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What is the contribution of respiratory viruses and lung proteases to airway remodelling in asthma and chronic obstructive pulmonary disease?

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Abstract

It is well known that the lungs of asthmatics show airway wall remodelling and that asthma exacerbations are linked to respiratory infections. There is some evidence that respiratory infections in early childhood may increase the risk of developing asthma later in life. Chronic obstructive pulmonary disease (COPD), by definition, involves structural changes to the airways. However, very little is known about what role virus infections play in the development of this remodelling. This review considers the role of matrix metalloproteases and neutrophil elastase in remodelling, and whether the induction of proteases and other mediators during respiratory virus infections may contribute to the development of airway remodelling.

Keywords: Matrix metalloprotease; Neutrophil elastase; Virus; Tissue inhibitor of metalloproteases; Exacerbation

1. Introduction: remodelling, asthma, COPD, and respiratory viruses

Airway remodelling (AR) is common in asthmatics. Clinically, it presents as airflow obstruction that is poorly reversible with bronchodilators, and laboratory findings include greater thickness of the airway wall, subepithelial layer and smooth muscle, and hyperplasia of goblet epithelial cells [1,2]. These structural changes may also contribute to, or worsen, bronchial hyperresponsivness. AR may partly explain why lung function declines more rapidly in asthmatics than non-asthmatics, but AR is difficult to study without invasive or costly imaging procedures [1,3]. There are conflicting data on reversibility of AR with corticosteroid treatment [2,4,5], with duration and dose of treatment, and duration of disease at the time of starting treatment, impacting on results. Despite a growing consensus that AR is an important component of asthma, and that amelioration of remodelling is an important therapeutic outcome, the molecular basis of this process remains obscure.

Chronic obstructive pulmonary disease (COPD) is a collective term for degenerative, obstructive lung disease, overwhelmingly due to cigarette smoking. COPD includes emphysema, chronic bronchitis and chronic obstructive bronchiolitis. While there is much variation in the lung pathology of COPD, typical features are alveolar destruction leading to permanent peripheral airspace enlargement, small airway fibrosis, increased numbers of inflammatory cells in the small airways, reduced lung elasticity, increased mucus production and declining lung function which is poorly reversible with bronchodilators [6–9]. Contributing factors to this AR include excessive protease activity and free radical damage, followed by induction of growth factors in a presumably aberrant repair process, which may be worsened by polymorphisms in enzymes that metabolize cigarette smoke components [6,10].

In both asthma and COPD, viral infections commonly precipitate severe and sustained disease exacerbation. Respiratory viruses were detected in 39% [11], 56% [12] and 64% [13] of patients with an acute exacerbation

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of COPD. Respiratory viruses were detected in 80–85% of school age children with an acute exacerbation of asthma [14]. Amongst adult asthmatics, 76% of patients requiring emergency treatment for acute asthma were infected with a respiratory virus [15]. COPD exacerbations are linked to worsening quality of life [16] and more rapid decline in lung function with more frequent and longer lasting hospital admissions [17]. The typical viruses known to cause exacerbations are rhinoviruses, which cause most common colds, followed by respiratory syncytial virus (RSV), influenza, coronaviruses and parainfluenza viruses (PIVs). In addition, Hogg [18] has proposed that latent adenovirus infection might also contribute to the pathogenesis of COPD. The detection rate and prevalence of specific viruses varies with patient age, time of year, site of sampling, method of detection, influenza vaccination status and that year's predominant influenza strain. In particular, older studies that use culture and/or serology have lower virus detection rates [19] than when PCR is used [11–13]. While respiratory symptoms are similar during infection with these pathogens, these are distinct viruses with very different replication strategies.

Very little is known about how respiratory virus infections worsen asthma and COPD. A landmark study by Corne et al. [20] found that asthmatics were no more likely to get rhinovirus colds than their non-asthmatic domestic partner, but asthmatics were more likely to develop lower respiratory tract symptoms that were more severe and long lasting. It is possible that mediators such as proteases, which are induced by the respiratory virus infection, contribute to more severe disease in these patients.

In this review, we will discuss the limited knowledge about induction of proteases in respiratory virus infections and the potential role of respiratory viruses in AR. More is known about proteases and their inhibitors in inflammatory lung disease; this will be briefly addressed but for more details, the reader should consult other reviews [7,21].

2. Respiratory viruses and airway remodelling

Very few studies have specifically addressed this issue. To our knowledge there are only three studies on this topic, and the variable results point to a need for further research.

