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Review

Matrix metalloproteinases in inflammation ☆

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ABSTRACT

Background: Matrix metalloproteinases (MMPs) are a family of ubiquitously expressed zinc-dependent endopeptidases with broad substrate specificity and strictly regulated tissue specific expression. They are expressed in physiological situations and pathological conditions involving inflammation. MMPs regulate several functions related to inflammation including bioavailability and activity of inflammatory cytokines and chemokines. There is also evidence that MMPs regulate inflammation in tumor microenvironment, which plays an important role in cancer progression.
Scope of review: Here, we discuss the current view on the role of MMPs in the regulation of inflammation.
Major conclusions: MMPs modulate inflammation by regulating bioavailability and activity of cytokines, chemokines, and growth factors, as well as integrity of physical tissue barriers. MMPs are also involved in immune evasion of tumor cells and in regulation of inflammation in tumor microenvironment.
General significance: There is increasing evidence for non-matrix substrates of MMPs that are related to regulation of inflammatory processes. New methods have been employed for identification of the substrates of MMPs in inflammatory processes *in vivo*. Detailed information on the substrates of MMPs may offer more specific and effective ways of inhibiting MMP function by blocking the cleavage site in substrate or by inhibition of the bioactivity of the substrate. It is expected, that more precise information on the MMP–substrate interaction may offer novel strategies for therapeutic intervention in inflammatory diseases and cancer without blocking beneficial actions of MMPs. This article is part of a Special Issue entitled Matrix-mediated cell behaviour and properties.

1. Introduction

Matrix metalloproteinases (MMPs) are a family of proteolytic enzymes involved in physiological situations including tissue homeostasis, host defense and tissue repair. There is also evidence, that MMPs play a role in the pathogenesis of inflammatory diseases with focal tissue destruction, such as rheumatoid arthritis, osteoarthritis, and chronic cutaneous ulcerations, as well as in cancer progression [1–4]. The expression and activity of MMPs are under strict control in physiological situations, whereas excessive activity of MMPs is often noted in pathological conditions [5]. MMPs were initially characterized as extracellular matrix (ECM) cleaving proteolytic enzymes, but during the past years, a growing number of non-matrix substrates for MMPs have been identified [5,6].

MMPs can orchestrate the inflammatory functions at various levels [5,6]. They can regulate transmigration of inflammatory cells from vasculature to the site of inflammation in tissue. They also regulate the recruitment and influx of inflammatory cells to the site of inflammation by processing ECM components, growth factors, cytokines and chemokines. While the role of the members of ADAM family of metalloproteinases (ADAM, a proteinase with a disintegrin and a metalloprotease domain) in inflammatory processes has been well characterized, in this review we focus on the role of MMPs in inflammation.

2. Matrix metalloproteinases

MMPs belong to the metzincin superfamily, which is characterized by the presence of a highly conserved motif containing three histidine residues, which chelate a zinc ion in the catalytic site [7]. Other families in the metzincin super family are ADAMs and ADAM-TSs (ADAM with thrombospondin like motif), astacins, and serralysins. MMPs are ubiquitously expressed zinc-dependent endopeptidases with wide substrate specificities. They are produced either as soluble or cell membrane anchored proteinases that cleave proteins and proteoglycan components of ECM. In addition, MMPs cleave a multitude of non-matrix substrates including cytokines, chemokines, growth factors, growth factor receptors and cell surface adhesion receptors (Table 1). The members of the MMP family display marked differences in their tissue specific

Abbreviations: ADAM, a proteinase with a disintegrin and a metalloprotease domain; ADAM-TS, ADAM with thrombospondin like motif; EGF, epidermal growth factor; IL, interleukin; MCP, monocyte chemoattractant protein; MMP, matrix metalloproteinase; TGF, transforming growth factor; TNF, tumor necrosis factor; ZO, zona occludens

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expression and substrate specificity making MMPs a diverse group of proteolytic enzymes with multiple physiological functions. Moreover, expression and activity of various MMPs has also been reported in pathological conditions, such as inflammatory diseases and cancer [1–5].

2.1. MMP structure and function

To date, 23 human MMPs have been identified. According to their structure, substrate specificity, and function, MMPs can be classified to different subgroups: *collagenases* (MMP-1, -8, and -13), *gelatinases* (MMP-2 and -9), *stromelysins* (MMP-3, and -10), *stromelysin-like* MMPs (MMP-11 and -12), *matrilysins* (MMP-7, and -26), *transmembrane* MMPs (MMP-14, -15, -16, and -24), *glycosyl-phosphatidyl-inositol (GPI)-type* MMPs (MMP-17, and -25), *MMP-19-like* MMPs (MMP-19, and -28), and *other* MMPs (MMP-18, -20, and -23) [8].

All members of the MMP family are homologous in their structure and most of them contain four distinct functional domains: *signal peptide*, *propeptide*, *catalytic domain* and *hemopexin-like domain*.

Table 1
Non-matrix substrates of MMPs.

