Biomechanics of the lung parenchyma: critical roles of collagen and mechanical forces

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Suki, Béla, Satoru Ito, Dimitrije Stamenović, Kenneth R. Lutchen, and Edward P. Ingenito. Biomechanics of the lung parenchyma: critical roles of collagen and mechanical forces. J Appl Physiol 98: 1892–1899, 2005; doi:10.1152/japplphysiol.01087.2004.—The biomechanical properties of connective tissues play fundamental roles in how mechanical interactions of the body with its environment produce physical forces at the cellular level. It is now recognized that mechanical interactions between cells and the extracellular matrix (ECM) have major regulatory effects on cellular physiology and cell-cycle kinetics that can lead to the reorganization and remodeling of the ECM. The connective tissues are composed of cells and the ECM, which includes water and a variety of biological macromolecules. The macromolecules that are most important in determining the mechanical properties of these tissues are collagen, elastin, and proteoglycans. Among these macromolecules, the most abundant and perhaps most critical for structural integrity is collagen. In this review, we examine how mechanical forces affect the physiological functioning of the lung parenchyma, with special emphasis on the role of collagen. First, we overview the composition of the connective tissue of the lung and their complex structural organization. We then describe how mechanical properties of the parenchyma arise from its composition as well as from the architectural organization of the connective tissue. We argue that, because collagen is the most important load-bearing component of the parenchymal connective tissue, it is also critical in determining the homeostasis and cellular responses to injury. Finally, we overview the interactions between the parenchymal collagen network and cellular remodeling and speculate how mechanotransduction might contribute to disease propagation and the development of small- and large-scale heterogeneities with implications to impaired lung function in emphysema.

connective tissue; structure; stiffness; mechanotransduction; heterogeneities

THE BIOMECHANICAL PROPERTIES of connective tissues play fundamental roles in the functioning of virtually every organ. These properties are critical determinants of how mechanical interactions of the body with its environment produce physical forces at the cellular level. In the lung, for example, mechanical forces can directly influence function via cellular signaling (94), such as during lung development (88), surfactant release by alveolar epithelial cells (93), the contractile properties of airway smooth muscle (26), or tissue remodeling (48). More generally, it is now recognized that mechanical interactions between cells and the extracellular matrix (ECM) have major regulatory effects on cellular physiology and cell-cycle kinetics that can lead to the reorganization and remodeling of the ECM (8, 13). This in turn influences the macroscopic biomechanical properties and function of the organ.

Traditional biomechanics has focused on characterizing the macroscopic structural and mechanical properties of living tissues and organs by establishing a mathematical relation, called the constitutive equation, that describes how mechanical stresses (force per unit area) change in response to a change in the size and/or shape of a body. The constitutive equation is often nonlinear and can describe the static relationship between stress and strain. When the constitutive equation also characterizes the time-dependent or dynamic stress-strain properties, the tissue is usually referred to as viscoelastic. Virtually every living tissue displays viscoelastic behavior (29). These constitutive equations are commonly determined from measured stress-strain relationships, and they reflect behavior emergent from the mechanical properties of the individual constituents as well as their structural arrangement in the tissue (29).

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most abundant and perhaps most critical for structural integrity is collagen. One might expect, therefore, that the amount of collagen in a tissue is the primary determinant of its mechanical properties. However, different connective tissues with similar collagen content can exhibit different mechanical behavior matching the specific needs of the organ (29). During the last decade, the advent of novel imaging techniques (17) and quantitative computational modeling (63) have allowed the study of micromechanics of specific components of tissues and hence the ability to understand the relationship between tissue composition, microstructure, and macrophysiology. In particular, it has become evident that macrophysiology reflects both the mechanical properties of the individual components of the tissues and the complexity of its structure (14).

