On the Progressive Nature of Emphysema

Roles of Proteases, Inflammation, and Mechanical Forces

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Emphysema is classically defined by pathologic criteria as destruction of lung parenchyma distal to the terminal bronchioles without associated inflammation or scarring (1–3). The primary risk factors for this disease are exposure to cigarette smoke, environmental irritants, genetic factors, and indoor pollutants (4). The major mechanisms thought to be responsible for the development and progression of emphysema include the protease–antiprotease hypothesis, inflammation, oxidative stress, and matrix remodeling (4). It is likely that these are not entirely distinct processes and that each contributes to the development of this complex disease. During the last few years, considerable progress has been made in describing the nature of inflammation in emphysema (5–8). Compelling evidence now suggests that inflammation can trigger a cascade of responses that culminate in tissue destruction that is characteristic of this disease (9).

It is reasonable to presume that once established, the progression of emphysema occurs through pathways that are similar to those that govern its initial development. However, disease progression is still poorly understood (4, 10) and may also be related to abnormal repair of the tissue after inflammation (11). One factor of potential importance in disease progression that is frequently overlooked is the role of mechanical forces. Clearly, the lung is a mechanical device. The alveolar walls at end expiration are under pre-existing mechanical stress (force per unit area), and breathing superimposes additional cyclic mechanical forces. Such forces are in fact capable of physically rupturing the entire alveolar wall after initial damage and repair (12). Thus, as suggested recently (13), mechanical factors may also contribute to disease progression, as measured by a decline in FEV_1 (14) or by changes in computed tomography (CT) images (15). In this Perspective, we review several mechanisms relevant for disease progression and propose a coherent view of how the intricate and complex interaction of inflammation, protease activity, repair, and mechanical forces contribute to the progressive nature of emphysema.

THE PROTEASE–ANTIPROTEASE HYPOTHESIS

The most widely accepted hypothesis of how tissue destruction occurs in emphysema is that an imbalance of protease and antiprotease activity exists within the lung that ultimately leads to enzymatic degradation of elastin (2, 4, 16). This hypothesis has been applied to the pathophysiology of emphysema in general, although it was developed on the basis of studies and clinical observations involving patients with inherited α1-antitrypsin deficiency (17). α1-Antitrypsin is an inhibitor of human neutrophil elastase, and a deficiency in this enzyme accounts for less than 1% of emphysema. However, there is a presumption that cigarette smoke produces protease–antiprotease imbalance among patients with normal α1-antitrypsin levels by causing an overly exuberant inflammatory response. The cigarette smoke model therefore provides a rational basis for the development and progression of emphysema in general.

Experimental findings also support the protease–antiprotease model but suggest that neutrophil elastase may not be the protease principally regulating tissue destruction in emphysema. For example, gene knockout studies suggest that macrophage elastase is sufficient to cause development of emphysema after chronic inhalation of cigarette smoke (18). Moreover, experimental emphysema can also be induced by a variety of other ways. These include transgenic mice overexpressing collagenase (19), which is not a developmental abnormality (20), or knockout mice that have defects in the ability to synthesize specific proteoglycans (21). Thus, there are pathways that lead to emphysema but do not directly involve elastin at all.

Biochemical and histologic studies suggest that both the organization and the amount of connective tissue fibers are important determinants of the loss of lung function in emphysema (22). Indirect evidence supporting this notion comes from observations that matrix metalloproteinases (MMP), enzymes that degrade tissue components, have been implicated in the pathogenesis of emphysema (23, 24). Alveolar macrophages from patients with emphysema produce elevated levels of matrix-degrading enzymes with both elastolytic and collagenolytic activities (25). These observations have led to a broadening of the original protease–antiprotease hypothesis to include the breakdown and resynthesis of a wide variety of matrix components (25–27). Nevertheless, even this new protease–antiprotease hypothesis does not provide a complete understanding of the progressive nature of emphysema.