MMP	Substrate	Response	Reference
MMP-1	α1-antitrypsin/α1-antichymotrypsin	Inactive serpins	[60]
	IL-1β	Inactivation of IL-1β	[61]
	Latent TNF-α	Bioavailable TNF-α	[60]
	MCP-1, -2, -3, -4	CC chemokine receptor antagonists	[58]
	IGFBP-2, -3	Bioavailable IGF	[87,88]
	SDF-1	Inactive chemokine	[57]
	VEGF	Activation	[89]
MMP-2	IL-1β	Inactivation of IL-1β	[61]
	Pro-IL-1β	Activation of IL-1β	[55]
	SDF-1	Inactive chemokine	[57]
	MCP-3	CC chemokine receptor antagonists	[58]
	IGFBP-3	Bioavailable IGF	[88]
	Latent TGF-β	Activation	[90]
	Latent TNF-α	Bioavailable TNF-α	[60]
	FGFR1	Bioactive FGFR1 ectodomain	[91]
	Pleiotrophin	Mobilization of VEGF	[92]
	CTGF	Mobilization of VEGF	[92]
MMP-3	α1-antitrypsin/α1-antichymotrypsin	Inactive serpins	[93]
	IL-1β	Inactivation of IL-1β	[61]
	Pro-IL-1β	Activation of IL-1β	[55]
	MCP-1, -2, -3, -4	CC chemokine receptor antagonists	[58]
	SDF-1	Inactive chemokine	[57]
	IGFBP-1, 3	Bioavailable IGF	[88,94]
	Latent TGF-β	Activation	[95]
	Pro-HB-EGF	Activation	[96]
	Latent TNF-α	Bioavailable TNF-α	[60]
	Osteopontin	Increased bioactivity	[97]
	VEGF	Activation	[89]
MMP-7	α1-antitrypsin	Inactive serpinA1	[93]
	Pro-HB-EGF	Activation	[98,99]
	Latent TNFα	Bioavailable TNFα	[59]
	Syndecan-1	CXC1-chemokine gradient	[62]
	Osteopontin	Increased bioactivity	[97]
	Cellular membrane bound FasL	Active/inactive soluble FasL	[100,101]
	VEGF	activation	[89]
MMP-8	α1-antitrypsin	Inactive serpinA1	[60]
	CXCL5	Increased bioactivity	[54]
	IL-8	Activation	[102]
MMP-9	α1-antitrypsin	Inactive serpinA1	[52]
	IL-1β	Inactivation of IL-1β	[61]
	Pro-IL-1β	Activation of IL-1β	[55]
	CXCL5	Inactivation	[54]
	IL-8	Potentiates the activity of IL-8	[65]
	SDF-1	Inactive chemokine	[57]
	Latent TGF-β	Activation	[90]
	Latent TNF-α	Bioavailable TNF-α	[60]
	IL-2Rα	Cleavage of IL-2Rα	[80]
	IGFBP-1	Bioavailable IGF	[94]
	VEGF	Activation	[89]
MMP-11	α1-antitrypsin	Inactive serpinA1	[103]
	IGFBP-1	Bioavailable IGF	[94]
MMP-12	Latent TNF-α	Bioavailable TNF-α	[104]
MMP-13	α1-antichymotrypsin	Inactive serpin	[60]
	Latent TNF-α	Bioavailable TNF-α	[39]
	Latent TGF-β	Activation	[105]
	MCP-3	CC chemokine receptor antagonists	[58]
	SDF-1	Inactive chemokine	[57]
MMP-14	MCP-3	CC chemokine receptor antagonists	[58]
	SDF-1	Inactive chemokine	[57]
MMP-16	VEGF	Activation	[89]
MMP-17	TNFα	Bioavailable TNF-α	[60]
MMP-19	VEGF	Activation	[89]
MMP-26	α1-antitrypsin	Inactive serpinA1	[106]

The N-terminal signal peptide is required for secretion of MMPs. All MMPs contain a highly homologous catalytic domain responsible for the proteolytic activity, as well as a propeptide, which regulates MMP activity by interacting with the Zn^{2+} ion in catalytic pocket through a conserved cysteine residue [7,8]. This covalent interaction, "cysteine switch" retains the enzyme in the latent, catalytically inactive state. The C-terminal hemopexin-like domain is present in all MMPs except matrilysins and MMP-23 and is involved in substrate recognition. Gelatinases contain a series of fibronectin type II inserts in the hemopexin domain, which alleviate binding to collagen and gelatin. MT-MMPs are localized on the cell surface by either a transmembrane domain followed by a short cytoplasmic tail or a GPI anchor.

Collagenases (MMP-1, 8, and -13) are abundant secreted MMPs and they are able to cleave native fibrillar collagens of types I, II, and III, which are resistant to proteolysis by most proteinases. They are expressed by various types of cells, but MMP-8 is mainly synthesized by neutrophils during their maturation and stored in their intracellular secretory granules [9]. Gelatinases were initially named due to their ability to cleave denatured collagen (gelatin). MMP-2 and -9 (gelatinases A and B, respectively) are expressed by several types of cells. Stromelysins, MMP-3 (stromelysin-1) and -10 (stromelysin-2) present a wide substrate specificity and cleave for example gelatin, fibronectin, and laminin in contrast to MMP-11 (stromelysin-3). Matrilysins are the smallest human MMPs lacking the C-terminal hemopexin-like domain. MMP-7 (matrilysin-1) is not able to cleave intact fibrillar collagens, but it can digest other ECM components, such as gelatin, laminin, fibronectin, vitronectin, and elastin. MMP-26 (matrilysin-2, endometase) has a more limited substrate specificity than MMP-7. It is the only MMP that does not contain the cystein switch mechanism to keep the molecule in latent form [10]. MT1-MMP and MT2-MMP (MMP-14 and -15, respectively) present largely overlapping substrate specificities and they are capable of cleaving many ECM proteins, *e.g.* native fibrillar collagens, gelatin, fibronectin, and vitronectin. MT3-MMP (MMP-16) and MT5-MMP (MMP-24) are less well characterized, but the structure of MT3-MMP shows close homology to MT1-MMP [11]. MT4- and MT6-MMPs (MMP-17, and -25, respectively) are structurally distinct from other MT-MMPs, since they are linked to cell membrane by a GPI anchor, whereas the other MT-MMPs contain a membrane spanning domain. MT4- and MT6-MMPs interact with lipid rafts on cell membrane *via* their GPI anchor and may this way be subject to internalization and recycling [12]. MT4- and MT6-MMPs cleave a limited number of ECM components, including gelatin. MT6-MMP also cleaves collagen type IV, fibronectin and laminin [12].

2.2. Regulation of MMP expression and activity

The proteolytic activity of MMPs is normally low in healthy, intact tissues. The production of MMPs by cells *in vivo* is induced by various stimuli and the proteolytic activity of the enzyme is in turn regulated by various activators and inhibitors. The expression of MMPs is upregulated at transcriptional level by many inflammatory cytokines including tumor necrosis factor-α (TNF-α), and by growth factors, including epidermal growth factor (EGF) and transforming growth factor-β (TGF-β). The expression of MMPs is also regulated by hormones, tumor promoters, cell–cell contact, and cell–ECM interactions [13,14]. Expression of certain MMPs, *e.g.* MMP-1, -3, and -2 is also regulated at post-transcriptional level by modulation of mRNA stability [15,16]. There is also increasing evidence for epigenetic regulation of MMPs and the promoters of several MMP genes contain CpG islands that can be methylated resulting in silencing of the gene [17].

In general, most MMPs are secreted as inactive zymogens and are subsequently activated in the extracellular space. The activation of proMMP requires disruption of the cystein switch, *i.e.* the covalent bond between the thiol group of cystein residue in the propeptide and the zinc ion in the catalytic site. Several proteinases, *e.g.* plasmin, trypsin, kallikrein, mast cell tryptase and other MMPs can cleave the propeptide and result in disruption of the cystein switch [7,8]. In addition, reactive oxygen and hypochlorous acid generated by leukocytes in inflammatory processes may interact with the cystein switch and regulate activity of MMPs [18]. The furin cleavage site positioned between catalytic domain and propeptide in MT-MMPs and in MMP-11 serves as an alternative activation site for furin, a calcium-dependent serine endopeptidase, in these MMPs [19]. Activation of MMPs by other MMPs by proteolytic processing results in generation of a complex proteinase web in tissue.

Once activated, the activity of MMPs is regulated by general protease inhibitors, *e.g.* α2-macroglobulin and α1-antiprotease, and by specific inhibitors, *i.e.* tissue inhibitors of metalloproteinases (TIMPs). The TIMP family consists of four members (TIMP-1, -2, -3, and -4), which competitively and reversibly inhibit the activity of all MMPs [20]. All TIMPs show different tissue specific expression reflecting differential regulation of their gene expression. In general, all TIMPs inhibit the activity of all MMPs except TIMP-1, which does not inhibit MT1-MMP or MT3-MMP [21,22]. TIMP-3 is sequestered to ECM, whereas all other TIMPs are present in soluble form *in vivo*. MMP/TIMP balance is an important factor in controlling the overall proteolytic activity *in vivo* [1–4].

3. MMPs and inflammation

Recent observations provide evidence, that MMPs modulate various aspects of inflammation. They can regulate the integrity of physical barriers and transmigration of leukocytes from vasculature to tissue. They also regulate the availability and activity of inflammatory mediators, such as cytokines and chemokines. MMPs also generate chemokine gradients in tissue to recruit inflammatory cells to the site of injury or inflammation and can also regulate survival of inflammatory cells [5,6].

3.1. MMPs in inflammatory conditions

Studies with MMP knockout mice have elucidated the specific roles of distinct MMPs in different experimental models involving inflammation (Table 2). Interestingly, the only inflammatory phenotype without challenge is detected in MT1-MMP deficient mice, which spontaneously develop arthritis [23]. Among challenges with different experimental models, MMP-9 has been shown to play a role in mouse models of myocardial infarction, cerebral ischemia, asthma, and multiple sclerosis (experimental autoimmune encephalomyelitis (EAE)) [24–27]. In addition, elevated levels of other MMPs, MMP-2, -7, and -8 have been reported in mice with EAE [28–30].

The mechanistic role of MMP-12 in a mouse model of emphysema has been elucidated, indicating that defective activation of latent TGF-β regulates the expression of MMP-12 in macrophages [31]. MMP-8 has been shown to regulate inflammation in skin and MMP-9 may also function as an anti-inflammatory mediator in skin inflammation and in glomerulonephritis [32,33]. The role of MMP-8 in the regulation of inflammation appears complex. Recruitment of neutrophils is impaired in chemically induced epidermal carcinomas in MMP-8 knock-out mice, as compared to wild type mice [34]. However, in MMP-8-null mice, neutrophil recruitment into alveolar space after lipopolysaccharide stimulation in mouse model of acute lung injury is increased, suggesting an anti-inflammatory potential of MMP-8 [35]. MMP-3 and -9 have also been shown to play an important role in cutaneous inflammation in the mouse model for contact hypersensitivity [32]. Specifically, MMP-3 appears to be required for cutaneous inflammation and loss of MMP-9 prolongs the inflammation in skin.

