Roles of extracellular matrix in lung diseases

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[Review]

Roles of extracellular matrix in lung diseases

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Abstract

Extracellular matrix (ECM) is a non-cellular constituent found in all tissues and organs. Although ECM was previously recognized as a mere "molecular glue" that supports the tissue structure of organs such as the lungs, it has recently been reported that ECM has important biological activities for tissue morphogenesis, inflammation, wound healing, and tumor progression. Proteoglycans are the main constituent of ECM, with growing evidence that proteoglycans and their associated glycosaminoglycans play important roles in the pathogenesis of several diseases. However, their roles in the lungs are incompletely understood.

Leukocyte migration into the lung is one of the main aspects involved in the pathogenesis of several lung diseases. Glycosaminoglycans bind to chemokines and their interaction fine-tunes leukocyte migration into the affected organs. This review focuses on the role chemokine and glycosaminoglycan interactions in neutrophil migration into the lung. Furthermore, this review presents the role of proteoglycans such as syndecan, versican, and hyaluronan in inflammatory and fibrotic lung diseases.

Key words : extracellular matrix, lung inflammation, lung fibrosis, syndecan

Introduction

Extracellular matrix (ECM) is a non-cellular constituent found in all tissues and organs. Recently, it has emerged that the ECM not only serves as a physical scaffold for cells, but also has important biological activities for tissue morphogenesis, differentiation, and homeostasis[1-5]. ECM includes two main types of macromolecules : fibrous proteins (collagen, elastin, *etc.*) and proteoglycans.

Proteoglycans are glycoproteins consisting of a core protein with glycosaminoglycan (GAG) side chains. Several types of proteoglycans exist in the lung as components of ECM[6], previously recognized as a mere "molecular glue" providing structural support to tissues. However, growing evidence demonstrates that proteoglycans have a variety of biological activities for fine control of inflammation, wound healing, development, and homeostasis[7-12].

There are four classes of GAGs : heparan sulfate, chondroitin sulfate/dermatan sulfate, keratan sulfate, and hyaluronan. All these classes are found in normal lungs, with heparan sulfate being the predominant GAG (40-60%), followed by chondroitin sulfate/dermatan sulfate (31%), hyaluronan (14%), and heparin (5%)[13]. GAGs consist of repeating disaccharide units of a hexosamine (glucosamine of galactosamine) and either a uronic acid (glucuronic acid or iduronic acid) or a galactose[14-17] (Figure 1). GAG side chains, which contribute to up to 90% of the molecular weight of proteoglycans, are highly sulfated and bind to a variety of proteins such as chemokines and growth factors[6,18-20].

Proteoglycans are named according to the core protein to which constituent GAGs are bound, e.g., heparan sulfate proteoglycan (HSPG), chondroitin sulfate proteoglycan, and dermatan sulfate proteoglycan[21,22]. Hyaluronan, a non-sulfated GAG, does not bind to a proteoglycan core protein. Proteoglycans can be classified based on their location as cell