ROLES OF INFLAMMATION

Numerous studies suggest that the presence of inflammation in the lung is an important contributor to the development of emphysema and perhaps to disease progression as well (4, 5, 6, 10). The specific inflammatory milieu that develops in response to cigarette smoke leads to damage to the fiber network of the lung. Using bronchial biopsy, a greater number of inflammatory cells, including neutrophils and CD8+ lymphocytes, have been found in the airways of patients with chronic obstructive pulmonary disease with airflow limitation than in smokers with normal lung function (28). Also, expression and release of MMP-9 (gela-

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tinase B) and a tissue inhibitor of MMP-1 (interstitial collagenase) by pulmonary macrophages are increased in smokers compared with nonsmokers, both at baseline and in response to cytokine challenge (29). Results of studies using knockout mice indicate that tumor necrosis factor–α, a neutrophil chemoattractant cytokine, plays a prominent role both in acute smoke-induced inflammation (8) and in elastase-induced emphysema (7). Furthermore, a new picture is emerging regarding the interaction of tumor necrosis factor–α and macrophage metalloelastase (MMP-12) during the early events of smoke-induced inflammation (9). After smoke exposure, MMP-12 expression is necessary for tumor necrosis factor–α release at the site of smoking-related inflammation, and tumor necrosis factor–α alters the endothelial cell phenotype in a manner that leads to neutrophil recruitment and local activation of macrophages. As a consequence, neutrophils are captured and release proteases, events that finally lead to matrix breakdown (9). It will be important to examine whether a similar mechanism exists in more advanced stages of emphysema in human subjects. Amplification of inflammation in response to nonspecific stimuli has also been reported in association with latent adenoviral infection (5). Persistent inflammation of this kind, even in the absence of cigarette smoking, may stimulate release of a variety of proteases that eventually lead to the progressive chemical degradation of lung tissue. If this hypothesis were correct, then providing sufficient amounts of protease inhibitors or anti-inflammatory agents should stop, or at least slow, the progression of the disease. However, the beneficial effects of antiprotease therapy and anti-inflammatory drugs in general are not clear. In one study, short-term supplementation of α1-antitrypsin did not consistently slow the rate of lung function decline in patients with known α1-antitrypsin deficiency (30), whereas in another study, α1-protease inhibitor reduced the rate of FEV_1 decline only in a subgroup of patients (31). Furthermore, inhaled corticosteroids, potent anti-inflammatory agents with demonstrated efficacy in asthma, another lung disease associated with inflammation, may have some benefits (32), but they do not appear to halt the progression of emphysema (33), and the issue remains controversial (34). New information suggests that combinations of phosphodiesterase inhibitors and steroids may be significantly more potent in preventing the type of inflammation that exists in emphysema, although there are few clinical data at present to support this notion (35).

These observations indicate that emphysema develops as a consequence of inflammation due to exposure to cigarette smoke, and yet, the role of inflammation in the progression of this disease is unclear. In this regard, chronic overexpression of MMP-1 in transgenic mice causes changes in lung morphology, which are similar to human emphysema in the absence of any provocative challenge and without associated inflammation (19). Thus, although many cytokines and proteases are known to be involved in the pathogenesis of emphysema, it appears that a link between inflammation and progression of tissue destruction is still missing.

ROLES OF MECHANICAL FORCES

Given the complex role played by inflammation in the development of emphysema, one may ask, Why is the progression of emphysema so relentless and why is it that medications administered specifically to halt inflammation are not very effective? Because so many factors appear to contribute to the development and progression of emphysema, it is not clear what a drug should target, and at least six different possible approaches have been proposed (14). An important notion, however, is that experimental emphysema can be induced in many different ways in animal models, and depending on the model selected for study, a different biochemical pathway will be of central importance (2, 18, 19, 21, 36–41). Independent of the biochemical pathway, however, the end result is always loss of alveolar attachments and enlargement of alveolar airspaces. The simple question of just how the alveolar wall is eliminated has not received much attention. One hypothesis implicit in the classic protease–antiprotease model is the concept that the tissue is slowly degraded by the continuous activity of enzymes until at a certain point nothing is left. However, as pointed out in the introduction, it is important to consider that the alveolar wall tissue is prestressed and continuously undergoing cyclic straining during breathing. Moreover, quiet breathing is regularly interrupted by deep inspirations in which tidal volume at least doubles and the forces on the tissue significantly increase. An important question arises: Is it possible that after an initial chemical injury and remodeling, the fibers and their connectivity in the alveolar walls become weakened to the extent that mechanical forces generated during the course of normal respiration could lead to mechanical failure of the alveolar wall?

