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The Role of MMPs in the Progression of Chronic Lung Inflammatory Diseases

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Additional information is available at the end of the chapter

1. Introduction

The alveolar extracellular matrix (ECM) and chronic lung inflammatory diseases, such as pulmonary fibrosis and chronic obstructive pulmonary disease (COPD), are closely connected. Pulmonary fibrosis is associated with ECM production, deposition and remodeling. In contrast, COPD is defined by a loss of the ECM. Matrix metalloproteinases (MMPs) regulate ECM remodeling, and therefore play an important role in the development of chronic lung diseases. MMPs constitute a family of endopeptidases that have a common zinc-based active site. In this chapter, the role of MMPs in pulmonary fibrosis and COPD are discussed, mainly based on the findings in animal models. The effects of MMPs inhibitor on chronic lung disease are also herein discussed.

2. Overview

MMPs constitute a family of endopeptidases with a zinc molecule in their active site and a dependency on Ca^{2+} for their activity. MMPs are thought to be responsible for the turnover and degradation of the ECM [1-3]. In the lungs, these proteinases are synthesized and secreted by diverse cell types, including mesenchymal cells, macrophages, polymorphonuclear cells, alveolar type II epithelial cells, fibroblasts, smooth muscle cells, the lung parenchyma and inflammatory cells [4].

Classification

The most commonly used classifications are based partly on the historical assessment of the substrate specificity of the MMPs, and partly on the cellular localization of the MMPs. They can be divided into two main groups based on their domain and compartment location: basic

secreted MMPs (collagenases, gelatinases and stromelysins) and membrane-anchored (the membrane-type) MMPs (MT-MMPs). The collagenases are capable of degrading triple-helical fibrillar collagens into distinct 3/4 and 1/4 fragments. These collagens are the major components of bone, cartilage and dentin, and MMPs are the only known mammalian enzymes capable of degrading them. The collagenases are MMP-1, -8, -13 and -18. In addition, MMP-14 has also been shown to cleave fibrillar collagen, and there is evidence that MMP-2 is capable of collagenolysis. The main substrates of the gelatinases are type IV collagen and gelatin, and these enzymes are distinguished by the presence of an additional domain inserted into the catalytic domain. This gelatin-binding region is positioned immediately before the zinc-binding motif, and forms a separate folding unit that does not disrupt the structure of the catalytic domain. The gelatinases are MMP-2 and MMP-9. The stromelysins display a broad ability to cleave extracellular matrix proteins, but are unable to cleave the triple-helical fibrillar collagens. The three canonical members of this group are MMP-3, -10, and -11. All six membrane-type MMPs (MMP14, -15, -16, -17, -24, and -25) have a furin cleavage site in the pro-peptide, which is a feature also shared by MMP-11. There are a number of MMPs that do not fit into any of the traditional groups, such as matrilysins (MMP-7, MMP-26). In addition, MMP-19, enamelysin (MMP-20), MMP-21, MMP-23A and 23B, MMP-27 and epilysin (MMP-28) have recently been reported and are still being characterized (Summarized in Table 1).

Structure

To be classified as an MMP, a protein needs to have at least the conserved pro-domain and catalytic domain (Figure 1). The pro-domain of a typical MMP is 80 amino acids, and contains the consensus sequence, PRCXXPD. The exception is MMP23, in which the crucial cysteine residue is found in a distinct amino acid sequence. The catalytic domain of a typical MMP contains a zinc ion (Zn^{2+}) in the active site that is ligated to three conserved histidine residues in the sequence HEXXHXXGXXH. The glutamic acid residue (E) in this catalytic motif provides the nucleophile that severs peptide bonds. The backbone structures of the MMP catalytic domain, include a characteristic Met turn on the carboxy side of the zinc active site, so matrix metalloproteinases have a methionine residue that is always conserved. This residue is part of a 1,4- β -turn that loops the polypeptide chain beneath the catalytic zinc ion and forms a hydrophobic base for the zinc-binding site. This is caused by a conserved methionine residue downstream of the zinc-binding site, which is similar to those of the astacin-, reprotolysin- (also known as a disintegrin and metalloproteinase (ADAMs)) and serralsin-family metalloproteinases.

