Mechanical ventilation and elastic fiber assembly

Barry Starcher
Department of Biochemistry, University of Texas Health Center at Tyler, Tyler, Texas

ELASTIN IS A CONSTITUENT of connective tissue that is present in virtually all vertebrate tissues and has an especially vital role in organs that undergo repeated cycles of extension and recoil such as the arteries, lungs, and skin. Elastic fibers consist of two morphologically distinct components, the microfibrils and polymerized tropoelastin. The current view is that elastin is secreted from cells of mesenchymal origin, such as smooth muscle cells, fibroblasts, chondrocytes, and endothelial cells, in a soluble form (tropoelastin) that coalesces on a scaffold of microfibrils and crosslink to form insoluble, functional elastic fibers. Microfibrillar proteins are generally expressed before tropoelastin during development and are always associated with elastin throughout early stages of fiber assembly. There are three major groups of microfibrils closely associated with elastin: fibrillin-1, -2, and -3, fibrillin-2, -4, and -5, and MAGP-1 (8, 11). Emilin-1 is another matrix protein that apparently stabilizes molecular interactions between elastic fibers and is required for normal elastic fiber assembly (4, 19). These proteins play a central role in elastogenesis by orchestrating the deposition of tropoelastin onto the developing elastic fiber, and their importance cannot be overstated. The study by Bland and colleagues (1) in this issue provides new insights into the importance of the elastin/microfibril relationship during the development of chronic lung disease.

For the successful transition of the structurally immature lung to an architecturally mature lung with a large internal surface area to occur, the lung is subdivided with the growth of secondary septae from primary alveolar walls. In rodents, the subdivision begins around 3–4 days after birth and is essentially completed within 14 days (6). In humans, septation begins during gestation and continues into early childhood (7). If the process of septation is blocked or impaired, there is a high risk for loss of internal surface area and emphysema-like changes. One of the critical extracellular matrix components required for the process of lung septation and alveolar formation is elastin. Elastin is expressed early during the pseudoglandular stage of lung development in areas of airway branching. After birth, elastin synthesis is greatly upregulated and is concentrated at the apex of developing secondary septal crests, forming rings that surround the mouths of alveoli and in bundles in the alveolar walls (13, 17). The signals that regulate alveologenesis are not fully understood, but a variety of agents, including oxygen, can arrest this process.

Bronchopulmonary dysplasia and neonatal chronic lung disease (CLD) are the most common causes of long-term disability in premature infants and typically develop after premature birth and lengthy mechanical ventilation with oxygen-rich gas. The pathogenesis of CLD is linked to structural lung immaturity and impaired alveolarization, with elevated levels of disorganized lung elastin (5, 15, 16). Elastin production is known to be markedly upregulated by strain or stretching of the cell matrix (9, 14). Lung histology of infants who have died with CLD shows thickened, tortuous, and irregular distribution of elastic fibers in the walls of distal air spaces, with reduced septation and fewer alveoli (5, 16). Bland and coworkers previously used an ovine model of CLD to study the effects of mechanical ventilation and high oxygen exposure on premature lambs. They reported an abnormal abundance and distribution of elastin in blunted secondary crests, where focal deposits of distally situated elastin are projected to be the loci of new alveoli during lung development (3, 15). They later accomplished a marvelous miniaturization of their procedures to do similar studies in mice (2) and now present a sophisticated model in the article in focus that permits the mechanical ventilation of newborn mice for up to 24 h (1). This provides a window to address some of the mechanisms responsible for the altered elastin metabolism observed in CLD. As predicted, tropoelastin expression as well as protein in general was upregulated. There was also a fivefold elevation in serum protease activity with no increase in inflammatory cells. The unexpected finding was that other genes so important for normal elastin assembly (fibrillin, fibrulin, and lysyl oxidase) either did not change or were actually downregulated.

From these observations, the authors offer a couple of novel proposals that are intriguing but are not yet verified. First, they suggest that the discordant expression of microfibrils, lysyl oxidase, and tropoelastin during mechanical ventilation may provide an environment hostile to elastic fiber assembly. The prolonged cyclic stretch of the developing lung stimulates the release of tropoelastin from myofibroblasts, without a corresponding increase in other matrix proteins that are essential for elastic fiber assembly. Compound this with an increase in protease activity and the result may be an accumulation of poorly organized elastic fibers and the associated failure of alveolar septation. This leads to impaired alveologenesis and emphysema-like lesions in the lung. Are these proposals sound? Their data suggest they are, and we know from many other studies that the absence or mutation of the fibrillins or the fibulins will result in altered elastin assembly (10, 18). We also know that knocking out the elastin gene results in massive lung defects (12). These deficiencies, however, are very extensive, whereas in the Bland study, they are looking at relatively minor changes in microfibril levels with elevated activity of the elastin gene. The ratios may change, but is this enough? In most biological systems, it requires quite significant changes in the level of a specific molecule to see any appreciable effect on the system involved. However, we have to recognize that the present studies were short term relative to CLD treatment regimens, and perhaps over an extended period of time, the subtle ratio changes observed here would become considerable. The authors also revisit the intriguing question of whether elastin so important in the initiation of alveologenesis. There is a growing list of growth factors and cytokines such as VEGF, PDGF, and retinoic acid that regulate septation (3). While elastin does not fit this list, if conditions for elastic fiber

Address for reprint requests and other correspondence: B. Starcher, Dept. of Biochemistry, Univ. of Texas Health Center at Tyler, 11937 U.S. