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Interplay of Extracellular Matrix and Leukocytes in Lung Inflammation

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Abstract

During inflammation, leukocytes influx into lung compartments and interact with extracellular matrix (ECM). Two ECM components, versican and hyaluronan, increase in a range of lung diseases. The interaction of leukocytes with these ECM components controls leukocyte retention and accumulation, proliferation, migration, differentiation, and activation as part of the inflammatory phase of lung disease. In addition, bronchial epithelial cells from asthmatic children co-cultured with human lung fibroblasts generate an ECM that is adherent for monocytes/macrophages. Macrophages are present in both early and late lung inflammation. Matrix metalloproteinase 10 (MMP10) is induced in alveolar macrophages with injury and infection and modulates macrophage phenotype and their ability to degrade collagenous ECM components. Collectively, studies outlined in this review highlight the importance of specific ECM components in the regulation inflammatory events in lung disease. The widespread involvement of these ECM components in the pathogenesis of lung inflammation make them attractive candidates for therapeutic intervention.

Keywords

Asthma; Extracellular matrix; Fibrosis; Hyaluronan; Immunity; Inflammation; Macrophage; Matrix metalloproteinase 10; Versican

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1. Introduction

The extracellular matrix (ECM) is a critical component of normal lung tissue that not only provides structural support for cells and tissue architecture of the airways and lung parenchyma, but also is a major effector of cell behavior and fate. Indeed, we now know that the ECM has considerable control over cellular function during lung development, homeostasis, normal repair, immunity, inflammation, and disease. The airways, blood vessels, interlobular septa, and visceral pleura are bordered and embedded in specialized ECM structures. As for all visceral organs, the lung ECM consist of two distinct compartments. One compartment is the basement membrane (basal lamina), which is a thin, organized layer of laminins, type IV collagen, nidogen/entactin, and perlecan, a heparan sulfate proteoglycan. Basement membrane is the substratum on which endothelial and epithelial cells reside and is well established as a key driver of differentiation and cell survival. The second compartment is the interstitium, which is mostly a loose connective tissue composed of an array of structural and nonstructural ECM components such as fibrillar collagens (e.g., types I and III), elastin, fibronectin, fibrillins, various proteoglycans, matricellular proteins (e.g., CCN proteins, SPARC, tenascins, thrombospondins) and polysaccharides, such as hyaluronan, an abundant and physiologically important glycosaminoglycan (GAG) [1, 2]. Within the interstitium are blood and lymph vessels, airway smooth muscle bundles and cartilage, and a range of cells types, including fibroblasts, pericytes, and resident leukocytes. Furthermore, the ECM includes numerous related proteins, such as the enzymes that form fibers, proteinases that remodel ECM, cytokines and growth factors that are stored within the ECM, and more.

Recent studies have further indicated that specific individual components of the ECM can impact developmental and pathological events within the lung. For the purpose of this review, we will focus on versican and hyaluronan, two interstitial ECM components [3] that can serve as ligands for leukocytes and impact immune and inflammatory responses in lung disease [3–7]. In addition, we will discuss how specific leukocytes, such as the macrophage, interact with the ECM and the importance of a specific matrix metalloproteinase (MMP), MMP10, in controlling the state of macrophage activation in lung disease.

2. The ECM as a regulator of the innate immune response

Inflammatory responses as a result of tissue infection require the emigration of leukocytes from the vasculature to the infected area as part of the innate immune response. Upon extravasation into the subendothelial and/or subepithelial compartments, leukocytes encounter an ECM enriched in versican and hyaluronan that functions as a scaffold or “landing strip” for cell adhesion and subsequent retention and activation [8] (Figure 1). These components are highly interactive and bind chemokines, growth factors, proteases, and receptors on the surface of the immune cells to provide intrinsic signals and influence immune cell phenotype [9–11]. We recently demonstrated that hyaluronan interacts with the surface of T-regulatory cells through CD44 and promotes their differentiation [12–14]. Furthermore, once bound, these leukocytes modify the ECM in such a way as to generate pro-inflammatory ECM fragments to further drive the inflammatory response [15, 16]. Fragments of ECM affect multiple functional properties of inflammatory and immune cells

[17]. Since different types of infection may demand extravasation of certain immune cell types, the ECM often undergoes compositional changes which regulate the appropriate cellular responses. Such compositional changes may enrich for specific ECM molecules that actively participate in the recruitment and activation of specific immune cell types to either promote or inhibit the inflammatory cascade [18]. Such findings suggest that the ECM may be a useful therapeutic target to control various aspects of the immune response associated with inflammation in a variety of diseases [19].

3. ECM components: interaction with leukocytes

A number of different ECM components interact with leukocytes and it has become clear that this interaction is a critical part of the inflammatory response [20]. It has also become clear that the ECM exhibits specificity for binding leukocytes and impacting their phenotype [6]. We have become interested in versican and hyaluronan, which increase during inflammation. Versican is a proteoglycan that exists in at least four different isoforms due to alternative splicing of the major exons that code for the attachment regions of the chondroitin sulfate (CS) GAGs attached to the core protein [21, 22]. Versican interacts with a number of other molecules, many of which are involved in promoting tissue inflammation [6]. For example, versican interacts with hyaluronan [23, 24], link protein, TSG-6, and CD44 through a common structural domain in each of the proteins called the link module [25, 26]. These macromolecules form higher ordered macromolecular complexes that increase as part of the inflammatory response [27–31]. Known functions for versican include controlling tissue space due to its ability to entrap water such as observed in the lung [32, 33], as well as influencing cell adhesion, proliferation, migration, and survival [21, 34–36]. Versican is highly interactive due to the negatively charged CS side chains. For example, versican regulates the availability and activity of several inflammatory chemokines [37–41]. In addition, the CS chains of versican interact with MMPs [42], influencing their catalytic activity [43–45]. As versican accumulates in diseased tissues, it can be degraded by a number of proteases including five members of the a disintegrin and metalloproteinase with a thrombospondin type-1 motif (ADAMTS) family of proteases [46, 47]. Cleavage of versican generates biologically active fragments that have been associated with inflammatory cytokine release and cell death through apoptosis [48, 49]. In addition, the G3 domain of versican can interact with P-selectin glycoprotein-1 (PSGL-1) and cause macrophage aggregation [50]. Several studies indicate that versican is a danger-associated molecular pattern (DAMP) molecule that interacts with toll-like receptors (TLRs), such as TLR2 on alveolar macrophages to promote production of inflammatory cytokines such as tumor necrosis factor α (TNFα), IL-6, and other pro-inflammatory cytokines [51–57]. As such, versican has been implicated in regulating several key events in the inflammatory response [3, 6, 36, 58, 59].