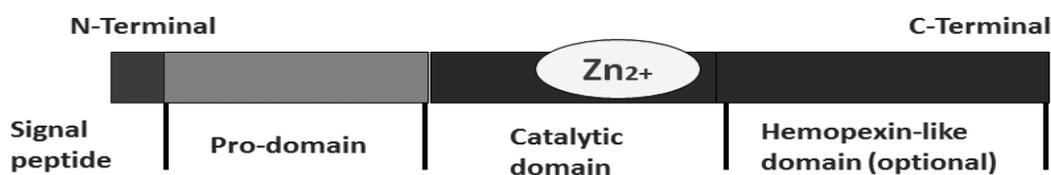


Figure 1. The structure of the MMPs

Group name	Number	Substrates
Collagenase-1	MMP-1	Collagen I, II, III, X, Casein
Gelatinase-A	MMP-2	CCL7, CXCL12, Collagens IV, V, VII, XI, Gelatin, Fibronectin
Stromelysin-1	MMP-3	E-cadherin, Laminin, Latent TGF-beta, Collagens III, IV, VII, IX, Casein, Fibronectin
Matrilysin	MMP-7	Pro-alpha-defensins, Fas L, Latent TNF, Syndecan-1, E-cadherin, Elastin, Collagens IV, Casein, Fibronectin
Collagenase-2	MMP-8	CXCL5, Collagens I, II, III, Casein
Gelatinase-B	MMP-9	Zona occludens 1, alpha1-antiproteinase, Latent TGF-beta, Latent VEGF, Fibrin, NG2 proteoglycan, Collagens III, IV, V, Gelatin
Stromelysin-2	MMP-10	Collagens III, IV, V, Casein, Fibronectin
Stromelysin-3	MMP-11	Fibronectin
Metalloelastase	MMP-12	Latent TNF, Elastin, Gelatin, Casein
Collagenase-3	MMP-13	Type I, II fibrillar collagen
MT1-MMP	MMP-14	ProMMP2, Fibrillar collagens, Fibrin, Syndecan-1, laminin
MT2-MMP	MMP-15	Fibrin
MT3-MMP	MMP-16	Fibrin, Syndecan-1
MT4-MMP	MMP-17	ND
MMP-19	MMP-19	ND
Enamelysin	MMP-20	Amelogenin
MMP-21	MMP-21	ND
MMP-23A	MMP-23A	ND
MMP-23B	MMP-23B	ND
MT5-MMP	MMP-24	ND
MT6-MMP	MMP-25	ND
Matrilysin-2	MMP-26	ND
MMP-27	MMP-27	ND
Epilysin	MMP-28	ND

ND=Not determined.

Table 1. A list of the currently known MMPs

Several MMPs have the hemopexin-like C-terminal domain, which is linked to the catalytic domain by a flexible hinge region. The minimum domain structure is characteristic of matrilysins (MMP-7 and MMP-26). Stromelysin (MMP-3 and MMP-10), collagenases (MMP-1, 8,

13), MMP-12, enamelysin (MMP-20) and MMP-27 have several hemopexin domains. A similar domain structure is present in MMP-11, MMP-28 and MMP-21, which have a furin-like target sequence inserted in their pro-domains. Membrane-type MMPs have membrane-anchored modules of glycosylphosphatidylinositol, which form type I or type II transmembrane segments. MMP-23A and 23B have an immunoglobulin-like domain. MMP-2 and MMP-9 are secreted MMPs with gelatinolytic activity, and are characterized by the presence of fibronectin type II modules [1-3].

Regulation

The activation of MMPs can be mediated by other MMPs or proteases, and some are activated intracellularly by furins. In addition, various chemicals, such as organomercurials, urea, some detergents and reactive oxygen species, can act as activators of MMPs. Although the healthy adult lung is not a major source of MMPs, parenchymal cells, such as the airway epithelium, fibroblasts and smooth muscle have the capacity to express active MMPs following stimulation by a variety of agents, such as infectious pathogens, environmental toxins, growth factors and cytokines.