In this review, we first summarize the constituents of the connective tissue of the lung and their complex structural organization. Next, we describe how the mechanical properties of the parenchyma arise from the constituents and structural organization of the alveolar walls. We will also argue that collagen is the single most important load-bearing element within the alveolar duct and wall and that it is critical to determining the homeostasis and cellular responses to injury. Finally, we will summarize what is known about the interactions between the collagen network and cellular remodeling and how mechanotransduction might contribute to impaired lung function in emphysema.

MAIN CONSTITUENTS OF THE LUNG CONNECTIVE TISSUE

Collagen. There are over 20 different types of collagen molecules. Most interstitial collagens (I, II, V, XI) are helical in structure, consisting of three polypeptide chains, each of which is a left-handed coil of ~1,000 amino acids, and the three chains form a right-handed super helix (10). These helical molecules are rodlike rigid structures with length and diameter of ~300 and 1.5 nm, respectively, and capable of spontaneous fibril forming (77). The helical subunits are first assembled in the endoplasmic reticulum of interstitial cells in precursor form called procollagens, which have amino- and carboxy-terminal globular regions known as propeptides. These serve to solubilize the procollagen and correctly align the individual peptide chains to facilitate helix formation (77). After secretion, the propeptides are enzymatically cleaved, which allows the collagen molecules to associate both axially and laterally to start forming fibrils. Apparently, type I collagen is thermally unstable at body temperature, and folding of the least stable micromdomains can trigger self-assembly of fibrils where the helices are protected from complete unfolding (49). The lateral and axial growth of the fibrils appears to be, in part, determined through interactions with other matrix components such as proteoglycans (38, 39, 62). The fibril structure itself also shows tremendous hierarchical complexity. For example, the lateral packing of molecules can exhibit significant fluidlike disorder (35, 38). The collagen fibrils can further organize into thicker fibers through cross-linking of lysine and hydroxylysine residues present within the overlapping terminal helical and telopeptide regions of the molecules (77). These fibrils and fibers go on to form random (lung tissue, cartilage) or quasi-deterministic (tendon) networks within an organ.

The interstitium of the lung parenchyma contains mostly type I and III collagen, which provide the structural framework for the alveolar wall. Fiber thickness ranges from several hundred nanometers to well over one micrometer (79). The distribution of fiber thickness is skewed, and has a long “tail” (79) similar to a power law (82), indicating broad variability of fiber structure. This blend of deterministic order (exact amino sequence and axial packing) and random disorder (from fluidlike lateral packing to random networks) may partly be responsible for the existence of a broad range of time constants that characterizes the viscoelastic properties of the connective tissue of the lung (6, 83). These collagen fibers in the parenchyma are further organized to form an axial fiber network extending down from the central airways to the alveolar ducts, a peripheral fiber network extending centrally from the visceral pleura, and a parenchymal interstitium that connects the two (90). Variations in the collagen content of the parenchyma during development (85, 86), in fibrosis (21) or after in vitro digestion (96) have suggested an important role for these protein fibers in the biomechanical properties of the parenchyma.

Elastic fibers. Elastic fibers are composed of elastin and microfibrils that are mostly fibrillin and fibulnin (64). The elasticity of microfibrils is controversial, and their role in lung elasticity has not been studied. Values of the Young’s modulus of microfibrils were reported to be as low as 0.2 MPa (87), which is about three to five times lower than the stiffness of elastin (29, 74), and as high as 96 MPa (75), which is closer to that of the collagen (29). The microfibrils often form a fibrous outer mantle surrounding the more amorphous elastin. The elastin is composed of insoluble flexible cross-linked polypeptides. Although the three-dimensional molecular structure of elastin fibers is not as well understood (38, 47), elastin organizes itself into easily extensible fibers and has a linear stress-strain relation up to 200% strain (29). The distribution of the diameter and length of elastin fibers in the lung are skewed with long tails and appear similar to the distribution of collagen fiber properties (79). Thus the elastic fibers exhibit significant structural heterogeneity and are also known to be mechanically connected to the collagen (11) via microfibrils and/or proteoglycans (38, 45, 62). Traditionally, elastin is thought to dominate lung elasticity at normal breathing lung volumes (73). However, a recent study comparing the effects of elastin and collagen digestion on the constitutive equation of parenchymal strips suggests that collagen may be equally important, even at lower lung volumes (96).