We can illustrate this process with a simple analogy. Imagine that we want to split a rope composed of many fibrils into two pieces. If the rope is lying free on a table, one must use scissors to cut every fibril individually. If the rope is prestressed (e.g., by hanging it and attaching a weight to its end), the situation drastically changes. The reason is that every material including biopolymers (e.g., collagen and elastin fibrils) has a mechanical failure threshold. When the force on a single fibril exceeds its failure threshold, the fibril breaks. Because the fibrils are in parallel, the total force is distributed among all the fibrils and the individual fibrils do not break initially. As we cut a few fibrils, the total force will be redistributed among the remaining intact fibrils. As the number of fibrils decreases, it becomes increasingly easier to cut the next fibril because the fibrils carry larger and larger loads. When there are only a few fibrils left, the force per fibril may exceed the failure threshold of one or more fibrils, and the rope ultimately fails due to mechanical force. Perhaps the failure of an alveolar wall is similar. Because the elastic fibers are under time-varying tension, it seems that the presence of mechanical forces cannot be neglected. The protease-induced degradation will initiate the process leading to the mechanical failure of the fibers and ultimately the alveolar wall. One is therefore compelled to conclude that mechanical forces play a role in the progressive nature of the disease.

The idea that mechanical forces are involved in the progression of emphysema is not new. In the 1920s through 1950s, mechanical force was, in fact, considered a potential etiologic factor in the development of emphysema, and early animal models were developed specifically to examine this hypothesis. One-way valves were placed in the airways to cause mechanical hyperinflation and produced emphysema-like changes in the remaining tissues (42). Despite the presence of tissue destruction, histology failed to demonstrate evidence of significant inflammation at the sites of emphysema. Subsequently, West (43) argued that because the uneven topographical distribution of mechanical stresses in the lung is closely related to the upper lobe predominance of emphysema, greater mechanical stresses on the nondependent alveoli contribute to the development of centrilobular emphysema.

Recently, more experimental evidence based on clinical observations among patients with advanced emphysema undergoing lung volume reduction surgery (LVRS) has emerged supporting the hypothesis that mechanical forces accelerate the progression of emphysema. LVRS involves surgical resection and resizing of the hyperexpanded lung to the chest wall (44). This therapy produces an immediate 30–50% increase in recoil pressure (45). Because the remaining lung of these patients is stretched to fill the thoracic cavity, mechanical forces on the

connective tissue must also increase. Many patients who undergo LVRS experience a deterioration in lung function over time, which is accelerated compared with their rate of lung function decline before surgery (45, 46) and is far greater than would be anticipated for nonsmokers. Also, it has been reported that there was a statistically significant correlation between the magnitude of short-term incremental improvement and the long-term rate of deterioration in FEV_1 after LVRS (44). Thus, the increased mechanical forces on the fiber network that follow LVRS and dictate immediate physiological benefits may also be responsible for an accelerated rate of mechanical damage of the alveolar walls and a subsequent deterioration of lung function. Finally, we recently provided direct evidence that alveolar walls in lung tissue samples from elastase-treated rats can break due to mechanical forces similar to those occurring during breathing (12).

ROLES OF COLLAGEN

If mechanical failure of the alveolar wall does occur as a result of the forces of normal breathing, then how do the individual components of the alveolar wall actually break? The primary load-bearing elements are the collagen, elastin, and perhaps the proteoglycan matrix. Collagen has a stiffness that is 50–100 times higher than that of elastin (47), and its failure threshold is similarly higher than that of elastin. The classic view of the physiological role of collagen is that it protects the lung from rupture at high lung volumes. Thus, under mechanical forces that occur during normal breathing, the collagen fibers do not break. If the collagen fibers do not break in the alveolar wall, how is it possible that the alveolar wall breaks? From the mechanical point of view, it is in fact not possible. The alveolar wall cannot fail until the collagen fiber itself breaks because the cells, proteoglycans, and elastin (48) are attached to the collagen fiber. This paradox can be resolved by postulating that the collagen network in the alveolar wall of the emphysematous lung cannot be normal. There are two possible etiologies for this: (*1*) interstitial collagenases (MMP) or other enzymes directly damage the collagen fibers leading to decreased collagen content which is not replaced; and/or (*2*) active collagen remodeling does occur, but the newly synthesized fibers are mechanically defective such that they yield at a lower force.