Since MMPs may cause significant host damage, they are tightly regulated. MMPs are regulated at four main levels: gene transcription, proenzyme activation, activity inhibition and compartmentalization. First, they are rarely stored, and require gene transcription before secretion, the exception being neutrophil MMP-8 and -9. Second, MMPs are either secreted as pro-enzymes that require proteolytic cleavage, or in the case of MT-MMPs, are activated intracellularly by pro-protein convertases, such as furin. This processing exposes the catalytic cleft, a mechanism known as the cysteine switch [5]. Third, specific inhibitors of MMPs, the tissue inhibitors of metalloproteinases (TIMPs), are secreted proteins that bind MMPs in a 1:1 manner to prevent their enzymatic activity [6]. TIMPs comprise a family of four protease inhibitors (TIMPs 1-4). The balance of MMPs to TIMPs therefore determines the matrix turnover, where either an excess of MMPs or a deficit of TIMPs may result in excess ECM degradation. The major endogenous MMP inhibitor in serum is α 2-macroglobulin, which binds MMPs and leads to their clearance by endocytosis. Finally, MMPs can be compartmentalized in close proximity to the cell.

Synthetic MMP inhibitors and clinical implications

A number of rationally-designed MMP inhibitors have shown some promise in the treatment of pathologies in which MMPs have been implicated. Two major approaches were undertaken to counterbalance such MMP activity: substrate peptide mimics and small synthetic molecules.

Macpherson and colleagues developed a nonpeptidic hydroxamic acid inhibitor (CGS 27023A) of the stromelysin group of MMPs, which was orally bioactive and blocked the erosion of cartilage matrix in an *in vivo* rabbit model of cartilage degradation [7]. Batimastat, a broad spectrum MMP inhibitor, showed prolonged survival in an animal model of cancer and some efficacy in phase I clinical trials, but its development was hindered by its low bioavailability and limited solubility [8]. Marimastat, a low-molecular-weight substrate peptide-based hydroxamate (inhibitor of MMPs -1, -8, and -13), and prinomastat, based on a sulphonamide-hydroxamate scaffold (inhibitor of MMPs -2, -3, and -13), failed during phase III clinical trials

for cancer treatment [9]. In addition, cipemastat (Ro 32-3555), an MMP-1-selective inhibitor, demonstrated limited efficacy in clinical trials. The development of several other MMP inhibitors was stopped due to their systemic toxicity, a lack of any correlation between the activity of MMP inhibitors and the MMP levels in the plasma and poor efficacy [10].

Doxycycline, at sub-antimicrobial doses, inhibits MMP activity, and has been used in various experimental systems for this purpose, such as for recalcitrant recurrent corneal erosions. It is used clinically for the treatment of periodontal disease, and is the only MMP inhibitor that is widely available clinically. Minocycline, another tetracycline antibiotic, has also been shown to inhibit MMP activity. For example, tetracyclines, which are used in the treatment of arthritis, have been shown to reduce the activity of MMPs -1, -2 and -9 [11].

3. The inflammatory process

The main activity of MMPs is considered to be the degradation of the ECM. However, matrix degradation is neither the sole function, nor the main function, of these proteinases. Recent findings indicate that MMPs play an important role in the regulation of cytokine and chemokine release and activation, which are key steps in the immune response [2, 3, 12-14]. For example, MMP-1, -2, -3, -7, -9, and -12 are able to process pro-tumor-necrosis factor (TNF)- α into soluble active TNF- α . MMP-2, -3 and -9 also have the ability to cleave interleukin (IL)-1 β , generating a more active form. MMP-9 controls the IL-2-dependent proliferation of T lymphocytes. MMP-8, -13 and -14 can cleave IL-8 to generate truncated forms with increased activity. Therefore, inflammatory cytokines and MMPs are interconnected.

