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Matrix Metalloproteinases as Modulators of Inflammation

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Abstract

An increased expression of members of the matrix metalloproteinase (MMP) family of enzymes is seen in almost every human tissue in which inflammation is present. Through the use of models of human disease in mice with targeted deletions of individual MMPs, it has become clear that MMPs act broadly in inflammation to regulate barrier function, inflammatory cytokine and chemokine activity, and the generation of chemokine gradients. Individual MMPs regulate both normal and pathological inflammatory processes, and therefore, developing rational therapies requires further identification of specific MMP substrates and characterization of the downstream consequences of MMP proteolytic activity.

Keywords

matrix metalloproteinase; inflammation; cytokine; chemokine

1. Introduction

The classic features of inflammation, as described by Celsus of rubor (redness), tumor (swelling), dolor (pain), and calor (heat) are the symptomatic manifestations of complex tissue responses to harmful stimuli such as invading pathogens, damaged cells, and other irritants. Acute and chronic inflammation are both characterized by several fundamental processes including exudation of plasma proteins, recruitment of leukocytes, and activation of cell and plasma derived inflammatory mediators. Increased expression of matrix metalloproteinases (MMPs) has been observed in almost every human disease in which inflammation is present, and recent insights from *in vitro* and mouse models of human disease processes suggest that MMPs have evolved to serve broad functions in defense, injury, inflammation and repair [1]. Although inflammation is essential for host defense and tissue repair processes, when unregulated or excessive, it can contribute to ongoing tissue injury, organ dysfunction, and chronic disease. Indeed, experimental evidence supports the idea that MMPs can either protect against or contribute to pathology in inflammatory processes.

The varied physiologic and pathologic inflammatory processes regulated by MMP proteolytic activity are dependent on multiple factors, including MMP expression, location, and substrate availability. Hence, multiple functions may be attributed to a single MMP depending on the

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cell type and disease state. Broadly speaking, MMPs contribute to inflammatory processes, and they do so by regulating physical barriers, modulating inflammatory mediators such as cytokines and chemokines, and establishing chemokine gradients in inflamed tissues that regulate the movement of leukocytes at sites of infection or injury. It has been hypothesized and demonstrated *in vitro* that leukocytes use MMPs to degrade matrix proteins to allow for egress; however, there is little direct evidence of this occurring *in vivo*. Rather, some mechanisms whereby MMPs do discretely affect leukocyte migration include proteolytic processing of chemokines and chemokine receptors, and release of chemotactic fragments or accessory proteins [2–6]. The attribution of specific roles for individual MMPs in inflammatory processes is best made by linking distinct proteolytic events to individual MMPs, therefore, the discussion here will focus on well-defined substrate cleavage processes and molecular mechanisms that illustrate MMP function in inflammation.

2. Identifying MMP substrates in inflammation

Although many MMPs have been causally linked to many diseases and inflammatory proteins, the substrates that are targeted to mediate these effects remain largely unknown. MMPs either shed or cleave proteins, thereby influencing the substrates' activity, localization and function. Importantly, MMPs can have more than one substrate, providing one explanation why multiple distinct injury and organ-dependent inflammatory phenotypes can be seen in one MMP-null mouse strain.

The identification of MMP substrates is not a straightforward process, and there are several approaches that have been used to identify candidates. Early approaches focused on incubating a purified proteinase with a candidate substrate and assessing for cleavage products. However, this *in vitro* approach does not demonstrate what the proteinase is actually doing *in vivo*. With the use of gene-targeting strategies, combined with observation and deduction, physiologic substrates have been identified (Table 1) [2,7,8]. More unbiased approaches include exosite scanning that employs protease substrate-binding domains as yeast two hybrid baits [9]. This technique has identified that the hemopexin domain of MMP2 binds to monocyte chemoattractant protein-3 (MCP-3), leading to its cleavage and converting it from a receptor agonist to a potent antagonist [4]. This method has also identified other MMP substrates, such as MCP-1, MCP-2, MCP-3, MCP-4, that are all processed by multiple MMPs, resulting in similar conversion from a receptor agonist to antagonist [4,5,10].

