The Stumbling Block in Lung Repair of Emphysema: Elastic Fiber Assembly

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The mechanical properties of the lung are largely determined by the connective tissue networks laid down during development. The macromolecules most important for lung mechanics and structural integrity are collagen, elastin, and proteoglycans. Members of the fibrillar collagen gene family provide the structural framework of the various lung compartments and elastic fibers provide elastic recoil. Elastin is also an important architectural component that influences lung development, predominantly during the alveolar stage. Previous studies have conclusively shown that elastin degradation is a key step in the pathogenesis of chronic obstructive pulmonary disease. Exacerbating the disease process is the inability of lung cells to repair damaged elastic fibers, which leads to permanently compromised lung function and ongoing degenerative disease. Elastic fibers are among the most difficult matrix structures to repair because of their size, molecular complexity, and the requirement for numerous helper proteins to facilitate fiber assembly. Recent studies of elastin assembly combined with new insight into the functional role of elastic fiber proteins obtained from gene inactivation studies and linkage of human disease to elastin mutations provide new insight into the molecular and cellular complexities of elastin homeostasis.

Keywords: elastin; elastin mutations; emphysema; extracellular matrix; repair

The discovery of an association between emphysema and α_1 -antitrypsin deficiency, in concert with the use of animal models that develop emphysema after intrapulmonary instillation of elastolytic enzymes, lead to the recognition that destruction of elastin is central to disease pathogenesis (i.e., the elastase:anti-elastase hypothesis). The best-known source of proteases in the lung is inflammatory cells recruited to the airspaces by stimulators of inflammation, such as cigarette smoke (reviewed in Reference 1). Analysis of the cell profile in alveoli and small airways of smokers shows an increase in all of the cell types implicated in chronic obstructive pulmonary disease (COPD), including macrophages, T lymphocytes, B lymphocytes, and neutrophils. For many years, neutrophils were thought to be the cell type most likely responsible for tissue destruction in emphysema through the release of neutrophil elastase (2, 3). Studies in knockout mice, however, found that the macrophage also plays a significant role in the pathophysiology of COPD and can account for many of the known features of the disease (4, 5).

Both neutrophils and macrophages secrete potent elastases that degrade elastin and other matrix proteins. Alveolar macro-

phages from patients with COPD secrete more inflammatory proteins and have a greater elastolytic activity at baseline than those from normal smokers and this is further increased by exposure to cigarette smoke (6). Elastin fragments liberated during elastic fiber degradation recruit more inflammatory cells to the lung, leading to enhanced lung tissue destruction by placing more macrophages, and thus more elastin-degrading enzymes, within close proximity of the airspace (4).

In addition to proteases, other factors have been implicated in tissue destruction leading to COPD, including oxidative stress and apoptosis of lung structural cells (reviewed in References 7 and 8). Inflammatory cells generate potent reactive oxygen and reactive nitrogen species that lead to oxidative stress when there is an imbalance between oxidants and antioxidants. Alveolar macrophages from smokers, for example, release more reactive oxygen species than do cells from nonsmokers and plasma antioxidant capacity is decreased by cigarette smoking. The effects of oxidants on elastic fiber homeostasis are most likely manifest through their ability to modulate the activity of proteinases, proteinase inhibitors, cross-linking enzymes, etc., as opposed to a direct effect on elastin.

THE ELASTIC FIBER: COMPOSITION, STRUCTURE, AND COMPLEXITY

Exacerbating the disease process is the inability of lung cells to repair damaged elastic fibers, which leads to permanently compromised lung function and ongoing degenerative disease. To fully understand why elastic fibers are difficult to repair one needs to understand the molecular complexities of elastic fibers and the unique relationship between the synthetic cell and the extracellular matrix (ECM) that it produces.

The elastic fiber is a complex structure that contains at least two morphologically distinguishable components: amorphous elastin and microfibrils. One reason that elastic fibers are difficult to repair is that replacing damaged fibers requires the coordinated reexpression of all of the molecules that make up the microfibril as well as the enzymes critical for cross-linking elastin. Expression of these proteins must be coordinated so that the correct temporal sequence is followed. In adult tissue, this appears to be a difficult task for the elastin-producing cells and most often results in production of elastin that does not polymerize or that does not organize into a functional three-dimensional fiber.