An essential pro-inflammatory mediator that is regulated by metalloproteinase activity is TNF, which is produced as a 26-kDa membrane-associated protein (proTNF) that is cleaved by TNF-converting enzyme (TACE) into a soluble 17.5-kDa cytokine. Because synthetic metalloproteinase inhibitors block this cleavage, it was suggested that TACE was an MMP. However, when the convertase activity was purified and cloned, TACE was found to be identical to ADAM17 [15, 16]. The cleavage of proTNF by ADAM17 is specific [17]. Since the release of active TNF is reduced by 90% in cells derived from ADAM17-deficient mice, ADAM17 seems to be the principal physiological TNF-converting enzyme *in vivo*. Several MMPs (including MMP-1, -2, -3, -9 and -17) can process proTNF to its active form *in vitro* [18, 19]. MMP-7 and MMP-12 also activate proTNF in macrophages. The high-level release of TNF in response to bacteria and toxic shock by MMP-7 and MMP-12 processing might elicit the constitutive release of TNF from macrophages that is required for common functions, such as tissue resorption and resolution, in response to injury.

Similarly, IL-1, a potent pro-inflammatory cytokine, requires proteolytic processing for activation, a process attributed to the IL-1-converting enzyme (ICE, caspase-1). Although the function of ICE had been well established *in vitro*, studies using ICE-deficient mice provided evidence of other mechanisms of IL-1 activation [20]. It was subsequently discovered that MMP-2, -3 and -9 can cleave and activate the IL-1 precursor [21]. Furthermore, after activating IL-1, MMP-3 degrades the biologically active cytokine [21], which can also be inactivated *in*

vitro by MMP-1, -2 and -9 [22]. These data indicate a dual role for MMPs in the biphasic modulation of inflammatory-mediator activity. MMPs are involved in both the activation and inactivation of these inflammatory molecules.

Moreover, several studies have indicated that MMPs can either directly or indirectly affect the activity interferon- γ [23], vascular endothelial growth factor [24], epidermal growth factors [25], fibroblast growth factors [26] and transforming growth factor (TGF)- β . As shown using TGF- β -deficient mice, this cytokine functions to restrain mononuclear inflammation [27-29]. In both cells and tissue-explant models, MMP-3 [30], MMP-9 [31] and MMP-14 [32] have been shown or suggested to activate a proportion of the total TGF- β .

Lopez-Boado et al. reported a 25-fold induction of MMP-7 in lung epithelial cells following infection with *Escherichia coli* [33] and *Pseudomonas aeruginosa*, [34] which could explain the upregulation of this enzyme in the airway of cystic fibrosis patients who are commonly infected with these bacteria. It has also been shown that proinflammatory cytokines, such as IL-1 β and TNF- α , upregulate the expression of MMP-9 in human airway epithelial cells following a one-day treatment [35].

4. Pulmonary fibrosis and MMPs

Lung inflammation is deeply associated with the process of pulmonary fibrosis. MMP-9 was observed in alveolar macrophages from idiopathic pulmonary fibrosis patients [36] and in the bronchoalveolar lavage (BAL) fluid from patients with bleomycin-induced pulmonary fibrosis [37, 38]. An mRNA study also supported that the activation of MMP-2 and MMP-9, both gelatinases, is involved in pulmonary fibrosis [39]. The function of other MMPs, such as collagenases or stromelysins, in pulmonary fibrosis is still unclear, despite their importance in ECM deposition. Edwards and colleagues reported that mast cells harvested from the tissues of patients with interstitial lung diseases demonstrated the expression of MMP-1. MMP-1 has thus been reported to be important for controlling fibrogenesis in humans [40]. Although the existence of MMP-1 is unclear in rodents [41], other collagenases, such as MMP-13, have been detected [42]. Similarly, collagenase activity has been observed after bleomycin administration [37]. An immunohistochemical analysis demonstrated that MMP-13 expression was present after bleomycin administration [43]. However, other researchers have reported that the MMP-9 (gelatinase B), MMP-3 (stromelysin-1) and interstitial collagenase gene expression did not significantly change after bleomycin administration [44].

5. Therapeutic trials for pulmonary fibrosis

As mentioned previously, doxycycline inhibits MMP activity. We demonstrated that the early administration of doxycycline inhibited early inflammation and resulted in an inhibition of the development of pulmonary fibrosis through the inhibition of early inflammation [45]. However, doxycycline did not affect established pulmonary fibrosis. A MMPs inhibitor,

batimastat, was reported to attenuate pulmonary fibrosis in mice [38]. Batimastat inhibited both MMP-2 and TIMP-1, and resulted in the attenuation of pulmonary fibrosis. In contrast, a MMPs inhibitor, CGS27023A, blocked the anti-fibrotic MMPs and resulted in an augmentation of the ECM [43].

