Matrix metalloproteinases in T cell mediated pulmonary diseases

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1. ABSTRACT

Lung transplantation is the only conclusive treatment for many patients suffering from end-stage pulmonary disease. Unfortunately, the leading cause of death in lung transplant recipients is the development of chronic rejection known as obliterative bronchiolitis, characterized by extensive remodeling. Matrix metalloproteinases (MMPs) are endopeptidases known for their role in matrix remodeling and their involvement in many biological processes including end-stage pulmonary disease and transplant rejection. Our understanding of MMPs involvement in pulmonary immunity is rapidly expanding. As a result there has been some focus on MMPs role in T cell-associated pulmonary diseases, such as pulmonary fibrosis, emphysema, asthma and bronchiolitis obliterans syndrome. However, not much is known about the role of MMPs in regulating immune cell function. It is now commonly known that MMP inhibition via, broad spectrum or specific synthetic or naturally occurring inhibitors (TIMPs) can down regulated many pulmonary disease states. In this review, we explore the idea that T cell targeted MMP inhibition may provide a novel approach of immune regulation in the treatment of T cell-mediated diseases.

2. INTRODUCTION

Lung transplantation is the only definitive treatment for many patients suffering from end-stage pulmonary disease. However, the development of chronic rejection known as obliterative bronchiolitis (OB), remains to be the leading cause of death in lung transplant recipients (1-2). Obliterative bronchiolitis-OB/bronchiolitis obliterans syndrome-BOS and the events leading to these devastating conditions are characterized by extensive matrix remodeling ultimately leading to fibrosis. These processes are believed to be the result of immune activation with the endpoint of scar formation. The various mechanisms regulating immune activation and matrix remodeling could be a final common pathway contributing to graft destruction.

Matrix Metalloproteinases (MMPs) constitute a family of over 25 secreted and cell surface zinc-dependent endopeptidases, known to be responsible for the turnover of the extracellular matrix (ECM) and basement membranes (BM). MMPs have been mainly classified based on their substrate specificity and structural similarities (3). Structurally, MMPs have a pro-peptide domain, a catalytic domain and a hemopexin-like domain. The pro-peptide
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domain is ~80 amino acids with a hydrophobic residue at the NH2-terminus, and contains a highly conserved cysteine residue in the conserved sequence (PRCGXPD). The cysteine within this conserved sequence is termed the “cysteine switch” due to its interaction with a Zn$^{2+}$ ion in the catalytic site. The catalytic domain is ~160 residues, contains the active site, and contains a Zn$^{2+}$ binding motif of the conserved sequence HEXXHXGXXXH (where X can be any amino acid). The three conserved histidine residues within the catalytic site are responsible for the coordination of the catalytic Zn$^{2+}$ ion. The catalytic domain also includes a conserved methionine, which forms a unique “met-turn” structure (XXMXP) and structural binding sites for 2-3 Ca$^{2+}$ ions, which are important for stability. The C-terminal hemopexin-like domain is ~ 200 residues and is thought to modulate substrate specificity and the binding of Tissue Inhibitors of MMPs (TIMPs) (3).

These endopeptidases have a broad range of substrate specificity, and participate in a plethora of biological processes, such as cellular proliferation, embryonic development, morphogenesis, bone remodeling, wound healing and inflammation. Apart from development, morphogenesis, bone remodeling, specific, and participate in a plethora of biological These endopeptidases have a broad range of substrate specificity, and participate in a plethora of biological processes, such as cellular proliferation, embryonic development, morphogenesis, bone remodeling, wound healing and inflammation. Apart from digestion the ECM, MMPS are capable of modulating the activity of other proteases, as well as cytokines and chemokines that are important in lung diseases (4).

Recently, studies have identified MMPs as being key players involved in pulmonary immunity by facilitating cell migration, matrix remodeling and modulation of other non-matrix substrates. Additionally, reports have highlighted MMPs’ role in a variety of pulmonary diseases associated with T cell activation such as pulmonary fibrosis (5), emphysema, COPD (6) asthma (7), as well as in bronchiolitis obliterans syndrome (8), which is the result of autoimmune-mediated injury following lung allograft rejection (9-11). It is thought that the exacerbation of many of these disease states is due to the unregulated expression of MMPs (12-13).