Tropoelastin

Elastin is secreted from the cell as a soluble monomer (tropoelastin) that must be cross-linked into a functional polymer (9). The first step in the cross-linking reaction is the formation of the δ -aldehyde allysine through oxidation of lysyl ϵ -amino groups by a member of the lysyl oxidase enzyme family (10). Approximately 40 lysine residues in 16 cross-linking domains of tropoelastin eventually participate in forming the bi-, tri-, and tetrafunctional cross-links that help make the resulting product a polymer with reversible deformation and high resilience. The association of elastin with fibrillin-containing microfibrils during the early stages of elastic fiber assembly has led to the supposition

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that an interaction between these two components is the first (and a required) step in the formation of an elastic fiber. Binding onto the microfibril is proposed to help align the cross-linking sites in tropoelastin so that intermolecular cross-linking can occur (reviewed in Reference 11). In this regard, tropoelastin has been shown to specifically interact with components of the microfibril, including fibrillin and microfibril-associated glycoproteins (MAGPs), and sites of interaction within the various proteins have been identified.

Microfibrils

Microfibrils are defined as 10–12 nm fibrils associated with elastic fibers or free in the ECM (12). It now appears that microfibrils have different compositions in different tissues and that this composition may change during development. In terms of elastic fiber formation, microfibrils appear first in development and associate close to the cell surface at foci of elastin synthesis. Ultrastructural studies suggest that tropoelastin interacts with the microfibrils in a way that facilitates its cross-linking to form the functional polymer. Hence, microfibrils are considered necessary components for the assembly of a functional elastic fiber. Microfibrils also have other functions important for tissue repair, including binding and sequestration of growth factors (13) and the capacity to provide direct signals to cells through interactions with integrins and cell-surface heparan sulfate-binding receptors.

To fully understand the intricate nature of the microfibril, we must consider the complexity of its molecular composition. More than 30 different proteins have been localized to microfibrils or to the elastic fiber–microfibril interface (reviewed in Reference 14). Below we consider some of the major players in microfibril function.

Fibrillins. Fibrillins are the major structural proteins of the elastic fiber microfibril. There are three members of the fibrillin family and each is a large glycoprotein (~350 kD) whose primary structure is dominated by calcium-binding epidermal growth factor (cbEGF) domains (15–18). All three fibrillins are expressed relatively early in lung development. In the mouse lung, expression of fibrillin-1 increases for about 3 wk postnatally then decreases to low adult levels. Expression of fibrillins-2 and -3, in contrast, decrease dramatically shortly before birth and remain low throughout adulthood (15, 17, 19). Fibrillin-1 and -2 have been shown to contain multiple binding sites for ECM proteins. Proteins that bind to fibrillin include tropoelastin, MAGPs, heparan sulfate proteoglycans, chondroitin sulfate proteoglycans, and various members of the transforming growth factor (TGF)- β superfamily, among others. Fibrillin-1 null mice die soon after birth from ruptured aortic aneurysm, impaired pulmonary function, or diaphragmatic collapse. Fibrillin-2 null mice, in contrast, have well developed elastic fibers, suggesting that fibrillin-2 plays a less significant role than fibrillin-1 in elastogenesis (20). It should be noted that fibrillin-3 has been inactivated in the mouse genome due to chromosome rearrangement (17).

MAGPs. MAGP-1 and -2 are found in most microfibrils and are expressed in mesenchymal cells throughout development. The proteins share an approximately 60-amino-acid region of sequence homology near the C-terminus that defines a matrix-binding domain in MAGP-1 (21, 22). Both proteins have been shown to bind to fibrillin, and interactions between MAGP-1 and tropoelastin were thought to be important for elastin assembly (23). Inactivation of each gene individually or together, however, has no obvious effect on elastic fiber formation in mice (our unpublished results).

Latent TGF- β binding protein. The latent TGF- β binding proteins (LTBPs) are members of the fibrillin superfamily based on repeating cbEGF domains within the molecules (24). A major

role for most members of the LTBP family is to maintain TGF- β in the latent state through the formation of the large latent complex. This complex has been shown to associate with ECM macromolecules and thereby establishes an extracellular storage site for positioning and concentrating growth factors in the ECM. LTBP-1, for example, has been shown to bind directly to fibrillin and thereby anchor TGF- β as the large latent complex directly to microfibrils (25). Fibrillin itself is also capable of binding TGF- β family members, specifically bone morphogenic protein-7 (26). It is interesting to note that perturbations in the sequestration of TGF- β into the ECM during lung development results in an emphysemalike phenotype (27). Providing further evidence for an important role of LTBPs and lung disease is a recent report documenting an association between single nucleotide polymorphisms in the LTBP-4 and TGF- β genes and COPD (28).