Several studies have demonstrated that hyaluronan, a binding partner of versican, influences inflammatory responses [60–62]. Hyaluronan interacts with the surface of many myeloid and non-myeloid cells through CD44, a major cell surface receptor for hyaluronan [63], to affect their phenotype. Lack of CD44 leads to excessive accumulation of hyaluronan in the lungs of bleomycin-treated animals due to the inability of lung cells to clear hyaluronan via CD44 [64]. As hyaluronan accumulates, hyaluronan fragments also accumulate and interact

with immune cells to promote the expression of specific inflammatory cytokines and chemokines to drive the immune response. Low molecular weight hyaluronan (LMW-HA) activates inflammatory gene expression in epithelial cells, dendritic cells, endothelial cells, fibroblasts, and macrophages [65–71]. Lack of CD44 limits macrophage recruitment to the lung when mice are challenged with lipopolysaccharide (LPS) [72]. Interestingly, alveolar macrophages isolated from CD44-deficient, LPS-treated mice secrete lower levels of TNFα, suggesting a key role for CD44 in the innate immune response to LPS. Recently, it has been recognized that it is possible to stimulate chemokine expression by immune cells in the absence of CD44 [73–75]. This stimulation involves the TLRs as part of the innate immune response [76]. Using a series of $TLR^{-/-}$ mice, it has been demonstrated that hyaluronan fragments stimulate elicited alveolar macrophages to express inflammatory chemokines via TLR2 and TLR4 pathways [75, 77]. TLRs are found not only on myeloid cells, but also on non-myeloid cells of the lung [78, 79]. While the above studies implicate TLR2 and TLR4 in the hyaluronan innate immune response, other studies suggest that TLR3 is involved since viral infection of synoviocytes causes hyaluronan synthase 1 (HAS1) activation with no effect on HAS2 or HAS3 [80]. Interestingly, overexpression of HAS2 in epithelial cells is associated with decreased hyaluronan cable structures and reduced monocyte binding to the ECM [81]. These findings, plus our own data, suggest that HAS1, together with versican, may be critical for the formation of this proinflammatory ECM following lung infection. In fact, a number of studies demonstrate that these ECMs are important for leukocyte adhesion during inflammation in the lung [64, 82], colon [83–85], kidney [86, 87], and skin [88, 89].

4. Versican and hyaluronan as components in lung disease

The observation that versican, a CS proteoglycan (CSPG), is abundantly expressed during lung development, is expressed at very low levels in lungs of healthy adults, but is re-expressed and accumulates in a number of lung diseases, including bacterial infection (Figure 2), suggests that versican functions in a number of overlapping processes in lung development, injury, and repair [32, 90–92]. Recent studies show that versican is expressed and accumulates in the lungs of mice in studies of gram-negative lung infection [59, 90], acute lung injury [93], allergen-induced airway inflammation [94], fibrosis [95], cancer [51, 55, 96, 97], and emphysema[98]. Similarly, in humans, versican accumulates in chronic lung diseases such as pulmonary fibrosis [99–101], acute respiratory distress syndrome [102, 103], asthma [104, 105], cancer [106], lymphangioleiomyomatosis [107], and chronic obstructive pulmonary disease (COPD) [108, 109]. Whereas numerous studies show that the re-expression and accumulation of versican is a common observation in lung disease, very little is known about the regulation of versican expression or the role of versican in the pathogenesis of lung disease.

Our recent work showing that versican expression and accumulation is rapidly increased in lungs of mice with gram-negative pneumonia suggests an important role for this CSPG in the innate immune response to lung infection (Figure 2) [59, 90]. There are multiple binding domains on versican for a number of cytokines, chemokines, adhesion molecules and growth factors, many of which are involved in the innate immune response [3, 36, 110]. The ability of versican to bind to chemokines is due in large part to the negatively charged CS side chains associated with the α- and β-GAG domains. For example, versican regulates the

availability and activity of several chemokines including CXCL2, CXCL10, CCL2, CCL5, CCL8, CCL20, and CCL21 [37–41, 111]. We previously showed that GAGs provide fine-tune control of the innate immune response in lungs by controlling the kinetics of chemokine-GAG interactions, chemokine diffusion, and leukocyte migration [9, 10, 112, 113]. Chemokine-GAG interactions are also known to regulate the oligomerization of chemokines in tissues [114, 115] and the ability of chemokines to bind to their high affinity receptor on leukocytes [116, 117]. More recently, studies show that the binding of versican to TLR2 reprograms macrophages and dendritic cells [51, 118]. The reprograming of dendritic cells by versican in a TLR2-dependent manner increases the amount of IL-10 and IL-6 receptors on the cell surface, resulting in a immunosuppressive phenotype [118]. As such, versican has been implicated in regulating several key events in the innate immune response [3, 6, 36, 58, 59]. The observation that versican is observed in a number of lung diseases and is able to modify the innate immune response in studies performed *in vitro* makes it an attractive target for therapeutic intervention. However, to advance these concepts into preclinical studies, we need to learn much more about the mechanisms whereby versican modifies outcomes in fundamental/experimental studies of lung disease.