Although the focus of this review is on the role of MMPs in T cell mediated diseases, it is important to note the involvement of other cell types capable of secreting MMPs and augmenting injury. Neutrophils are thought to be one of the major sources of MMPs. They synthesize MMP-9 during maturation in the bone marrow which is then stored in granules and readily released (14). To name a few others, bronchial epithelial cells (15), Clara cells (16), alveolar type II cells (17), fibroblasts (18), epithelial cells (19), eosinophils (20) and macrophages (21) can all produce MMPs. Many of these cell types work in concert by either direct cell-cell interaction or indirectly by cytokine/chemokine secretions, thereby mediating lung injury. Ferrari-Lacraz et al. demonstrated that human interstitial lung macrophages secrete MMPs following direct contact with activated T cells which lead to tissue remodeling (21). It is important to emphasize that even though T cells have been found to be upregulated in many lung disease states, the true role of T cells and MMPs in lung disease exacerbation remains unknown and highly controversial.

Interestingly, the gelatinases (MMP2 and MMP9) have been shown to play critical roles in T cell infiltration into tissues, suggesting their importance in T cell-mediated injury (22). Indeed, elevated levels have been identified in the airway and parenchyma of the lung, as well as in sputum and bronchoalveolar lavage (1, 23-24). In this regard, studies have shown that CD4+ and CD8+ T cells, among others, have the ability to produce MMP2 and MMP9 upon stimulation (25), which implies that T cell derived gelatinases may play a pivotal role in the pathogenesis of T cell-mediated lung injury.

To date, many studies have been aimed at developing strategies to block or inhibit MMP activity using broad-spectrum as well as, mechanism-based specific MMP inhibitors, with the goal of identifying novel approaches to abrogate the immunopathogenesis of lung disease as well as transplant rejection.

2. MMPS AND ORGAN TRANSPLANTATION

Recently, reports have begun to show the functional role of MMPs in allograft rejection and their role in T cell alloreactivity. In a orthotopic rat lung transplant study, we reported that acute lung allograft rejection was associated with an up-regulation of MMP-2 expression (26). When these transplant recipient rats were treated with COL-3, a chemically modified tetracycline and broad-spectrum MMP inhibitor, not only was MMP activity blocked, but the expression of two cytokines reported to be elevated in the BAL fluid following transplantation, IL-1beta and TNF-alpha, was also abrogated (26-27). Moreover, lymph node lymphocytes from the COL-3 treated transplant recipient rats proliferated poorly in response to donor alloantigens (26). Although treatment with COL-3 did not prevent the rejection response, transplant recipient rats exhibited a clinical condition known as post-transplant lymphoproliferative disorder (PTLD), a B cell lymphoma that correlates with severe T cell dysfunction (immunosuppression). In another study assessing ischemia reperfusion injury and MMP inhibition, we reported that in addition to blocking MMP-9 and TNF-alpha expression, COL-3 down-regulated IL-8 mediated PMN infiltration and improved systemic oxygen and lung histology (28). More importantly, MMP-9 inhibition down-regulated the release of type V collagen (colV), a sequestered autoantigen that is intercollated with type I collagen in the lung and thought to be only exposed in response to remodeling. In accordance with these findings, a prior study showed that COL-3 blocks the development of T cell mediated immune responses to col (V) (28). These studies suggest that dampening the T cell response to alloantigens or col (V) improves lung function and suggests that global MMP inhibition may mediate this response.

