Biochimica et Biophysica Acta 1825 (2012) 29–36

Contents lists available at SciVerse ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbacan

Review

New facets of matrix metalloproteinases MMP-2 and MMP-9 as cell surface transducers: Outside-in signaling and relationship to tumor progression

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ARTICLE INFO

Article history:
Received 15 June 2011
Received in revised form 3 October 2011
Accepted 4 October 2011
Available online 12 October 2011

Keywords:
Gelatinase
Cell surface binding
Cancer
Inhibitor
Function
Outside-in signaling

ABSTRACT

This review focuses on matrix metalloproteinases (MMPs)-2 (gelatinase A) and -9 (gelatinase B), both of which are cancer-associated, secreted, zinc-dependent endopeptidases. Gelatinases cleave many different targets (extracellular matrix, cytokines, growth factors, chemokines and cytokine/growth factor receptors) that in turn regulate key signaling pathways in cell growth, migration, invasion, inflammation and angiogenesis. Interactions with cell surface integral membrane proteins (CD44, αVβ/αβ1/αβ2 integrins and Ku protein) can occur through the gelatinases' active site or hemopexin-like C-terminal domain. This review evaluates the recent literature on the non-enzymatic, signal transduction roles of surface-bound gelatinases and their subsequent effects on cell survival, migration and angiogenesis. Gelatinases have long been drug targets. The current status of gelatinase inhibitors as anticancer agents and their failure in the clinic is discussed in light of these new data on the gelatinases' roles as cell surface transducers — data that may lead to the design and development of novel, gelatinase-targeting inhibitors.

Contents

1. Introducing MMPs and their roles in cancer

The matrix metalloproteinase (MMP) family consists of at least 23 structurally related, zinc-dependent endopeptidases [1,2]. The family shares specific functional and structural components, including a hydrophobic signal peptide for secretion, a propeptide domain for enzyme latency, a catalytic domain with a highly conserved zinc-binding site and (for the majority of MMPs) a hemopexin-like C-terminal domain (PEX) linked to the catalytic domain *via* a flexible hinge region (Fig. 1A) [1,2]. The PEX domain binds endogenous tissue inhibitors of MMPs (TIMPs) and certain MMP substrates and is involved in MMP activation [1]. TIMPs include four members originally described as inhibitors of MMP activities, which also have biological activities that are independent of MMP inhibition and regulate cell growth, migration, survival and angiogenesis [3–5]. MMPs include membrane-

Abbreviations: MMP, matrix metalloproteinase; PEX, hemopexin-like C-terminal domain; TIMP, tissue inhibitor of metalloproteinase; MT, membrane type; CBD, collagen-binding domain; ECM, extracellular matrix; MMPI, matrix metalloproteinase inhibitor; CLL, chronic lymphocytic leukemia; AML, acute myeloid leukemia; EGF, epidermal growth factor; VEGF, vascular endothelial growth factor; TGF-β, transforming growth factor-β; FGF, fibroblast growth factor; TNF, tumor necrosis factor; IL, interleukin; IFN, interferon; IGF-BP, insulin-like growth factor-binding protein; ICAM, intercellular adhesion molecule; PF4, platelet factor-4; SDF-1, stromal-cell derived factor-1; IP-10, IFN-γ-induced protein of 10 kDa; MCP, macrophage chemotactic protein; I-TAC, IFN-γ-induced T cell-activated chemokine; MIG, monokine induced by interferon-γ; RECK, reversion-inducing cysteine-rich protein with Kazal motif; LRP, low density lipoprotein-related scavenger receptor; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; ERK, extracellular signal-regulated protein kinase; FAK, focal adhesion kinase; CAM, chick chorioallantoic membrane; HIF, hypoxia-induced transcription factor

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doi:10.1016/j.bbcan.2011.10.001