5. Chronic changes to airway ECM in asthma

Bronchial biopsies from asthmatic adults and children demonstrate features of airway remodeling, including excessive subepithelial ECM protein/proteoglycan deposition that are already present by early childhood [119–122]. Excessive ECM production by human lung fibroblasts (HLFs) and the role of epithelial regulation of fibroblasts have been extensively studied in the context of pulmonary fibrosis [123]; however, there is less data on the role of epithelial regulation of ECM production by fibroblasts in asthmatic airway remodeling [124, 125]. Previous work has demonstrated that mesenchymal cells are the predominate source of many ECM constituents. This is particularly true for fibroblasts that have undergone transforming growth factor-β (TGF-β)-dependent fibroblast-to-myofibroblast transition (FMT), differentiating into a phenotype expressing cytoskeletal alpha smooth muscle actin (α-SMA) [126, 127]. Myofibroblasts are the primary source of types I and III collagen in fibrotic lesions [128–130]. Additionally, myofibroblasts represent a contractile phenotype that may directly participate in scar formation and contraction in the asthmatic airway [131]. Other important ECM constituents such as fibronectin, hyaluronan, and versican are also primarily secreted by fibroblasts and may play important roles in airway remodeling. Hyaluronan is major component of the ECM and its clearance is essential for resolution of local inflammation during acute injury [132, 133]. Furthermore, expression of airway hyaluronan [134, 135] and versican [136, 137] is higher in asthmatics and correlates with asthma severity [138]. Hyaluronan has also been linked to localized collagen deposition in animal models of asthma [139]. Interestingly, fibroblasts from patients with airway hyper-responsiveness demonstrate greater overall ECM production than those from healthy individuals [140, 141]. Collagens I and III, hyaluronan, and versican are, therefore, potentially important constituents of altered basement membranes and may be differentially regulated in asthma [128, 132, 142, 143].

5.1. Role of the airway epithelium in regulating ECM in asthma

The current mainstay of therapy for persistent asthma is suppression of airway inflammation using corticosteroids. However, clinical trials in asthmatic children show that although inhaled corticosteroids improve symptoms and prevent exacerbations, they do not alter the natural course of asthma [144, 145]. Because the airway epithelium undergoes significant structural changes early in asthma, and is the first contact point between the host airways and the environment, a new paradigm of asthma pathogenesis has emerged to partially explain asthma pathogenesis and airway remodeling, wherein ongoing injury, irritation, and/or viral infection of airway epithelial cells results in disordered wound repair in asthmatics, including disordered regulation of lung fibroblast and airway smooth muscle activity and altered airway ECM deposition (Figure 3) [146]. *In vivo* animal models of airway remodeling [147–149] and descriptive data from human bronchial biopsies [150–152] suggest the airway epithelium secretes proteins that regulate lung fibroblasts and airway remodeling with increased ECM deposition, including TGF-β [150, 153–155], VEGF [151, 156–159], periostin [160, 161], activin A [162–164], and follistatins [165, 166]. Furthermore, recent *ex vivo* investigations using primary bronchial epithelial cells (BECs) from asthmatic and healthy children demonstrated that when co-cultured with BECs from healthy children, lung fibroblast expression of types I and III collagen, hyaluronan, as well as expression of α-SMA, indicative of a myofibroblast phenotype, are downregulated [167, 168]. This downregulation is diminished in fibroblasts co-cultured with asthmatic BECs [167, 168], suggesting that, in addition to stimulatory signals, there must be epithelial-derived factors that inhibit fibroblasts and FMT, such that in normal airways, a balance of epithelial-secreted stimulatory and inhibitory factors that regulate fibroblasts and ECM deposition. Other studies have shown that airway epithelial cells synthesize hyaluronan and its degradative enzymes, the hyaluronidases (Hyals), in response to oxidative stress and other injurious agents [169–174] and that hyaluronan-enriched ECM synthesized by respiratory epithelial cells can impact monocyte adhesion [175].

5.2. Effects of airway ECM on immune cells in asthma

In addition to its role as a structural component of the airway, the ability of the ECM to modulate the recruitment and adhesion of inflammatory cells in the airway is an emerging area of investigation [20]. ECM, enriched in hyaluronan and versican, is synthesized by various lung cells in response to allergens, inflammatory cytokines, and other infectious agents [3]. Hyaluronan and its degradation products, are key ECM components that are believed to be involved in modifying immune cell recruitment, activation, and retention during inflammation [176]. Additional studies have demonstrated that hyaluronan binding partners such as versican [59] are also critical to the recruitment and activation of leukocytes in hyaluronan-enriched matrices. Versican accumulation in the subepithelial layer in airways of atopic asthmatics has been described and correlates with the degree of airway hyper-responsiveness [99].

In recent years, there has been an emerging appreciation for the role of ECM in leukocyte trafficking and modulation of local airway inflammation [20, 177, 178]. Evidence from both animal and human cell culture models has demonstrated that modulation of hyaluronan occurs in the setting of infection and/or viral mimetics [84, 179]. Hyaluronan levels in lung

tissue and bronchoalveolar lavage fluid (BALF) are elevated and correlate with the degree of inflammation in animal models of lung injury [139, 180, 181]. Furthermore, concentration of airway hyaluronan is higher in asthmatics and correlates with asthma severity [105, 134, 135, 138]. Blockade of the major hyaluronan receptor, CD44, reduced hyaluronan and eosinophil accumulation in animal models of antigen-induced eosinophilia [177]; however, CD44-deficient mice suffer from increased inflammation and increased deposition of hyaluronan suggesting that CD44 is critical for hyaluronan turnover [64, 182]. Indeed, Hyal1 and Hyal2, two principal hyaluronidases, have been shown to be dependent on an association with CD44 for their activity [183]. Turnover of hyaluronan by Hyals is important in fibrotic lung disease and diverse biological activity can be stimulated by differing sizes of hyaluronan fragments [31, 132, 184]. For example, high molecular weight hyaluronan (HMW-HA) has been shown to stabilize inflammatory cell activation, inhibit scar formation, and suppress inflammation [31, 185]. In contrast, LMW-HA has been found to stimulate gene expression in macrophages, endothelial cells, and epithelial cells and to enhance scar formation [66, 186–188]. Furthermore, LMW-HA has been found to increase production of TGF-β by eosinophils and prolong their survival in a dose-dependent, CD44-mediated fashion [189]. The latter finding is of significant interest in the context of activation of resident lung fibroblasts.