LTBP-2 is the only member of the family that is a candidate to serve as an integral structural protein of microfibrils (29). Interestingly, LTBP-2 has an altered disulfide bond structure in the TGF- β binding domain and hence cannot bind TGF- β . Mice with a targeted disruption of the LTBP-2 gene die between Embryonic Days 3.5 and 6.5 (30). Inactivation of LTBP-3 and -4 results in emphysema-like lung morphology (31, 32).

Fibulins. Another family of cbEGF-containing proteins shown to associate with elastic fibers is the fibulins (33, 34). Members of this six-member family are hypothesized to function as intramolecular bridges that stabilize the organization of supramolecular ECM structures (33). Fibulins-1, -2, -4, and -5 all bind to tropoelastin and have been localized to elastic fibers in developing tissues. Mice deficient in fibulins-4 and -5 show defective elastic fiber assembly with concomitant emphysemalike lung morphology (35, 36). Mutations in fibulin-5 have also been linked to severe lung disease in humans (37).

Lysyl Oxidases

Lysyl oxidases are copper-requiring enzymes that catalyze the covalent cross-linking of collagen and elastin. In addition to the first characterized lysyl oxidase (LOX), there are four lysyl oxidase-like (LOXL1–4) proteins that resemble LOX in containing a conserved amino oxidase domain. Because lysyl oxidases are critical for elastin and collagen cross-linking, they associate with these proteins early in the assembly phase. LOXL1, for example, has been localized to the elastin globules that form on the cell surface (38) and antibodies to LOX have been localized to microfibrils. LOXL1 has also been shown to interact with fibulin-5, fibrillin, and with tropoelastin in ligand-binding assays (38, 39). Inhibition of LOX activity through copper deficiency (copper is a required cofactor) or through the administration of enzymatic inhibitors results in weakened connective tissue throughout the body. Inhibition of LOX activity during the critical period of postnatal lung growth results in irreversible structural changes, including larger airspaces, that may predispose the lung to injury in later life (40). Not surprisingly, inactivation of LOX and LOXL1 individually leads to enlarged airspaces in the lung (39, 41).

In addition, it has long been known that cigarette smoke blocks cross-linking of elastin *in vitro* (42). Recent studies using cigarette-smoke-condensate-treated cells have demonstrated decreased levels of LOX protein accompanied by decreased LOX catalytic activity when compared to smoke-condensate-free controls (43). This decrease in protein in cigarette-smoke-condensate-treated cells is thought to be the result of oxidant-induced down-regulation of LOX steady-state mRNA through inhibition of transcription initiation and increased instability of LOX mRNA transcripts (44).

EXPRESSION OF ELASTIC FIBER PROTEINS DURING TISSUE DEVELOPMENT: A TRANSCRIPTIONAL PROGRAM THAT MUST BE RECAPITULATED FOR REPAIR

Expression profiles of elastic fiber proteins have recently been obtained using large-scale gene expression analysis of mouse lung development (19). They show elastin expression increasing rapidly beginning at Embryonic Day 18 and reaching its highest level at Postnatal Days 10 to 14, coincident with alveogenesis. Between Postnatal Days 14 and 21, levels decrease rapidly and then remain low throughout adulthood. A comparison of relative expression levels across the developmental time series shows that the ratio of elastin to microfibrillar proteins and the ratio of microfibrillar protein to each other are quite different. An example is shown in Figure 1 where the expression profile of elastin, the two fibrillins, and lysyl oxidase is shown as a function of lung development. The inability to repair damage to elastic tissue in the adult period may reflect an inability of the cell to reactivate the many required genes in the appropriate ratios and in the temporal sequence required for normal elastic fiber assembly.

THE ROLE OF THE CELL IN ELASTIC FIBER ASSEMBLY

Elastic fibers are the largest ECM structures in the lung. In contrast to collagen fibrils that have defined molecular diameters (e.g., type I collagen fibers are ~ 35 nm in diameter), the diameter of elastic fibers appears not to be restricted by constraints of molecular packing. Their large size and unique position in the ECM creates special problems for the elastin-producing cells.