An additional approach that is being employed is proteomics [11]. By comparing proteins from tissue or cell models under conditions where the enzyme is expressed versus that from an MMP-null mouse, one can identify new (i.e., shed) or lost proteins (i.e., cleaved or degraded). These proteins are then identified by mass spectrometry. The traditional method of separating the proteins is two-dimensional polyacrylamide gel electrophoresis (2-D PAGE), and a 2-D gel-based approach was used to identify Ym1, S100A8 and S100A9 as potential substrates of MMP2 and MMP9 in a mouse model of allergic airway inflammation (discussed in further detail below) [12]. However, gel-based approaches lack proteome coverage for proteins having extreme isoelectric points or molecular masses. Consequently, alternative strategies using protein separation by chromatography followed by mass spectrometry have improved the resolution of protein separation, and subsequently, that of substrate identification [13].

After candidates have been identified, these potential substrates need to be verified by more basic biological testing. Such approaches include evaluating co-localization of the proteinase and its substrate, determining the cleavage site(s) and specificity by targeted mutagenesis, and evaluating loss-of-function and gain-of-function in *in vivo* systems [1]. Thus far, these techniques have identified novel MMP substrates in inflammation that serve as key effectors of leukocyte trafficking (Table 2). However, further studies are needed not only to identify

additional MMP substrates but also to verify that MMP-mediated proteolysis of candidate proteins occurs *in vivo*, and to determine the physiologic and pathologic consequences of these protein cleavage processes.

3. MMPs in barrier function

A breakdown of epithelial and endothelial barriers is both a stimulus for inflammation in tissue injury and a component of normal inflammatory processes that permits leukocyte influx into areas of infection and tissue damage. The regulation of vascular permeability and transmigration of leukocytes across endothelial surfaces includes the disassembly of intercellular junctions between endothelial cells, and one mechanism of this regulation is MMP proteolysis of endothelial cell junctional proteins. Matrix metalloproteinases, including MMP7 can shed VE-cadherin, a major component of endothelial adherens junctions [14]. Similarly, MMP2 and MMP9 can regulate endothelial permeability by cleaving occludin, the transmembrane component of endothelial tight junctions, in the opening of the blood-brain barrier (BBB) [15], a process that may contribute to enhanced permeability and inflammation in autoimmune encephalitis, hypoxic brain injury, and other CNS inflammatory diseases [16, 17]. MMP-dependent VE-cadherin proteolysis may also contribute to blood-retinal-barrier disruption in early diabetic eye disease [18]. BBB tight junctions are also targets of leukocyte-derived MMP activity. Dendritic cells (DC) migration across the blood brain barrier is increased in CNS autoimmunity and inflammation and a recent report demonstrates that MIP-1 alpha stimulated DC transmigration across brain endothelial cells is in part mediated by MMP-mediated disruption of endothelial occludin [19]. Similarly, dengue virus infected dendritic cells overproduce MMP9, and to a lesser extent MMP2, that is associated with decreased endothelial PECAM-1 and VE-cadherin staining in vascular endothelium *in vitro* and *in vivo*, which may contribute to the marked increase in vascular permeability seen in dengue hemorrhagic shock [20]. Thus, opening of endothelial barriers by MMP activity may be a mechanism that allows passage of plasma proteins and inflammatory cells into otherwise privileged compartments. Further work needs to be done to define the relative physiological and pathological contributions of these processes.

