OCCASIONAL REVIEW

Matrix metalloproteinases in destructive pulmonary pathology

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Matrix metalloproteinases (MMPs) are a family of proteolytic enzymes that have a number of important physiological roles including remodelling of the extracellular matrix, facilitating cell migration, cleaving cytokines, and activating defensins. However, excess MMP activity may lead to tissue destruction. The biology of MMP and the role of these proteases in normal pulmonary immunity are reviewed, and evidence that implicates excess MMP activity in causing matrix breakdown in chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome (ARDS), sarcoidosis, and tuberculosis is discussed. Evidence from both clinical studies and animal models showing that stromal and inflammatory cell MMP expression leads to immunopathology is examined, and the mechanisms by which excess MMP activity may be targeted to improve clinical outcomes are discussed.

Normal lung function requires alveolar support by the extracellular matrix (ECM). In many pulmonary diseases abnormal remodelling or destruction of the ECM occurs, leading to impaired lung function and, if extensive, death. Consideration of the biochemistry of the lung matrix predicts that the matrix metalloproteinase (MMP) family of enzymes is likely to be involved in this pathology. MMPs are proteases that collectively can degrade all components of the ECM, but also have important roles in normal immunity.[1] Thus, MMPs may modulate appropriate responses to exogenous stimuli but may also contribute to immunopathology that leads to aberrant turnover of the ECM. We review the roles of MMPs in normal pulmonary immunity and discuss four diseases where excess MMP activity may contribute to pulmonary destruction: chronic obstructive pulmonary disease (COPD), the acute respiratory distress syndrome (ARDS), sarcoidosis, and tuberculosis (TB).

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THE PULMONARY ECM

The pulmonary interstitium forms the mechanical scaffold of the lung, while the basement membrane supports alveolar epithelial cells and in part determines the resistance of the diffusion barrier.[2] The primary structural fibrils of the lung are type I collagen which provides tensile strength, and elastin which allows distensibility.[3] Elastin fibres are usually highly stable and often last life-long.[4] The alveolar wall is primarily made from type III collagen[5] while the basement membrane is rich in type IV collagen. Large collagen and elastin fibres are connected by a variety of smaller fibrils. Degradation of the primary structural fibrils of the lung will therefore first involve cleavage of the cross linking fibrils to expose enzyme binding sites.[6] Consequently, multiple enzymes are likely to be involved in the turnover of the ECM, and it may be impossible to specify a single protease as the critical mediator of any particular pulmonary pathology. MMP involvement in degradation of the lung ECM is predicted since fibrillar type I collagen is highly resistant to enzymatic degradation and only certain MMPs can degrade it at neutral pH.[7] Furthermore, multiple MMPs are elastases and MMPs also degrade type IV collagen.[1]

MATRIX METALLOPROTEASES

MMPs are a family of zinc dependent proteases that were initially identified in the involuting tail of tadpoles by their ability to degrade collagen.[8] MMPs can be broadly classified on the basis of substrate specificity into collagenases (MMP-1, -8 and -13), gelatinases (MMP-2 and -9), stromelysins (MMP-3, -10, -11), elastases (MMP-7 and -12), and membrane type MMPs (MT-MMPs, MMP-14, -15, -16 and -17) which are surface anchored. MMP-1 (interstitial collagenase), MMP-8 (neutrophil collagenase), MMP-13 (collagenase 3), and MMP-14 (MT1-MMP) can cleave the triple helix of native type I collagen,[7] the primary architectural collagen of the lung.[3] Elastolytic MMPs include MMP-2 (gelatinase A), MMP-7 (matrilysin), MMP-9 (gelatinase B), and MMP-12 (macrophage metalloelastase).