Proteoglycans. Within the lung, collagen and elastin fibers of the connective tissues are embedded in a hydrated gel, often called the “ground substance.” The composition of the matrix and the ratio of fiber to gel vary among tissues (38) and change during maturation and with certain disease states (44). A critical constituent of this matrix are the glycosaminoglycans (GAG), a family of highly charged polysaccharides (38). There are several different types of GAGs (e.g., hyaluronic acid, chondroitin sulfate, dermatan sulfate, keratan sulfate) whose molecular weights vary over three orders of magnitude, implying that the polymer chains can contain as many as 10^6 units with a huge variability in size and structure (12, 72). Within the lung parenchyma, the most abundant GAGs are heparin sulfate and chondroitin sulfate. Most GAGs are usually covalently linked to a core protein to form proteoglycans. Similar to collagen, GAGs can also have secondary and tertiary structures by forming helical and randomly organized regions depending on the ionic environment and pH of the matrix (72). Proteo-

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glycans can also associate ionically with one another to form large aggregates that exhibit an even higher level of hierarchical organization. Images of the proteoglycans obtained by electron microscopy reveal an extraordinarily complex structure (12, 23). The majority of the above studies on proteoglycan mechanics has been done in cartilage, and it is likely that the role of proteoglycans in lung function has been underestimated. Indeed, only a few studies have examined their role in lung mechanics (1, 14).

**Interstitial cells.** The lung parenchyma contains a variety of cell types. From the point of view of mechanics, the most important ones are the contractile cells, including smooth muscle cells in the alveolar duct and vessel walls and the myofibroblasts and fibroblasts in the alveolar walls (89). Stimulation of these cells with different agonists induces local internal stresses in the fiber network that can lead to changes in the viscoelastic properties of the lung tissue (22, 25, 59, 67, 95). However, during contractile challenge, the mechanical properties of tissue strips have also been found to vary with the number of medium-size airways in the sample (67). It is therefore possible that part of the previously observed changes in mechanics during agonist challenge were in fact related to smooth muscle contraction and airway-parenchymal interaction. Nevertheless, the viscoelastic properties of the lung parenchyma are only moderately affected by the active tone of the interstitial cells (22, 95). A more important function of the interstitial cells is to actively remodel and repair the connective tissue during growth or after injury. As a result of such cellular processes, the nonlinear viscoelastic properties of the lung tissue can significantly change both at the organ and the alveolar wall levels (9). Thus, although cells contribute little to the biomechanical properties of the tissue in response to physical (e.g., deformation) or chemical (e.g., histamine challenge) stimuli over a short time period, they are responsible for the longer term maintenance as well as the remodeling of the composition and structure of the matrix.

**Surface tension at the air-liquid interface.** The airways and alveoli are lined with a thin liquid film containing pulmonary surfactant, which derives from type II epithelial cells. During the deflation of the lung from total lung capacity, the recoil pressure significantly decreases in fluid-filled compared with air-filled lung, implying that the surface film significantly contributes to lung elasticity (5, 31). In addition to its direct effects on recoil, the surfactant also influences lung macrophysiology by ensuring alveolar stability and preventing collapse at low lung volume (4). Among the various components of the surfactant, phospholipids and low-molecular-weight hydrophobic surfactant proteins play a critical role in determining its biophysical properties and in maintaining low surface tension (42). The amount and composition of surfactant released by the type II epithelial cells into the air-liquid interface are largely determined by the dynamic stretching pattern of the lung parenchyma (3, 60, 93). The surfactant generates prestress on the alveolar ducts, and, by distorting their geometry, it indirectly alters the elastic properties of the associated connective tissues (80, 92). For small deformations, similar to those that occur during normal tidal breathing, the hysteresis of the surface film is small and surface film viscoelasticity may be less important than lung tissue viscoelasticity (71). Indeed, tissue hysteresis, defined as energy dissipation normalized by stored elastic energy per cycle (27), was found to be very similar in isolated lungs with intact surfactant and in lung tissue strips that lack air-liquid interface (66).