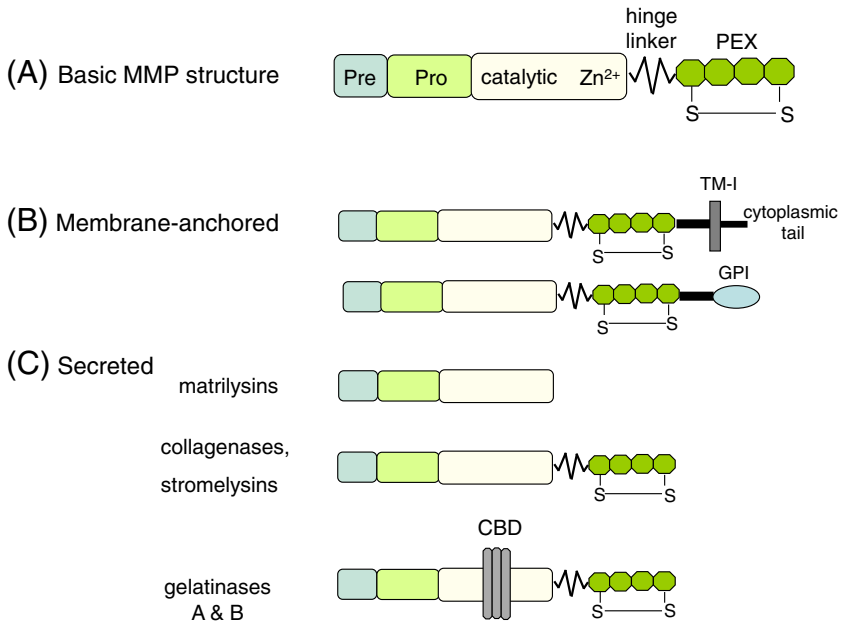

Fig. 1. Structures of the MMPs. (A) The general domain structure of MMP family members. The signal peptide (Pre) guides the MMP into the rough endoplasmic reticulum during synthesis. The propeptide domain (Pro) sustains the latency of MMPs. The catalytic domain houses a highly conserved Zn^{2+} binding region. The hemopexin-like-C-terminal domain (PEX) is linked to the catalytic domain by a short hinge region. (B) MT-MMPs include membrane-anchored MMPs localized at the cell surface through a C-terminal (type I) transmembrane domain (TM-I) or by a glycosylphosphatidylinositol anchor (GPI). (C) Secreted MMPs include stromelysins, matrilysins, collagenases and gelatinases. The gelatinases (MMP-2 and MMP-9) contain repeats of fibronectin type II-like domains (the collagen binding domain, CBD) that interact with collagen and gelatin.

anchored and secreted MMPs. The membrane-anchored MMPs (MT-MMPs) are localized at the cell surface by a C-terminal (type I) transmembrane domain or a glycosylphosphatidylinositol anchor (Fig. 1B) [4,6]. A type II transmembrane MMP (MMP-23) has also been described [6]. TIMP-1 has a relatively low affinity for the MT-MMPs [5]. MMPs secreted as latent pro-enzymes include collagenases, stromelysins, matrilysins and two gelatinases (A and B) (Fig. 1C) [4]. Removal of the prodomain by the endopeptidase furin leads to MMP activation. TIMPs inhibit most of the secreted MMPs [5]. The gelatinases differ from most of the other MMPs in that they have a collagen-binding domain (CBD) within the catalytic domain (Fig. 1C). The CBD is composed of three fibronectin type II repeats and is involved in the binding of collagenous substrates, elastin, fatty acids and thrombospondins [7].

Matrix metalloproteinases selectively degrade various components of the extracellular matrix (ECM) and release growth factors and cytokines that reside in the ECM [8,9]. The MMPs are also capable of activating various latent growth factors, cytokines and chemokines and cleaving cell surface proteins (cytokine receptors, cell adhesion molecules, the urokinase receptor, etc.) [1,2,10,11]. Through their proteolytic activity, MMPs play crucial roles in invasion and metastasis and regulate signaling pathways that control cell growth, survival, invasion, inflammation and angiogenesis