Since MMPs may cause significant host damage, they are tightly regulated. Firstly, they are rarely stored but require gene transcription before secretion, the exception being neutrophil MMP-8 and -9. Secondly, they are either secreted as pro-enzymes that require proteolytic cleavage or, in the case of MT-MMPs, activated intracellularly by pro-protein convertases such as furin. This processing exposes the catalytic cleft, a mechanism known as the cysteine switch.[9] Thirdly, specific inhibitors of MMPs—the tissue inhibitors of metalloproteinases (TIMPs)—are

Abbreviations: MMP, matrix metalloproteinase; ECM, extracellular matrix; COPD, chronic obstructive pulmonary disease; ARDS, acute respiratory distress syndrome; TB, tuberculosis; MTb, *Mycobacterium tuberculosis*; BAL, bronchoalveolar lavage

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secreted which bind MMPs in a 1:1 manner to prevent enzymatic activity.[10] The balance of MMPs to TIMPs therefore determines matrix turnover, where either an excess of MMPs or a deficit of TIMPs may result in excess ECM degradation. Finally, MMPs can be compartmentalised in close proximity to the cell.

The majority of MMPs are not expressed in normal healthy tissues but are expressed in diseased tissues that are inflamed or undergoing repair and remodelling.[11] MMP expression may be upregulated by exogenous stimuli, cytokines and cell-cell contact. Conversely, cytokines such as interferon (IFN)-γ and interleukins (IL)-4 and -10 may downregulate MMP expression. Both inflammatory and stromal cells can express MMPs, although the profile is both cell and stimulus specific. For example, macrophages express a wider profile and greater quantities of MMPs than monocytes.[12] Pulmonary epithelial cells may also be a significant source of MMPs as they express MMP-1, -2, -7 and -9.[13–15] Intracellularly, MMP secretion is primarily regulated by the prostaglandin (PG) and mitogen activated protein kinase (MAPK) signal transduction pathways.[15–17]

The complexity of proteinase interactions is illustrated by the manner in which MMP-9 deficiency prevents neutrophil elastase induced immunopathology. In a model of autoimmune skin disease, MMP-9 deficient mice were found to be resistant to blister formation.[18] However, a direct role for MMP-9 was not identified. Instead, MMP-9 is responsible for cleaving the serpin α_1-proteinase inhibitor which then results in uninhibited neutrophil elastase activity. Multiple proteases may therefore be involved in a cascade, with a single one causing the final pathology but upstream enzymes being equally critical to the process.

MMPs IN PULMONARY IMMUNITY

Although MMPs are implicated in numerous diseases characterised by abnormal turnover of the ECM such as arthritis, malignancy, and atherosclerosis, they also have multiple functions in the normal immune response.[7] Therefore, before discussing how MMPs may contribute to immunopathology in specific lung diseases, we will review the biology of MMPs in pulmonary immunity.

Cell migration

The pulmonary surface is exposed to exogenous injury and, when damaged, ECM remodelling is required to allow epithelial repair. Migration of stromal and inflammatory cells occurs and MMPs are involved in this process. MMP-7 expression is increased in wounded epithelial cells and MMP-7 knock-out mice have deficient epithelial cell migration during wound healing, demonstrating the functional importance of MMP activity.[14] Similarly, MMP-9 accumulates at the leading edge of migrating pulmonary epithelial cells and inhibition of MMP activity prevents cell migration, suggesting that MMP-9 is also important in pulmonary epithelial repair.[19] This hypothesis is supported by the observation that MMP-9 deficient mice display abnormal alveolar bronchiolisation in a bleomycin model of lung injury.[20]

In addition to facilitating epithelial cell migration, MMPs are involved in the matrix remodelling necessary for the egression of inflammatory cells. For example, MMP inhibition prevents the extravasation of lymphocytes across high endothelial venules.[21] In an immune complex model of lung injury MMP-3 deficient mice have reduced neutrophil influx,[22] possibly due to the ability of MMP-3 to cleave type IV collagen, the primary collagen of the basement membrane.[1] Similarly, MMP-9 null mice display reduced dendritic cell recruitment to the airways in an allergen exposure model.[23] MMP activity is therefore required for both stromal and immune cell migration in the lung.