MMPs also function during tissue injury via proteolysis of epithelial cell junction proteins and regulation of cell-matrix interactions. In vaginal epithelium, estrogen-dependent down-regulation of tight junctions and vaginal epithelial permeability is mediated by MMP7 generation of a 50kD occludin cleavage product that is distinct from occludin cleavage products generated by proteinase-K, plasmin, or MMP2 [21]. MMP9 contributes to the skin blistering seen in a mouse model of autoimmune bullous pemphigoid by regulating neutrophil elastase (NE) cleavage of the hemidesmosomal protein, bp180, by proteolytic inactivation of the serpin alpha-1 proteinase inhibitor [22]. MMPs also promote re-epithelialization and restoration of epithelial barriers to bacteria or other invading pathogens. In damaged airway mucosa, MMP7 is expressed by wound-edge epithelial cells, and in MMP7-null mice, airway mucosal wound healing is markedly impaired [23]. MMP7 facilitates re-epithelialization by shedding E-cadherin from adherens junctions to remodel cell-cell contacts and facilitate cell migration [7]. Migrating keratinocytes in healing skin wounds up-regulate the expression of MMP1, which cleaves type 1 collagen to alter its affinity for $\alpha_2\beta_1$ -integrins expressed on wound-edge keratinocytes. This mechanism allows the migrating cells to detach and reattach as they move across the provisional wound matrix [24]. MMP3 also functions in skin wound repair. Healing of excisional wounds is impaired in MMP3-null mice because of inadequate organization of actin purse-string formation in stromal fibroblasts and failure of wound contraction during the first phase of wound healing [25].

4. MMPs regulate inflammatory mediators

Inflammation is propagated from the initial site of tissue injury or infection by the diffusion of small molecules that act locally and more distantly. Exogenous mediators, including bacterial products and toxins such as endotoxin, or lipopolysaccharide, a cell-wall component of gram-negative bacteria, are potent activators of host immune responses. To date, no pathogen protein has been demonstrated to be a substrate of MMP activity, although there are numerous examples by which pathogens activate MMP expression in host cells (reviewed in [26]). Among the endogenous inflammatory mediators are cytokines and chemokines that induce the migration of leukocytes to sites of injury or infection and activate the cells to mount an immune response [27]. Several lines of evidence show that MMPs can either promote or repress inflammation by the direct proteolytic processing of inflammatory cytokines and chemokines to activate, inactivate, or antagonize chemokine function [3–5].

4.1. Cytokine activation

MMP cleavage of specific protein substrates often results in a gain-of-function. MMP substrates that are important in activating or amplifying inflammatory responses include cytokines, chemokines, and accessory proteins that bind, retain or concentrate chemokines. Tumor necrosis factor- α (TNF- α) is a potent pro-inflammatory cytokine, and increased production of TNF- α is seen in septic shock and several autoimmune diseases including rheumatoid arthritis, Crohn's disease, and multiple sclerosis [28]. TNF- α is expressed on T-cells and macrophages as a 26 kDa membrane-bound protein (pro-TNF- α) that is activated by cleavage to a 17 kDa soluble cytokine by TNF converting enzyme (TACE), identical to ADAM17, a member of the disintegrin family of metalloproteinases [29,30]. However, several MMPs also have TNF converting activity *in vitro* (including MMP1, -2, -3, -9, -12, -14, -15, and -17), and MMP-7 and MMP-12 have been shown to activate pro-TNF in isolated macrophages [31,32]. MMP-7 processes TNF- α to release active TNF from macrophages to generate an MMP-3 dependent chemoattractive gradient regulating macrophage infiltration in resorption of herniated discs [33,34]. Thus, whereas TACE is likely the primary TNF converting enzyme in sepsis or chronic inflammation, in tissue resorption or resolution of injury, MMPs may have physiological roles in constitutive TNF- α shedding.

Interleukin IL-1 β is another potent pro-inflammatory cytokine that requires proteolytic processing for activation. Similar to the case for TNF- α , the primary physiological protease IL-1 β is IL-1 β -converting enzyme (ICE, also known as caspase-1), but the presence of active IL-1 β in ICE-null mice suggests roles for other proteases. Indeed, several MMPs (MMP2, -3, and -9) can activate the IL-1 β precursor to the active 17-KDa form [35]. Interestingly, MMP3 (and to a lesser extent, MMP1, -2, and -9) can degrade the mature IL-1 β cytokine, suggesting potentially dual roles for MMPs in either promoting or repressing IL-1 β effects [36]. Thus, further investigation into the MMP regulation of IL-1 β activity in normal and pathological processes is warranted.