Several MMPs have been shown to be involved in joint destruction in animal models of inflammatory arthritis [3,36]. For instance, expression

Table 2
Inflammatory phenotypes of MMP-deficient mice.

Genotype	Phenotype	Reference
MMP-2$^{-/-}$	Reduction of leukocyte influx to bronchoalveolar lavage	[64]
	More severe antibody induced arthritis	[107]
	Earlier onset and more severe EAE	[108]
	More severe experimental colitis	[109]
	Exacerbation of myocardial inflammation in TNF-α-induced cardiomyopathy	[110]
	Reduced vein wall inflammation and fibrosis following venous thrombosis	[111]
MMP-3$^{-/-}$	More severe collagen induced arthritis	[112]
	Impaired neutrophil influx in experimental acute lung injury	[113]
	Reduced skin inflammation in contact hypersensitivity	[32]
	Reduced neutrophil influx through blood–brain barrier	[114]
	Diminished cartilage derived chemoattractant activity of macrophages	[59]
	Decreased macrophage accumulation in atherosclerotic plaque	[59]
	Delayed appearance of lymphocytes into intestinal mucosa	[102]
	Protection against bleomycin-induced pulmonary fibrosis	[115]
MMP-7$^{-/-}$	Lack of activation of TNF-α displayed by macrophages	[59]
	Reduced neutrophil influx into the alveolar space in bleomycin-induced lung injury	[62]
	Impaired epithelial repair and shedding of E-cadherin in bleomycin-induced lung injury	[41]
	Decreased shedding of Fas ligand and apoptosis of epithelial cell	[101]
	Augmented ciliated cell formation after injury of lung epithelium	[116]
MMP-8$^{-/-}$	Increased incidence of cutaneous tumors in male mice and decreased neutrophil influx to dermis around skin tumor	[34]
	Delay in neutrophil influx into cutaneous wound	[47]
	Inhibition of LPS induced leukocyte recruitment	[117]
	Resistance to bleomycin-induced lung fibrosis	[118]
	Increased severity of arthritis	[119]
MMP-9$^{-/-}$	Less severe antibody induced arthritis	[107]
	Prolonged skin inflammation in contact hypersensitivity	[32]
	Less susceptible to development of EAE	[27]
	Reduced extent and severity of colitis	[120]
	Attenuated influx of macrophages and collagen deposition in atherosclerosis	[121]
	Resistant to bullous pemphigoid antibody induced skin blister formation	[122]
	Altered chemokine gradient and leukocyte influx in allergen-induced airway inflammation	[63,123,124]
	Increased number of leukocytes and neutrophils in IL-13-induced lung injury	[125]
	More severe lung injury in IL-1β-induced bronchopulmonary dysplasia	[126]
	Enhanced and prolonged central nervous system inflammation	[127]
MMP-10$^{-/-}$	Increased severity of ulcerative colitis	[128]
MMP-12$^{-/-}$	Decreased recovery of leukocytes, eosinophils, and macrophages in IL-13-induced lung injury	[125]
	Reduced neutrophil migration into alveolar space in acute lung injury	[129]
	Impaired TNF-α release from macrophages after smoke exposure	[103]
	Decreased influx of macrophages in smoke-induced emphysema	[130]
MMP-13$^{-/-}$	Reduced inflammatory response in cholestatic liver	[131]
	Less severe systemic inflammation of bowel disease	[39]
	Impaired experimental granulation tissue formation	[45]
MMP-14$^{-/-}$	Development of spontaneous arthritis	[23]
	Decreased macrophage infiltration in arterial aneurysms	[132]
MMP-19$^{-/-}$	Enhanced Th2-driven inflammation in allergen challenged lung	[133]
MMP-24$^{-/-}$	Abnormal degranulation of mast cells	[134]
MMP-28$^{-/-}$	Reduced inflammation in myocardial infarction	[135]
	Accelerated influx of macrophages to lung in pneumonia	[136]

Experimental autoimmune encephalomyelitis, EAE.

of MMP-9 and -13 is potently upregulated in murine antigen induced arthritis model and the expression pattern correlates with the course of synovial inflammation [37]. Furthermore, expression of MMP-13 in mouse synovial tissue induced the onset of inflammation characterized by increased cytokine and chemokine production and inflammatory cell influx [38]. Additional evidence for the proinflammatory role of MMP-13 was provided by a recent study, showing that activation of TNF-α by MMP-13 plays an important role in the mouse model of inflammatory bowel disease (Fig. 1A), suggesting also a possible mechanistic role for MMP-13 in pathogenesis of intestinal ulcerations [39,40].