Intercellular signalling

In addition to degrading components of the ECM, MMPs may act on a variety of non-matrix substrates. MMPs can proteolytically process cytokines and chemokines to both augment and reduce their activity. For example, MMPs can both activate and inactivate pro-IL-1β, thereby providing both positive and negative regulation.[24 25] Several MMPs can release surface bound tumour necrosis factor α (TNF-α) by a similar mechanism to TNF-α converting enzyme (TACE, A disintegrin and metalloprotease (ADAM)-17).[26] In addition to processing cytokines, MMPs also cleave chemokines. MMP-9 processes CXCL8 (IL-8) to a fragment with 10 times the potency of the parent molecule.[27] Conversely, CCL7 (MCP-3) is cleaved from an active to an inactive form by MMP-2, and the CCL7 fragment acts as a receptor antagonist.[28] This has led to the hypothesis that MMP activity may act as a tuner and amplifier of immune responses, regulating both positive and negative feedback to facilitate the appropriate influx of inflammatory cells and the timely resolution of inflammation.[29]

MMPs are involved in regulating chemokine activity not only by proteolytically processing them, but also by releasing them from cell surface anchors. MMP-7 knock-out mice fail to recruit neutrophils to the alveolar space in a bleomycin injury model. Neutrophils leave the circulation but become trapped in the interstitium.[30] The migration deficit did not result from insufficient matrix degradation but was secondary to the failure to release a surface bound molecule, syndecan-1, which acts as an anchor for the chemokine KC. MMP-7 activity is required to cleave syndecan-1 on pulmonary epithelial cells, thereby releasing and activating KC, permitting KC to exert its biological activity and thus drive neutrophil influx.

In addition to modulating the activity of cytokines and chemokines, MMPs can mediate intercellular signalling directly. MMP-1 can cleave proteinase activated receptor 1 (PAR-1) on the cell surface, initiating a G-protein dependent intracellular signalling cascade and calcium flux.[31] In a model of malignant invasion, activation of PAR-1 by MMP-1 led to increased tumour invasiveness. MMP-1 was derived from fibroblasts, not malignant cells, which shows that MMPs may modulate interactions between invading and stromal cells.

Defensin activation

In the gut MMP-7 activates the antimicrobial peptides pro-α-defensins[32] and may play a similar role in the lung. The functional importance of α-defensin activation is shown by the delayed clearance of bacteria from the bowel in MMP-7 deficient mice.[32] MMP-7 expression in airway epithelial cells is upregulated in diseases characterised by chronic infection such as cystic fibrosis, supporting the hypothesis that MMP-7 contributes to pulmonary immunity.[14] Furthermore, bacterial components alone can actively drive MMP-7 secretion from cultured pulmonary epithelial cells.[33] Together with the release of anchored chemokines by MMP-7, these results have led to the hypothesis that MMP-7 secretion may be part of a generalised activation response to bacteria.[1]

The data outlined above indicate that MMPs play important roles in normal pulmonary immunity by facilitating cell migration, modulating chemokine and cytokine activity, activating defensins, and mediating intercellular signalling. However, extensive evidence has accumulated that altered MMP activity can lead to disease. The number of pulmonary conditions in which MMPs have been implicated in the pathology encompasses much of thoracic medicine (table 1) and so cannot be addressed within a single review. Here, we examine four conditions—COPD, ARDS, sarcoidosis, and TB—where destruction of the pulmonary ECM is a

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Table 1 Pulmonary diseases in which dysregulated MMP activity is implicated in the pathology

Diseases	References
Lung cancer	34 (R)
Asthma	35 (R)
COPD	36–58
ARDS	59–70
Sarcoidosis	71–75
Tuberculosis	76–88
Idiopathic pulmonary fibrosis	73, 89–93
Silicosis	94
Cystic fibrosis	14, 95, 96
Pneumonia	97
Lymphangioleiomyomatosis (LAM)	98, 99
Cryptogenic organising pneumonia	100
Bronchiolitis obliterans	101, 102
Langerhans' cell granulomatosis	103
Radiation pneumonitis	104