Similarly, in a heterotopic murine heart transplant study, Ogawa et al., reported that clarithromycin (CAM), a 14-membered ring macrolide and potent antibiotic, inhibited MMP-9 expression and suppressed acute and chronic rejection (29). Interestingly, the authors found that CAM altered expression of inflammatory cytokines (IFN-gamma, IL-6, IL-15 and IL-10), suppressed migration and proliferation of smooth muscle cells and attenuated macrophages and CD4+ and CD8+ T cell infiltration. In this regard, an earlier study by Morikawa et al., demonstrated
demonstrated that global MMP inhibitors are quite effective at modulating the rejection response, although the exact mechanism by which this occurs remains unknown. It is interesting to speculate regarding possible mechanisms by which MMP inhibition abrogates T cell proliferation. With the similarities seen in these studies, it may be that COL-3 and CAM have similar functions despite the fact that COL-3 is a chemically modified tetracycline that lacks antibiotic activity, whereas CAM is a potent antibiotic. In this regard, Kikuchi et al., reported in a chronic inflammatory airway model, that CAM modified inflammation by suppressing IL-8 production through the transcription factors AP-1 and NF-kappa B (32). It is possible that a similar mechanism may be involved in COL-3 inhibition of IRI. COL-3 may act to inhibit IL-8 production through AP-1 or NF-kappa B, thereby suppressing IL-8 mediated PMN infiltration. Additionally, AP-1 and NF-kappa B have been shown to play important regulatory roles in T cell proliferation (33). COL-3 may also perturb IL-2 gene promoter transcription factors AP-1 and AP-1/NFAT binding complexes, thereby abrogating T cell proliferation.

Thus far, many of the known MMPIs such as batimastat, GM6001, doxycycline and chemically modified tetracyclines (COL-3), are global inhibitors, which are designed to non-specifically inhibit MMP activity by chelating the active-site zinc ions within the MMPs. The lack of specificity has made studying individual MMPs challenging. For example, Sandler et al. reported that COL-3 inhibits the activity of protein kinase C (PKC) in mast cells, suggesting that COL-3 functions as more than just an MMPI and can negatively affect cell growth and differentiation (34). Additionally, Kikuchi et al., reported that CAM also has multiple biological effects, such as alteration of inflammatory factors (32). These findings suggest that global MMP inhibitors may mediate other signaling pathways involved in immune regulation. As such, studies have begun to use more specific means of studying MMP biology by utilizing MMP deficient animals as well as MMP specific inhibitors.

For example, Fernandez et al. reported in a tracheal allograft obstructive airway disease (OAD) model, that increased intragraft expression and activity of MMP-2 and MMP-9 correlated with OAD development, and host mice that lacked MMP-9 expression did not develop OAD when transplanted with wild-type tracheas, which correlated with significantly lower levels of graft infiltrating CD4+ and CD8+ T cells (10). They also reported that alloreactivity was enhanced in MMP9 deficient bulk T cells stimulated with allogeneic BALB/c DCs. It has been reported that T cells and macrophages are important to the development of OAD (35-36), as studies have shown that mice with a genetic T cell deficiency, such as severe combined immunodeficient (SCID) mice or recombinase activating gene 1-deficient (RAG-/-) do not develop OAD (37). These studies provide strong evidence that T cells are important in the development of OAD and suggest that T cell derived MMP-9 may play an important role in this development.

In another study using a mouse model to study the role of MMP-2 and MMP-9 in the pathogenesis of cardiac allograft rejection, Campbell et al. reported that rejection was inhibited in MMP-2 deficient host mice, and exacerbated in MMP-9 deficient host mice (9). They suggest that the protective effects seen in MMP-2 deficient mice were due to an inhibition of mononuclear cell infiltration into the allograft, resulting in lower levels of collagen deposition and tissue remodeling.

Examination of T cell alloreactivity revealed that MMP-2 deficient T cells displayed an innate defect in their alloreponsive capacity. These data demonstrate that the absence of a T cell-derived MMP can alter T cell alloreactivity, which is in essence effecting T cell activation. Taken together, these two studies illustrate the different roles MMP-2 and MMP-9 play in the process of activation and expansion of alloreactive T cells during the process of cardiac allograft rejection or OAD. These data highlight the complexity of MMPs in immune responses, and suggest that prevention of T cell-derived MMPs can result in decreased T cell activation, which provides protective effects in response to a variety of pathogenic states.

Table 1 summarizes the roles of MMPs that have been reported in organ transplant rejection.