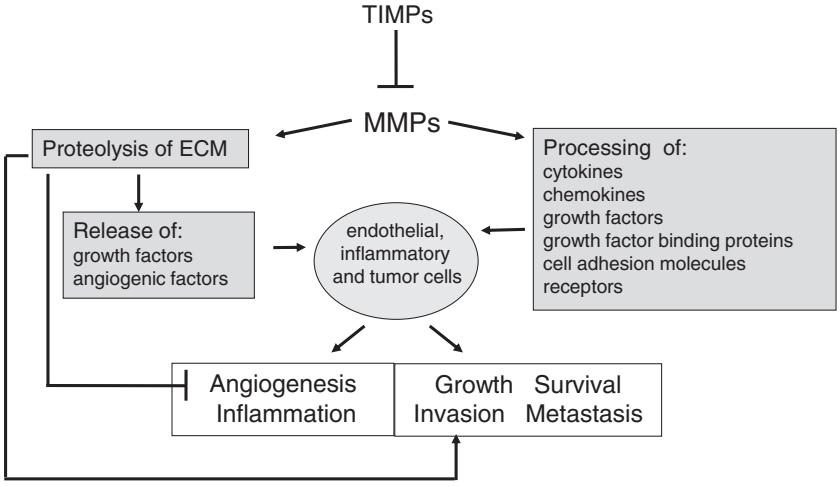

Fig. 2. A schematic overview of the roles of MMPs in cancer. MMPs degrade structural components within the ECM, facilitating tumor cell invasion and metastasis and thus releasing growth factors, cytokines and angiogenic factors embedded in the ECM (VEGF, TGF-β, bFGF, IFN-γ, etc.). MMPs also generate angiogenesis inhibitors, such as angiostatin, endostatin and tumstatin. MMPs process and activate or inactivate signaling molecules (cytokines, chemokines, growth factors) that target immune cells (inflammation), endothelial cells (angiogenesis) and tumor cells (cell growth, survival, migration, invasion and metastasis). MMP-mediated cleaving of adhesion molecules (E-cadherin, ICAM-1, integrins, etc.) enhances tumor cell migration and invasion. (⊣ negative regulation, ➡ positive regulation).

(Fig. 2). A number of excellent reviews have discussed the MMPs' roles in cancer [1,2,8,12–14].

2. Development of synthetic MMP inhibitors as cancer drugs

Many different MMP inhibitors (MMPIs) have been designed to target MMPs in cancer [13,15,16]. Although these compounds differ in their inhibitory potencies towards MMPs, none of them are selective for a given MMP (including the gelatinases).

The first generation of MMPIs were peptidometics (such as batimastat and marimastat) that mimic the structure of collagen. They act as competitive inhibitors and chelate the zinc ion present at the MMP's active site. To improve specificity and oral bioavailability, non-peptidometics (such as tanomastat, prinomastat, BMS-275291, CGS27123A, etc.) were synthesized on the basis of the active site's three-dimensional conformation. Other MMPIs include tetracycline derivatives (such as metastat/COL-3, minocycline and doxycycline) that inhibit both the MMPs' enzymatic activity and their synthesis (by blocking gene transcription) [17,18]. To date, all clinical trials of these MMPIs in advanced cancer patients have failed, with the exception of metastat (which has entered Phase II trials for Kaposi's sarcoma and brain tumors) [19,20]. The latest generation of MMPIs includes biphosphonates [21,22] and S-3304, a D-tryptophan derivative that primarily inhibits gelatinases [23]. Novel biphosphonate derivatives show benefits as a result of altering the expression pattern of MMPs/TIMPs in breast cancer cells [13]. A Phase I clinical trial of S-3304 in patients with advanced and refractory solid tumors found that the compound was safe, well tolerated and achieved plasma concentrations above those required to inhibit gelatinases [24]. However, it is not yet known whether S-3340 will be effective in Phase II/III clinical trials.

There are several possible reasons for the failure of MMPIs in the clinic. Firstly, most MMPIs have dose-limiting musculoskeletal toxicity that limits efficacy. Secondly, the clinical trials were performed on patients with terminal-phase cancer, where several overlapping pathways come into play. Thirdly, the structural similarity of the various MMPs' catalytic domains makes it difficult to design MMPIs with high selectivity [25]. Moreover, the role of MMPs in cancer progression appears not to be restricted to their ECM-degrading activity, with involvement in many signaling pathways that influence tumor cell behavior [26,27]. Lastly, recent evidence shows that MMPs may have opposing functions in primary and metastatic cancer sites; hence, MMPIs may produce protumorigenic effects in some situations and may counterbalance the benefits of target inhibition [26,28,29].

3. Gelatinases (MMP-2 and MMP-9) as cancer biomarkers

Of the various MMPs thought to be involved in cancer, attention has focused on the gelatinases because (i) they are overexpressed in a variety of malignant tumors and (ii) their expression and activity are often associated with tumor aggressiveness and a poor prognosis. Elevated levels of MMP-2 and/or MMP-9 are found in breast, brain, ovarian, pancreas, colorectal, bladder, prostate and lung cancers and melanoma [2,8,30–32]. Dysregulated MMP expression is also observed in hematological malignancies such as acute lymphoblastic leukemia, adult T-cell leukemia, chronic B lymphocytic leukemia (CLL), acute myeloid leukemia (AML), chronic myeloid leukemia, myelodysplastic syndromes and Hodgkin's and non-Hodgkin's lymphoma [31,33].