4.2. Chemokine activation

The N-terminal domain of the mature CXC chemokine CXCL8 (IL-8) and LIX (the mouse equivalent of human CXCL5 and CXCL6) are processed by MMP9 and MMP8 respectively, resulting in products that have more potent chemoattractant activities than the full-length molecules [37,38]. Similar to other cytokines, CXCL5 can be processed by several proteinases, including MMP9, and indeed high concentrations of cleaved CXCL5 were recovered from inflamed lungs of MMP8-null mice [39]. The *in vivo* relevance of MMP8 processing of LIX was demonstrated using a TNF- α /GalN model of lethal hepatitis in MMP8-null mice. MMP8 is primarily expressed by neutrophils, and these mice had impaired LIX release from the ECM with reduced mortality and neutrophil influx into the liver suggesting that MMP8 proteolysis

of either LIX or an accessory protein that restrains LIX, is required for generation of a key chemokine gradient. If release of LIX is achieved by MMP8 proteolysis of the N-terminus, then neutrophil influx would be enhanced via the generation of a more potent chemoattractant [40]. MMP8-dependent neutrophil recruitment and resolution has been shown to be altered in other injury models. Fewer neutrophils are detected in the dermis surrounding chemical-induced skin tumors in MMP-8-null mice compared to wildtype mice [39], and a follow-up study showed that neutrophil influx into skin wounds was delayed early after injury [41]. However, at later time points the wounds of MMP8-null mice showed impaired wound closure as compared to wounds in wildtype mice, and this was associated with persistent neutrophil inflammation and reduced neutrophil apoptosis. This defect could be rescued with bone marrow transplantation. These results suggest roles for MMP8 both in initiation and resolution of inflammation. Further evidence for a role for MMP8 in limiting inflammation is provided by observations of increased neutrophil recruitment into the alveolar space after intratracheal LPS administration in these same MMP8-null mice as compared to wildtype mice [42]. Indeed, the studies discussed here indicate that multiple proteinases, including MMPs, can process various cytokines and chemokines, and suggest that different mechanisms of processing may be cell-type and disease process specific.

4.3. Chemokine inactivation and antagonism

MMPs also modulate inflammation by proteolytic modification of chemokines to inactive or antagonistic derivatives. Several MMPs can cleave the CXC-chemokine ligand 12 (CXCL-12/SDF-1) *in vitro* including MMP1, -2, -3, -9, -13, and -14, and MMP cleavage of CXCL-12 results in loss of its ability to bind its cognate receptor, CXCR4 [3]. Another consequence of MMP chemokine cleavage is the conversion of the active chemokine to an antagonist. CC chemokine ligand 7 (CCL7/MCP3) is cleaved by MMP2 in which removal of the four (N)-terminal amino acids from the active CCL7 chemokine molecule converts it to a truncated form that can still bind to its CC chemokine receptor, but cannot activate it, thus functioning as a receptor antagonist [4]. Similarly, (N)-terminal cleavage of CCL2 (also known as MCP1), CCL8 (MCP2), and CCL13 (MCP4) by MMP1, -3, -13, and -14 generate truncated forms that function as potent receptor antagonists of their cognate CC chemokine receptors in cell migration assays *in vitro* [5]. Additionally, in an *in vivo* model of carrageenan-induced inflammation in rat paws, the MMP-truncated CC chemokines induced a greater than 66% reduction in inflammatory edema progression after 12 hours [5].