This list is not exhaustive. (R) denotes review article.

key component of the disease process, and review evidence that excessive MMP activity contributes to this pathology.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

The observation that smokers with α_1-antitrypsin deficiency develop COPD provided the initial indication that a protease/antiprotease imbalance can drive pulmonary pathology.[105] Since neutrophil elastase is one of the enzymes inhibited by α_1-antitrypsin, excess elastase activity was initially thought to be responsible for the destructive pathology in COPD. However, although there is considerable evidence for the involvement of neutrophil elastase in COPD, it now seems that multiple proteases acting in concert cause pathology.[106] The turnover of the lung ECM will involve the interaction of several enzymes as cross linking fibrils must first be cleaved to expose the major fibres to allow their degradation.[6] Since MMPs degrade all components of the ECM including type I collagen and elastin, they are likely to be involved in tissue remodelling in COPD.

Animal models

Mice that constitutively overexpress human MMP-1 develop spontaneous air space enlargement, showing that MMP-1 can drive pulmonary destruction.[36] Since that report, numerous transgenic mouse models have been developed in which emphysema-like changes develop. For example, targeted overexpression of IFN-γ, IL-13, or TNF-α causes inflammation and air space enlargement accompanied by the upregulation of numerous proteases.[37–39] Similarly, macrophage colony stimulating factor (M-CSF) deficient mice, surfactant protein D deficient mice, and integrin $\alpha_v\beta_6$ deficient mice also develop air space enlargement.[40–42] In all these models increased MMP activity has been demonstrated and, furthermore, mice deficient in MMP-12 are resistant to the pathological changes of cigarette smoke exposure.[43] The absence of MMP inhibitors can also result in abnormal pulmonary matix turnover as TIMP-3 deficient mice spontaneously develop air space enlargement at 2 weeks of age.[44]

The functional importance of MMP activity in these models is confirmed by crossing emphysema developing mice with MMP-knockout mice. For example, in the IL-13 overexpression model, deficiency of MMP-9 or MMP-12 results in reduced pathological changes and less respiratory failure.[45] Similarly, crossing integrin $\alpha_v\beta_6$ deficient mice with MMP-12 deficient mice prevents the development of age related emphysema.[42] However, these studies are limited by the lack of a functional murine orthologue of human MMP-1. The proposed orthologue, Mcol-A, has greatly reduced activity against type I collagen compared with human MMP-1,[107] and in human disease MMP-1 may play a primary role, as outlined below. Secondly, in some models changes develop early in life so may result from developmental abnormalities as opposed to reflecting the exogenous insults that cause COPD in humans.[108]

The guinea pig presents an alternative to the mouse in the study of cigarette smoke induced lung damage and MMP activity has also been implicated in this model. Smoke exposed guinea pigs have increased pulmonary collagenase levels as analysed by gene expression, immunoreactive protein, and activity.[46] This upregulation of collagenase activity is associated with a reduction in total lung collagen. Furthermore, the pathological changes are reduced by a broad spectrum MMP inhibitor, demonstrating the therapeutic potential of targeting MMPs in COPD.[47]

Human studies

The models described above indicate that MMP-9 and MMP-12 play key roles in destructive pulmonary pathology in mice and that collagenase activity is important in guinea pigs. However, studies in patients suggest that the spectrum of MMPs in human disease may differ significantly from these models. Clinical studies are often limited by demonstrating association as opposed to causation, but clinical investigation is essential to identify which proteases are critical in pulmonary disease in man.