4. Proteolysis-dependent functions of gelatinases

Gelatinases are secreted as inactive zymogens (proMMP-2: 72 kDa, proMMP-9: 92 kDa), with cleavage of a prodomain yielding the active form (MMP-2: 65 kDa; MMP-9: 82 kDa). An 85 kDa proform of MMP-9 lacking complex carbohydrates has been reported in breast tumors and AML cell lines [34,35]. Several mechanisms can stimulate the activation process. The main route for activation of proMMP-2 on the cell surface occurs through the formation of a molecular complex containing proMMP-2 (*via* its PEX domain), MT1-MMP (*via* its catalytic domain) and TIMP-2 (reviewed in [2]). This cell surface interaction leads to clustering of proMMP-2 near a TIMP-free, active MT1-MMP which initiates activation of proMMP-2. MMP-2 can also be activated by MMP-1, MMP-7, thrombin and activated protein C [7,36]. MMP-9 can be activated by plasmin, trypsin-2, MMP-2, MMP-13 (activated by MMP-2) and MMP-3 (activated by plasmin) [7,36]. Other activation mechanisms have been suggested in order to explain proMMP-2 and proMMP-9's catalytic activity in the presence of the propeptide. For example, binding of proMMP-9 to a gelatin- or type IV collagen-coated surface could lead to reversible activation of MMP-9 *via* disengagement of the propeptide from the active site [37]. Interaction of hemin or β-hematin with the proMMP-9 PEX domain primes MMP-9 activation *via* an autocatalytic process [38]. Interaction of proMMP-2 with low concentrations of collagen α2 VI chain induces its auto-activation [39]. Lastly, the reversion-inducing cysteine-rich protein with Kazal motifs (RECK, an integral membrane protein that forms a complex with MT1-MMP) has been found to inhibit gelatinase secretion and activity [40,41]. Whether these mechanisms occur *in vivo* remains to be established.

Activated gelatinases are able to degrade various components of the ECM and non-matrix proteins (Table 1) [1,2,8,11,12]. Cell migration and invasion are complex processes that involve the ECM, proteinases, chemokines, adhesion receptors and (for invasion) basement membrane. Angiogenesis (defined as the generation of new blood vessels from preexisting ones) is critically important for tumor growth and metastatic spreading. It was initially suggested that gelatinases played a dominant role in basement membrane-invasive events because of their ability to degrade collagen IV [42]. However, studies in MMP-$9^{(-/-)}$ and MMP-$2^{(-/-)}$/MMP-$9^{(-/-)}$ murine models of inflammation [43], cancer cells engineered to express active MMP-2 and MMP-9 [44] and fibroblasts isolated from MMP-$2^{-/-}$ and MMP-$9^{-/-}$ mice [45] strongly suggest that gelatinases do not promote basement membrane invasion. In fact, recent evidence shows that gelatinases play major but indirect roles in cell signaling by controlling the bioavailability and bioactivity of molecules that target specific receptors regulating cell growth, migration, inflammation and angiogenesis (Table **1**).

Table 1
Gelatinase substrates.

Substrates	MMP-2/gelatinase A	MMP-9/gelatinase B
ECM substrates	Collagens I, IV, V, VII, X and XI	Collagens III, IV and V
	Gelatin	Gelatin
	Tenascin	Elastin
	Elastin	Vitronectin
	Fibronectin	Entactin
	Laminin-5	
Other substrates	proTGF-β	proTGF-β
	proIL-1β	proTNF-α
	proTNF-α	IL-2Rα
	proHB-EGF	ICAM-1
	FGFR-I	EGFR-1
	IGFBP-3, -5, -6	Kit ligand
	CXCL12/SDF-1	CXCL1/GRO-α
	CCL7/MCP-3	CXCL4/PF4
	CX3CL1/fractalkine	CXCL8/IL-8
	KISS-1	CXCL9/MIG
		CXCL11/ITAC
		CXCL12/SDF-1
		α1 proteinase inhibitor
		Plasminogen
		KISS-1
		IFN-β