**Interaction among the tissue components and lung structure.** Conventional histological or immunohistochemical techniques may not truly reflect the spatial orientations of different tissue components in vivo due to artifacts resulting from fixation. Recent atomic force microscopic studies have demonstrated the existence of ridges and filaments along the surface of unfixed, untreated collagen fibrils from rat tail tendon (66), which likely represent the core protein and the GAG side chains of proteoglycans, respectively. These data suggest that the organized network of proteoglycan aggregates have multiple interactions, including chemical and topological, with collagen fibril surfaces as well as with each other. Collagen may reinforce the proteoglycan and water gel and provide a safety limit against excessive stretching of the matrix. This results in a composite structure with significant load-bearing capacity over a wide range of external forces to which the lung is exposed. An additional level of structural complexity comes from the fact that the fibers of the lung parenchyma within the alveolar walls are arranged in a hexagonal-like lattice (46, 80). By combining fluorescent imaging of the alveolar walls with computational modeling after external deformation, it appears that interconnectedness of the alveolar wall network also contributes to parenchymal viscoelasticity (9).

**MECHANICAL PROPERTIES OF THE NORMAL LUNG**

**Molecular, fibril, and fiber elasticity.** The structure of the lung is largely determined by the connective tissue network. The complex organization and the nonlinear mechanical properties of these tissue components lead to complex mechanical behavior. The Young’s modulus of the type I collagen molecule has been estimated to be between 3 and 9 GPa (69, 77). The elasticity of a single collagen molecule has been attributed to the existence of amino acid sequences along the triple helix that lack proline and hydroxyproline (78). These regions are more flexible than other regions of the helix. Such variation of rigid and flexible regions likely has a significant effect on the fibril-forming ability and hence the elasticity of the fibrils. Additionally, the unfolding of thermally activated molecular kinks or “crimps” along the molecule may also contribute to molecular elasticity (58). The stress-strain curve of fibrils appears reasonably linear (up to 3–5% strain) with a modulus in the order of 0.5–5 MPa (77). It is notable that the stiffness of elastin is at least two orders of magnitude smaller than that of collagen (29).

Crimps also exist at the fibril and fiber level (77). When thicker fibers in the tissue are stretched, it is the crimps along the fibers that first unfold followed by an unfolding of the crimps in the fibrils (58). Further stretching the fibers results in stretching of the triple helices and the cross-links, which also raises the possibility of slipping of molecules and fibrils within the fiber (24). In addition to the elasticity of a single molecule, collagen fiber stiffness may depend on the number of fibrils through a given cross section, i.e., the diameter as well as the type of cross-linking between molecules and fibrils. Both increasing diameter and cross-linking tend to increase fiber stiffness in normal collagen (2, 77). Furthermore, fibril length as well as small proteoglycan bridges between fibrils can contribute to the stiffness of collagen fibers (63). The stress-
strain curve of tendon composed of many fibrils arranged in parallel is nonlinear with a toe and a steepest region (68, 81). The toe region is usually attributed to the crimps along the fibrils, which, on stretching, straighten out (32). The composition of the fibrils and fibers is also important because fibers can contain a mixture of different collagen types. It has been argued that type I collagen is stiffer than type III (78), implying that fiber stiffness can depend on the relative amounts of type I and type III within the fiber. Furthermore, there are notable species-related differences. A small amount (5–10%) of variation in amino acid composition between bovine and equine collagen can lead to a two- to threefold difference in elastic modulus of in vitro cross-linked collagen gels (2). All these factors can give rise to significant inter- and intraspecies variability in the mechanical properties of the alveolar walls. However, because both mechanical and biochemical factors contribute to collagen production and assembly, it is likely that there are significant regional variabilities in collagen fiber properties within a single lung. This variability is in addition to the different fiber content and mechanical properties of alveolar ducts and alveolar walls (20, 54). The former has been argued to be stiffer and hence contribute more to lung elasticity at higher lung volume (55). Such differences in local matrix stiffness may have important consequences on cell signaling as discussed below.