MMPs play an important role in the development of pulmonary fibrosis. However, there are conflicting hypotheses regarding whether MMPs have anti-fibrotic properties [46]. Researchers should focus on when and what type of MMPs inhibitor(s) should be used for pulmonary fibrosis.

6. COPD and MMPs

Both alveolar and bronchial inflammation have been shown to be present in human COPD. Hence, chronic inflammation contributes to the development of COPD through the destruction of alveoli and the induction of MMPs. Recently, the role of MMPs has been given increasing attention as a possible mechanism underlying the development of pulmonary emphysema. Additionally, the inflammatory cells invading the lung during the course of COPD are also a major source of different MMPs. It has been shown that neutrophils and macrophages are the predominant inflammatory cells in the lungs of COPD patients [47, 48].

Lipopolysaccharide (LPS) is a strong proinflammatory compound present in the cell wall of gram-negative bacteria. Acute LPS instillation induces apoptotic cell death in bronchial epithelial cells at early time points, and neutrophil apoptosis in the lungs at later time points [49, 50], and this is associated with the production of MMPs, mainly gelatinase [51]. LPS leads to the recruitment of neutrophils and macrophage activation with concomitant airspace enlargement [52, 53]. Although humans tolerate bacterial pneumonia without any residual emphysema, the chronic instillation of LPS was found to induce COPD-like changes. Bacterial endotoxin was demonstrated to be present in high concentrations in tobacco (approximately 20 $\mu\text{g}/\text{cigarette}$), and bioactive LPS could be detected in both mainstream and sidestream cigarette smoke (approximately 0.12-0.2 $\mu\text{g}/\text{cigarette}$) [54, 55]. Repetitive LPS instillation for 12 weeks led to COPD-like changes [56]. This mouse model mimicked several important pathological changes that are observed in COPD patients. These mice demonstrated goblet cell metaplasia in the larger airways, thickening of the airway walls and irreversible alveolar enlargements [57]. It is well known that LPS induces TNF- α . TNF- α overexpression in mice has been reported to have diverse effects, including the induction of pulmonary emphysema and pulmonary fibrosis. At first, the overexpression of TNF- α in the lungs of mice was thought to lead to pulmonary fibrosis [58, 59]. In contrast, TNF- α overexpressing mice bred in Denver demonstrated pulmonary emphysema [60]. Chronic inflammation, a reduced elastic recoil, a huge lung size and an activation of MMPs (mainly MMP-2 and MMP-9) were all observed in these mice, along with a progression of pulmonary hypertension [61]. In addition, this mouse model was insensitive to fibrogenesis factor, bleomycin and TGF- β [62]. Many evidence have demonstrated that TNF- α plays a critical role in smoking-related emphysema [63]. Taking these findings into considera-

tion, TNF- α is considered to play a crucial role in the development of COPD and MMPs, mainly MMP-2 and MMP-9 is associated with the COPD pathogenesis.

Several transgenic mouse strains with targeted expression of cytokines show COPD-like lesions, such as airspace enlargement, thickening of the airway walls and subepithelial fibrosis without any exposure to a specific agent [64, 65]. An overexpression of IL-13 in the murine lung caused an asthma-like eosinophil- and lymphocyte-rich inflammation, goblet cell hyperplasia, airway fibrosis and alveolar enlargement [66, 67]. The induced overexpression of interferon (IFN)- γ in the lungs of mice caused a phenotype mimicking human COPD [68]. In these models, the overexpression of these inflammatory cytokines was associated with an increased expression of MMPs (mainly gelatinase) and cysteine proteases, including cathepsins. Similarly, macrophage colony stimulating factor (M-CSF)-deficient mice, surfactant protein D (SP-D)-deficient mice and integrin $\alpha\beta6$ -deficient mice also develop air space enlargement [69-71]. The macrophages of SP-D-deficient mice have increased oxidant production, which activates nuclear factor (NF)- κ B and subsequently leads to MMP expression [72]. NF- κ B is also well known to be a transcription factor involved in the induction of TNF- α . Inflammation and MMPs activation (mainly gelatinase) contribute to the development of COPD.