Fractalkine (CX₃CL1) is the first member of the CX₃C family of chemokines and has been suggested to have a proinflammatory role in monocyte chemotaxis in rheumatoid arthritis [43]. Fractalkine can exist as a membrane-anchored adhesion molecule, and as a soluble form shed from the cell membrane by ADAM10 and ADAM 17 that functions as a chemoattractant [44,45]. An *in vitro* study demonstrated that soluble fractalkine can also inhibit inflammation by antagonizing MCP-1 induced transendothelial migration and chemotaxis of the monocyte cell line MonoMac6 and freshly isolated human monocytes [46]. Employing a new proteomics strategy with amine-labeled iTRAQTM mass tags (Applied Biosystems, Foster City, CA), Dean and Overall identified that fractalkine is an MMP2 substrate [47]. Moreover, they found that similar to MMP2 (N)-terminal processing of CC chemokines, (N)-terminal tetrapeptide truncation of the fractalkine chemokine domain causes loss of chemotactic activity and converts the chemokine to a potent antagonist of the CX₃CL1 receptor CX₃CR. Thus, MMP-dependent (N)-terminal processing of mature chemokines is likely a common mechanism for regulating chemokine/receptor interactions.

4.4. Chemokine gradients

Another mechanism by which MMPs control inflammation is the regulation of chemokine gradients. The function of chemokines is regulated by the level of biosynthesis, the expression

of cognate receptors, proteolytic processing, and by compartmentalization. This latter mechanism includes both the immobilization of chemokines to cell surfaces or ECM proteins, and the generation of chemotactic concentration gradients which provide directional cues for leukocyte migration. Thus, MMPs can indirectly control influx of inflammatory cells by cleaving proteins in the pericellular environment that bind chemokines.

One such example of this mechanism is MMP7-dependent shedding of syndecan-1 in acute lung injury. Syndecan-1 is a ubiquitous heparan sulfate proteoglycan (HSPG) present on the basolateral surface of epithelium. By way of its HS chains, syndecan-1 is capable of binding numerous extracellular ligands and can direct these ligands for recycling or degradation, enhance ligand-receptor interactions, or release the entire complex via shedding [48]. The neutrophil chemokine, CXCL1 (KC), is one such ligand that binds to and is spatially restrained by the HS chains of syndecan-1 at the basolateral surface of epithelial cells. In response to lung injury, both CXCL1 and MMP7 are induced, and MMP7 sheds syndecan-1 that releases the CXCL1-syndecan-1 complex to generate a chemokine gradient. MMP7-null mice that lack this shedding are unable to create a CXCL1 gradient, and thus, neutrophils fail to efflux into the alveolar space and instead remain in the perivascular space. [2,8].

MMP are capable of forming cleavage products that function similarly to chemokines. For example, MMP9-null mice are protected from lung injury and lethality of pulmonary infection with *Francisella tularensis* [49]. These mice have diminished neutrophil accumulation in the lung with no difference in neutrophil chemokines, CCL2 (MCP-1) and CXCL1 (KC) early in the injury. However, there was a significant decrease in Pro-Gly-Pro (PGP), which is a chemotactic fragment generated from MMP9-mediated hydrolysis of collagen that has homology to CXCL8 (KC) and binds and activates the CXCL8 (KC) receptor, CXCR1/2 [50]. A similar finding of diminished neutrophil recruitment was observed in *Escherichia coli*-induced abdominal sepsis. However, in this model, MMP9-null mice developed more severe sepsis and end-organ damage with reduced neutrophil recruitment to the peritoneum and impaired bacterial clearance [51]. These differences likely reflect differences in propagation and clearance of host pathogens, with *F. tularensis*, an intracellular pathogen, requiring host leukocytes for growth. In contrast, early recruitment of neutrophils is vital for *E. coli* clearance, and loss of this important innate immune response proves lethal. However, if bacterial clearance is removed from this equation, MMP9 deficiency protects against mortality in an LPS model of peritoneal sepsis, presumably by mitigating systemic inflammatory responses that can have deleterious effects on the host [52].