3.2. MMPs in tissue injury

Proteolysis is an important feature of tissue repair. Wound healing in the skin can be divided to three stages: 1) hemostasis and inflammation, 2) re-epithelialization and 3) granulation tissue formation and tissue remodeling [2]. The cells participating in wound repair specifically produce several MMPs and regulate their activity. For example, MMP-7 regulates cell-cell contacts and epithelial cell migration by shedding E-cadherin from adherent junctions [41]. MMP-7 also plays an important role in tissue repair in airway epithelium [42]. MMP-1 and MMP-9 play a role in reepithelization in tissue repair in skin and lung, respectively. Expression of MMP-1 is specifically upregulated in migrating keratinocytes in the edge of healing cutaneous wound. MMP-1 cleaves collagen type I and thus alters the affinity of keratinocyte α2β1 integrin to type I collagen [43]. MMP-9, a proteinase, which cleaves and inactivates the serine protease inhibitor α1-antitrypsin (SerpinA1), is released by activation of neutrophils. α1-antitrypsin in turn is a potent inhibitor of neutrophil elastase, which exerts anti-microbial activity. Thus, MMP-9 can this way indirectly promote the activity of neutrophil elastase. MMP-3 and -13 are also involved in cutaneous wound repair. In MMP-3 deficient mice healing of excisional wounds is impaired [44]. Recent observations with MMP-13 null mice show that MMP-13 plays an important role in growth of granulation tissue, and regulates angiogenesis, inflammation, and proteolysis in granulation tissue [45]. Although inflammation is an important feature of normal wound repair, persistent inflammation results in impaired wound healing and plays an important role in the pathogenesis of chronic dermal ulcers [46]. Accordingly, a delay in wound closure was noted in MMP-8 deficient mice, associated