Another mechanism for COPD involves macrophage elastase (MMP-12). MMP-12 is nearly undetectable in healthy macrophages, while MMP-12 is expressed in the alveolar macrophages of human cigarette smokers. Of note, MMP-12 knockout mice did not develop emphysema in response to long-term cigarette smoke exposure [73, 74]. MMP-12 knockout mice also failed to recruit macrophages into their lungs in response to cigarette smoke. Neutrophil elastase-deficient mice were significantly protected from the development of pulmonary emphysema after cigarette smoke exposure [75]. Mice that constitutively overexpress human MMP-1 develop spontaneous air space enlargement, showing that MMP-1 can drive pulmonary destruction [76]. Since that report, numerous transgenic mouse models have been developed, in which emphysema-like changes are induced. The absence of MMP inhibitors can also result in abnormal pulmonary matrix turnover, as TIMP-3 deficient mice spontaneously develop air space enlargement at two weeks of age [77].

The functional importance of MMP activity in these models was confirmed by crossing emphysema-developing mice with MMP-knockout mice. For example, in the IL-13 overexpression model, a deficiency of MMP-9 or MMP-12 results in reduced pathological changes and less respiratory failure [78]. Similarly, crossing integrin $\alpha\beta6$ -deficient mice with MMP-12-deficient mice prevents the development of age-related emphysema [79].

MMPs seem to be strongly related to the development of COPD [80]. In a clinical study, there were increases in the pulmonary expression of MMP -1 [81], MMP-2 [82], MMP-8 [83], MMP -9 [84], MMP-12 [85] and MMP-14[82] in COPD patients. For example, Finlay and colleagues detected collagenase activity in BAL fluid samples from 100% of emphysematous patients but in only 10% of smoking controls; and MMP-9 was present in 60% of patients compared to 20% in the control group [84]. Segura-Valdez and colleagues showed a significant upregulation of MMPs -1, -2, -8, and -9 in the BAL fluid samples obtained from COPD patients [86]. In another study, Imai and colleagues reported the detection of MMP-1 mRNA by *in situ* hybridization,

and also found protein expression and enzymatic activity in the lung samples of patients with emphysema. However, there was no MMP-1 detected in the lungs of normal control subjects [81]. Additionally, Ohnishi and colleagues documented a more than three-fold increase in the level of MMP-2 protein and activation in lung samples from emphysematous patients compared to subjects in the control group [82]. Another study reported an increase in the MMP-9 protein level in 40% of COPD patients compared to healthy subjects. The location of the MMP-9 expression was confirmed by an immunohistochemical analysis to be in the bronchial epithelium and submucosal areas [87]. Furthermore, an extracellular MMP inducer, called basigin, a member of the immunoglobulin G (IgG) superfamily, were increased in smokers' BAL fluid samples [88]. The extracellular MMP inducer was prominent in the bronchial glands, bronchial epithelium and alveolar macrophages. An increase in the level of MMP-9 has also been reported in the sputum of patients with chronic bronchitis compared to control subjects [89].

MMP-9 and MMP-12 play key roles in the development of COPD in mice. However, studies in patients suggest that the spectrum of MMPs in human disease may differ significantly from these models. Studies of MMP activity demonstrate divergent results at different stages of disease evolution, and lead to controversy about which MMPs are critical in pulmonary disease in humans. Taking the data from both clinical and animal studies into consideration, MMP-9 is the most compelling molecule related to the development of COPD. In contrast, MMP-12 is essential for the cigarette smoke-induced pathology in the mouse, but may not be equally critical in human disease.