3. MMPS AND T CELL MEDIATED DISEASES

With much of the focus of MMPs being on their extracellular regulation and with studies highlighting the role of MMPs in the pathogenesis of many T cell mediated lung diseases, as well as transplant rejection, it is of interest to better understand the interconnection between MMPs and T cells. As such, many reports have confirmed that T cells can express MMPs (9-10). A recent study by Oviedo-Orta et al. compared gelatinase production in CD-1 murine splenic Th0, Th1 and Th2 cell phenotypes in the context of atherosclerotic plaques, and found that Th1 cells expressed higher levels of both MMP-2 and MMP-9 as compared to Th2 or Th0 cells (38). These data suggest that T cell-derived MMPs promote inflammation, consistent with previous reports implicating T cell-derived gelatinase activity contributing to atherosclerotic plaque inflammation in atherosclerosis (38).

Additionally, Beck et al., using a murine model of contact hypersensitivity (CHS), which is in part a CD8+ T cell-dependent disease, reported that MMP19 deficiency
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Table 1. Summary of role of MMPs in transplant rejection

<table>
<thead>
<tr>
<th>ROLE OF MMPs IN LUNG/PATHOLOGY/TRANSPLANT REJECTION</th>
<th>Human Lung Transplant</th>
<th>Orthotopic Rat Lung Transplant</th>
<th>Heterotopic Murine Tracheal Transplant</th>
<th>Intrapulmonary Murine Tracheal Transplant</th>
<th>Heterotopic Murine Cardiac Transplant</th>
<th>Ischemia Reperfusion Injury (IRI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute/Chronic rejection; Interstitial remodeling; OB; Increase in MMP-2, -8, -9 in BAL and sputum.</td>
<td>-Acute rejection; Increase in MMP-2, IL-1beta and TNF-alpha (MMP inducers) -Inhibition of MMPs: using COL-3 blocked IL-1beta and TNF-alpha and lymphocyte proliferation.</td>
<td>-Acute rejection; Increase in MMP-2 and -9</td>
<td>-Obstructive airway disease (OAD) Increase in MMP-2 and -9 -Inhibition of MMPs: using doxycycline blocked OAD and mononuclear cell infiltration -Inhibition of MMP-9 using MMP9-/- recipient mice: blocked OAD, decreased graft infiltrating CD4+ and CD8+ T cells.</td>
<td>-Acute/Chronic rejection; OB; Increase in MMP-9 and -12 -Inhibition of MMPs: using GM6001 and doxoyxilone prevented rejection, decreased remodeling, cell migration and increased alloreactive T cell proliferation.</td>
<td>-Acute/Chronic rejection; Increase in MMP-2 and -9 -Inhibition of MMPs: using CAM suppressed acute/chronic rejection, blocked MMP-9, altered IFN-gamma, IL-6, IL-15 and IL-10, decreased cell migration, proliferation and CD4+ and CD8+ T cell infiltration.</td>
<td>-Increase in MMP-2 and -9; Neutrophil influx; Increase in TNF-alpha and collagen V (Col V) -Inhibition of MMPs: using COL-3 blocked MMP-9, decreased PMNs, leukocytes, antigenic Col V and TNF-alpha.</td>
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In our investigation of gelatinase inhibition in an in vivo murine model of antigen specific CD8+ T cell mediated airway hyperresponsiveness using CC10-OVA mice, we found a significant decrease in the percentage of CD8+ Thy1.1+ T cells in the lung of CC10-OVA mice, suggesting that gelatinase inhibition may affect T cell migration and/or decrease cellular activation. Additionally, we found a decrease in GR-1+ cell infiltration, corresponding to a decrease in neutrophil accumulation in the BAL. Further analysis of CD25 surface expression on CD8+ Thy1.1+ T cells in the lung revealed a dramatic decrease in CD25 surface expression suggesting decreased cellular activation. These findings are similar to the in vitro data demonstrating a significant decrease in CD25 mRNA and cell surface expression in response to gelatinase inhibition (40). These findings are corroborated by a study by Vermaelen et al., demonstrating in a murine asthmaic airway inflammatory model that MMP-9 deficient mice exhibited reduced airway inflammation as compared to wild-type mice (41-42). Their data also suggested that in the absence of MMP-9, the airway DCs were depleted. This may also imply that if the DC population was diminished or non functional, then this would in turn dampen T cell activation since DCs process and present antigens to T cells, thereby reducing airway inflammation.