Cellular control of matrix polymer assembly has been shown to be important for several matrix proteins, including fibronectin, collagen, and laminin. Assembly of all three proteins requires an interaction with integrins and perhaps other cell-surface receptors (45). Like these other ECM proteins, elastic fibers are assembled extracellularly in a process directed by the elastin-producing cell. Dynamic imaging of elastic fiber formation by

cells expressing tropoelastin tagged with the fluorescent Timer construct (BD Biosciences Clontech, San Jose, CA) suggests that the initial step in elastin assembly is the formation of small elastin aggregates on the cell surface (46). These initial aggregates then coalesce to form larger globules that are transferred to fibrillin-containing microfibrils already present in the ECM (Figure 2). The early organization of tropoelastin monomers into aggregates most likely occurs through self-association when the proteins are brought to assembly sites on the cell surface. Particle tracking studies show that the globules remain associated with the cell during early phases of assembly, thereby implying a direct association between elastin and the plasma membrane.

Elastin binds to cells in a specific and saturable manner with kinetics typical of a receptor-ligand interaction (47). The nature of the elastin-binding proteins that participate in assembly, however, is unclear, with $\alpha\text{v}\beta 3$ integrin, several nonintegrin proteins, elastin-binding protein arising from an alternatively spliced form of β -galactosidase, and cell-surface glycosaminoglycans representing possible binding partners (48).

Figure 1. Individual expression profiles for four elastic fiber genes during lung development. Shown are mean normalized mRNA values over a developmental series beginning at Embryonic Day 12 (E12), continuing through postnatal development (D1–D21), and ending at the adult stage (AD). Note that the relative expression of each gene is different at every developmental period and is at its lowest level at the adult stage. Gray squares, elastin; solid squares, fibrillin-1; solid triangles, fibrillin-2; solid circles, lysyl oxidase. Data compiled from Reference 19.

Figure 2. Model of elastin assembly. *Step 1:* Tropoelastin monomers (shaded circles) are secreted to the plasma membrane where they self-assemble into aggregates. Fibrils associated with the globules (black lines) may assist in this process by providing a nucleation scaffold that initiates and directs aggregation, or alternatively, the fibers may serve to limit the rate or extent of tropoelastin self-assembly so that fiber formation can be directed and controlled. Although the composition of these early fibers is unknown, it is possible that lysyl oxidase is a component because cross-linking (gray lines) must occur as tropoelastin assembles into the cross-linked polymer. Other possible fibrillar proteins include fibulin-5 and fibrillin. *Step 2:* Tropoelastin aggregates move over the cell surface, perhaps through associations with the cytoskeleton, and merge to form larger globular structures. Lysyl oxidase must also be present at this stage to covalently join the aggregates into globules. *Step 3:* Elastin globules leave the cell surface where they interact with fibrillin-containing microfibrils (large gray line) in the extracellular space. Once associated with the microfibril, the globules condense with other globules to form larger aggregates (*Step 4*). Fiber maturation consists of removal of the initial elastin-associated fibers and cross-linking of globules as they coalesce to form larger fibers (*Step 5*).

CHANGES IN ECM COMPOSITION MAY RESTRICT FIBER ASSEMBLY PROCESSES ASSOCIATED WITH CELL MOVEMENT

As cells move through the ECM, they thereby extend and align a network of microfibers as well as interacting with adjacent elastin-containing aggregates. As a result of coordinated cell motility, two distinct elastic fiber aggregates can approach each other and attach to the same cell. Subsequently, by local ECM reorganization at the cell surface, the two ECM structures can unite to form a larger composite structure. From repetitions of the ECM movements and aggregation steps over time, progressively larger units emerge. Parallel to this large-scale, hierarchical assembly, newly secreted elastin-containing globules may also be added to the aggregates. In adult tissue the preponderance of collagen changes the material properties of the ECM, which may restrict cell movement and not allow for the sculpturing of matrix that is possible in the early embryonic stages.

ELASTIN IS CRITICAL FOR NORMAL LUNG GROWTH AND DEVELOPMENT

A rich structural network of elastic fibers within the pulmonary ECM supplies elasticity to the parenchyma and airways as they cycle through repeated inflation (stretch) and deflation (recoil) throughout the life of the organism (49). Organization of the elastin network begins during the pseudoglandular stage of lung development, increases during the canalicular and saccular stages, and peaks during alveogenesis, which occurs postnatally (50). Expression of elastin by cells actively participating in alveogenesis suggests that elastin is the driving force for septal generation and alveolar growth. In mice deficient for elastin ($ELN^{-/-}$), or in mice deficient in key growth factors such as platelet-derived growth factor that have an effect on the onset of elastin expression, perinatal development of terminal airway branches is arrested, resulting in distal air sacs that are dilated with attenuated tissue septae (51, 52).