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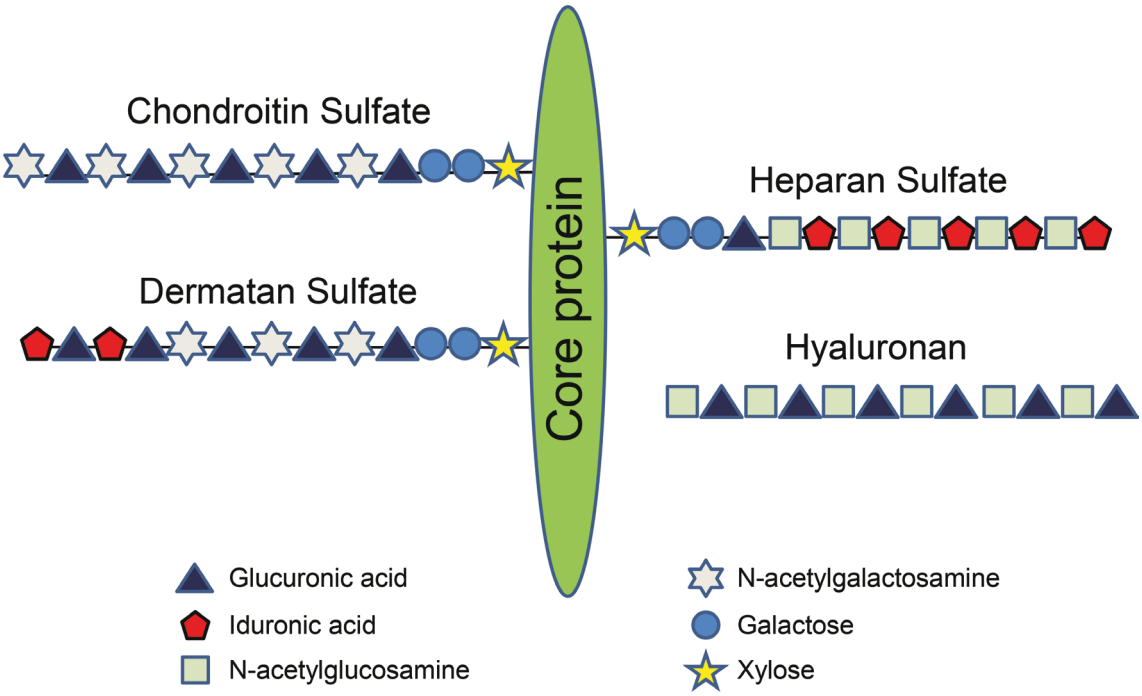

Fig. 1. Schematic representations of glycosaminoglycan and proteoglycan. The composition of disaccharide unit repeats is schematically illustrated for heparan sulfate, dermatan sulfate (DS), keratan sulfate (KS), chondroitin sulfate (CS) and hyaluronan (HA). Hyaluronan is the only glycosaminoglycan in a free and unsulfated form. All the other glycosaminoglycans are attached to a protein, forming proteoglycans.

surface, pericellular, extracellular, and intracellular proteoglycans[23].

Clinical significance and research implications

Roles of GAGs on neutrophil migration into the lungs

GAGs bind to various cytokines and chemokines, and sulfation of GAGs provides sites to which chemokines bind[24-26]. Chemokines are a family of chemotactic cytokines which promote leukocyte migration into the tissues. Several studies have reported that chemokine-GAG interaction is critical for recruitment of leukocytes into the peritoneum and lungs[20,27-29].

Neutrophil migration into the lungs is involved in the pathogenesis of several lung diseases, particularly in lung infection and acute respiratory distress syndrome[30,31]. IL-8/CXCL8 is a potent neutrophil chemokine which is produced by alveolar macrophages in the lungs during acute bacterial pneumonia and acute respiratory distress syndrome[30-32]. All chemokines have a GAG-binding domain. The binding of chemokines to GAGs plays critical roles in leukocyte recruitment into tissues by facilitating both the formation of tissue-bound chemokine gradients and the presentation of chemokines to leukocytes in tissues[25,33,34].

The GAG-binding domain of CXCL8 includes basic residues located in the proximal loop (K20) and C-terminal α-helix (R60, K64, K67, and R68)[35] (Figure 2). In the lungs, CXCL8 binds to heparin sulfate and chondroitin sulfate GAGs, and these interactions promote the dimerization of CXCL8, resulting in an increase in the amount of CXCL8 bound in lung tissues[20,24]. Although these results suggest that the interaction of CXCL8 and GAGs plays a critical role in neutrophil migration in the lung and results of *in vitro* experiments support its possible role[36-38], the precise role of this interaction had not been clarified *in vivo*. Our research group uncovered the role of CXCL8 in neutrophil migration in the lung by conducting an *in vivo* experiment using two mutant forms of CXCL8 (R68A-CXCL8 and K64A/K67A/R68A-CXCL8), which do not bind to GAGs[39]. When intratracheally instilled into the lungs of mice, the CXCL8 mutants recruited more neutrophils into the lungs and appeared more rapidly in systemic circulation than recombinant CXCL8 (Figure 3a). In addition, the CXCL8 mutants appeared in plasma at significantly higher concentrations (Figure 3b) and diffused more rapidly across the ECM *in vitro*. Furthermore, when we instilled