Alveolar macrophages from patients with COPD express more MMP-1 and -9 than those from normal volunteers, and this is associated with increased secretion of active enzymes.[48] No increase in MMP-12 expression or activity was found. MMP-9 secretion is further increased in response to inflammatory stimuli.[49 50] The increased MMP-9 expression in macrophages is associated with increased MMP-9 activity in bronchoalveolar lavage (BAL) fluid.[51 52] Alveolar macrophages secrete several elastolytic proteases and the contribution of MMPs to elastin degradation increases with time.[53]

Although BAL fluid analysis provides a good indication of protease activity within the airways, it may not provide an indication of events within the interstitium where most of the tissue remodelling occurs. Also, studies using BAL fluid derived alveolar macrophages assume that they are the primary source of MMPs in emphysema, but stromal cells may make a greater contribution to ECM turnover. Immunohistochemistry does not have these limitations, and in an analysis of collagenase and gelatinase expression in COPD, MMP-1, -2, -8 and -9 were found to be upregulated.[54] Neutrophils were identified as the primary source of MMP-8 and -9, while MMP-1 and -2 were expressed by macrophages and epithelial cells.[54] Increased MMP-14 expression has also been demonstrated in emphysematous lungs by immunohistochemistry and by western blotting.[55] In a study combining RT-PCR, ELISA, immunohistochemistry and a collagen degradation assay to analyse MMP-1, -9 and -12, increased MMP-1 expression was observed in patients with COPD.[56] Type II pneumocytes were identified as a main source of MMP-1, suggesting that inflammatory cells may not be exclusively responsible for tissue destruction in emphysema.[56] MMP-1 expression correlated with increased collagenase activity in homogenised lung samples. In contrast to the BAL fluid studies, MMP-9 expression did not differ between emphysema and control samples. Again, no MMP-12 expression was found in human disease, despite the critical role for MMP-12 in the mouse model of emphysema. However, another study did show increased MMP-12 expression in smokers with COPD compared with normal smokers.[57] Increased MMP-1 expression in epithelial cells of

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smokers may result from prolonged activation of the ERK mitogen activated protein kinase pathway, providing a potential regulatory point to suppress activity.[15]

Taking clinical and animal studies together, the evidence linking MMP-1 and MMP-9 to emphysema is the most compelling. MMP-12 is essential to cigarette smoke induced pathology in the mouse but may not be equally critical in human disease. MMP-7 has not been specifically studied in human emphysema, despite being a potent elastase secreted by human macrophages.[109] The ease of detection of MMP-9 may have caused over-representation in clinical studies relative to MMPs that are more difficult to quantify. Whether MMP-9 is primarily responsible for pathology or part of the inflammatory and reparative process remains an area of debate.[110] The nature of MMP biology allows MMP-9 to be both involved in the initial pathological insult when released in excess, but also to be necessary for tissue repair when secreted at appropriate levels. Studies of MMP activity may therefore give divergent results at different stages of disease evolution and lead to controversy about which MMPs are critical in pulmonary disease.

ACUTE RESPIRATORY DISTRESS SYNDROME

ARDS may result from a wide spectrum of systemic insults such as septicaemia which precipitate increased permeability of the alveolar–capillary barrier causing impairment of gas exchange. Chronically, the disease may progress to fibrotic lung injury.[111] Since the alveolar basement membrane is primarily type IV collagen, MMPs are likely to be involved in the extensive ECM remodelling that occurs in ARDS. In the acute phase of ARDS increased MMP-9 levels have been identified in BAL fluid[59–61] and are associated with markers of basement membrane disruption.[60] However, when ARDS patients were compared to those with hospital acquired pneumonia, no increase in MMP-9 levels was found.[62] Lung tissue remodelling may be exacerbated by treatment since hyperoxia upregulates collagenase and gelatinase activity in rat lungs.[63] The complexity of the events in early ARDS is highlighted by the observation that not only are protease levels increased, but markers of collagen synthesis are also raised.[61 64] The response to the initial insult may therefore drive both ECM destruction and synthesis and, in some cases, may ultimately result in fibrosis.

The functional importance of MMP activity in ARDS has been investigated in animal models of acute lung injury. In an immune complex deposition model in the mouse, mice deficient in MMP-3, -9 or -12 had less severe lung injury than wild type mice.[22 65] Additionally, neutralising the inhibitor TIMP-2 exacerbates lung damage in this model, demonstrating once more that the balance between MMPs and their inhibitors is critical in determining pathological outcomes.[66] Similarly, mice deficient in TIMP-3 develop worse lung injury in a model of sepsis associated with reduced collagen and fibronectin levels.[67]

These data indicate that MMPs may contribute to the initial lung insult in ARDS, suggesting that MMP inhibition may prevent acute lung injury. In a cardiopulmonary bypass model, inhibition of MMP and neutrophil elastase activity by a chemically modified tetracycline reduced lung injury.[68] Similar protective effects by inhibiting these enzymes have been demonstrated in animal models of sepsis.[69 70] Modulation of MMP activity therefore has the potential to prevent acute lung injury, but the challenge will be to give treatment sufficiently early in the course of the disease to halt the pathological cascade initiated by excessive protease activity. Furthermore, comparison between studies is difficult because of the diverse models and different MMPs investigated.

SARCOIDOSIS

Sarcoidosis is a syndrome affecting multiple organs with diverse clinical presentations. Granuloma formation is common to all disease manifestations and results in extensive ECM remodelling. Collagenase activity can be detected in the BAL fluid of patients with sarcoidosis and, when present, is associated with a lower carbon monoxide transfer factor.[71] Furthermore, the decline in lung function is more rapid in collagenase positive patients.[72] MMP-8 appears to be responsible for this activity since MMP-8 levels and collagenase activity correlate.[73] MMP-9 levels are also increased in the BAL fluid and induced sputum of patients with sarcoidosis, with no compensatory increase in the levels of the inhibitor TIMP-1.[73 74] The cellular source of MMPs may primarily be multinucleate giant cells since they are highly immunoreactive for MMP-1 and -9.[75] The pathological result of this unopposed protease activity is disruption of the basement membrane as focal damage is observed on staining for type IV collagen.[75] Such data implicate MMP activity in initiating ECM breakdown and remodelling that can lead to the decline in lung function that occurs in advanced pulmonary sarcoidosis.

TUBERCULOSIS

Mycobacterium tuberculosis is one of the most successful human pathogens of all time and remains a global health crisis. ECM destruction is fundamental to the success of *M tuberculosis* since it allows cavitation and thereby creates an immunoprivileged site within which the organism can proliferate and then spread to new hosts.[112] The reduced immune surveillance of the cavity is demonstrated by the ability of less virulent pathogens such as *M intracellulare*, *M xenopi*, and *Aspergillus fumigatus* to occupy a pre-existing pulmonary cavity. However, the ability to create a cavity in previously normal lung distinguishes *M tuberculosis* from these opportunist infections. If *M tuberculosis* infects organs other than the lung it will usually reach a biological dead end, killing its host and failing to spread to a new one. Surprisingly, the mechanisms by which it causes lung destruction are poorly understood. As collagen and elastin must be degraded to allow cavity formation, MMPs are likely to be involved in the pathology of TB.

Animal studies

Guinea pigs present a relatively good model of human TB, with granuloma morphology that is similar to human disease but cavitary disease rarely develops. The water soluble fraction of *M smegmatis* can increase collagenase secretion by guinea pig macrophages,[113] but more extensive analysis of MMP activity in guinea pig TB has not been undertaken. Mice are a very useful model of immunity to *M tuberculosis*, with many findings such as the key roles of CD4+ cells, TNF-α and IFN-γ first identified in the mouse later confirmed in man.[114] However, the pulmonary pathology of TB infection in the mouse is very different from that in humans. Mice develop progressive pulmonary fibrosis, as occurs in advanced human TB, but do not cavitate.[114 115] We hypothesise that this difference may result in part from the lack of a functional homologue of human MMP-1 in the mouse.[107]