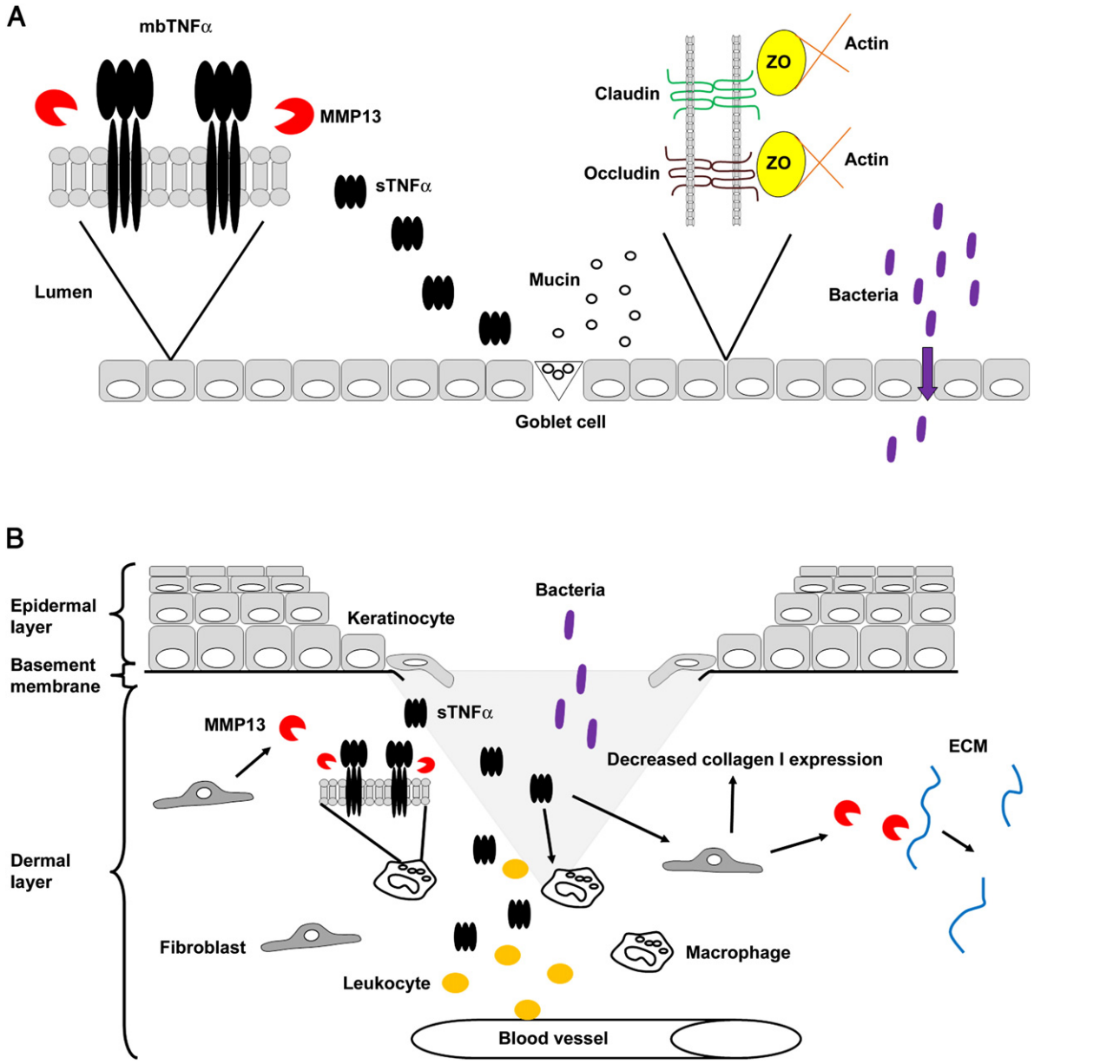

Fig. 1. Regulation of inflammatory responses by MMP-13. **(A)** The role of MMP-13 in inflammatory bowel disease. The lipopolysaccaride challenge in the intestine induces production of MMP-13. This leads to increased cleavage of the cell membrane anchored TNF-α (mbTNFα) by MMP-13 to soluble, bioactive TNF-α (sTNFα), which induces mucin expression and secretion in Goblet cells. Furthermore, sTNF-α induces caveolin dependent endocytosis, which results in destabilization of tight junctions consisting of claudin, occludin and zona occludens-1 (ZO) protein, and in increased permeability of epithelial cell layer. Modified from [39]. **(B)** A proposed model for the role of MMP-13 in the pathogenesis of chronic dermal ulcers. Fibroblast-derived MMP-13 activates TNF-α by cleaving it to soluble form (sTNFα) on the cell surface of macrophages. TNF-α stimulates the inflammatory process by attracting inflammatory cells to the wound tissue. TNF-α also inhibits the production of collagen type I by fibroblasts and enhances the expression of MMP-13 by fibroblasts. Increased activity of MMP-13 promotes degradation of collagen type I and other extracellular matrix (ECM) components, and this way inhibits the migration of keratinocytes. Impaired reepithelialization of the wound allows colonization of the wound bed with bacteria, which further promote inflammation.

with delayed initial influx of neutrophils followed by persistent inflammation [47]. In this context, it is also interesting to note, that MMP-13 is expressed by fibroblasts in chronic dermal ulcers characterized by persistent inflammation [48]. It can therefore be proposed, that fibroblast derived MMP-13 regulates activation of TNF-α in chronic ulcers and may this way promote persistent inflammation (Fig. 1B).

3.3. MMPs and barrier function

Loosening of intercellular junctions between endothelial cells increases vascular permeability and leukocyte transmigration through endothelial cell surface. MMPs have been revealed to cleave endothelial cell junctional proteins and thus allow extravasation of plasma proteins and inflammatory cells. MMP-2 and -9 can cleave occludin, a transmembrane component of endothelial tight junctions [49]. MMP-13 has also been shown to promote disorganization of tight junction protein ZO-1 and hyperpermeability of blood–brain barrier in response to hypoxia [50]. In addition, vascular endothelium (VE)-cadherin, a major component of endothelial adherent junctions is cleaved by MMP-7, increasing vascular permeability [51]. MMP-9 has been shown to play a role in skin blister formation in a mouse model of bullous pemphigoid, by promoting degradation of basal keratinocyte hemidesmosomal proteins by neutrophil elastase by inhibiting α1-

antitrypsin [52,53]. In addition to promoting inflammation, MMP-13 can participate in the disruption of intestinal barrier in a mouse model of inflammatory bowel disease (Fig. 1A) [39].

3.4. MMPs and inflammatory cytokines and chemokines

Chemokines control migration and activation of inflammatory cells. Evidence emerging from several studies has revealed a potential role for MMPs in the regulation of chemokine gradients in inflamed tissue, this way regulating inflammatory cell recruitment to the site of inflammation or injury. Depending on the context, MMPs can activate, inactivate or antagonize the biological functions of cytokines and chemokines by proteolytic processing and this way either promote or suppress inflammation (Table 1) [39,54–58]. Furthermore, stimulation of inflammatory cells by cytokines and chemokines may in turn induce production of MMPs. A list of non-matrix substrates of MMPs relevant in inflammation is presented in Table 1.

Both TNF-α and IL-1β are potent pro-inflammatory cytokines regulated by MMPs. Several MMPs can cleave and activate TNF-α (Table 1) [39,59,60]. TNF-α plays a central pathogenic role in autoimmune diseases, such as rheumatoid arthritis [3]. IL-1β produced by macrophages is also an important mediator in inflammatory responses. MMPs present a dual role in processing of IL-1β, since certain MMPs (MMP-2, -3, and -9) can activate IL-1β, but proteolytic activity of these MMPs against active form of IL-1β has also been demonstrated [55,61].

As discussed above, chemokines play an important role in inflammation by attracting inflammatory cells to the site of inflammation in tissue. Chemokines can be divided to two subgroups: *CC chemokine* family (containing MCP-1, -2, -3, and -4 and macrophage inflammatory peptide-1α and -1β) and *CXC chemokine* family (containing IL-8, neutrophil activating peptide 2 (NAP-2) and stromal cell-derived factor-1 (SDF)-1α and -1β). The bioavailability of chemokines is regulated at the level of biosynthesis, proteolytic processing, and also by mobilization of the chemokines from cell surface molecules or ECM proteins. In addition, the activity of chemokines depends on the expression of the specific receptor on target cell surface. Various MMPs are able to control the mobilization of chemokines. For example, syndecan-1 binds neutrophil chemokine CXCL1 *via* its heparan sulphate side chains on the surface of epithelial cells. In lung injury, MMP-7 cleaves and sheds the ectodomain of syndecan-1 on airway epithelial cell surface releasing CXCL1–syndecan ectodomain complex and this way generating a gradient of CXCL1 chemokine [62]. In the model of allergic lung inflammation, reduction in the influx of inflammatory cells to the alveolar space was noted in MMP-9-null mice [63]. In the same model the role of MMP-2 in leukocyte migration to the inflammation site was also demonstrated. MMP-2 deficient mice presented diminished CCL11 chemokine gradient and influx of eosinophils into airway lumen [63,64]. However, loss of MMP-9 has a more potent effect on inflammation in this model than MMP-2 since various chemokines are affected by lack of MMP-9 resulting in disturbed influx of both neutrophils and eosinophils [63].