7. Therapeutic trials for COPD

MMP inhibition could be a promising candidate therapy for COPD. In fact, a MMP inhibitor, GM6001, has been reported to block the emphysematous changes associated with methylprednisolone-induced emphysema in rats [90]. However, past experiences, including our own study, have shown that a broad spectrum MMP inhibitor would be of limited benefit [91-93]. In fact, our preliminary study using CGS27023A, an MMP inhibitor, or doxycycline, did not improve the COPD in mice with TNF- α overexpression (unpublished data). Nonselective MMP inhibitors, such as marimastat, have major side effects. Isoenzyme-selective inhibitors or inhaled delivery may be needed. A dual MMP9-MMP12 inhibitor (AZ11557272) was shown to prevent emphysema, small airway fibrosis and inflammation in guinea pigs that were exposed to cigarette smoke over a six-month period [94], but its clinical development has now been stopped for some unknown reason. MMP-9 is potentially a good target for patients with emphysema, but progress in the development of drugs targeting MMP-9 has been disappointing, because it has proved to be difficult to discover safe and selective MMP-9 inhibitors [93]. A more sophisticated approach is therefore required in the future.

8. Conclusion

There is a controversy concerning the role of MMPs in the development of chronic inflammatory lung diseases. There were two possible but conflicting roles of MMPs: promoting the deposition of the ECM by facilitating fibroblast migration, or degenerating the ECM. MMPs play important roles in the degradation of the ECM and recovery from lung damage. Similar to inflammation, MMPs activation was observed in both pulmonary fibrosis and COPD. The role of MMPs in inflammatory lung diseases is therefore complex. The different MMPs show variations in terms of their effecting depending on different condition. In addition, MMP inhibitors appear to work in different ways. More precise and specific studies of both the proteins themselves and their specific inhibitors will be needed in the future. Moreover, there are discrepancies between mice and humans. Novel therapeutic agents targeting MMPs for use against chronic inflammation are currently under development, and more will likely be developed as more is learned about the MMPs and their functions. This information is summarized in Figure 2.

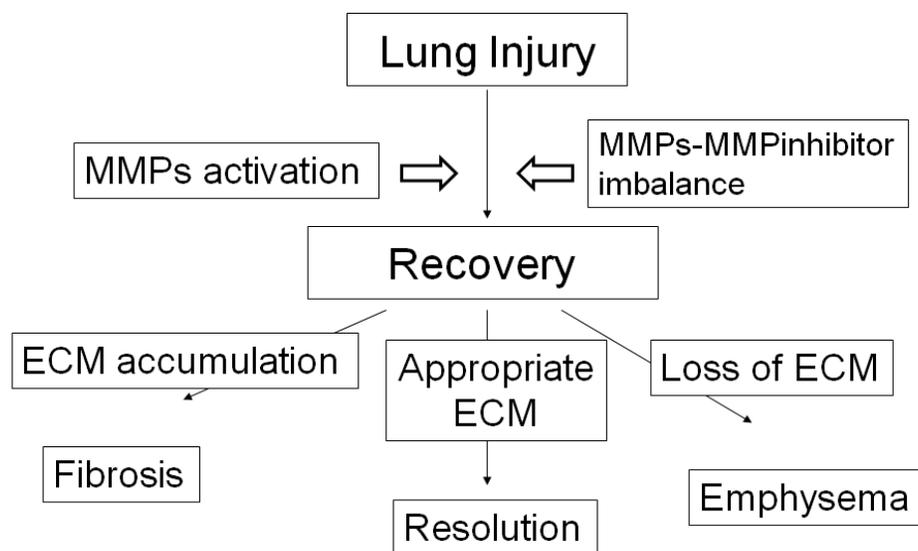


Figure 2. A schematic drawing of the relationship between MMPs and lung injury.

Abbreviations

a disintegrin and metalloproteinase (ADAMs)

bronchoalveolar lavage (BAL)

chronic obstructive pulmonary disease (COPD)

extracellular matrix (ECM)

IL-1-converting enzyme (ICE)

immunoglobulin G (IgG)
interleukin (IL)
interferon (IFN)
lipopolysaccharide (LPS)
macrophage colony stimulating factor (M-CSF)
matrix metalloproteinases (MMPs)
membrane-type MMPs (MT-MMPs)
nuclear factor (NF)
surfactant protein D (SP-D)
tissue inhibitors of metalloproteinases (TIMPs)
tumor-necrosis factor (TNF)
TNF-converting enzyme (TACE)
transforming growth factor (TGF)

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