By degrading the ECM, gelatinases generate or release bioactive molecules that influence tumor progression. Gelatinase activity can cause the release of cryptic information from the ECM, leading to cell migration and angiogenesis. For example, the proteolytic cleavage of collagen IV by MMP-9 unmasks cryptic sites that are critical for angiogenesis [46,47]. Similarly, cleavage of laminin-5 by MMP-2 results in the exposure of a cryptic epitope that enhances endothelial cell migration [48]. MMP-9 can release ECM-sequestered factors VEGF, TGF-β and FGF-2, which stimulate proliferation and migration of endothelial cells and thus promote angiogenesis and tumor growth [49–53]. In contrast, tumstatin and endostatin (generated by the MMP-9-mediated proteolysis of type IV collagen and type XVIII collagen, respectively) are active inhibitors of angiogenesis [54,55].

Gelatinases target immunomodulating cytokines and growth factors and cytokine/growth factor receptors. For example, gelatinases shed and activate TNF-α, TGF-β and IL-1β, which are intimately involved in the regulation of growth, angiogenesis and inflammation [56,57]. FGF-R1 may be a specific cell-surface target for MMP-2, yielding a soluble FGF receptor that modulates the mitogenic and angiogenic activities of FGF-2 [58]. MMP-9 cleaves IFN-β and thus kills the cytokine's antiviral and immunotherapeutic activity [59]. MMP-2 is able to cleave certain insulin-like growth factor-binding proteins (IGFBPs) and thus release active insulin-like growth factors (IGFs) involved in tumor cell growth [11,60]. Both gelatinases process the tumor suppressor protein KISS-1 to generate metastin, which enhances cell invasion [61,62]. MMP-9 suppresses the proliferation of T lymphocytes through disruption of the IL-2Rα signaling that may constitute a mechanism of cancer-mediated immunosuppression [63]. Moreover, MMP-9 releases Kit-ligand, which plays a crucial role in tumor growth and angiogenesis [64,65]. MMP-9-dependent shedding of ICAM-1 augments tumor cell resistance to natural-killer-cell-mediated cytotoxicity [66].

Chemokines play an essential role in modulating tumor growth *via* regulation of tumor-associated angiogenesis, activation of host immunological responses and direct inhibition of tumor cell proliferation. Gelatinases generate either inactivated chemokine fragments (*e.g.* GRO-α, PF4, SDF-1, MCP-3, IP-10, MIG) or truncated chemokines with enhanced activity (IL-8, I-TAC) [9]. The gelatinase-mediated proteolysis of chemokines might have direct consequences on tumor growth (*e.g.* I-TAC), migration (*e.g.* SDF-1 and MCP-3) and angiogenesis (*e.g.* IL-8, PF4, MIG, IP-10 and SDF-1) [7,9,11]). For example, the MCP-3 generated by MMP-2 can bind to CC chemokine receptors and inhibit migration, and suppresses inflammation [67]. In contrast, processing of IL-8 by MMP-9 increases its chemotactic activity in neutrophils [68].

5. Cell surface-associated gelatinases

Gelatinases have been shown to interact with the cell surfaces of leukocytes and epithelial and endothelial cells [7,36,69,70]. As mentioned above, the activation of proMMP-2 requires interaction with MT1-MMP and TIMP-2 [7]. Furthermore, gelatinases bind to collagens and fibronectin at the surface of cancer cells through their CBD domain [7]. Gelatinases also bind to the low-density lipoprotein-related scavenger receptor (LRP), which is responsible for the internalization of various ligands including these enzymes [71–73].

In addition to these cell surface associations, gelatinases reportedly bind to other integral membrane proteins, such as the DNA repair protein Ku (*via* its integrin I-like domain) [74], CD44 [50,75–80] and the integrins (αVβ3, αVβ1, αβ2, αVβ5, α4β1 and α5β1) [70,80–93] (Table 2). The gelatinases' catalytic and PEX domains are variously involved in these interactions (Table 2). For example, the integrin α_M, α_L and β2 subunits can bind to MMP-9's catalytic domain, whereas CD44 and the β5, α4 and β1 subunits interact with the PEX domain (Table 2). However, doubt has been cast on the reported molecular interaction between MMP-2 and integrin αVβ3 *via* the PEX domain in endothelial cells [82], with a suggestion that the recombinant PEX polypeptide was possibly contaminated by lipopolysaccharide [94]. On mesenchymal cells, active MMP-2 can bind to αVβ3 *via*

Table 2
Examples of binding between gelatinases and integral membrane proteins.