As mentioned above, MMPs also present anti-inflammatory effects by cleaving chemokines to their receptor antagonists (Table 1) [58]. For example, CC-chemokine ligand 7 (MCP-3) is cleaved by MMP-2 generating a truncated form of the chemokine, which is still able to bind to the receptor but serves as an antagonist, this way inhibiting inflammatory response [56]. Similarly, MCP-1, -2, and -4 are substrates for MMPs (MMP-1, -3, -13, and -14), which also generate antagonistic cleavage products of these chemokines [58]. CXC ligands (CXCL) may also serve as substrates for MMPs. Processing of CXCL8 (IL-8) by MMP-9 increases the chemotactic activity of IL-8 but processing of other CXC-ligands, like CXCL5 and -6 by MMP-9 results in inactivation of these chemokines [65]. Similarly, proteolytic processing of SDF-1 inhibits its ability to bind to its receptor (Table 1) [57]. The role of MMP-8 in cleavage of mouse CXCL5 and neutrophil influx has been highlighted in several studies. MMP-8 deficient mice show impaired CXCL5 release from ECM and reduced mortality in the TNFα-induced lethal hepatitis mouse model [66]. In addition, MMP-8 activity is required for lipopolysaccharide (LPS) induced neutrophil chemotaxis (Fig. 2). TGF-β produced by stromal fibroblasts induces the expression of MMP-2 that is a potent inactivator of MCP-2 (CCL8) [16,58].

4. MMPs and inflammation in cancer

Immune system plays an important role in cancer cell surveillance by recognizing and attacking cancer cells *in vivo*. However, cancer cells can escape the immune attack in various ways. On the other hand, chronic inflammation is associated with progression of several types of cancer, *e.g.* in skin, prostate, liver, breast, urinary bladder, and gastric mucosa [67]. Inflammation is necessary to promote cancer initiation and progression *via* vascularization and remodeling of tumor microenvironment, which are important for tumor cell survival [68]. Inflammation in cancer tissue is also necessary for suppression of innate immune response against tumor cells. MMPs may exert immune regulatory function in tumor microenvironment and they may help cancer cells escape immune surveillance [67,68].

The role of MMPs in cancer progression has been extensively studied in various animal models [1]. In addition to tumor cells, stromal cells play an important role in cancer progression, for example by producing MMPs. One example of this is stromal fibroblast derived MMP-11, which has been demonstrated to support the growth of breast cancer cells *in vivo* [69]. The association between MMPs and inflammation in cancer progression has also been emphasized. A good example of this association is that transplantation of wild-type mouse MMP-9 expressing bone marrow cells to MMP-9 deficient mice effectively restores development of cutaneous squamous cell carcinoma [70].

Cancer progression is regulated by growth factors, chemokines and cytokines either directly *via* their angiogenic or angiostatic activity or indirectly by attracting anti- or precancerous inflammatory cells [71]. As discussed above, several studies have unveiled the proteolytic activation or inhibition of growth factors, cytokines, and chemokines by various MMPs (Table 1). Several types of malignant cells produce TNF-α, which can promote cancer cell survival *via* NF-κB pathway [72]. As discussed above, various MMPs can activate cell surface bound TNF-α (Table 1) and this may be an important step in tumor progression [72,73]. As also noted above, MMPs can process chemokines to antagonistic anti-inflammatory modulators [58]. For example, CCL/MCP and CXCL chemokines and their receptors are also processed by MMPs (Table 1). MMPs also regulate T cell responsiveness, which may have an important effect on the adaptive antitumor immune response. For example, MMP-8, -9, and -12 modulate the bioactivity of CXCL11, a Th1 lymphocyte-attracting chemokine. The receptor for this chemokine, CXCR7, is expressed on various types of tumor cells and activates signaling pathways that support cancer cell survival and growth [74]. MMP-1 and -3, among others have been shown to cleave CCL8/MCP-2 and proteolytic processing of this molecule may suppress the antitumor activity of CCL8/MCP-2 in melanoma [75]. CXCL12 (SDF-1) serves as a ligand for CXCR4 receptor expressed by various types of cancer cells, and function blocking of this receptor has been shown to inhibit breast cancer metastasis [76]. Interestingly, CXCL12 is cleaved and inactivated by several MMPs, which this way may inhibit the prometastatic effect of CXCL12 [77].

Proteolytic remodeling of ECM may also have secondary effects on immune control, as some ECM components processed by MMPs may exert chemotactic function. In airway inflammation ECM degradation generates a peptide that presents chemotactic activity through activation of CXC chemokine receptor on neutrophilic granulocytes [78]. Furthermore, MMP-12 cleavage of neutrophil elastase has been shown to generate neutrophil attracting peptides [79].