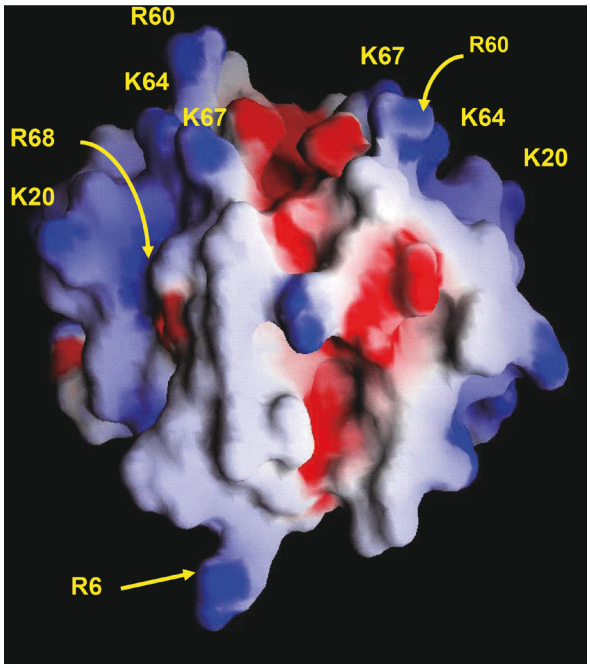

Fig. 2. Glycosaminoglycan-binding domain on CXCL8 dimer. CXCL8 has three binding domains : a high-affinity binding domain, which mediates binding to specific receptors on polymorphonuclear neutrophils ; the glycosaminoglycan-binding domain (K20, R60, K64, K67, R68) ; and the dimer interface (R6), where CXCL8 molecules bind to each other to form dimers. Blue and red show positively and negatively charged regions, respectively.

another mutant CXCL8 (I64K-CXCL8), which has more binding activity to GAGs, into the lungs of mice, it recruited fewer neutrophils than recombinant CXCL8 (unpublished data). These results show that GAGs control the spatiotemporal formation of chemokine gradients and neutrophil migration in the lungs.

Syndecan

Syndecan is one of the transmembrane HSPGs and consists of four isoforms. Syndecan-1, -2, and -3 are specifically expressed on the surface of epithelial cells or plasma cells, fibroblasts or endothelium, and nerve cells, respectively. On the other hand, syndecan-4 is expressed on a variety of cells[12,40-43]. Heparan sulfate is the most abundant GAG in healthy lungs[13], and several types of proteoglycans exist in the lung as components of ECMs[6]. Heparan sulfate GAG side chains of syndecans bind to various proteins such as cytokines, chemokines, and growth factors, and mediate biological activities of these proteins[19,20,44,45]. However, the role of HSPGs in the lung had not been clarified in detail.

To clarify the role of HSPGs in acute lung inflammation, we evaluated mRNA expression of HSPGs using an LPS-induced murine lung inflammation model. After LPS instillation, syndecan-4 mRNA was rapidly and selectively upregulated among the HSPGs studied[46] (Figure 4a). Therefore, we focused on syndecan-4 for our further studies. In the LPS-induced lung inflammation model, more neutrophils were found in bronchoalveolar lavage fluid (BALF) in syndecan-4 deficient mice compared to wild-type mice[46] (Figure 4b, c). Moreover, in a model of lung inflammation induced