Given that a compelling argument for a critical role of hyaluronan in the establishment and regulation of airway inflammation is building, the study of hyaluronan binding partners has also become an important area of investigation. Versican content in normal lung is typically low; however, it increases dramatically in the context of disease and inflammation and is known to interact closely with hyaluronan, TSG-6, and CD44 [25, 26]. Additional studies have confirmed that increases in versican expression influence cell adhesion, proliferation, migration, and survival, as well as regulation of key inflammatory responses [6, 34, 59]. Accumulation of versican in the subepithelial layer in airways of atopic asthmatics has been described previously and correlates with the degree of airway hyper-responsiveness to methacholine challenge [99]. In addition, increased accumulation of versican has been associated with both small and large airway remodeling seen in autopsy specimens following fatal asthma exacerbations [136]. Subjects with uncontrolled asthma demonstrate increased accumulation of versican in biopsy specimens from their central airways compared to healthy subjects with well controlled asthma [104]. Interestingly, these same subjects also demonstrated a greater number of myofibroblasts per unit area in tissue samples. Of note, HLFs obtained from asthmatic adults produce greater amounts of proteoglycans, including versican, *in vitro* compared to HLFs obtained from healthy adults [141]. Additional studies have confirmed the presence of versican in the sputum of adults with severe asthma, which correlates negatively with their forced expiratory volume over one second (FEV_1), indicating a correlation with airway obstruction [105]. In animal studies, rats sensitized with ovalbumin displayed increased deposition of proteoglycans in the airways and BALF. Increased staining for versican was observed in the airways and blood vessels of the ovalbumin-exposed rats, which co-localized with α-SMA staining, suggesting an association with myofibroblasts in these tissues. Furthermore, these changes were not reversible following treatment with budesonide, a commonly used inhaled corticosteroid [190]. More recently, in a mouse model of allergic airway inflammation using cockroach

antigen (CRA), we found increased subepithelial accumulation of versican and hyaluronan that paralleled monocyte/macrophage infiltration (Figure 4) [94], supporting a role for these ECM components in leukocyte retention. Of interest in this same study, differentiated primary human airway epithelial cells from asthmatic children expressed elevated levels of versican and hyaluronan when compared to epithelial cells from healthy children, suggesting that epithelial cells may also be a source of these ECM components and that their production may be dysregulated in asthma.

Respiratory viruses also play a significant role in asthma inception and exacerbation and are a major cause of morbidity in asthma [191]. Our group [59, 176, 179] and others [84] have shown that HLFs and smooth muscle cells treated with respiratory syncytial virus and/or the viral mimetic, poly I:C, produce a complex viscous ECM that is enriched in hyaluronan and versican, and displays extensive hyaluronan- and versican-enriched “cables” extending into the ECM. Monocytes, eosinophils, and lymphocytes specifically adhere in much larger numbers to this enriched ECM rather than directly to the cell surface [179]. Furthermore, we have shown that formation of a monocyte-retaining ECM can be blocked by the presence of anti-versican antibodies [179]. Since viral infection is the most common trigger of acute asthma exacerbations, these exacerbations may be caused by changes in ECM remodeling that take place in the lung, creating a microenvironment that supports inflammatory cell invasion and adhesion. Presently, data regarding the regulation of HLF deposition of ECMs enriched in hyaluronan and versican, and the role that viral infection and/or aeroallergen stimulation of airway epithelial cells may play in modifying ECM in asthmatic lungs is lacking, but may offer valuable insight into the regulation of airway inflammation.

6. The macrophage, ECM and lung inflammation

6.1. Macrophage heterogeneity

Macrophages play essential, yet distinct, roles in both promoting and resolving inflammation as well as in both in facilitating tissue repair and contributing to its destruction [192]. That a single cell type can serve opposing functions may seem counterintuitive, but dramatic phenotypic changes occur when macrophages respond to local stimuli [192–197]. Based on patterns of gene and protein expression and function, macrophages are commonly classified as classically activated (M1) or alternatively activated (M2) cells (as well as sub-M2 types) [192–194, 197]. The M1 phenotype is induced by infection and pro-inflammatory T_H1 cytokines [196]. M1 macrophages are effective at killing bacteria and release pro-inflammatory cytokines, such as IL-1β, IL-12, and TNFα. In contrast, the M2 phenotype is induced by the T_H2 cytokines IL-4 and IL-13 and other factors [196, 197]. M2 macrophages release anti-inflammatory factors, such as IL-10 and TGF-β1, are weakly microbicidal, and promote repair [196]. However, dividing macrophages into M1 vs. M2 classes oversimplifies the complex continuum of functional and reversible states that these immune cells exist in *in vivo* [198, 199].

6.2. Macrophages and fibrosis

Macrophages present early in inflammation are functionally distinct from those at later stages [197, 200–207]. Depletion of macrophages in the early phases of wound repair

significantly impairs scar formation [208, 209], whereas depletion of macrophages during later stages leads to an inability to resolve scars [204, 210]. Hence, early phase macrophages, which are predominately M1-biased cells, contribute to ECM deposition and fibrosis likely by producing profibrotic cytokines that promote the activation of resident fibroblasts and pericytes into ECM-producing myofibroblasts [197, 200–203, 211–215]. During the later resolution phase, macrophages tend to be alternatively activated, remodeling-competent M2-biased macrophages [202, 213, 216] (Figure 5). Although far from being fully understood, resolution of scarring and fibrosis appears to be – not surprisingly – the responsibility of macrophages and, in particular, M2 macrophages [202, 204, 217–221].

