Proteoglycans and pathophysiology

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VENTILATION-INDUCED LUNG INJURY (VILI) is an important clinical entity whose pathophysiology is incompletely understood. The article by Moriondo and coworkers (14) in the Journal of Applied Physiology offers new insights into potential mechanistic pathways. These authors report that one of the earliest responses to mechanical ventilation in healthy rats is evidence of proteoglycan (PG) fragmentation. Changes in glycosaminoglycan (GAG) sidechain binding to core protein, as demonstrated by enhanced washout of GAG fragments, preceded changes in lung mechanical behavior. With larger tidal volumes, the effect of ventilation on pulmonary GAGs progressively increased. In contrast, only at the highest level of tidal volume ventilation was a consistent change in lung compliance observed. One may conclude that monitoring changes in extracellular matrix PG may be a more reliable indicator of ventilation-induced lung injury than pulmonary mechanics.

Proteoglycans, a key component of extracellular matrices, are macromolecules consisting of a protein core and GAG sidechains (8). The GAG sidechains include chondroitin sulfate (CS), keratin sulfate (KS), heparan sulfate (HS), dermatan sulfate (DS), and hyaluronic acid (HA), a GAG that is not bound to a protein core. Different subclasses of proteoglycans have been described and include large, aggregating proteoglycans, such as versican and aggregan; basement membrane proteoglycans, such as perlecan; small leucine-rich repeat proteoglycans (SLRP), such as decorin, biglycan, lumican, and fibromodulin; and cell surface proteoglycans, such as syndecan (8). Members of all these PG families have been identified in the lung.

Proteoglycans subserve a number of different biologic functions. Versican, because of the high ionic charge of its multiple GAG sidechains, plays a critical role in determining the water content or turgor of extracellular matrices. Via this mechanism, versican influences tissue viscoelastic behavior, as well as cell migration and proliferation. Basement membrane proteoglycans are important components of alveolar and pulmonary capillary basal laminae; perlecan is likely the predominant molecule in the lung (15). These molecules help define functional compartments and act as filtration barriers. Cell surface PGs, such as syndecan, have been described in lung epithelial cells and function primarily as cell surface receptors for matrix ligands (12). The SLRPs, decorin and biglycan, bind to collagen and affect collagen fibrillogenesis and matrix assembly. Through their coating of collagen fibrils, they can also act to protect the fibrils from cleavage by collagenases (7). These molecules also bind different growth factors, such as transforming growth factor (TGF)-β and fibroblast growth factor (FGF), and by influencing their bioavailability, modulate their ability to influence cell proliferation and matrix deposition (19).

There is some information reported in the literature documenting alterations in extracellular matrix (ECM) molecules in response to abnormal ventilatory regimens. Berg and colleagues (3) reported that high lung inflation resulted in increased mRNA for various ECM components. In an in vitro system, Breen (4) showed that collagen mRNA was upregulated in response to excessive mechanical strain. Increased message for ECM molecules could represent an autoregulatory response to strain-induced increases in ECM breakdown. Little information is available, however, concerning the effects of mechanical strain on the PG components of the ECM. We showed in a model of large tidal volume ventilation in healthy rats (2) that, at the largest tidal volume, expression of versican, HSPG, and biglycan protein core in extracts of lung tissue was increased. We did not, however, examine changes in GAG per se or level of GAG fragmentation. Alveolar overdistension leads to plasma membrane stress failure (23). Syndecan, the most common cell surface PG, has primarily HS sidechains. Increased HS fragmentation, such as was seen in the experiment of Moriondo et al. (14), may be a consequence of ventilation-induced plasma membrane disruption.

Changes in PG in response to mechanical perturbations would be expected to lead to alterations in the mechanical properties of the lung. Proteoglycans contribute to the viscous properties of the lung parenchyma. The hydrophilic GAG sidechains attract ions and fluid into the matrix, thereby affecting tissue turgor and viscoelasticity (5, 8). Versican is a large, hydrodynamic molecule with numerous CS sidechains (8). As versican is the predominant PG present in the ECM of the lung parenchyma, it seems likely this PG plays a key role in determining the turgor of the parenchymal tissues. Cavalcante et al. (5) postulated that PG act to stabilize the collagen-elastin network of connective tissues via their effects on tissue osmolarity. Negrimi and colleagues (13, 16) published a series of papers showing that proteoglycans critically influence the development of edema via their effects on interstitial tissue compliance. We published experimental data that directly implicate proteoglycans as determinants of the viscoelastic behavior of the lung tissues (1). Parenchymal strips were excised from rat lungs, and tissue viscoelastic properties were measured in the organ bath. Exposure of the tissues to the specific degradative enzymes, chondroitinase and heparitinase, which digest GAG sidechains, resulted in alterations in tissue viscoelastic behavior, including increased tissue elastance (1). We also obtained data in decorin-deficient mice, characterizing the viscoelastic behavior of the lung, both in intact animals, and again, in isolated lung parenchymal strips (6). The in vivo and in vitro lung elastic properties of decorin-deficient mice were different from those of wild-type, decorin-replete mice. Hence, alterations in GAGs in response to mechanical ventilation, such as was documented by Moriondo et al. (14), may represent a primary event that ultimately leads to the altered physiology characteristic of VILI.

A further mechanism by which altered PG may contribute to the pathology seen in response to excessive ventilation is
through their putative proinflammatory effects. GAGs have been shown to demonstrate highly specific interactions with various chemokines, such as CCL5/RANTES, CCL2, MCP-1, and CXCL8/IL-8 (11). Furthermore, PGs may act as ligands for proinflammatory Toll-like receptors (20). Hence, fragmentation of GAGs and breakdown of PG may have an impact on the development of the inflammatory response seen in VILI.

Finally, the concept of “matrikines” is worth considering. Matrikines are a new class of ligands that exist as a domain within an ECM protein. Natural matrikines are those that signal directly from the ECM, and cryptic matrikines are those that require proteolytic breakdown for the ligand to be revealed (21). Decorin is an example of a proteoglycan matrikine; it functions through the EGF receptor and activates downstream signaling pathways, such as ERK1/ERK2 (17). It is plausible that the breakdown of ECM proteins observed in the rat ventilation model leads to exposure of matrikines, which can then act as ligands to induce subsequent biologic effects.

The observation that mechanical ventilation results in PG breakdown and GAG fragmentation is an important one, and highlights the potential role that these molecules may play in the subsequent pathophysiological process. They may be important in influencing the altered mechanical behavior of the lung and in contributing to subsequent inflammatory events and the altered biology characteristic of ventilation-induced lung injury. The observation of early GAG fragmentation may also have pertinence to other disease processes characterized by abnormal mechanical strain or stress. Suki and colleagues (9, 10) recently highlighted the potential importance of altered mechanical stress in the development of emphysema. It is possible that a part of the process relates to the excessive breakdown of matrix components and the subsequent effects on lung biology. Excessive mechanical strain may also play a role in the airway wall remodeling typical of asthma; proteoglycan deposition is altered in the asthmatic airway (18, 22). Hence changes in proteoglycans in response to mechanical stimuli may potentially contribute to the pathophysiology of a number of clinically important lung diseases.

REFERENCES