In mice, *M tuberculosis* results in increased levels of MMP-2 and MMP-9 in infected tissues[76] and infection of murine macrophages increases MMP-9 secretion.[77] Broad spectrum MMP inhibition in a mouse model of TB led to more rapid disease progression and a deficiency in IL-1 and IL-2 secretion with a relative excess of IL-4, demonstrating a deviation in the immune response to a Th2 profile.[78] In another murine study MMP inhibition was reported to lead to reduced bloodborne *M tuberculosis* with smaller granulomas, less cell recruitment, and more collagen deposition.[79]

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This suggests that MMP activity may contribute to mycobacterial dissemination by facilitating erosion from the alveolus. However, the lack of specificity of BB-94, the MMP inhibitor used in these two studies, makes interpretation difficult. BB-94 also inhibits members of the ADAM family including ADAM-17 (TNF-α cleaving enzyme, TACE), so the deviated immune response may be due to inhibition of TNF-α release which is vital to an effective immune response to *M tuberculosis*.[114]

Human studies

The first indication that MMPs may be involved in tissue destruction in TB came in 1996 when it was shown that mycobacterial lipoarabinomannan (LAM), a major antigenic cell wall component of *M tuberculosis*, increases MMP-1 and MMP-9 gene expression in the human THP-1 cell line.[80] Furthermore, MMP-9 mRNA accumulation was shown in cells isolated by BAL from two patients with active pulmonary TB.[80] Circulating MMP-9 levels correlate with disease severity of TB, with highest levels in those with the most extensive disease, while MMP-2 levels do not differ between groups.[81] In an analysis of TB pleural effusions, higher levels of MMP-1, -2 , -8 and -9 were found in patients with TB than in patients with congestive heart failure (unpublished data).[82 83]

In TB meningitis our group has shown a matrix degrading phenotype in the cerebrospinal fluid where increased MMP-9 concentrations are unopposed by a compensatory increase in TIMP-1 levels.[84] Extensive disease occurs in TB despite a relatively low bacterial load, suggesting that host immunity and intercellular networks may drive MMP secretion. Consistent with this, the immunohistochemistry of TB lymph node granulomas shows extensive MMP-9 staining with minimal TIMP-1 expression despite the presence of only small numbers of bacilli.[85] However, the ECM of the lung differs from that of brain and lymph nodes, so the key MMPs in pulmonary TB and extrapulmonary disease may not be the same.

We have recently studied MMP expression in pulmonary TB. In a global analysis of MMP and TIMP gene expression in *M tuberculosis* infected human macrophages, MMP-1 and -7 were most potently upregulated.[86] The induction of these specific MMPs may drive matrix destruction, as MMP-1 degrades type I collagen[7] and MMP-7 is a potent elastase.[109] MMP-9 gene expression and secretion was unchanged, showing that MMP regulation differs between human cell lines, undifferentiated monocytes, and macrophages. This suggests that MMP-9 expression may occur at specific phases of granuloma development. MMP-1 and -7 were expressed in caseating granulomas of patients with active culture proven TB but not in control patients. Airway epithelial cells were also strongly immunoreactive for MMP-1, showing that stromal cells may contribute to tissue destruction (fig 1).[87] In culture, epithelial cell MMP-1 expression is driven by a monocyte dependent network. *M tuberculosis* therefore drives a matrix degrading phenotype both by direct infection of macrophages and by an intercellular network that increases MMP secretion by epithelial cells (fig 2).