Despite the compelling data in various tissue models with macrophage-depletion and direct proteolysis strategies, M2 macrophages – or specific subsets of M2 macrophages – have been considered to be profibrotic [222] for two key reasons. One, M2-like macrophages (or M2 markers) are present in scars and fibrotic tissue. However, these are mostly correlative data, whereas functional studies – such as our data below – indicate that M2-biased macrophages are working to resolve fibrosis, not promote it. A couple of studies concluded that M2 macrophages are profibrotic in interstitial lung disease, including idiopathic pulmonary fibrosis (IPF). One study relied on one M2 marker [223] and the other on three, including CD163 [224], but no M1 markers. Although the use of M1 and M2 makers may be convenient – and provides a reasonably good lexicon for discussion of macrophage subtypes – we hold that assessing functional read outs is more critical to understanding macrophage biology.

The second reason why M2 macrophages are thought to be profibrotic is because they express known or suspected profibrotic factors, particularly TGF-β1 and arginase-1, a cytosolic enzyme that functions in the synthesis of proline, an abundant amino acid in collagens. However, depletion of TGF-β1 or arginase-1 from macrophages does not affect fibrosis [225, 226]. It is likely that macrophage-derived TGF-β1 is a functionally distinct pool from the well-established profibrotic TGF-β1 produced by resident epithelium and interstitial cells.

6.3. Collagen degradation

Current models indicate that ECM turnover involves two sequential steps: limited extracellular proteolysis followed by uptake and lysosomal degradation [227, 228]. For the first step, some MMPs cleave the large collagen fibrils into fragments that are then endocytosed and degraded intracellularly [218, 229–231]. However, because MMPs act on much more than ECM, they can contribute to resolution of fibrosis by directly degrading ECM or indirectly by shaping the proteolytic phenotype of cells [232–234]. Based on published data [218, 221], we propose that MMP10 is a critical effector controlling the ability of M2-like macrophages to clear fibrotic ECM.

6.4. MMPs: effectors of immunity

Several proteins influence macrophage behavior, including some MMPs. For example, MMP12 and MMP28, both macrophage products, either promote or restrict macrophage

influx into lung [235, 236], and MMP28 and TIMP3 regulate M1 activation of macrophages in lung [237, 238]. As their name (matrix metalloproteinases) implies, MMPs are thought to degrade ECM proteins, a function that is indeed performed by some members [239–242]. However, ECM degradation is neither the sole, nor predominant function of these enzymes. Findings from several groups demonstrate that individual MMPs regulate specific immune processes, such as leukocyte influx and activation [243–248]. MMPs control immune functions typically by gain-of-function processing of non-ECM proteins, such as cytokines, chemokines, surface proteins, etc. [248–253]. Two other important concepts, both supported by many observations with gene-targeted mice [243, 245, 247], are that i) individual MMPs perform specific, non-redundant functions with no evidence of functional compensation by other MMPs; and ii) in normal processes, such as repair and immunity, MMPs typically serve beneficial roles. However, if their expression is prolonged or misregulated, then their catalytic activity can lead to disease.

Recent findings suggest that MMP10 impacts macrophage functions with different outcomes in different conditions and at different stages. In an acute setting, MMP10 moderates the proinflammatory activity of macrophages, which appears to be a beneficial effect [254]. Later on, MMP10 facilitates scar resolution and limits fibrosis by activating the ability of M2-biased macrophages to degrade ECM. This remodeling activity is beneficial in a setting with excess ECM, such as a wound (scar) or fibrotic tissue, as found in IPF. However, this MMP10-dependent ECM degrading activity of macrophages can be damaging when sustained in an otherwise structurally normal lung, such as the development of emphysema after many years of smoking. For example, blocking MMP10 activity or the pathways it controls or altering macrophage activation status could reduce the destructive potential of M2 cells in chronic conditions (e.g., COPD), whereas stimulating these mechanisms could be beneficial in IPF.

The importance of MMP10 in human lung disease is being recognized by others. Both Sokai *et al.* [255] and Vuga *et al.* [256] proposed that MMP10 is a predictor of outcomes in IPF, complementing earlier work showing that MMP10 is among the genes that are over-expressed in acute exacerbations of IPF [257]. In addition, MMP10 is expressed by lung macrophages in human smokers with emphysema [258], and MMP10 is one of two genes whose levels are significantly related to a decline in FEV_1 in human smokers with COPD [259], findings we validated with functional studies as part of large genome-wide association study (GWAS) on obstructive lung disease (discussed below) [260]. Furthermore, because macrophages and MMPs are important effectors in many conditions, such as asthma, vascular disease, cancer, and more, MMP10's control of macrophage activation may be relevant to a wide range of models and diseases.

6.5. MMP10 promotes ECM degradation by M2 macrophages

In models of excess ECM deposition in lung (bleomycin fibrosis; WCP, unpublished observations) and skin (scarring in wounds) [221], macrophage MMP10 functions to reduce collagen accumulation. In both models, levels of deposited collagen were greater in bleomycin-treated lungs and skin wounds in *Mmp10*$^{-/-}$ mice than in wildtype mice, with no differences in collagen expression or other synthetic endpoints between genotypes [221].

Net collagen deposition is the sum of collagen production minus turnover, and we determined that significantly less collagenase activity is released from *Mmp10*$^{-/-}$ macrophages. The missing activity is not that of MMP10; it cannot cleave fibrillar collagens [243, 261]. Depletion of macrophages in wildtype tissue reduced collagenase activity to the levels seen in *Mmp10*$^{-/-}$ samples, but ablation did not further lower the activity in *Mmp10*$^{-/-}$ tissue. Selective ablation of M2 cells [262] led to decreased collagenase activity in wildtype explants, but not in *Mmp10*$^{-/-}$ samples. In addition, whereas M2 polarization in culture increased the collagenolytic activity released from wildtype macrophages, it had no effect on the activity released from *Mmp10*$^{-/-}$ macrophages.

