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The role of proteoglycans in pulmonary edema development

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Abstract Pulmonary gas exchange critically depends upon the hydration state and the thinness of the interstitial tissue layer within the alveolo-capillary membrane. In the interstitium, fluid freely moving within the fibrous extracellular matrix (ECM) equilibrates with water chemically bound to hyaluronic acid and proteoglycans (PGs). The dynamic equilibrium between these two phases is set and maintained by the transendothelial fluid and solutes exchanges, by the convective outflows into the lymphatic system, and by the mechanical and hydrophilic properties of the solid elements of the ECM. The fibrous ECM components, in particular the chondroitin sulfate proteoglycan (CS-PG) and the heparan-sulfate proteoglycan (HS-PG) families, play a major role in the maintenance of tissue fluid homeostasis. In fact, they provide: (a) a perivascular and interstitial highly restrictive sieve with respect to plasma proteins, thus modulating both interstitial protein concen-

tration and transendothelial fluid filtration; (b) a mechanical support to lymphatic vessels sustaining and modulating their draining function, and (c) a rigid three-dimensional low-compliant scaffold opposing fluid accumulation into the interstitial space. Fragmentation of PG induced by increased plasma volume, by degradation through proteolytic or inflammatory agents, by exposure to inspiratory gas mixture with modified oxygen fraction, or by increased tissue strain/stress invariably results in the progressive loosening of PG intermolecular bonds with other ECM components. The loss of the PGs regulatory functions compromises the protective role of the tissue solid matrix progressively leading to interstitial and eventually severe lung edema.

Keywords Interstitial tissue matrix · Proteoglycans · Interstitial pressure · Tissue safety factor · Tissue compliance · Thoracic lymphatic system

Introduction

The lung is supported by a network of blood capillaries surrounded by a thin layer of interstitial space interposed between the vascular endothelium and the alveolar epithelium. During the respiratory cycle the interstitium undergoes variable mechanical stresses associated with alveolar volume reduction during expiration, followed by inspiratory re-expansion; therefore, the alveolo-capillary

barrier must be strong enough to withstand local tissue stresses and, in the meantime, thin enough to facilitate respiratory gas exchange. Both these functions are optimized by the composition and structure of the pulmonary extracellular matrix (ECM), a mesh of fibrous macromolecules immersed in the interstitial extravascular fluid [1]. Fibrillar macromolecules, such as collagen type I and III or elastin (Table 1), play a main structural function, providing tensile strength and/or lung elastic recoil. Other