
proposed a three-step theory to explain how calls can overcome this barrier
(Figure 4). First, the tumour cells attach to the matrix macromolecules of the
basement membrane or stroma via specific cell-surface receptors. This is followed
by local degradation of the ECM. At this point, the anchored tumour cell needs
to utilize proteolytic enzymes, which may arise from the tumour cell itself or come from the surrounding stroma. Finally, the cell migrates towards the degraded ECM, which dictates the directionality of cell locomotion. Continued invasion of tumour cells into the tissue is achieved by cyclic repetition of these three steps. It is now widely accepted that MMPs play the major role in breaking down the ECM and creating a path for cancer cells. There have been numerous reports showing a correlation between increased expression of various MMPs and tumour progression in a range of cancer cells as well as in surrounding stromal cells [7]. These include MMP-1 (collagenase 1), MMP-2 (gelatinase A), MMP-3 (stromelysin 1), MMP-7 (matrilysin 1), MMP-9 (gelatinase B), MMP-10 (stromelysin 2), MMP-11 (stromelysin 3), MMP-13 (collagenase 3), and MT1-MMP (MMP-14). The involvement of MMPs in cell invasion is also supported by

Figure 2. MMP-3–TIMP-1 complex
Ribbon representation of the structure of MMP-3 catalytic domain–TIMP-1 complex (Protein Data Bank entry 1UEA) [23] where MMP-3 is shown in blue and TIMP-1 in orange. The catalytic domain of MMP-3 consists of three α-helices and five β-strands (sky blue), one catalytic and one structural zinc ions (pink) and three calcium ions (orange). TIMP-1 consists of N-terminal (contains α-helix 1, β-sheets A, B, C, and D, and α-helices 2 and 3) and C-terminal (contains β-sheets G and H, α-helix 4, and β-sheets I and J) domains. The N-terminal inhibitory domain forms a β-barrel structure similar to that of the oligosaccharide/oligonucleotide-binding (OB)-fold family proteins. Six conserved disulphide bonds are shown in yellow. An enlarged image of the complex around the catalytic zinc atom of the MMP-3 is shown in the inset. The catalytic zinc atom (pink) is held by three histidine residues [His_201, His_205 and His_211 (sky blue)] in MMP-3. The α-amino group (blue) and the carbonyl oxygen (red) group of the N-terminal Cys_1 in TIMP-1 chelate the zinc atom of the active site (pink). The figure was prepared with the SWISS PDB viewer [24] and rendered by POV-Ray software.
the series of inhibitor studies using TIMPs or synthetic MMP inhibitors in vivo as well as in vitro. However, it has not been clear which MMP or MMPs are functionally involved in the invasive process in vivo. It is likely that multiple MMPs are involved and that these may vary in different types of cancer.

**Importance of pericellular proteolysis in tumour cell invasion**

When cells invade a tissue, it is not necessary to degrade a large area of ECM, but a more focal pericellular area (the area immediately surrounding cell) in the direction of the migration. Thus, proteinases that are bound to the plasma membrane are likely to be more suitable for this purpose than soluble enzymes. Hotary et al. [8] reported that the overexpression of soluble MMPs, including MMP-1, -3, -7, -9, -11, and -13, did not modify the invasion ability
of Madin–Darby canine kidney epithelial cells into a collagen matrix, whereas
overexpression of membrane-bound MT1-MMP did. Yu and Stamenkovic [9]
also showed that a membrane-anchored chimaera mutant of MMP-9 and the
transmembrane and cytoplasmic domains of CD44 (a cell surface adhesion
molecule that binds to ECM components including hyaluronan, collagens and
fibronectin) enhanced cellular invasion into the matrix compared with the
wild-type soluble form. Despite the fact that the expression of many soluble
MMPs is upregulated at the invasive sites of tumours, these studies emphasize
that pericellular proteolysis is closely associated with the invasive phenotype
and malignancy of cancer cells. Indeed, MT1-MMP has been shown to be one
of the key enzymes in this process. This enzyme is found on the cell surface in
its active form and degrades local ECM components [2,3]. MT1-MMP also
activates the zymogens of MMP-2 and MMP-13, which degrade different
ECM components at or near the cell surface [3,10]. The activation of MMP-2
is considered to be especially important, as MMP-2, but not MT1-MMP, can