Regarding the first mechanism, it is known that several MMPs are capable of degrading type-I collagen (24, 49). Because alveolar macrophages are certainly involved in at least the early phase of emphysema (25, 18), it is important to realize that alveolar macrophage–derived MMP-1, neutrophil collagenase (MMP-8), and collagenase-3 (MMP-13) all cleave fibrillar collagen helices (24). A recent study suggests that even neutrophil elastase is capable of degrading type-I collagen (50). More importantly, perhaps, epithelial type-II cells in lungs of smokers also express MMP-1, suggesting that damage to essential components of the interstitium can result from cells not traditionally considered inflammatory cells (51). Thus, it appears that many different proteases can break down or at least weaken type-I collagen in the lung.

Regarding collagen remodeling, morphometric and biochemical studies suggest that collagen in the emphysematous lung is abnormal. Snider and coworkers (52), using an animal model of emphysema induced by cadmium chloride exposure, showed airspace enlargement with a significant increase in lung collagen. Short-term exposure of rats to high concentrations of oxygen also leads to emphysema with degradation of collagen but no changes in elastin (38). In human lungs (53), elastin content was decreased in panacinar and severe centriacinar emphysema, but collagen content was increased in centriacinar, distal acinar, and irregular emphysema. Wright and Churg (26) reported that cigarette smoke–induced emphysema in guinea pigs is associated with the breakdown and repair of collagen fibers. Furthermore, in human emphysematous tissue, the mean linear intercept directly correlated with the increase in septal wall thickness, which was accompanied by significant increases in both elastin and collagen content (27). Stone and coworkers (54) evaluated markers of collagen and elastin turnover in emphysema by assaying for urinary desmosine and hydroxylysylpyridinoline, specific markers for the degradation of mature cross-linked elastin and collagen, respectively. They found that both desmosine and soft tissue–related hydroxylysylpyridinoline levels were elevated in smokers. Stone and coworkers (54) concluded that the excess elastin and collagen degradation associated with chronic obstructive pulmonary disease appears to persist even after the cessation of smoking. Lucey and coworkers (37) found that in hamsters, elastase-induced emphysema triggered an immediate (within 6 hours) remodeling response characterized by an increased expression of elastin and α1(I) collagen type-I subunit messenger RNA. The collagen message returned to control levels, and the elastin message decreased but stayed slightly above normal by 1 month after treatment. Interestingly, whereas the messenger RNA levels were nearly normal 1 month after treatment, the mean linear intercept appeared to further increase with time, although this increase was not statistically significant, most likely due to the large variations in the signal. In summary, traces of collagen involvement (i.e., damage and/or remodeling) can be found in nearly all animal models of emphysema and many studies using human lung tissue.

PROPOSED MECHANISM OF DISEASE PROGRESSION

On the basis of the arguments described previously here, we propose that after the initial insult due to cigarette smoke–induced inflammation, there exists a common pathway that leads to the characteristic structural alterations of emphysema. First, inflammation occurs, and the balance between enzymes degrading the extracellular matrix (e.g., MMP) and their inhibitors is disturbed. This leads to a direct chemical injury followed by cellular remodeling of the matrix. As a consequence of degrading and/or remodeling, the collagen fibers become weaker. Indeed, the ultrastructure of collagen from human emphysematous lungs reveals thickened and disorganized fibrils after remodeling (55). The weakening of the fibers may itself lead to mechanical stress concentration within a single alveolar wall (56). The additional mechanical forces due to breathing eventually lead to the failure of collagen. It is important to note that at this early stage of disease, substantial collagen weakening through inflammation and proteolytic activity must be present to produce fiber rupture because many fibers are functioning in parallel with the damaged and weakened fibers to counteract the mechanical forces of normal breathing. However, after the failure of a collagen fiber, all the matrix attachments and hence the entire alveolar wall can also fail. The lung recoil is subsequently reduced, operating lung volume may increase, and locally, the mechanical load carried by the wall is redistributed among the neighboring alveolar walls. If the increased force on the neighboring alveolar wall exceeds the failure threshold of the collagen, the collagen and the wall will rupture, i.e., mechanical forces propagate tissue breakdown. It is also possible that the lung remains stable for an extended period because both the number of fibers and mean recoil pressure decrease. During this period, disease progression is dictated principally by inflammation, protease activity, and remodeling, which act together to cause weakening of a larger and larger population of lung fibers. The end result is weakened fibers and alveolar walls, which become prone to mechanical failure. In addition, once the fibers break, fragments of various