Guinea pigs infected with RSV develop viral bronchiolitis. 100 days after RSV infection, guinea pigs had significantly increased eosinophilia and airway hyperresponsiveness (AHR). Between virus infected guinea pigs and controls, there was no significant difference in the thickness of subepithelial connective tissue or smooth muscle [22]. Infected animals may need to be kept for longer times for remodelling to be apparent, although there is evidence from occupational asthma research that remodelling in humans can occur after fairly short-term exposure to allergens [1]. RSV infected airway epithelial cells secrete increased amounts of basic fibroblast growth factor (bFGF), in comparison to uninfected cells [23]. This could contribute to remodelling.

Mice infected only once with Sendai virus (a paramyxovirus and natural rodent pathogen that is moderately related to RSV and PIVs) had both acute and chronic airway hyperreactivity. Virus was undetectable by culture at 12 days post-infection (p.i.) and by real time PCR at 21 days p.i. [24]. Increased numbers of mucus-producing goblet cells and increased staining for the mucin MUC5AC were seen at 21 days p.i., which is similar to the profile of acute fatal asthma in humans [25]. The increased airway hyperreactivity and goblet cell hyperplasia were partly reduced by corticosteroids but unchanged in IFN-γ knockout mice. The authors interpreted these overall findings to mean that a single virus infection can lead to permanent changes in the epithelium and airways, and this chronic phenotype in mice can be genetically segregated from the acute antiviral response [24].

3. Features of lung proteases

At first glance it seems odd that proteases contribute to AR, as their main task is to degrade proteins [10]. However, increased protease activity can have a major impact on the overall level of inflammation.

There are at least 25 matrix metalloproteases (MMPs), which can be secreted or associated with the cell membrane. Some MMPs, such as MMP-7 are constitutively expressed in healthy tissue (generally epithelial surfaces) but most secreted MMPs are only expressed in tissues undergoing angiogenesis, disease, inflammation and repair [21]. In contrast, the mRNAs for the six membrane-type MMPs are constitutively expressed in many normal cells and tissues, including leukocytes, lung and spleen [26]. In older papers, names of MMPs reflect the best studied of its substrates, whereas more recent terminology uses numbers as many MMPs can cleave multiple substrates. For example, gelatinases A and B are, respectively, known as MMP-2 and MMP-9 [21].

MMP-9 is important in the lung, and while it is not normally made by resident lung cells, it can be made by leukocytes, bronchial epithelial cells and other cell types in response to various stimuli [27]. Macrophages, neutrophils, lymphocytes, fibroblasts and smooth muscle cells produce a range of MMPs, depending on the stimulus [7]. More detail on MMPs and their role in normal and diseased lung can be found in other recent reviews [21,27,28].

The activity of MMPs is controlled at four levels [21,27]: *gene expression*, *compartmentalization*, e.g. by anchoring of some MMPs to the cell membrane, or neutrophils storing MMPs in granules, *proteolysis* (cleaving off the pro region by MMPs or serine proteases), and *enzyme inactivation* (e.g. binding to endogenous inhibitors). These activation processes can be influenced by inflammatory

mediators [27]. Anchoring of some MMPs at the cell surface provides better control of proteolysis, and in addition to proteases designated as membrane-type MMPs [26], cell surface association of MMP-9 on human neutrophils has been reported [29].

There are five known tissue inhibitors of metalloproteases, or TIMPs. Aside from their main role in MMP regulation, TIMPs are also involved in regulation of other proteases and apoptosis [30,31], and hence the (at least transient) dysregulation of TIMPs in asthma and COPD [7] could have a systemic impact. Other inhibitors exist; the main circulating inhibitor of MMP-9 is α_2-macroglobulin [27] and any study of MMPs from body fluids must consider that some MMPs may be complexed with inhibitors.

Neutrophil elastase (NE) is a serine protease critical for the antimicrobial activity of neutrophils. Other serine proteases relevant to COPD are proteinase 3 and cathepsin G [10]. NE is stored in primary (azurophilic) granules, released upon neutrophil degranulation and it can degrade almost all extracellular matrix proteins and key plasma proteins, as well as innate immune proteins such as complement receptors and lung surfactant proteins [32]. While NE is generally a pro-inflammatory molecule, it can also turn down inflammation by cleavage of pro-inflammatory cytokines such as IL-6. The main endogenous inhibitors of NE are α_1-protease inhibitor, α_2-macroglobulin and secretory leukocyte protease inhibitor or SLPI [32]. Increased net activity of NE is seen in acute lung injury [32], acute viral exacerbations of asthma [15] and COPD, where it stimulates release of mucus and is strongly linked to alveolar destruction [10]. MMP-1 (a collagenase) and MMP-12 or macrophage metalloelastase are also implicated in alveolar destruction [10].