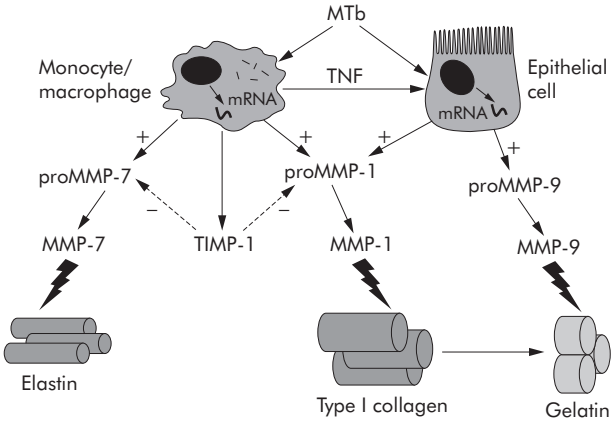


Figure 2 Schematic representation of *Mycobacterium tuberculosis* (MTb) driven tissue destruction. MTb infection of monocytes/macrophages increases MMP-1 and MMP-7 gene expression and secretion. No compensatory increase in secretion of the inhibitor TIMP-1 occurs. A monocyte dependent network also drives MMP-1 and -9 secretion from pulmonary epithelial cells. After activation, MMP-1 cleaves type I collagen fibrils to gelatin which is, in turn, degraded by MMP-9 and MMP-7 degrades elastin.

MMPs AS THERAPEUTIC TARGETS

The data outlined above implicate excess MMP activity in the pathogenesis of COPD, ARDS, sarcoidosis, and TB. It therefore follows that modulating MMP activity may reduce immunopathology. The initial interest in therapeutic targeting of MMPs concentrated on cancer, although to date the results have been disappointing.[34] However, in pulmonary disease, MMP inhibition can prevent pathological changes of emphysema[47] and ARDS[69 70] in animal models. In human disease, global MMP inhibition may have deleterious effects as it may suppress the key immunoregulatory functions of MMPs. Mechanisms to target specific MMPs are therefore required. This may be achieved either by generating new chemical inhibitors with a narrower spectrum of activity than those available or by targeting the pathways that regulate MMP secretion such as the mitogen activated protein kinases. In order to realise the potential of MMP inhibition

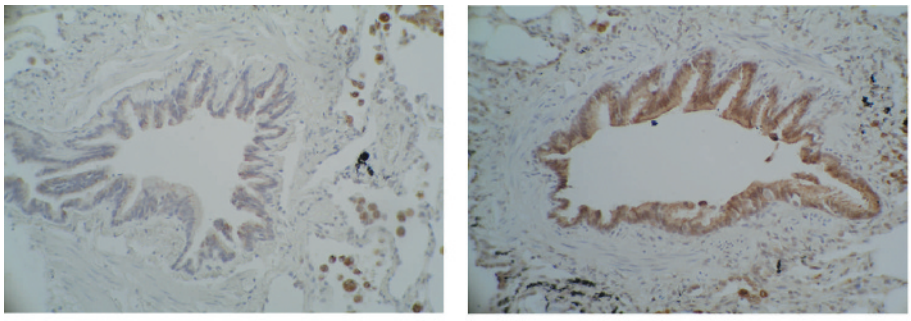


Figure 1 Pulmonary epithelial cells express MMP-1 in patients with tuberculosis. MMP-1 immunoreactivity is brown against the blue counterstain. In uninfected lung, pulmonary epithelial cells do not express MMP-1 (left panel). In active pulmonary TB epithelial cells adjacent to TB granulomas are strongly immunoreactive for MMP-1 (right panel). From Elkington *et al*[87] with permission. © The American Association of Immunologists Inc, 2005.

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in human pulmonary disease, we must first dissect the balance between the immunological and pathological roles of critical MMPs. Next, the differences between animal models of lung disease and human disease must be further defined to ensure that animal studies of MMP inhibition reflect human disease more closely. If this can be achieved, suppression of excess MMP activity may reduce immunopathology in several pulmonary diseases.

CONCLUSIONS

MMPs are very likely to have a central role in destructive pulmonary diseases where excess proteolytic activity causes aberrant degradation of the lung ECM. Although MMPs play important roles in normal pulmonary immunity, in excess they can contribute to immunopathology that leads to morbidity and mortality. Further definition of the roles of individual MMPs in health and disease is required to allow targeted treatment that will protect the lung from excess MMP activity without compromising normal matrix remodelling and immunity.

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