Another study by Jung et al., reported in a murine model of airway hyperresponsiveness, that MMP-8 and MMP-9 inhibition in vivo reduced airway recruitment of Th1 and Th2 cells and consequently the recruitment of other inflammatory cells (42).

In addition to the important role of CD4 and CD8 T cells, CD425+ regulatory T cells (Tregs) have key roles in regulating immune responses. In a murine experimental model of asthma, Goswami et al., reported that in response to proteinase allergen, mouse airway epithelial cells express MMP7, which is in accordance with humans studies identifying increased MMP7 expression in patients with chronic asthma (43). In the absence of MMP7, mice exhibited attenuated allergic responses to challenge with proteinase allergen and enhanced expression of retinal dehydrogenase 1 (RALDH-1), an enzyme involved in the production of retinoic acid. Moreover, MMP7 deficient mice exhibited more Tregs in the lung parenchyma. RALDH-1 has been shown to induce and promote the development of immunosuppressive regulatory T cells (44). The study suggests that in vivo, this RALDH-1 is regulated by epithelial-derived MMP-7, and that this enzyme may function as a negative regulator of allergic inflammation.

Collectively, these studies demonstrate that T cells play a significant role in many inflammatory diseases and suggest a link between MMPs and T cell activation/function. Additionally, MMPI clearly affects T cell function, which many studies have addressed. However, further studies are needed to elucidate the exact mechanism by which MMPIs mediate T cell function as well as the role that MMPs play in normal T cell homeostasis. For additional review of MMPs in pulmonary disease see (45).

In addition to the importance of synthetic MMPIs, the major physiologic inhibitors of MMPs in vivo, are a group of specific tissue inhibitors of MMPs (TIMPS).
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These naturally occurring inhibitors consist of a family of four structurally similar members, TIMP-1, -2, -3, and -4. TIMPs have an NH$_2$- and C-terminal domain, each of which contains three conserved disulfide bonds. These secreted proteins bind to the catalytic site of active MMPs with 1 : 1 stoichiometry, resulting in their loss of proteolytic activity. Of the four TIMPs, TIMP-1 and -2 have been shown to have key roles in the pathogenesis of lung disease. The balance between TIMPs and MMPs is believed to be important in regulating protease activity, suggesting that disruption of this balance can lead to serious pathological conditions (1-2). Kumagai et al. demonstrated in a murine model of asthma that high local levels of TIMP-1 or TIMP-2 abrogated allergen-induced airway inflammation (46). Hubner et al. found that low levels of TIMP-1 relative to MMP-9 are associated with fibroproliferation in the pathogenesis of obliterative bronchiolitis after lung transplantation (1). However, in the OAD model reported by Fernandez et al., mice that do not express TIMP-1, which has strong affinity to inhibit MMP-9, fail to develop OAD in trachea allografts (10). Additionally, we reported that using local gene therapy to induce intragraft expression of TIMP-1 or TIMP-2, had differential effects on delayed type hypersensitivity (DTH) responses to donor antigens and col (V), but neither affected rejection pathology compared to untreated allograft recipients (47). Alternatively, it was reported in an organ culture model of type 1 diabetes mellitus, an autoreactive T-cell disease, that TIMP-2 is inhibits infiltration of autoreactive T-cells into target pancreas tissue thereby preserving pancreatic beta-cell mass. Although not many studies have assessed the role of TIMPs on T cell function in the lung, collectively, these studies suggest that TIMPs may block the activation or function of T cells.