Although mice lacking elastin do not undergo normal alveogenesis, $ELN^{+/-}$ mice, which have elastin levels about half those of wild-type (WT) animals, have essentially normal lungs (51). When compared with WT lungs, the lungs of $ELN^{+/-}$ mice are macroscopically normal, with normal lobe numbers and major airway branching patterns. On microscopic examination, neither the pulmonary parenchyma, nor the resident inflammatory cells offer an obvious difference from the WT control mice, and chord-length measurements show no difference between the two genotypes. Mice with less than 50% normal elastin levels, however, show abnormal lung development. We have recently rescued the elastin null mouse from perinatal lethality by expressing elastin from a bacterial artificial chromosome containing the complete human elastin gene. Quantitation of lung ECM shows that these animals contain approximately 30% of the elastin content of WT mice. Although the animals live well into adulthood, they demonstrate a remarkable lung phenotype at both the macroscopic and microscopic levels. They have enlarged thoracic cavities occupied by highly distended lungs that are larger than both WT and $ELN^{+/-}$ lungs at identical inflation pressures. Microscopic evaluation reveals massively dilated airspaces with no abnormal inflammatory phenotype—a feature typical of congenital emphysema (manuscript in preparation).

Together, these findings demonstrate that normal lung development can occur with lower than normal elastin levels as long as they do not drop below a critical threshold. Data from the $ELN^{+/-}$ mice tell us that approximately 50% of WT level is sufficient elastin to promote alveogenesis and normal lung function. Below that level, lung development is compromised.

ALTERED ELASTIN GENE DOSAGE PREDISPOSES MICE TO EMPHYSEMA

Although lower than normal levels of elastin can support normal lung development, we have recently found that elastin insufficiency makes mice more prone to develop severe lung disease when exposed to injurious environmental stimuli. This finding strongly suggests that the quantity of elastin in the lung may be an important factor in determining susceptibility to lung injury. On exposure to cigarette smoke (representing ongoing pulmonary injury), $ELN^{+/-}$ mice develop 1.8 times greater airspace enlargement than WT littermate control mice (manuscript in preparation). The mechanism responsible for the augmented airspace enlargement in the $ELN^{+/-}$ animals is most likely elastin degradation in that $ELN^{+/-}$ animals demonstrate a significantly increased macrophage inflammatory response when compared to WT control mice.

LUNGS WITH MISASSEMBLED ELASTIN ARE MORE SUSCEPTIBLE TO ENVIRONMENTAL DAMAGE

Elastin assembly is directed by molecular interactions between assembly domains within tropoelastin and the microfibrillar scaffolding proteins. In this regard, important functional properties have been mapped to the C-terminal region of tropoelastin encoded by exons 29–36. Tropoelastin molecules that lack this region associate with normal elastin but do not undergo usual cross-linking (53). Within this domain, the amino acid sequence encoded by exon 30 has been shown to mediate intermolecular interactions between tropoelastin monomers and may be important for the accretion of tropoelastin onto the growing elastic fiber. Exon 36, in contrast, defines an important cell-interaction site that may play a role in the early phases of elastin assembly on the cell surface (48). As described below, mutations that alter these regions of the protein can have either subtle or profound effects on elastin assembly or elastic fiber integrity. As a result, these abnormal fibers are more susceptible to environmental damage that leads to disease.

A MISSENSE ALLELE IN THE TERMINAL EXON OF ELASTIN IN SEVERE, EARLY-ONSET COPD

We have described above how loss-of-function mutations may heighten susceptibility to lung damage through elastin insufficiency. Elastin gain-of-function mutations that modify key assembly domains in elastin can also lead to lung disease by altering the ability of elastin to assemble into the functional polymer. In collaboration with Dr. Edwin Silverman and Dr. Benjamin Raby at Harvard University, we have described a novel variant in the terminal exon of human elastin (c.2318 G > A) resulting in an amino acid substitution of glycine 773 to aspartate (G773D) in a pedigree with severe early onset chronic obstructive pulmonary disease (COPD) (54). Transfection studies with elastin cDNAs demonstrate that the glycine to aspartate change compromises the ability of the mutant protein to undergo normal elastin assembly. The mutant protein associates with normal elastic fibers but is undercross-linked compared with the WT protein. Other functional consequences of this amino acid substitution include increased proteolytic susceptibility of the C-terminal region of elastin and reduced interaction of the exon 36 sequence with matrix receptors on cells. In the severe early onset pedigree harboring the G773D variant, evidence of airflow limitation was most severe among those mutation carriers who smoked, suggesting a gene-by-environment interaction. These results suggest that the G773D variant confers structural and functional consequences relevant to the pathogenesis of COPD and that individual carriers

of this polymorphism could be at increased risk for developing lung disease (54).