MMP regulation of chemokine gradients may also function in resolution of inflammation. For example, in models of allergic lung inflammation, MMP2-null mice have diminished egression of leukocytes into the alveolar space with concomitant accumulation of inflammatory cells, namely eosinophils, in the lung parenchyma. This impairment in leukocyte trafficking is associated with a diminished CCL11 (eotaxin) chemokine gradient in the alveolar space [53]. In similar models, MMP9-null mice also have diminished egress of leukocytes into the alveolar space with accumulation in the lung parenchyma. However, the effects of MMP9 are broader, as both neutrophil and eosinophil egress is affected by disruption of multiple chemokine gradients, including CCL11, CCL7, and CCL17 [54]. The *in vivo* substrate(s) mediating these effects are unknown, but possible mechanisms include MMP-mediated proteolysis of cell surface proteoglycans that bind and regulate chemokines gradients [48,54]. In a follow-up study, to identify candidate substrates underlying the observed MMP2 and MMP9 effects on allergic inflammation, Kheradmand and colleagues used a high-throughput proteomic analysis of to compare bronchoalveolar lavage fluid (BALF) from allergen-challenged mice deficient in both MMP2 and MMP9 to that from wildtype mice. Among the proteins that were differentially present in the MMP-null mice as compared to wildtype mice were three with potential chemotactic activity, including Ym1, S100A8, and S100A9, which exhibit altered

chemoattractant properties *in vitro* upon MMP-mediated proteolysis. Using function-blocking antibodies to S100A8 and S100A9, inflammatory cell egress into the alveolar space was reduced, suggesting a role for these proteins in resolution of allergic inflammation [12]. Collectively, these data support a mechanism of resolution of inflammation in allergic airway disease by the generation of chemotactic gradients to stimulate egress of inflammatory cells from tissues into the airways where they can then be cleared.

In contrast to the observed phenotypes above, MMP2-null mice exhibit more severe antibody-induced arthritis and experimental autoimmune encephalomyelitis with enhanced lymphocyte transmigration [36,55]. These enhanced inflammatory phenotypes may be mediated, in part, by a compensatory upregulation of MMP9 in MMP2-null lymphocytes and not altered chemokine gradients as seen in other injury models [55]. These observations further underscore the point that individual MMP enzymes can function differently in varying conditions, and thus points to the necessity for defining disease specific mechanisms of MMP function.

5. Conclusion

MMPs have evolved as important regulatory enzymes in both pro- and anti-inflammatory pathways. MMP expression and activity are typically increased in any tissue injury and inflammatory disease process, and there is a growing body of evidence that indicates these proteinases function in inflammation primarily to modulate leukocyte influx, either through regulation of barrier function, cytokine/chemokine activity, or gradient formation. The generation of mice with targeted deletions of individual MMPs has demonstrated their importance in host inflammatory responses and reveals non-redundant mechanisms that may be potentially targeted therapeutically to enhance or mitigate inflammation.

Because MMPs can be both beneficial in regulating host defense and pathological in inflammatory disease, it is essential to define the specific molecular mechanisms by which individual MMPs function in normal and abnormal inflammatory processes. Broad-spectrum metalloproteinase inhibitors have not proven beneficial in cancer [56], and it would be expected that their lack of specificity might limit their usefulness in inflammatory disease. Similarly, because an individual MMP can have both physiological and pathological functions that depend on cell type, substrate, and disease process, even targeted inhibition of a single MMP may be of limited benefit, and may even be harmful. However, further understanding of the downstream pathways by which MMPs function in specific health and disease states may identify therapeutic strategies that inhibit detrimental MMP effects, while preserving their beneficial effects. Thus, further exploration and understanding of MMP function in tissue injury and inflammation, with a particular focus on defining their substrates and the downstream consequences of MMP proteolytic activity will have important implications for health and disease.