In vitro studies provide indirect evidence that MMP-9 is involved in migration of T lymphocytes [33], eosinophils [34] and neutrophils [35] across basement membranes, and that elastase contributes to this process by activation of the proform of MMP-9 [35].

Involvement of a certain protease in some process does not mean that it is essential, as there can be redundancy in proteases. In mice, MMP-9 is not needed for neutrophil migration into the lung and in vitro neutrophil bacteriocidal activity [36]. Indeed, most mice that are 'knockouts' for specific MMPs are normal when unchallenged [28]. This redundancy could limit the therapeutic use of protease inhibitors.

There are many studies on proteases and their inhibitors in asthma and COPD [7]. The general picture is higher overall protease activity, but specific conclusions depend on site of sampling [bronchoalveolar lavage (BAL), sputum, nasopharyngeal aspirate, immunohistochemistry of lung biopsies], method of assay, stimulus (if patient derived cells are used in in vitro studies), patient status at time of sampling (stable or exacerbation, medication use, smoking status) and nature of controls (the same patients after recovery, healthy controls or healthy smokers). The increased protease activity observed in most studies need not mean that inhibitors are concurrently downregulated [7].

4. Relevance of MMPs to airway remodelling

Few studies have directly looked at proteases and remodelling. In mice sensitized with ovalbumin and then challenged with aerosolized ovalbumin, MMP-2 and MMP-9 were upregulated in BAL, which was accompanied by infiltration of eosinophils and lymphocytes. The movement of cells into the airway lumen was inhibited by treating mice with TIMP-1 and TIMP-2 [37], and a subsequent histology study showed that the epithelial basement membrane was damaged by transmigration of inflammatory cells [38]. Furthermore, treatment of mice with dexamethasone or TIMP-2 greatly reduced both the transmigration of inflammatory cells and damage to the epithelial basement membrane [38].

On the basis of their in vitro properties, many growth factors and inflammatory mediators are implicated in AR. Possible mediators include TGF-β, platelet-derived growth factor, bFGF, TNF-α and IL-4. Their relevant properties are mitogenic activity for fibroblasts and/or airway smooth muscle cells, and promotion of connective tissue synthesis by these cells [1]. MMPs can directly impact on the activity of growth factors and chemokines, such as TGF-β, TNF-α, insulin-like growth factor (IGF)-1, EGFs, FGFs and monocyte chemoattractant protein (MCP)-3. Products of MMP activity can act as chemoattractants [21]. Intratracheal instillation of elastase into mice led to a time-dependent release of FGF-2 and TGF-β from the lung into the BAL, and much of the TGF-β was in the active form. In pulmonary fibroblast cultures, elastase treatment caused the release of TGF-β [39].

Adults with a respiratory virus infection and acute exacerbation of asthma have increased sputum neutrophils and increased neutrophil elastase, compared to their baseline samples 4–5 weeks later [15]. While viruses are the main cause of COPD exacerbations, many patients with stable COPD show colonization of the normally sterile lower airways with potentially pathogenic bacteria. This is a risk factor for more frequent and more severe exacerbations of COPD [40]. MMP-7 (matrilysin) is rapidly induced in airway epithelial cells exposed to bacteria; this activates anti-bacterial defence but could contribute to remodelling [41].

As both inflammatory lung disease and respiratory virus infection can induce key lung proteases, viral exacerbations could lead to hyperinduction of active proteases and accelerated remodelling.

5. What do we know about protease induction during virus infections?

A PubMed search for 'MMPs and Virus' (words in title/abstract) yielded 134 hits, and those that focussed on actual induction of MMPs *by* a virus (as distinct from using viral vectors for gene expression) were mostly limited to hepatitis viruses, neurotropic viruses and retroviruses such as HIV. Coxsackie B3 virus infection of weanling BALB/c mice was associated with cardiac fibrosis from 2 to 4 weeks p.i. [42]. None of these viruses are closely related to common respiratory viruses. To our knowledge, there are only three studies that look at induction of MMPs upon infection with respiratory viruses.