We compared the expression of MMPs with known or suspected macrophage-derived collagenase activity (i.e., MMP2, 8, 9, 13, 14, 16 [263, 264]) between wildtype and *Mmp10*$^{-/-}$ tissue and M0-, M1-, and M2-polarized macrophages. Consistently, we found reduced expression of MMP8 (collagenase-2) and MMP13 (collagenase-3) in *Mmp10*$^{-/-}$ samples and M2-biased macrophages. We found no expression difference between wildtype and *Mmp10*$^{-/-}$ M0-and M1-biased cells. We assessed the relative contributions of MMP8 and MMP13 to M2 collagenase activity. Whereas anti-MMP13 removed essentially all activity, anti-MMP8 removed none [221]. Overall, these data indicate that MMP10 functions in M1 macrophages to moderate their pro-inflammatory behavior and to transition them into ECM remodeling-competent M2 cells (Fig. 5)

6.6. MMP10 and emphysema

If MMP10 controls the ECM remodeling activity of M2 macrophages, then this MMP could be detrimental in long-term conditions, such as cigarette smoke-induced emphysema. Indeed, a multi-center study identified *MMP10* as a candidate gene for COPD in humans [260]. Using a model of chronic (6-mo) exposure to cigarette smoke, we found that *Mmp10*$^{-/-}$ mice are fully resistant to the development of emphysema. As stated above, MMP10 is produced by macrophages from human smokers with emphysema [258] and is one of two genes whose expression correlates with reduced lung function in smokers [259].

These findings indicate that macrophage MMP10 contributes to disease progression in emphysema, which is seemingly opposed to the protective role for this MMP in acute models, such as bleomycin fibrosis. However, there are important differences between these models, especially with respect to macrophage biology. As discussed above, macrophages that function early in inflammation are functionally distinct from those that function late in inflammation or in a persistent inflammatory response, like long-term smoke exposure. Whereas acute infection and injury bias macrophages toward an M1 phenotype [197], cigarette smoke promotes expansion of M2 macrophages [265]. Macrophages are considered to be the destructive cell in emphysema [266, 267], and our findings indicate that MMP10 promotes the ECM-degrading activity of M2 macrophages [221]. Thus, in acute or fibrotic settings, MMP10 is beneficial by moderating the pro-inflammatory activity of M1-biased macrophages and by stimulating the ability of M2-biased macrophages to remodel scar tissue. But in a chronic setting, MMP10-driven ECM remodeling could be excessive and detrimental, as suggested in our smoke-exposure studies. Still, the common conclusion among these models is that MMP10 functions to control macrophage behavior.

7. Conclusions

The ECM serves as a template for adhesion once leukocytes invade tissue in immune and inflammatory responses in diseases of the lung. Within the lung, there is a complementary set of ECM components that characterize each cellular compartment and any disturbance in the composition and/or organization of these components disrupts lung architecture and destroys lung function. Specific components of the ECM, such as versican and hyaluronan, are dramatically altered in all forms of lung disease, including bacterial and viral infection as well as asthma. These changes promote leukocyte invasion and retention and significantly affect normal tissue architecture and lung function. The macrophage is a critical player in lung disease. These cells come into contact with the ECM through a specific set of ECM receptors on the cell surface. Such interactions impact the ability of these cells to proliferate, migrate, and degrade the ECM via a specific set of proteases including MMP10. Defining precise roles for these specific ECM components in lung disease is critical if effective therapeutic interventions are to be developed in the future.

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Abbreviations

ECM	extracellular matrix
GAG	glycosaminoglycan
MMP	matrix metalloproteinase
CS	chondroitin sulfate
ADAMTS	a disintegrin and metalloproteinase with a thrombospondin type-1 motif
PSGL-1	P-selectin glycoprotein-1
TLR	toll-like receptors
TNFα	tumor necrosis factor α
LMWHA	low molecular weight hyaluronan
LPS	lipopolysaccharide
HAS1	hyaluronan synthase 1
CSPG	chondroitin sulfate proteoglycan
COPD	chronic obstructive pulmonary disease
HLF	human lung fibroblast
TGF-β	transforming growth factor-β

FMT	fibroblast-to-myofibroblast transition
α-SMA	alpha smooth muscle actin
BEC	bronchial epithelial cell
Hyal	hyaluronidase
BALF	bronchoalveolar lavage fluid
HMW-HA	high molecular weight hyaluronan
FEV_1	forced expiratory volume over one second
CRA	cockroach antigen
M1	classically activated macrophages
M2	alternatively activated macrophages
IPF	idiopathic pulmonary fibrosis

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Highlights

1. Leukocytes interact with lung extracellular matrix (ECM) during inflammation
2. This interaction affects how leukocytes accumulate, migrate, and differentiate
3. Versican and hyaluronan are ECM components that regulate leukocyte phenotype
4. Versican and hyaluronan increase in a range of lung diseases
5. Macrophages can both promote and resolve inflammation and are influenced by MMP10

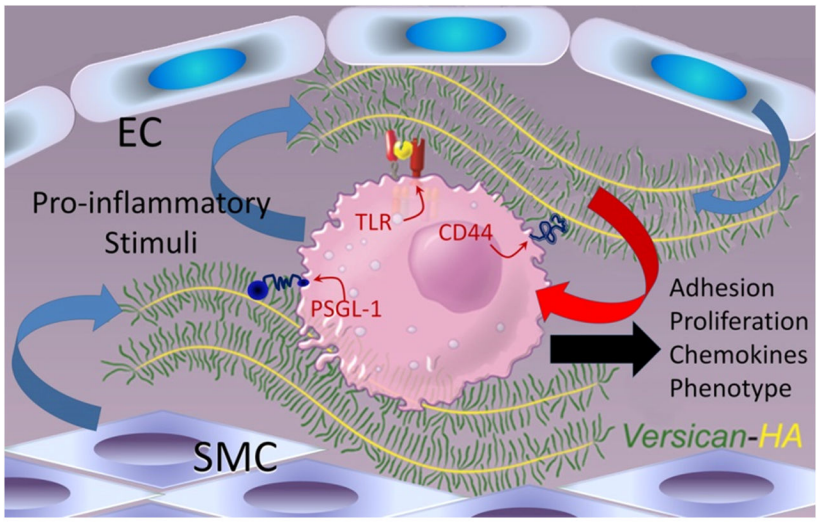

Figure 1.