Elasticity of lung collagen, alveolar wall, tissue strip, and whole lung. For larger lung tissue pieces, the stress–strain curve often exhibits exponential stiffening (28, 56, 59, 96). Maksym et al. (51, 52) showed that such behavior can be explained by the ensemble behavior of collagen fibers. They used a triangular network of line elements, each containing a parallel combination of a crimped collagen and an elastin fiber. They found that the exponential nonlinearity could be explained by a power law distribution of collagen fiber properties. On the basis of morphometric data of collagen in the lung (54, 79), this hypothesis may be reasonable and the distributed nature of collagen properties likely contribute to tissue elasticity. However, the collagen fibers are inside the alveolar walls, which form a hexagonal-like network. Triangular networks are inherently stable against shear or uniaxial stretching, whereas hexagonal networks collapse under such deformations (80), and thus the model of Maksym et al. (52) may not be used to extract microscopic parameters of the tissue. The more realistic hexagonal geometry has important implications on the mechanism of alveolar wall deformation. Recently, simulations using a hexagonal network to mimic the observed deformation of the alveoli in normal, hypotonic, and hypertonic solutions suggest that the folding of the alveolar wall and collagen during uniaxial stretching is elastically limited by the proteoglycan matrix (14). By incorporating this interaction into a hexagonal network model, the average Young’s modulus of a single alveolar wall was calculated to be ~5 kPa. Furthermore, by taking into account the volume fraction of collagen fibers in the alveolar walls, a lower limit of collagen fiber stiffness in the alveolar wall was also estimated, and a value of 300 kPa was obtained when tissue strips were stretched to 30% uniaxial macroscopic strain (14).

The elasticity of the whole lung can be described on the basis of the quasi-static pressure-volume curve using various models that include surface tension, alveolar duct properties, and constitutive equations for the lung fibers in an average alveolar duct unit (19, 80, 92). Another approach is the distributed fiber models by Maksym and coworkers (51, 52) mentioned above that takes into account the heterogeneity of lung properties. Nevertheless, it remains difficult to directly relate any of the parameters in these models to the physicochemical properties of collagen unless the spatial distribution of collagen and elastin (54) as well as the alveolar duct and septal geometry (89) together with their distributed nature (14) are appropriately taken into account.

In summary, whereas the phenomenological quasi-static stress-strain curve of the lung tissue can be completely accounted for by various models, the relationship between the molecular organization of collagen and elastin fibers and the in vivo pressure-volume curve is not fully understood. Such a mechanistic link would obviously be valuable to better understand the pathophysiology observed in emphysema and fibrosis, two diseases in which the pressure-volume curve and hence the mechanical properties of the lung change in a manner that implies alteration in collagen elasticity.

EFFECTS OF MECHANICAL FORCES ON THE PARENCHYMA

Mechanical forces, cell signaling, and biomechanical properties of the ECM. The lung tissue is constantly under a preexisting tensile stress or prestress that is a result of the distension of the lung by the transpulmonary pressure. The regional distribution of the prestress is determined by the hydrostatic pressure in the pleural space and the shape of the lung (36, 91). Additionally, prestress also changes cyclically and irregularly with breathing. This prestress in the alveolar walls is transferred through the ECM to the adhering cells with important consequences on cellular biophysics, biochemistry, and phenotype (30). Indeed, mechanical interactions between cells and the ECM are known to modulate cell contractility and myosin light chain phosphorylation (61), cell rheology (65), and focal adhesion assembly (15), all of which are critical for control of cell adhesion, migration, growth, contractility and viability. Additionally, the mechanical properties of the ECM may influence angiogenesis (41), as well as connective tissue homeostasis itself (16). The direct interaction between the ECM and cellular biochemistry also has important implications for the biomechanical properties of the connective tissues.