Figure 4. Molecular events that take place during cell invasion: three-step theory
The cell attaches to the ECM via specific ECM receptors on the cell surface (Step 1). The cell
then starts to express proteinases (MMPs) that degrade ECM at the attachment site (Step 2). It
then migrates to the area where the ECM was degraded (Step 3). Repetition of these steps
results in cellular invasion.
 degrade type IV collagen, a major component of the basement membrane. In addition, both MT1-MMP and MMP-2 can cleave the \( \gamma_2 \) chain of laminin 5, another major component of the basement membrane. The resulting fragments promote the migration of epithelial cells with a low invasive potential [11,12]. More recently, it has been shown that MT1-MMP sheds CD44 from the cell surface, an activity that is essential for migration of the MIA PaCa-2 pancreatic cancer cell line [13]. CD44 is a major hyaluronan receptor and is expressed in many malignant tumour cells. It is therefore proposed that these invasive tumour cells use the CD44/MT1-MMP system for migration in vivo.

**Activation mechanism of proMMP-2**

The activation of proMMP-2 by MT1-MMP is thought to be an integral part of tumour cell invasion. The mechanism is not a simple bimolecular interaction of proMMP-2 and MT1-MMP; several protein–protein interactions are involved, with the endogenous inhibitor TIMP-2 functioning as a bridging molecule [2,3]. The initial step is the binding of TIMP-2 to active MT1-MMP on the cell surface. This interaction is between the active site of the enzyme and the N-terminal inhibitory domain of TIMP-2. The MT1-MMP–TIMP-2 complex then acts as a receptor to recruit proMMP-2 produced by surrounding stromal cells. This binding occurs through the C-terminal Hpx domain of proMMP-2 and the C-terminal domain of TIMP-2. Since the MT1-MMP component of the MT1-MMP–TIMP-2–proMMP-2 complex is inhibited by TIMP-2, it is postulated that a second molecule of MT1-MMP is required for the activation of proMMP-2. Many of the recent studies support this notion [3], and more recently, it has been demonstrated that MT1-MMP forms a complex through the Hpx domains to keep the ‘receptor MT1-MMP’ and the ‘catalytic MT1-MMP’ close together [14] (Figure 5). The homophilic complexes of MT1-MMP (intermolecular interaction of identical molecules) are formed exclusively at the lamellipodia (a large plasma membrane protrusion that extends from the leading edge of the cell), indicating that MMP-2 activation and ECM degradation take place at the migration front of invading cells. Earlier histological studies showed that an elevated MMP-2 mRNA level is primarily found in cancer stromal cells, but that the MMP-2 protein is often associated with the malignant epithelium. In retrospect, these phenomena can be explained by the active recruitment of proMMP-2 by cancer cells through the molecular assembly of proMMP-2, MT1-MMP and TIMP-2.

**MMPs and tumour neovascularization**

In order for tumours to grow to the size of more than a few millimetres in diameter, neovascularization or angiogenesis (the formation of new blood vessels from existing ones) must take place to supply oxygen and nutrients. Vascularization of the tumour also facilitates the invasion of the blood stream by tumour cells. To achieve neovascularization, it is generally thought that tumour
cells produce angiogenic factors such as vascular endothelial cell growth factor (VEGF) or fibroblast growth factor (FGF) to stimulate local neovascularization. However, Bergers et al. [15] have found that VEGF and FGF-1 (acidic FGF) are present in both the normal tissue of control mice and in the tumour tissue of a transgenic mouse model; however, neurovascularization is only observed in the tumour tissue. Furthermore, in this tumour model there were no differences in the expression of two VEGF receptors (Flk-1 and Flt-1) before and after angiogenesis took place, although VEGF signalling was still essential for angiogenesis. Therefore, what regulates angiogenesis in tumour tissue? What are the differences before and after angiogenesis? These researchers found that MMP-9 expression was upregulated in the tumour tissue and that it released VEGF that was bound to the ECM. The increased availability of VEGF activated quiescent endothelial cells to the angiogenic state.

VEGF increases vascular permeability, causing the leakage of blood proteins from the vascular bed. This is accompanied by activation of the blood clotting cascade and the formation of cross-linked fibrins. The deposited fibrin network then serves as a scaffold for angiogenic endothelial cells, but at the same time the highly cross-linked fibrin structure is also a major barrier for endothelial cell migration. Therefore, angiogenic endothelial cells need to utilize fibrinolytic proteinases for sprouting and capillary formation. Plasminogen activator and plasmin, well characterized fibrolytic proteases,
were the prime candidates for this process, but Hiraoka et al. [16] found that inhibition of these serine proteinases did not influence the ability of endothelial cells to invade into cross-linked fibrin and to form capillaries. This process was inhibited by the MMP inhibitor TIMP-2, but not by TIMP-1. TIMP-2 inhibits MT1-MMP, but TIMP-1 does not. Based on a series of additional experiments, it was concluded that membrane-bound MT1-MMP is the key fibrinolytic enzyme in this system and promotes angiogenesis [16].