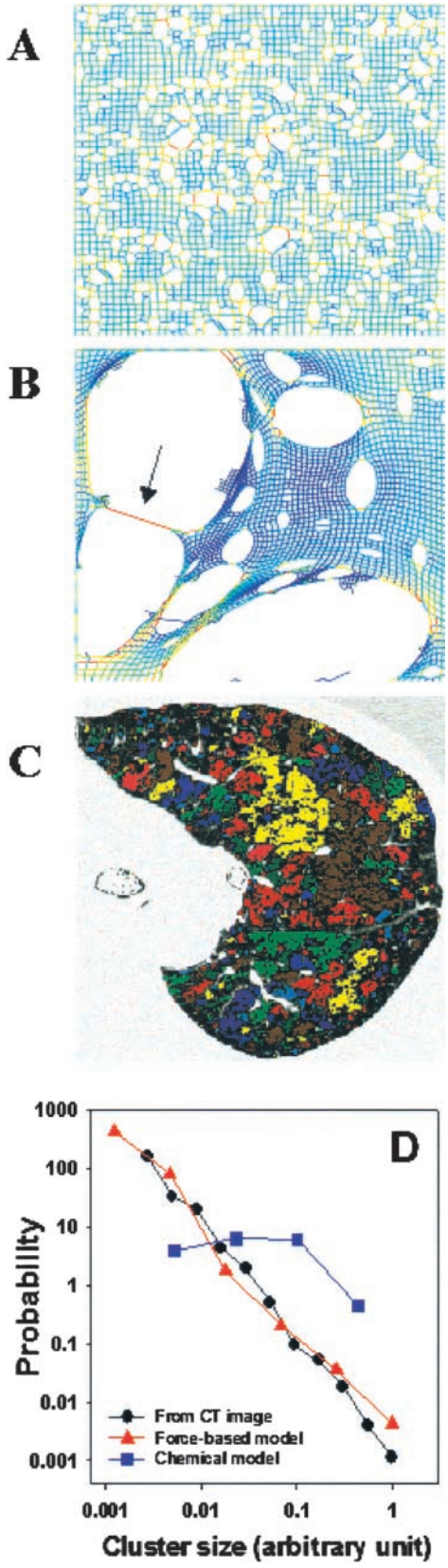

Figure 1. Network model simulations of the progression of emphysema and comparison with the structure seen on a computed tomography (CT) image of a subject with advanced emphysema. (*A*) Chemical breakdown of lung tissue simulated by randomly cutting the connections in the model. In (*A*) and (*B*), color is proportional to force. Note the uniform spatial distribution of colors and defect clusters. (*B*) Force-based breakdown of the model. Note the heterogeneous distribution of defect clusters and that high forces (*red*) occur around the perimeter of the clusters especially in regions where a "thin wall" separates two clusters (*arrow*). (*C*) Color-coded CT image of a patients with emphysema. (Reprinted with permission from Reference 15.) The different colors represent contiguous low attenuation areas. Note the heterogeneity of cluster sizes and their spatial distribution. (*D*) Size distributions of defect clusters from chemical (*blue*) and force-based (*red*) model as well as the size distribution of low attenuation area clusters from (*C*) (*black*). To obtain good statistics, the simulations were done in larger networks than in *A* and *B*.

matrix molecules will be exposed. Elastin (57) and proteoglycans (58) can attract and activate macrophages, which can lead to sustained inflammation and potentially a new supply of proteases. Such chemical feedback can further weaken the fiber network, and mechanical forces would break the tissue at points of stress concentration. We propose that the embedded loops of enzymatically initiated but mechanical force-driven tissue destruction can result in a self-propagating process that could be a major contributor to the progressive nature of emphysema, especially in its late stages.