MDCK cells (dog kidney) and Vero cells (monkey kidney) support the growth of most influenza viruses. Zymography (running of biological fluids such as BAL into a gel containing a protease substrate) showed that influenza infected MDCKs secreted more MMP-2 and less MMP-9 than uninfected cells [43]. In infected Vero cells, MMP-2 activity was unaffected while MMP-9 activity increased slightly. TIMP-1 levels in MDCK cells were unaffected by influenza, but in Vero cells, influenza infection caused a 2.3 fold increase in TIMP-1 at the peak of virus infection. Influenza shuts off the synthesis of most host cell proteins [44], which must be considered when measuring mediators in infected cells or animals.

Influenza infection of humans causes significant pathology in the lower respiratory tract; common features include desquamation of the epithelium, mucosal oedema and leukocyte infiltration [44]. These are complex processes but it is feasible that host proteases are involved. Proteases could trigger detachment from the epithelial monolayer and basement membrane, which may serve to limit virus spread [43], although dead infected cells can still trigger inflammation.

RSV-infected Hep-2 (human airway epithelium) cells showed more secretion and cell surface association of MMP-9 than uninfected cells [45]. Inhibitors of MMP-9 significantly reduced RSV replication, but only if the inhibitors were added early in infection. RSV mostly spreads by cell-to-cell fusion, forming characteristic 'giant cells' or syncytia, although extracellular spread does occur [46]. Enlarged syncytia were seen in transfected Hep-2s overexpressing MMP-9, but smaller syncytia were seen in transfected Hep-2s overexpressing TIMP-1 [45].

These data suggest a role for virus-induced MMP-9 in virus spread. It is possible that enhanced MMP-9 activity in RSV-infected cells may facilitate cell–cell spread in vivo [45], and one can speculate that RSV-induced proteases contribute to the spread of virus from the upper to lower respiratory tracts that is seen in 25–40% of infants [47]. RSV cytopathology in A549 cells is enhanced by trypsin, thrombin and plasmin although it is not known if enhanced cytopathology was linked to higher virus titres [48]. The precise mechanism of RSV spread is unknown; this is of great interest since the poor immune response to RSV in humans leads to persistent re-infections, and there are no effective drugs to treat RSV [47].

The only in vivo study of protease induction by a respiratory virus looked at the arterivirus porcine reproductive and respiratory syndrome virus (PRRSV) in piglets [49]. The BAL (but not serum) of infected piglets had significantly increased activity of MMP-2 and MMP-9, with the peak at days 7–14 (this correlates well with virus replication, lung histological lesions and increased monocytes and lymphocytes) and levels returned to normal by 6–7 weeks p.i.

While there are no direct in vivo studies, a role for MMPs in AR in response to viral infections can be inferred from the following sequence of observations: infection with respiratory viruses such as RSV [47] and influenza [44] induces pro-inflammatory cytokines such as TNF-α, IL-1β and IL-8, which stimulate production and release of MMP-9 [27]; MMP-2 and MMP-9 can cleave elastin [50], elastin-derived peptides are chemotactic for monocytes, and to a lesser extent neutrophils and alveolar macrophages [51] and elastin-derived peptides (made by human neutrophil elastase digestion of elastin) are chemotactic for fibroblasts [52].

6. Therapeutic potential

Many MMP inhibitors exist, but since MMPs have structural similarities, the inhibitors are often not specific enough for therapeutic use. Furthermore, many MMPs overlap in their cellular functions and multiple MMPs are upregulated in many disease states [29]. At least in mice, broad MMP inhibition can be harmful [7] and cancer patients treated with broad spectrum MMP inhibitors developed reversible skin thickening and shortening of muscle tissue in joints [21]. A specific NE inhibitor is effective in treating acute lung injury in animals and humans [32]. Upregulation of MMPs is seen in HIV-associated neurological disease, and it is interesting that clinically useful anti-HIV drugs reduce MMP activity in lipopolysaccharide stimulated brain cells [53].

7. Conclusion

Patients with asthma and COPD are often more severely affected by respiratory virus infections than the general population. AR contributes to lung dysfunction in asthma and COPD. While little research has been done in this area, it is possible that lung proteases are a factor in AR. There are many triggers that lead to a net increase in activity of a range of lung proteases, and the possible role of respiratory virus infections in increasing lung protease levels deserves further study.

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