Cell type	Gelatinase (domain involved in the binding)	Integral membrane protein	Refs	Positive effect on cell process(es)
Melanoma				
Primary and metastatic melanomas	active MMP-2	αVβ3	[81,85]	Growth collagen IV degradation
MC cells	pro/active MMP-9	CD44	[76]	Growth migration [1]
Squamous cell carcinoma				
SCC12F2 cells	pro/active MMP-9	α5β1	[88]	Migration [2]
Breast cancer				
MCF7, MCF10A cells	pro/active MMP-2	αVβ3	[82,83	Migration angiogenesis[3]
Met-1, MDA-MB435 cells	active MMP-9	αVβ3	[75,87	Migration[4, 5]
MMP-9 transfected MCF-7 cells	proMMP-9 (PEX)	CD44	[78,79	Migration[5]
Lung cancer				
A549 cells	MMP-2 (catalytic)	αVβ3	[93]	VEGF release and angiogenesis[6]
Fibrosarcoma				
HT1080 cells	proMMP-9 (PEX)	αVβ5	[89]	Migration[5,7]
AML				
THP-1, OCI-AML3 cells	pro MMP-2 (catalytic)	$\alpha_M\beta2$, $\alpha_L\beta2$	[90]	migration[5]
THP-1 cells	proMMP-9 (catalytic)	$\alpha_M\beta2$, $\alpha_L\beta2$	[90,91]	Growth migration[5] transendothelial migration[8]
U937, HL-60, THP-1, primary AML blasts	proMMP-9 (PEX)	Ku protein	[35,74]	Migration[9]
CLL				
Primary CLL cells	pro/active MMP-9 (PEX)	α4β1 and CD44v	[80,96]	Survival Migration[5]
Leukocytes				
Neutrophils, monocytes	proMMP2 and proMMP-9 (catalytic)	$\alpha_L\beta2$, $\alpha_M\beta2$	[91]	Transendothelial migration[8]
Monocyte-derived dendritic cells	active MMP-9 (catalytic)	$\alpha_M\beta2$ and CD44	[77]	Migration[10]
Endothelial cells				
ECV304 cells	proMMP-2	αVβ3	[82,85]	Growth angiogenesis[3]
HUVEC cells	active MMP-2	αVβ1	[86]	Apoptosis

[1] *In vitro* culture of TA3 cells on G8 myoblast monolayers; *in vitro* endothelial tube formation; [2] cell migration in fibronectin-coated Transwell® chambers; [3] CAM angiogenesis assay; [4] cell migration in purified ECM proteins-coated Transwell® chambers; [5] cell migration in Transwell® chambers with 10% fetal calf serum as chemoattractant in the lower chamber; [6] *in vitro* culture of HMEC-1 cells on Matrigel® and formation of capillary-like structures; xenograft mice; [7] cell migration in Matrigel®-coated Transwell® chambers; [8] transendothelial cell migration in HMECs-coated Transwell® chambers; [9] cell migration in collagen IV-coated Transwell® chambers; [10] cell migration in Matrigel®-coated Transwell® chambers with chemokine in the lower chamber.

PEX [92]. It therefore remains to be definitively established whether αVβ3 can bind to the PEX domain of MMP-2.

Consequently, cell growth, migration and angiogenesis appear to depend on cell surface associations between gelatinases and these integral membrane proteins (Table 2). For example, disrupting MMP-2/αvβ3 binding on the surface of melanoma cells is associated with the inhibition of tumor growth and migration [84,95]. Similarly, the complex formed by Ku protein and proMMP-9 (*via* the latter's PEX domain) is involved in the migration of AML cells [35]. Both proMMP-9 and active MMP-9 bound to the membrane *via* α4β1 and CD44 are involved in the survival of CLL cells [80,96]. ProMMP-9 enhances epithelial cell migration *via* a non-proteolytic mechanism that involves its PEX domain and CD44 [78]. Mesenchymal invasive behavior might be dependent on MMP-2/αVβ3 binding [92]. In neutrophils, both the active site and PEX domain of MMP-9 are involved in the induction of FGF-2-mediated angiogenesis [53].

6. Outside-in signaling by cell surface-associated gelatinases

Observation of these binding associations between surface receptors and gelatinases raised the possibility that the latter have the potential to directly influence cell behavior and to activate the classical signaling pathways involved in major biological events (cell growth, migration, survival, etc.).