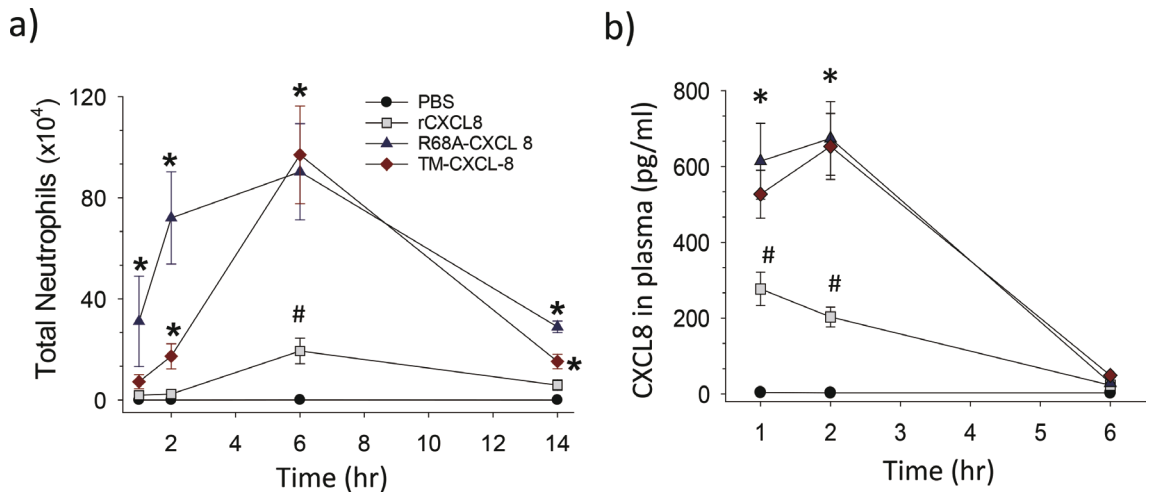

Fig. 3. Neutrophil migration in response to rCXCL8 and CXCL8 mutants. a) The CXCL8 mutants (R68A-CXCL8 and K64A/K67A/R68A-CXCL8 : TM-CXCL8) recruited more neutrophils into the lungs than recombinant CXCL8 (rCXCL8). b) The CXCL8 mutants appeared more rapidly in plasma after intratracheal instillation than rCXCL8.
* : $p < 0.05$ vs rCXCL8. # : $p < 0.05$ vs control.