Extravasation of leukocytes across the endothelium and/or epithelium (E) into the interstitium of the tissue during an inflammatory response. The leukocytes interact with specific ECM components, such as versican and hyaluronan, generated by resident cells of the tissue, such as endothelia and epithelia, and stromal cells, such as fibroblasts and smooth muscle cells. This interaction involves receptor-mediated interactions with hyaluronan and versican via cell surface receptors such as PSGL-1, TLR2, and CD44. These interactions in turn influence leukocyte phenotype by stimulating intracellular signals that promote their adhesion, proliferation, migration, differentiation, and activation. Furthermore, the leukocytes themselves may produce versican and hyaluronan in response to inflammatory stimuli to further enrich the matrix with these specific components. Such matrices, depending on their interactive partners, may exhibit either pro-inflammatory or anti-inflammatory properties. Figure from: Thomas N. Wight, Inkyung Kang, Mervyn J. Merrilees, *Matrix Biology.* 35:152–161, 2014, http://dx.doi.org/10.1016/j.matbio.2014.01.015. Reuse permitted under Creative Commons Attribution-NonCommercial-No Derivatives License (CC BY NC ND).

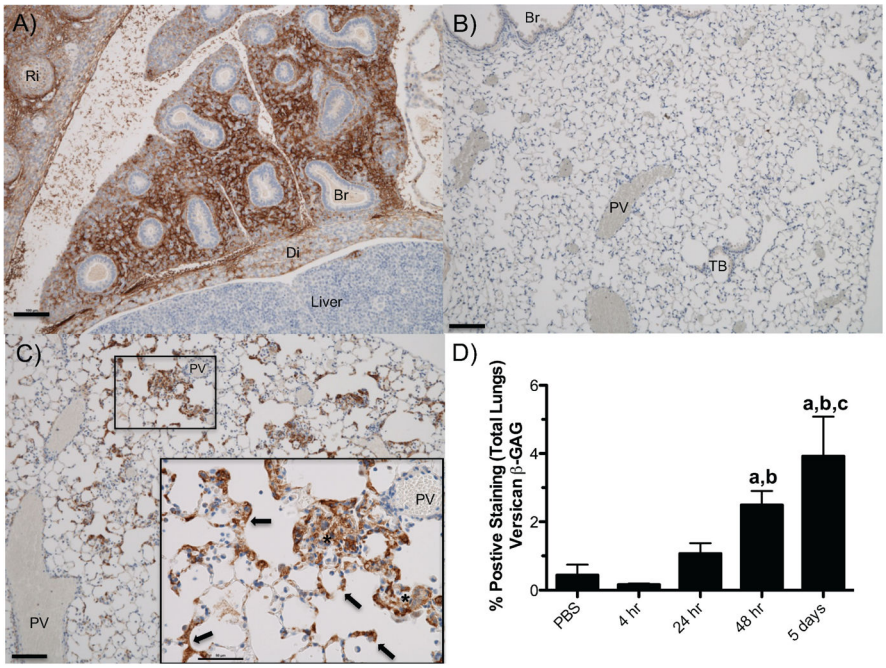

Figure 2.

Versican accumulation during embryonic mouse development and in lungs of a mouse with *Pseudomonas aeruginosa* lung infection. (A) Versican accumulation in fetal lung tissue at E14.5 days. (B) Versican accumulation in the lung of a 16-week-old mouse treated with PBS as a vehicle control. (C) Versican accumulation from a 16-week-old mouse infected with live *Pseudomonas aeruginosa* for 5 days. Brown indicates positive staining for versican β-GAG; blue, hematoxylin counterstain. Br, bronchiole; Di, diaphragm; Ri, rib; PV, postcapillary Vein; TB, terminal bronchiole. Arrows indicate versican staining in the alveolar septa; * marks an area of positive staining of the alveolar septa; cells in alveolar space makes it difficult to distinguish these two anatomical compartments. (D) The amount of versican-stained lung tissue as a percentage of total lung tissue in control mice (PBS) and those exposed to live *P. aeruginosa* for up to 5 days. Values are the mean β SEM (n = 3–6). [a]significantly different from PBS, [b]significantly different from 4 hr, [c]significantly different from 24 hr. p<00001 using a one-way ANOVA with Tukey's multiple comparison test. Scale (A–C) 100 μm; (C inset) 50 μm. Figure reused with permission from: Jessica M. Snyder, Ida M. Washington, Timothy Birkland, Mary Y. Chang, Charles W. Frevert, *Journal of Histochemistry & Cytochemistry* (Volume 63 Issue 12) pp. 952–967, copyright c 2015 by The Authors. Reprinted by Permission of SAGE Publications, Inc.