Experiments with inhibitors strongly suggest the involvement of cell signaling pathways in MMP-9-mediated cell migration. For example, the JNK inhibitor SP600125 blocked MMP-9-mediated dendritic cell migration [97], whereas the MAPK inhibitor PD98059 and the PI3K inhibitor LY-294002 inhibited MMP-9-induced epithelial cell migration [78]. By studying the adenovirus-mediated delivery of MMP small interfering RNA, Rao, Bhoopathi and colleagues showed a clear relationship between the loss of MMP-9 expression and apoptosis induction in medulloblastoma cells (associated with the activation of β1 integrin, ERK and NF-κB) [98,99].

By using a combination of strategies to respectively target MMPs (with siRNA, recombinant MMPs and enzyme inhibitors), gelatinase-integral protein interactions (with antibodies) and signal transduction pathways (with signaling inhibitors and siRNA), three recent studies have described the signaling properties of MMP-2 and MMP-9. Redondo-Munoz and colleagues showed that the binding of proMMP-9's PEX domain to its docking receptors α4β1 integrin and CD44 induces an intracellular signaling pathway that favors the survival of CLL cells [96]. This pathway (Fig. 3A) consists of Lyn kinase activation, STAT3 phosphorylation and up-regulated expression of the pro-survival protein Mcl-1 (a member of the Bcl-2 family). Accordingly, high levels of proMMP-9 and Mcl-1 are found in CLL cells from blood [100,101] and lymphoid organs [96]. The data presented by Dufour et al. [79] indicate that MMP-9-dependent epithelial cell migration involves the heterodimerization of the PEX domain of proMMP-9 with CD44, leading to activation of the tyrosine kinase epidermal growth factor receptor (EGFR) and subsequent phosphorylation of its downstream kinase effectors ERK, AKT and FAK (focal adhesion kinase) (Fig. 3B). Indeed, EGFR can stimulate various downstream cell signaling cascades, including the PI3K/AKT pathway that favors cell migration and cancer cell invasion [102]. Moreover, FAK reportedly coordinates cell adhesion, polarization, migration, survival and death [103]. Chetty and colleagues suggested a role for MMP-2 in VEGF-induced lung tumor angiogenesis [93]. The interaction of proMMP-2 with integrin αvβ3 on A549 epithelial cells induces PI3K/AKT-mediated VEGF expression and related angiogenesis *in vitro* (Fig. 3C). The part of MMP-2 that binds to αvβ3 remains to be determined. Importantly, these results have been validated *in vivo* in a spontaneous lung metastasis mouse model [93].

7. Open questions and conclusions

The gelatinases' established functions depend on their proteolytic activity. By cleaving ECM components, releasing ECM-associated growth factors, shedding membrane-anchored cytokines and receptors and regulating chemokine activity, gelatinases process signaling molecules that in turn influence tumor cell growth, migration, invasion and angiogenesis. The publications detailed in this review highlight the ability of cell-surface-associated gelatinases to directly trigger intracellular signaling pathways that control the aforementioned critical cellular processes and behavior. The observed cell surface association of gelatinases with integrins or other integral