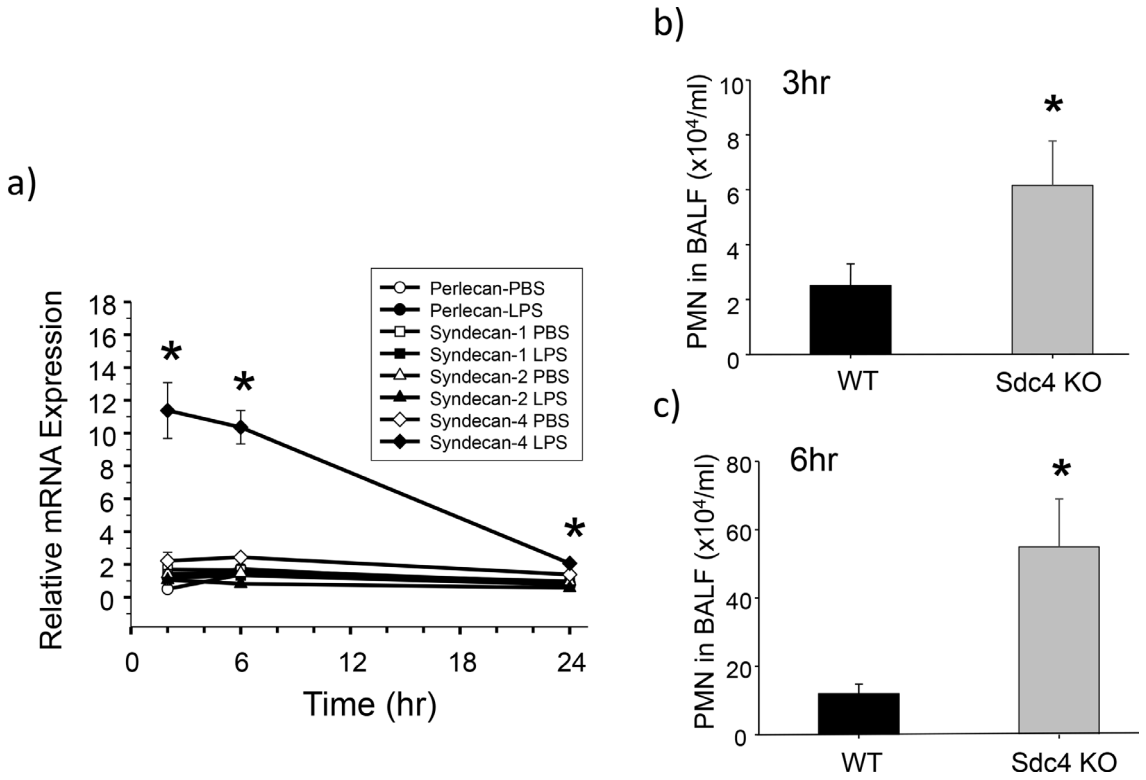

Fig. 4. Role of syndecan-4 in lipopolysaccharide-induced lung inflammation. a) Changes in mRNA for the heparan sulfate proteoglycans after intratracheal instillation of lipopolysaccharide (LPS) into wild-type mice. Among heparan sulfate proteoglycans, syndecan-4 mRNA was rapidly and selectively up-regulated. * : $p < 0.05$ vs syndecan-4-PBS. b, c) Intratracheal instillation of LPS induced more neutrophil recruitment into the lungs in syndecan-4 deficient mice (Sdc4 KO) than wild-type mice (WT). * : $p < 0.05$ vs WT.

by *S. pneumonia*, the survival rate of the syndecan-4 deficient mice was significantly lower than wild-type mice (Figure 5), while their total neutrophil counts in BALF, bacterial counts in blood, and plasma levels of inflammatory cytokines were significantly higher[47]. In addition, pretreatment of recombinant syndecan-4 significantly inhibited LPS-induced CXCL8 upregulation in BEAS-2B bronchial epithelial cells[46]. These results indicate that syndecan-4 can inhibit acute inflammation in the lungs. Furthermore, we evaluated the role of syndecan-4 in lung fibrosis[48]. In a bleomycin-induced lung fibrosis model, the histopathological lung fibrosis score and collagen content in lung tissues were significantly higher in syndecan-4 deficient mice compared to wild-type mice at 21 days after intratracheal bleomycin instillation. In *in vitro* experiments using lung fibroblasts, TGF-β-induced Smad3 activation as well as collagen and α-smooth muscle actin upregulation were significantly inhibited by co-incubation of recombinant syndecan-4. These results show that syndecan-4 is involved in the pathogenesis of lung fibrosis.

To further explore the role of syndecan-4 in lung diseases, we analyzed the serum levels of syndecan-4 in patients with acute pneumonia and idiopathic interstitial pneumonia (IIP)[47,49]. Although syndecans exist on cell surfaces, cell surface syndecans can be cleaved by several inflammatory factors such as matrix metalloproteinase (MMP)-7 and

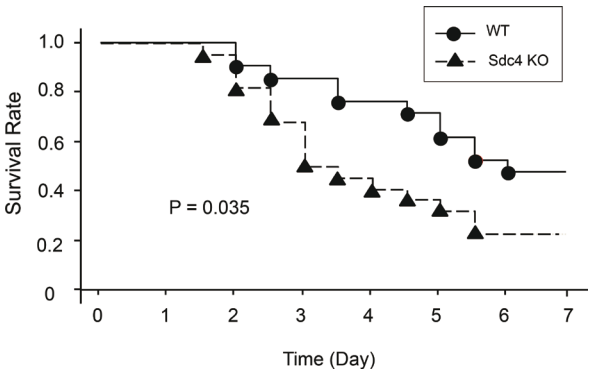

Fig. 5. Survival of wild-type and syndecan-4 deficient mice after intranasal instillation of *S. pneumoniae*. The survival rate of syndecan-4 deficient (Sdc4 KO) mice was significantly worse after intranasal instillation of *S. pneumoniae* (5.0×10^6 CFU) than wild-type mice (WT).

-9, or a disintegrin and metalloproteinase 17[44,50-54]. In patients with acute pneumonia, serum syndecan-4 levels were significantly higher than those in healthy volunteers and were correlated negatively with the pneumonia severity score. Moreover, among patients who improved with short-term antibiotic therapy, serum syndecan-4 levels on admission were higher than in those who did not improve and gradually increased during the antibiotic therapy[47]. IIP, including idiopathic pulmonary fibrosis (IPF), is a chronic, progressive, and intractable fibrosing lung disease[55-57]. During its clinical course, acute respiratory failure (also referred to as acute exacerbation) may occur, and this is reported to be the most common cause of death (40%) in Japanese IPF patients[58]. We found that serum syndecan-4 levels were significantly lower in patients with acute exacerbation of IIP than in those in the clinically stable phase, and the prognosis after acute exacerbation onset was significantly worse in the patients with higher baseline serum syndecan-4 levels than in those with lower baseline levels[49]. Furthermore, the clinical significance of serum syndecan-4 levels in preterm infants with chronic lung disease was recently demonstrated[59]. These results show that serum syndecan-4 is a clinically significant biomarker in lung diseases.