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TABLE 1
INFLAMMATORY PHENOTYPES OF MMP-NULL MICE

MMP2-null	Impaired eosinophil egression in allergic lung inflammation [53] Increased immune-mediated arthritis [57] Enhanced myocardial inflammation in TNF α -induced cardiomyopathy [58] Enhanced autoimmune encephalomyelitis [55] Enhanced experimental colitis [59]
MMP3-null	Decreased neutrophil recruitment in model of acute lung injury [60] Decreased neutrophil recruitment in LPS-induced neuroinflammation [61] Impaired contact hypersensitivity [62] Enhanced collagen-induced arthritis [63] Reduced accumulation of macrophages in atherosclerotic plaques [64] Reduced macrophage-chemoattractant activity [33] Reduced recruitment of CD4+ Lymphocytes into intestinal mucosa [65]
MMP7-null	Reduced neutrophil efflux in bleomycin-induced lung injury [2] Lack of activation of TNF α on macrophages [34]
MMP8-null	Delayed neutrophil recruitment and resolution. Reduced neutrophil apoptosis [41] Decreased neutrophil recruitment to dermis surrounding chemical-induced skin tumors [39]
MMP9-null	Reduced inflammation in experimental colitis [66] Diminished egression of leukocytes in allergic lung inflammation [54] Enhanced airway inflammation in allergic lung inflammation [67] Decreased lymphocyte recruitment and mononuclear inflammation in allergic lung inflammation [68] Decreased immune-mediated arthritis [57] Protected from lethal endotoxic shock [52] Prolonged contact hypersensitivity [62] Reduced experimental autoimmune encephalomyelitis [69] Diminished Dendritic cell migration [70] Increased neutrophil recruitment in IL13-induced lung injury [71] Impaired macrophage infiltration in atherosclerosis [72] Reduced neutrophil influx, mortality and bacterial burden during infection with <i>Francisella Tularensis</i> [49]
MMP10-null	Altered inflammatory responses [†]
MMP11-null	ND
MMP12-null	Decreased eosinophil and macrophage recruitment in IL13-induced lung injury [71] Reduced macrophage migration and influx in smoke-induced emphysema [73,74] Reduced macrophage recruitment and improved function in spinal cord injury [75] Reduced neutrophil influx to alveolar space in acute lung injury [60] Reduced release of TNF α from macrophages after smoke exposure [76]
MMP13-null	Attenuated inflammatory reaction during cholestasis [77]
MMP14-null	ND
MMP20-null	ND
MMP28-null	Altered inflammatory responses [†]

[†] Unpublished observations. ND, no inflammatory phenotype determined.

TABLE 2
MMP SUBSTATES & ALTERED GRADIENTS RELATED TO INFLAMMATION

MMP	Substrate [‡]	Altered Chemokine Gradient
MMP1	MCP-1, MCP-2, MCP-3, MCP-4 [5] SDF-1/CXCL12 [3] IL-1 β [36]	
MMP2	MCP-3/CCL7 [5] SDF-1/CXCL12 [3] Ym1, S100A8, S100A9 IL-1 β [35,36] Fractalkine/CX ₃ CL1 [47]	CCL11 [53]
MMP3	Osteopontin [78] Latent TGF- β 1 [79,80] MCP-1, MCP-2, MCP-3, MCP-4 [5] SDF-1/CXCL12 [3] IL-1 β [35,36]	Macrophage Chemokine [33]
MMP7	Latent TNF [34] Syndecan-1 [2] Osteopontin [78]	KC/CXCL1 [2]
MMP8	LIX/CXCL5 [39]	LIX/CXCL5 [40]
MMP9	Latent TGF- β 1 [81] Latent VEGF [82] SDF-1/CXCL12 [3] IL8/CXCL8, CTAP-III, platelet factor-4 (PF-4), and GRO-alpha [37] Ym1 [12] SDF-1/CXCL12 [3] CCL11, CCL7, CCL17 [54] IL-1 β [35,36]	CCL11, CCL7, CCL17 [54] PGP [50]
MMP12	Latent TNF- α [76]	
MMP13	MCP-3/CCL7 [5] SDF-1/CXCL12 [3]	
MMP14	ProMMP2 [83] Syndecan-1 [84] MCP-3/CCL7 [5] SDF-1/CXCL12 [3]	

[‡]The list of substrates includes proteins that have been shown to be MMP substrates *in vitro*.