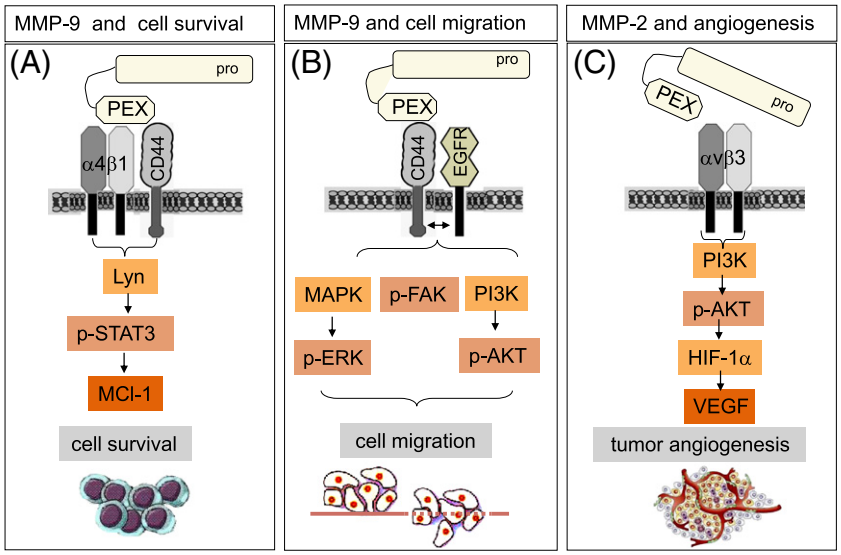

Fig. 3. Schematic representations of the signaling pathways induced by gelatinases and integral receptors. (A) ProMMP-9 interacts (*via* its PEX domain) with α4β1 and CD44 on B-CLL cells, leading to Lyn activation, STAT3 phosphorylation and MCL-1 up-regulation. Mcl-1 (a member of the Bcl-2 family) is essential for lymphocyte survival. (B) The PEX domain of proMMP-9 interacts with CD44 on tumor epithelial cells (COS-1/kidney, HT1080/fibrosarcoma, MDA-MB435/breast cancer cells) leading to the activation of EGFR and stimulation of various downstream cell signaling cascades, such as PI3K/AKT, ERK and FAK signals that coordinate cell migration. (C) The interaction of proMMP-2 with integrin αvβ3 on lung cancer cells (A549 cells) activates PI3/AKT signaling, leading to the activation of hypoxia-induced transcription factor-1α (HIF-1α). The latter regulates the expression of the primarily pro-angiogenic vascular endothelial growth factor VEGF-A. VEGF/VEGFR activation drives vascular sprouting, endothelial cell differentiation and then microtubule formation.

membrane proteins suggests that the signals triggered by these enzymes are intertwined with those triggered by integral proteins; hence, gelatinases may be involved in regulating other aspects of cell behavior, such as proliferation, differentiation, adhesion and apoptosis. Furthermore, the sheer variety of well-known and newly discovered functions for gelatinases (*i.e.* secreted forms *versus* membrane-bound forms, proforms *versus* active forms, etc.) begs several questions. To what extent are catalytic and non-catalytic activities (*via* CBD and PEX) related or interdependent? Are all cell types able to activate signaling cascades in response to membrane-bound gelatinase? Is MMP-2- and MMP-9-mediated outside-in signaling relevant in other disease states (*e.g.* inflammation and cardiovascular disease)? Does gelatinase-mediated outside-in signaling extend to other secreted MMPs that might colocalize with integral proteins? At present, it is thought that proMMP-1 interacts with $\alpha 2\beta 1$ integrin on epithelial cells [104] and on keratinocytes *via* its PEX domain [105], whereas MMP-19 binds to myeloid cells *via* its PEX domain [106].

Antiproteolytic therapies have sought to target the MMPs' catalytic activity and thus inhibit tumor progression [25]. The failure of MMPIs as cancer drugs in the clinic may be explained by their lack of selectivity towards MMPs (including gelatinases). In light of our current knowledge of the gelatinases' proteolytic and non-proteolytic (*i.e.* outside-in signaling) roles, the enzyme inhibitor approach may no longer be sufficient because it does not affect the gelatinases' interactions with cell surface proteins and consequent signaling. New therapeutic strategies are focusing on more selective MMPIs and targeting motifs outside the active site (the "exosite") of individual MMPs; newly designed inhibitors include peptides that block exosite-mediated cell surface interactions and function-blocking anti-MMP antibodies [28,107,108]. These approaches have already been used to target MMP-9 [79,89,109]. A neutralizing antibody targeting the PEX domain of MMP-9 bound to LRP-1 at the surface of Schwann cells, blocks cell migration *in vitro* [109]. An inhibitory peptide that binds selectively to the MMP-9 PEX domain has already been developed [89]. This small inhibitor prevents PEX from binding to $\alpha 1\beta 5$ integrin and blocks cell migration *in vitro* and tumor xenograft growth *in vivo* [89]. Synthetic peptides targeting specific sites of the PEX domain of MMP-9 inhibit the motility of HT-1080 and MDA-MB-435 tumor cells [79]. These studies indicate that targeting the PEX domain of MMP-9 by antibodies or peptides may be a viable approach to abrogate MMP-9-mediated cell function.

In conclusion, recent insights into the potential role of gelatinases as outside-in signaling molecules may provide opportunities for the development of new gelatinase inhibitors (such as antibodies and peptides) and validation in relevant animal models, before use as independent agents or in combination with other cancer treatment strategies.

Acknowledgement

Funding for this work was from the Institut National de la Santé et de la Recherche Médicale (INSERM).

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