It has been suggested by Ingber (40) that cells in the interstitium sense mechanical forces via the integrin adhesion receptors that connect the cytoskeleton to the ECM. In addition to collagen, integrin receptors can also anchor to other ECM molecules such as fibronectin or laminin. However, because the collagen is the main load-bearing component of the connective tissue, any prestress in the lung would likely be transferred from the collagen to the other ECM molecules. Although the exact molecular mechanisms by which this mechanotransduction occurs is not entirely clear (76), it has been found that modulation of stresses on the cell surface leads to a dynamic remodeling of focal adhesion (18). Thus integrins serve as a mechanotransduction device and can activate various cellular processes (30) when the forces along the collagen change. For example, integrins have been shown to downregulate collagen α1(I) and upregulate interstitial collagenase when fibroblasts were grown on a collagen matrix without prestress (48). However, mechanical forces can also induce direct se-
cretion of various growth factors that accelerate the remodeling of the matrix. For example, tensile force-mediated upregulation of the α1(I) procollagen gene was found to depend on the release of transforming growth factor-beta (TGF-β) (34). Tensile force also appears to regulate the connective tissue growth factor that is able to stimulate extracellular protein release through a TGF-β independent pathway (70). Additionally, fibroblasts appear to respond differentially to various types of mechanical stimuli (e.g., uniaxial vs. biaxial deformation) (7). It is clear that the presence of specific types of mechanical forces and various signaling cues in the ECM jointly regulate how the cells create their microenvironment to maintain an optimal structure and biomechanical properties of an organ (37). Thus cells and the prestressed ECM live in a dynamic balance that results in a continuous remodeling of the matrix with a rapid synthesis of collagen in the normal lung of ~10% of total collagen per day, 40% of which is immediately degraded (53). A schematic diagram of the hierarchical transmission of mechanical stimuli from the level of the whole lung down to single cells and the various possible feedback loops controlling ECM remodeling and ultimately organ-level mechanics are shown in Fig. 1. We note, however, that several other important mechanisms related to the effects of mechanical forces of lung biology such as surfactant secretion (93) or smooth muscle contractility (26, 61) are not considered here.

Mechanical forces in the diseased lung. In diseases, the biochemical cues within the alveolar walls change either because of the expression of enzymes and/or cytokines or secondary to the injury that external agents such as cigarette smoke cause. The turnover half time of matrix molecules can drastically change. For example, an increased collagen mRNA expression in the lung was detected within 6 h of elastase treatment of hamsters (50). In this case, matrix remodeling was directly initiated by the acute injury caused by elastase. It is conventional to think that diseases such as emphysema or fibrosis develop as a result of the changes in the biochemical microenvironment. However, as soon as the composition of the ECM is altered, either because of the direct injury or cellular remodeling, there are corresponding changes in the biomechanical properties of the matrix and consequently of the alveolar wall. Such alteration in matrix properties would lead to a change in the local deformation of the alveolar wall. The network of the alveoli would then have to reorganize itself to satisfy the condition of mechanical equilibrium. Consequently, local prestress on the alveolar walls would change, which in turn could have a feedback effect on cell signaling leading to further assembly of matrix molecules.

The possibility that mechanical forces contribute to the progression of emphysema has been put forth by West in 1971 (91). He showed that the topological distribution of emphysema scores closely resembled the regional distribution of mechanical stresses in the lung due to its own weight. Consequently, he argued that mechanical forces should also contribute to the local development of tissue disease. This idea has been revisited more recently using imaging of the alveolar walls and simultaneously measuring the mechanical properties of tissue strips during uniaxial stretching (46). It was found that the alveolar walls from elastase-treated rats could break under the influence of mechanical forces akin to what would likely occur in vivo in the lung. The assumption that mechanical force contributed to tissue destruction was also consistent with computed tomography images (57). The breakdown of the alveolar network driven by mechanical forces has been shown to lead to significant heterogeneities at the parenchymal tissue level, and it was argued that, being the most important load-bearing constituent of the alveolar wall, the collagen is expected to play a major role in this process (84).