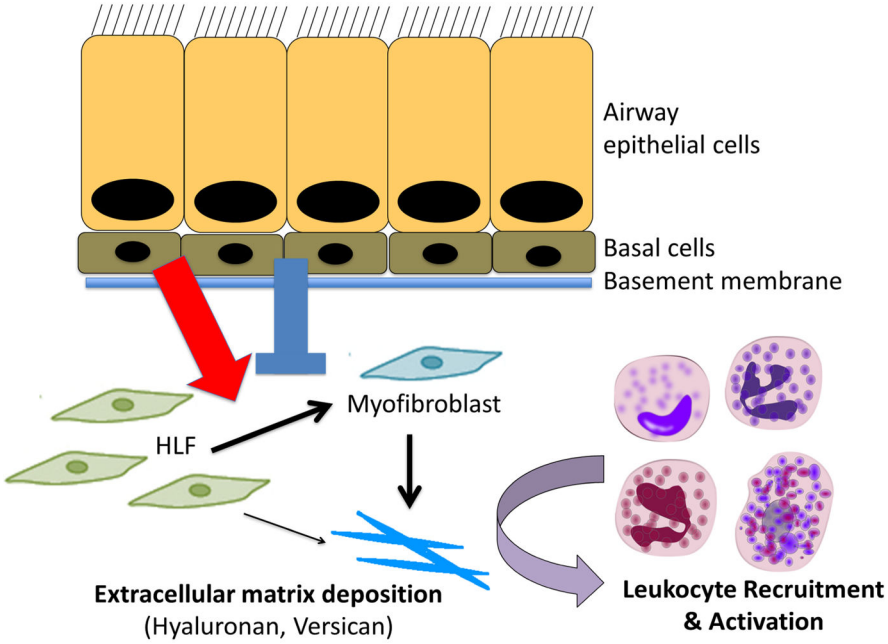

Figure 3.

Working hypothesis of leukocyte/ECM interaction in asthma suggesting that ongoing injury, irritation, and/or bacterial/viral infection of the epithelial cells results in signals that promote disordered wound repair resulting in altered ECM remodeling and the formation of a versican-/hyaluronan-rich ECM that promotes leukocyte recruitment and activation. Blue arrow indicates agonists that promote ECM accumulation and red arrow indicates antagonists the prevent ECM accumulation.

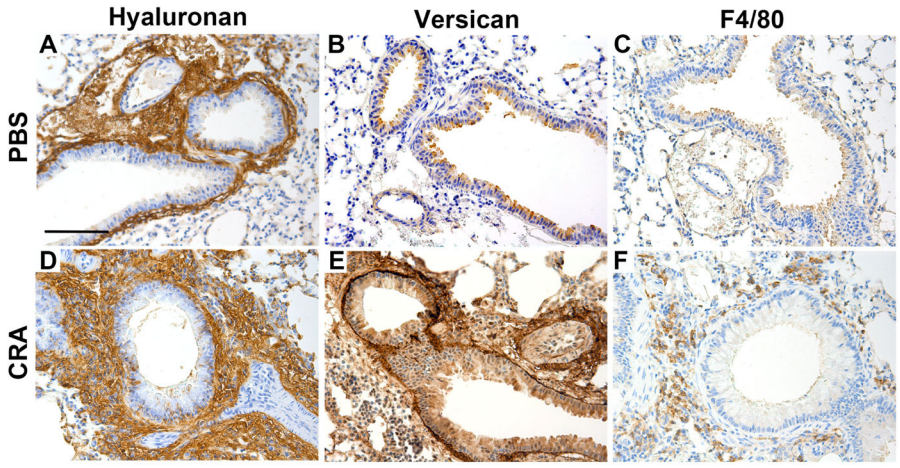

Figure 4.

Hyaluronan (A,D), versican (B,E) and macrophage (C,F) involvement (brown color) in control- and CRA-treated mouse lungs showing increases in hyaluronan and versican content in the subepithelial region of airway bronchioles in the CRA-treated lungs. These areas were also enriched in F4/80 positive macrophages. Figure adapted with permission from: Stephen R. Reeves, Gernot Kaber, Alyssa Sheih, Georgiana Cheng, Mark A. Aronica, Mervyn J. Merrilees, Jason S. Debley, Charles W. Frevert, Steven F. Ziegler, Thomas N. Wight. *Journal of Histochemistry & Cytochemistry* (Volume 64, Issue 6) pp. 364–380, copyright c 2016 by The Histochemical Society. Reprinted by Permission of SAGE Publications, Inc.

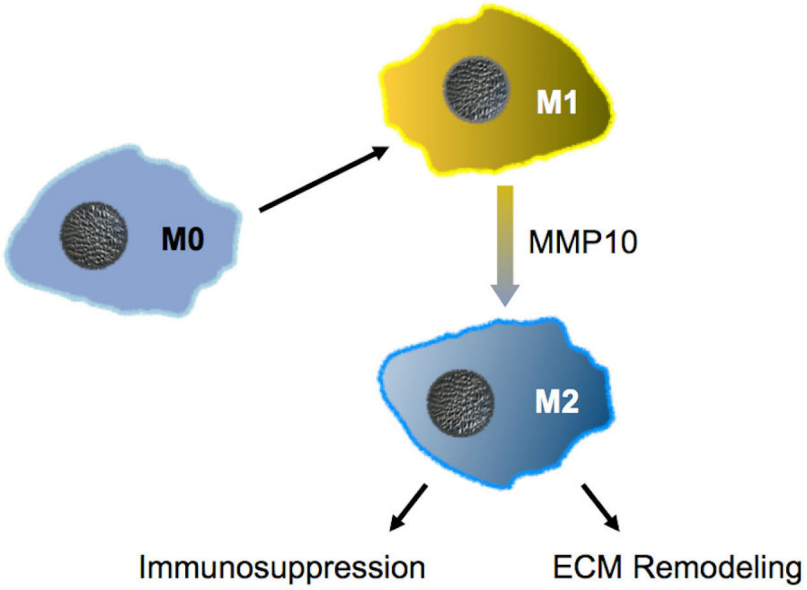

Figure 5.

MMP10 functions in a cell-autonomous manner to control the state of macrophage activation. Likely via shedding of a yet-to-be-identified surface protein, MMP10 drives the conversion of pro-inflammatory M1-biased macrophages towards immunosuppressive M2-biased cells. In addition, MMP10 controls the activation of ECM degrading activity in M2 macrophages, such as by promoting expression of MMP13, a collagenolytic proteinase.