Versican and hyaluronan

Versican, a large chondroitin sulfate proteoglycan belonging to the aggrecan family, has a molecular weight >1,000 kDa in its four isoforms, V0-V3, produced by alternative splicing[60]. Versican alters the pericellular environment by binding to various mediators via the GAG domain. In addition, versican modifies the bioactivities of ECM proteins, such as hyaluronan, and plays important roles in cell morphology, adhesion, proliferation and migration[61,62]. Hyaluronan, a non-sulfated GAG, is a major constituent of the ECM, and growing evidence shows its important roles in inflammation, injury, and repair in the lung[63,64].

In an LPS-induced murine lung inflammation model, we demonstrated that a rapid increase in mRNA expression of versican and hyaluronan synthase was associated with increased immunohistochemical staining for versican and hyaluronan. In addition, *in vitro* studies showed that LPS caused a rapid increase in versican mRNA, proteins, and hyaluronan synthase in M1 macrophages, but not in M2 macrophages[65]. These results show important roles of versican and hyaluronan in the innate immune response to gram-negative lung infection.

In patients with IIP, significantly higher levels of serum hyaluronan were found compared to healthy volunteers, and positive correlations of hyaluronan levels in BALF with the percentage of inflammatory cells and the amount of CXCL8 were shown. In addition, patients with acute exacerbation had significantly higher serum hyaluronan levels compared with those in the stable phase, and patients with the highest serum hyaluronan had the worst 60-day outcomes[66]. These results show that hyaluronan is involved in the pathogenesis of IIP, and serum hyaluronan is a possible biomarker in patients with IIP.

Proteases such as MMPs are involved in the pathogenesis of lung fibrosis, and MMP-1 and MMP-7 levels in blood, in particular, are reported to be prognostic biomarkers for IPF[67,68]. In addition, it is reported that the serum levels of ECM products degraded by MMPs increased and were related to disease activity in IPF[69]. In the PROFILE study, increased serum levels of proteoglycans degraded by MMPs were reported to be associated with disease activity in patients with IPF[70]. We analyzed the serum levels of ECM degradation products in IIP patients, and found that type IV and VI collagen degradation products were significantly higher, while elastin and versican degradation products were lower during acute exacerbation than during the stable phase of IIP. Furthermore, lower levels of versican degradation products during acute exacerbation were associated with an increased risk of mortality[71].

Decorin

Decorin is a small, leucine-rich proteoglycan with one chondroitin/dermatan sulfate GAG side chain[72]. Decorin binds to collagen and plays important roles in collagen fibril formation and fibrous spacing[73-75]. It is reported that decorin-deficient mice have a phenotype of abnormal collagen fibril morphology and skin fragility[73,76]. In addition to its role in collagen fibrogenesis, decorin also plays important roles in angiogenesis, innate immunity, inflammation, fibrosis, wound healing, tumor growth and autophagy[73,74,77,78].

In IPF, decorin is reportedly expressed in fibrotic collagen-deposited lesions and fibroblastic foci[79]. We analyzed the serum decorin levels in IIP patients in the stable phase and at the time of acute exacerbation, and found that serum decorin levels at the time of acute exacerbation were significantly lower compared with those in the stable phase or in healthy volunteers. In addition, serum decorin lev-

els in clinically stable IIP patients were significantly lower than those in healthy subjects. Moreover, those with serum decorin levels lower than the median, especially the patients with acute exacerbation of IPF, had significantly higher survival rates compared to those with higher-than-median serum decorin levels[80].

Conclusion

ECM is involved in the pathogenesis of several lung diseases, and ECM in biological samples, such as serum and BAL fluid, is a potential biomarker in patients with lung diseases.

Acknowledgements

None

Conflict of interest disclosure

The author has no conflicts of interest to declare.

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