4. INTRACELLULAR MATRIX METALLOPROTEINASES AND IDENTIFIED SUBSTRATES

Taken together, these data support the notion that MMPs have a regulatory role in T cells and pose a question as to whether they function extracellularly or intracellularly. Recent publications have identified the presence of intracellular MMPs. A report by Luo and colleagues found a variant of MMP-11 that is expressed as an intracellular active form (48). Another group identified the nuclear localization of an active form of MMP-2 in cardiac myocytes, suggesting a potential biological role for MMPs in the nucleus (49). An intriguing study by Si-Tayeb et al. elucidated a mechanism for nuclear localization of an MMP by identifying a nuclear localization signal and showed that nuclear MMP-3 can induce apoptosis via its catalytic activity (50). Since MMPs are generally thought to be secreted or transmembrane proteins, studies showing their intracellular presence or regulation are of great importance and suggest a potentially new path of MMP regulation and activity. The new identification of intracellular MMP activity, offers a new potential mechanism of action for MMPs. Although studies have demonstrated the presence of MMPs within T cells, the specific role that MMPs may play in regulating T cell activation remains unknown. More importantly, few reports have identified potential intracellular MMP substrates that may be involved in regulating T cell signaling events. This understanding would shed light on the potential mechanism of action that MMPs may be exerting in T cells to regulate their activation.

In this regard, a recent study using a proteomics approach to analyze bronchoalveolar lavage fluid (BALF) from the lungs of wild-type and MMP2/9 double deficient mice following allergen-challenge, Kheradmand et al., reported three new in vivo substrates for MMP2 and MMP9; Ym1, S100A8 and S100A9, all of which are involved in chemotaxis (12). Ym1, a member of the chitinase family of proteins and has been identified in macrophages and airway epithelium of airway challenged mice (12, 51). S100A8 and S100A9 are small calcium-binding proteins of the S100 protein family that are highly expressed in neutrophil and monocyte cytosol and are found at high levels in the extracellular milieu during inflammatory conditions (52). Intracellular S100A8/A9 complexes play an important role in cell trafficking (53).

Increased levels of Ym1 were identified in the BALF of MMP2/9/- mice and not in wild-type allergen-challenged mice, demonstrating that MMP2 and or MMP9 are needed to process Ym1. Additionally, the authors reported that Ym1 is in fact a substrate of MMP2 and MMP9. Due to the size of the S100 proteins, in vitro cleavage assays were performed which revealed that S100A8 and S100A9 are substrates of MMP2. In an in vivo model of asthma, it was found that inhibition of S100 proteins by function-blocking Abs to S100A8 and S100A9, altered migration of allergic inflammatory cells in the alveolar space (12). These proteins have been identified in adult and juvenile rheumatoid arthritis, chronic bronchitis, cystic fibrosis, systemic lupus erythematosus, langerhans cell histiocytosis (54) and granulomatous conditions, such as tuberculosis and sarcoidosis (52). The identification of these new in vivo intracellular substrates, suggest a potential intracellular role for MMP2 and MMP9.

5. SUMMARY

Although active MMPs have been associated with many lung diseases, including lung transplant rejection, their specific role in regulating T cell activation remains to be elucidated. Understanding these effects are not only critical to define MMP function post transplant, but recent evidence suggests a role for MMP activation in the donor pre-transplant. Trauma-induced brain death is the leading indicator for organ donation. Head injury-induced lung pathology has been well documented. Recent studies indicate that trauma-induced brain death is associated with accumulation and activation of MMP2 and MMP9 in the lung (55). Both of these MMPs have been implicated in ischemia reperfusion injury (IRI), and T cell depletion may attenuate this process (56). Therefore, it is interesting to speculate that MMP inhibition in the donor, pre-transplant, may prevent lung allograft pathologies post transplant. In addition, MMP inhibition post transplant may be a novel therapeutic to prevent acute rejection and OB/BOS.
Although our understanding of MMPs in T cell mediated diseases is increasing, there is still much to be understood. Particularly, more investigation is needed to shed light on the role of MMPs in immune cell function, including T cells. The new identification of intracellular MMP activity, offers a new potential mechanism of action for MMPs. Although studies have demonstrated the presence of MMPs within T cells, the role that MMPs may play in regulating T cell activation remains unknown. More importantly, no reports have identified potential intracellular MMP substrates that may be involved in regulating T cell signaling events. This understanding would shed light on the potential mechanism of action that MMPs may be exerting in T cells to regulate their activation. The more we understand the role of MMPs and their function in various pulmonary disease states, the more effective we will be at finding ways to alter their function and design novel therapeutics to combat pulmonary disease, ultimately increasing quality of life.

6. ACKNOWLEDGEMENTS

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7. REFERENCES


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**Key Words:** Matrix metalloproteinases, MMP, Lung transplantation, T cells, Review

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