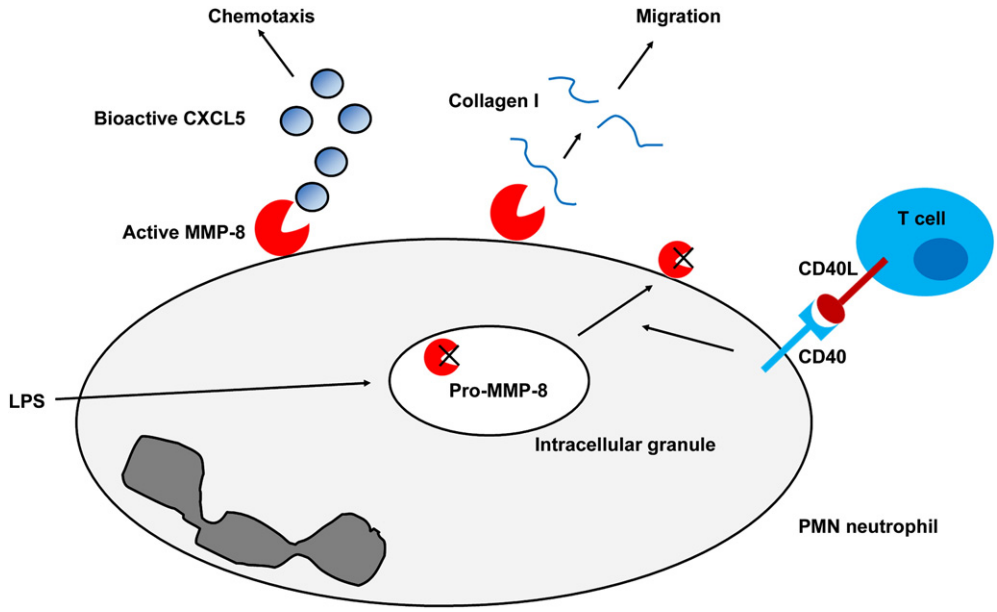

Fig. 2. Regulation of inflammation by neutrophil MMP-8. Latent MMP-8 (pro-MMP-8) is stored in intracellular secretory granules of neutrophils. The exocytosis of the secretory granules is induced by external stimuli such as lipopolysaccharide (LPS) or CD40 signaling and the secreted latent MMP-8 is activated in pericellular space. Cell surface bound MMP-8 is more stable than the soluble one. Active MMP-8 increases bioavailability of the chemokine CXCL5, which enhances chemotaxis of neutrophils. Thus, LPS-induced MMP-8 release from neutrophils and subsequent CXCL5 activation provides a cellular activation mechanism which acts in a feed-forward manner to promote neutrophil recruitment to the site of inflammation. In addition, active MMP-8 cleaves collagen type I and this way promotes the migration of neutrophils to the site of inflammation.

MMPs play a role also in cancer-mediated immune suppression by regulating the response of T lymphocytes against tumor cells. TGF-β-elicited inhibition of T cell response against cancer cells may be regulated by MMPs, as several MMPs can cleave latent TGF-β to active form (Table 1). IL-2 is a cytokine, which stimulates proliferation of T cells by activating cell signaling *via* IL-2Rα. Certain MMPs can cleave IL-2Rα on T cell surface and this way regulate proliferation of these cells (Table 1). For instance, in cervical cancer MMP-9 produced by the tumor cells cleaves IL-2Rα on the surface of activated T cells and suppresses their proliferative capacity [80]. The proteolytic product of α1-antitrypsin generated by MMP-11 has been shown to decrease the sensitivity of cancer cells against the cytotoxic effect of natural killer cells [81].

The neutrophil influx into the tumor microenvironment may also correlate with poor prognosis [82]. MMP-9 induces the chemotaxis for neutrophils by cleaving neutrophil-attracting IL-8 and MMP-7 releases chemotactic complex of CXCL1 and syndecan-1 by cleaving syndecan-1 from the cell surface [5,62]. MMP-13 promotes growth of cutaneous SCC xenografts *in vivo* [83]. The tumor growth promoting mechanism of MMP-13 is not known but it might involve the cleavage and activation of TGF-β, which exerts an immune suppressive effect (Table 1).

5. Concluding remarks

In this review we discuss the role of MMPs as regulators of inflammatory responses. MMPs are clearly important effectors in inflammation both in physiological situations, such as tissue repair, and in pathological inflammatory conditions and cancer, as has been demonstrated with MMP null mice in various models (Table 2). The association of MMPs with various human inflammatory diseases and cancer has obviously suggested them as potential therapeutic targets in these diseases. However, it is evident, that MMPs serve both as targets and antitargets in inflammatory diseases, as they can exert both proinflammatory and anti-inflammatory effects [84]. This may be one of the reasons for disappointing outcome of the previous clinical trials with broad spectrum MMP inhibitors [84,85].

There is increasing evidence for non-matrix substrates of MMPs that are related to regulation of inflammatory processes (Table 1). In addition, new methods have been developed for identification of the substrates of MMPs *in vivo e.g.* in inflammatory processes in tissues [86]. Detailed information on the substrates of MMPs may offer a more specific and effective way of inhibiting MMP function in specific conditions, for example by blocking the cleavage site in specific substrates or by inhibition of the bioactivity of the substrate. Thus, more precise information on the MMP–substrate interaction may offer novel strategies for therapeutic intervention in inflammatory diseases and cancer without interfering with the beneficial effects of MMPs.

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