**MMPs and tumour development**

The involvement of MMPs in tumour invasion and angiogenesis has been demonstrated as we have just discussed, but a number of observations have suggested that MMPs also play a role in tumorigenesis at a much earlier stage. For example, attenuating the TIMP-1 production in mouse fibroblasts by antisense RNA made them tumorigenic and metastatic in nude mice [17]. Overexpression of TIMP-1 or TIMP-2 in melanoma cells markedly reduced not only the invasive ability of those cells, but also primary tumour growth in vivo [18,19]. The role of MMP-7 in the development of intestinal tumours was investigated using a mouse strain which spontaneously develops intestinal tumours. This mouse model closely mimics the hereditary human colon cancer syndrome, familial adenomatous polyposis. MMP-7 production is elevated in the human intestinal tumour. As expected, MMP-7 was also expressed in epithelial-derived tumour cells in these mice, but not in normal intestinal mucosa. When these mice were crossed with MMP-7-deficient mice, the generated MMP-7-null mice developed 58% less tumours and the size of the tumours was 20% smaller than those of the wild-type [20]. This is further supported by inhibition of tumorigenesis by a synthetic MMP inhibitor. The mechanism underlying this phenomenon is not clear, but the proteolytic activity of MMP-7 is likely to be required for tumour growth. Sternlicht et al. [21] also reported that the overexpression of active MMP-3 in the mouse mammary gland results in aggressive malignant mammary tumours that exhibit genomic alterations, suggesting that changes of microenvironment by the overexpression of MMPs can lead to DNA damage, which results in tumour generation. It is likely that soluble MMPs are suitable for such activities, as they can modify a broader area of the ECM. It is possible that other soluble MMPs that are overexpressed at or near the tumour may play such a role.

**Conclusions**

Cellular and molecular biological studies have indicated that MMPs play a crucial role in cancer cell invasion and migration, in neovascularization and in tumorigenesis. Therefore, MMPs are certainly a suitable molecular target for cancer treatment. In the past decade, a large number of MMP inhibitors have been synthesized and have been shown to be effective against cancer in animal models. Unfortunately, when several of these inhibitors were tested clinically
on patients with advanced cancer, they were, disappointingly, not effective. Therefore, are MMPs still suitable target molecules for therapeutic intervention? Is the investigation of MMPs in cancer still valid? The answer to these questions are certainly “Yes”. Zucker et al. [22] commented that the failure in clinical efficacy may be due to the trials being conducted with advanced cancer patients, and it is emphasized that MMPs are more likely to play a critical role in the earlier stages of disease progression. The involvement of individual MMPs in each stage of cancer progression should now be analysed critically. It is important to investigate at what stage of the disease MMP inhibitors can work effectively. In addition, MMP inhibitors often have broad specificity and inhibit other types of metalloproteinases that are also biologically important such as ADAM enzymes (see Chapter 11). Therefore, there is a need to develop more specific inhibitors of a particular MMP to reduce possible side effects (e.g. joint pain, stiffness, oedema and reduced mobility). An understanding of the detailed interactions between MMPs and other related molecules may help us to develop new ways of blocking the function of a particular MMP with greater specificity. The engineering of mutant TIMPs specific to each MMP may also be considered because TIMPs have poor inhibitory activity against ADAM enzymes. TIMPs, on the other hand, have cell growth regulatory activities distinct from their MMP inhibitory function, and therefore, the inhibition of MMP by selective TIMP variants may have unexpected consequences. Further biochemical, molecular and cell biological investigations of MMPs and TIMPs are essential for our understanding of the molecular events in cancer progression, which will generate innovative ideas to fight this deadly disease in the future.

Summary

- **MMPs are the major group of proteinases that degrade ECM macromolecules.**
- **Cancer cells utilize MMPs to invade into tissue.**
- **MT1-MMP, which participates in pericellular proteolysis of ECM, is one of the key enzymes involved in the invasive process of cancer cells.**
- **MMP-9 expressed in tumour tissues triggers an angiogenic switch by releasing VEGF from the ECM.**
- **Endothelial cells utilize MT1-MMP as a fibrinolytic proteinase to promote capillary formation.**
- **MMP-7 is involved in intestinal tumour generation.**
- **Aberrant ECM degradation by MMP may cause cellular transformation and cancer.**
References


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