In an effort to test whether the proposed mechanism is consistent with clinical findings, we used a previously developed computer model of the lung tissue (15) to compare the effects of chemically mediated and mechanical force–based tissue destruction. The model consisted of a network of linearly elastic springs arranged in a squared lattice representing a slice of lung tissue. We assumed that the effects of gravity were negligible. The border of the lattice was fixed, whereas the internal nodes connecting the springs were free to move. The spring constants had a small amount of heterogeneity, and the entire network was prestressed. The equilibrium configuration of the network was solved as by Mishima and coworkers (15). To simulate disease progression, two extreme cases of network breakdown were considered: (*1*) Chemical breakdown that modeled the damage associated with inflammation and protease activity secondary to smoking. Because within an isogravity plane there is no reason to assume that chemical activity would prefer one location to another, the springs were randomly eliminated from the network. (*2*) Force-based breakdown of the network. Here we implemented our previous findings that mechanical forces can break the alveolar wall (12) by always eliminating the springs from the network that carried mechanical force exceeding the fiber failure threshold. The pattern of defects generated by the two approaches is shown in Figures 1A and 1B. Although in both cases 10% of the total number of springs were eliminated, the structures of the two models were drastically different. The chemical breakdown model showed holes or "defect clusters," which were reasonably similar in size and distributed evenly over the network. In contrast, the force-based approach led to a very different structure with a few giant defect clusters surrounded by many smaller clusters. The color is proportional to force, so it is evident that the force distribution is more homogeneous in the chemical model, whereas there are large stress concentration areas in the force-based model. These stress concentrations occur around the perimeter of large clusters, especially where two clusters are spatially close. Animations of the breakdown process in several models are presented in the online supplement.

We compared the patterns of defect formation predicted by the two models with those observed in a CT image of a lung in a patient with advanced emphysema (Figure 1C). To make the comparison quantitative, we measured the areas of the clusters

in the network models and calculated the histogram or distribution of low tissue density clusters as by Suki (59). In Figure 1D, we compare on a double logarithmic graph these distributions with the size distribution of contiguous regions of low attenuation areas from the CT image. It is clear that the chemical model provides a nearly uniform distribution of clusters, whereas the force-based model has a distribution that decreases linearly on the log–log graph following a power law distribution (59), in quantitative agreement with the distribution obtained from the CT image. Thus, the hypothesis that mechanical forces govern the pattern of destruction results in a structure that is consistent with the macroscopic structure of the emphysematous lung observed in CT images. An important consequence is that compared with the chemical tissue destruction, stress concentration in the force-based model is more localized, and regional stresses are much larger (maximum force in the force-based model is 2.5 times higher than that in the chemical model), a situation that may lead to a self-propagating process of disease progression.

Here, we considered only the two extreme cases for demonstration purposes. In reality, the breakdown process in the three-dimensional lung is likely to be much more complex whereby mechanical failure may initiate additional local remodeling and/or inflammation as described previously. The distribution of chemical activity may not be uniform in the three-dimensional lung because the distribution of inspired smoke is not uniform. In addition, chemical breakdown could be concentrated around regions where cytokine and protease activity is strong, resulting in local propagation of chemical breakdown. However, even such a process does not lead to the characteristic power law distribution of cluster sizes (Figure 1D) without considering the effects of mechanical forces (*see* online supplement). Thus, despite the simplicity and limitation of our two-dimensional model simulations, these results demonstrate that the progressive breakdown of the tissue cannot be a pure chemical process.

CONCLUSIONS

We have reviewed several existing hypotheses and experimental results about the roles of proteases and inflammation in the pathophysiology of emphysema. We have argued that inflammation alone does not satisfactorily explain the progressive nature of emphysema. We have also proposed a complex mechanism in which inflammation, remodeling, mechanical forces, and collagen failure each plays crucial roles in the progressive nature of emphysema. The proposed model does not consider the susceptibility of an individual for emphysema. However, the concept of force-based deterioration of lung tissue may have relevance to normal aging, exacerbations of chronic obstructive pulmonary disease, pulmonary rehabilitation, or optimization of the success of LVRS (60). To better understand the specific interactions among inflammation, protease activity, remodeling, and mechanical force–induced failure, detailed analysis of the micromechanical and ultrastructural properties of the damaged connective tissue fibers as well as information on the regional distribution of inflammation and protease activity will be necessary.

Conflict of Interest: B.S. has no declared conflict of interest; K.R.L. has no declared conflict of interest; E.P.I. is cofounder and part owner of Bistech, Inc., a biotechnology company whose mission is the development and testing of novel tissue engineering treatments for advanced lung diseases such as emphysema.

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