At high lung volumes the collagen in the alveolar wall protects the parenchyma from rupture. Therefore, the fact that the alveolar walls in the emphysematous lung can break at strains corresponding to normal breathing suggests that the yield stress of the collagen must be weaker after the remodeling process induced by elastase treatment (46). Interestingly, in a more recent study it was reported that, whereas the elastase treatment of mice led to a 50% increase in total collagen content of the lung, the stress at which tissue strips from these lungs failed decreased by ~50% compared with control (43). It is important to mention, however, that the mean linear intercept, a measure of alveolar air space size, also increased. Because the number of alveolar walls that can support the stress per unit cross-sectional area perpendicular to the direction of stretching is reduced, one may argue that the reduction in failure stress is simply due to the larger stress per alveolar wall in the emphysematous tissue. It has been argued, however, that the increase in mean linear intercept cannot fully explain the decrease in failure stress, especially when the collagen content per alveolar wall is increased (43). Therefore, despite increased collagen content per alveolar wall in the emphysematous lung, the wall stiffness is smaller than in healthy.

Fig. 1. Schematic diagram of force transmission from the level of the whole lung to single cell with various feedback mechanisms influencing extracellular matrix composition and lung mechanics. 3-D, three-dimensional.
animals. Thus the normal dynamic equilibrium between matrix turnover and mechanical forces is disturbed, which would lead to additional feedback loops in Fig. 1. (e.g., direct injury to the alveoli leading to an alteration in matrix turnover and reduction in collagen failure strength that ultimately results in the breakdown of alveolar wall network). Such feedback loops can represent a continuous deterioration of lung function and may offer an explanation for the progressive nature of emphysema (84). These findings are in stark contrast to the mechanics of the fibrotic lung in which total collagen content also increases but is accompanied by an increase in stiffness (21, 33). The conclusion is thus inescapable that, after the remodeling process, the internal structural organization of the collagen fibers in the alveolar wall should be drastically different in the emphysematous and the fibrotic lung. Currently, it is unknown whether it is only the biochemical milieu that is responsible for the different matrix properties. It is possible that, as a feedback mechanism, the grossly different mechanical properties of the ECM also contribute to the different intracellular and/or extracellular assembly of the collagen. Finally, we speculate that the progression of emphysema and likely most other diseases should necessarily lead to an increasing spatial heterogeneity of tissue remodeling and biomechanical properties of the ECM because, as we argued above, local changes in composition alter biomechanical properties and the distribution of mechanical forces, which in turn can act as a feedback mechanism to produce additional remodeling.

SUMMARY

The connective tissue of the lung is not a static structure, even during normal functioning. The tissue is the end result of a molecular hierarchical organization living in a dynamic balance between continuous breakdown and remodeling that is also modulated by mechanical forces. When this delicate dynamic balance is perturbed by external or internal chemical changes, such as those occurring in a disease process or environmental stimuli, the system dynamically remodels itself by an excess or lack of producing or breaking up these large complex macromolecular structures. The result is a chemically and structurally different tissue with accordingly altered biomechanical properties. We have also argued that the changes in matrix stiffness will alter the mechanical forces on the cells, which in turn may also influence the way cells remodel the interstitium. An important consequence is that a complete understanding of tissue biomechanics and lung function will not result solely from biochemical purification and biophysical study of the molecules. Connective tissues must be studied as an integrated system within their natural biochemical and mechanical environments. Additionally, to fully appreciate how diseases propagate spatially in the tissue and how they progress with time, it will be essential to map the regional correlation between cell signaling, matrix composition, and the local biomechanical properties of the tissue.

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