OTHER ELASTIN GENE MUTATIONS ASSOCIATED WITH ENHANCED LUNG DISEASE SUSCEPTIBILITY

Autosomal dominant cutis laxa (ADCL) is an inherited connective tissue disorder characterized by redundant, loose, and inelastic skin. The disease is a consequence of frameshift mutations near the 3' end of the gene that result in missense sequence through the critical assembly domain in exon 36. Similar to what happens with the G773D mutation outlined above, ADCL mutations alter the ability of the protein from the mutant allele to assemble properly. There is also the likely possibility that the mutant product may act in a dominant-negative fashion to alter the assembly of the protein from the normal allele.

Several studies have documented severe COPD in individuals with ADCL who smoke. For example, Urban and colleagues (37) have described a family with ADCL with severe, early-onset emphysema. In the family described, one of the probands had clinical COPD by 23 yr of age, and another had the disease at 36 yr. Both were notably smokers, although the duration of smoking was extremely short by conventional standards. Elastic staining of skin and bronchial biopsy sections revealed a normal quantity, but abnormal quality, of elastic fibers with a fragmented and clumped morphology.

ELASTIN DOSAGE AND LUNG DISEASE: THE THRESHOLD THEORY

We have presented data showing that lungs from $ELN^{+/-}$ mice, which have approximately 50% the amount of elastin of WT lungs, are morphologically identical to, but develop worse emphysema on cigarette-smoke exposure than WT mice. The data presented also show that mice possessing around 30% of normal elastin levels have congenital emphysema. In addition, clinical studies suggest that mutations (particularly those affecting exon 36) that alter the integrity of the elastic fiber predispose to emphysema in human populations. Together, these findings imply that a threshold level of functional elastin is critical for normal lung development and for both timely and efficient repair following lung injury. When elastin levels are below this critical threshold, repair is unproductive and the lungs are more prone to developing emphysema.

This hypothesis is shown schematically in Figure 3. The heavy dashed line represents an arbitrary threshold level of lung elastin concentration that defines whether injury will be repaired or progress on to clinical disease. Because $ELN^{+/-}$ mice have normal lung structure and function, this threshold level is likely to be lower than 50%. Individuals (or mice) with normal elastin levels (top solid line) have the capacity to accommodate and repair lung damage because they are well above the threshold level. For individuals (or mice) with elastin insufficiency or dysfunctional elastic fibers (middle dotted line), a similar injury will drop them below the threshold, where efficient repair cannot occur. In this case, early developmental perturbations in elastin homeostasis may predispose to smoking-induced emphysema and perhaps other forms of lung disease later in life. Finally, if elastin levels never exceed the threshold (bottom dashed line), lung development is perturbed and the lung is congenitally impaired. This might provide a mechanistic explanation for the congenital emphysema phenotypes observed frequently in mouse knockouts.

CONCLUSIONS

The ECM is a complex integrated system of interacting molecules required for the normal functioning of the lung. Elastic

Figure 3. Elastin threshold hypothesis of lung injury. The heavy dashed line represents an arbitrary threshold level of elastin concentration that defines whether injury will be repaired or progress on to clinical disease. Individuals with normal elastin levels (top solid line) have the capacity to accommodate and repair lung damage because they are well above the threshold level. For individuals with elastin insufficiency or dysfunctional elastic fibers (e.g., individuals with autosomal dominant cutis laxa or the G773D mutation; middle dotted line), a similar injury will drop them below the threshold, where repair cannot occur. If elastin levels never exceed the threshold (bottom dashed line), lung development is perturbed and the lung is functionally impaired. In theory, gradations of repair and disease might relate to both the extent of injury and the level of elastin.

fibers are a major component of this ECM and are essential for lung development and response to injury—both functions being affected by the genetically determined quantity and quality of elastin. Assigning a direct role for elastin in the pathogenesis of lung disease, however, is complicated by mutations in other components of the ECM that can result in defective elastic fiber formation and impaired pulmonary function. Understanding the critical role for elastin in lung development and disease will facilitate the discovery of therapies aimed at promoting pulmonary regeneration through alveolation and lung growth in an effort to improve the outcomes of patients afflicted with emphysema.

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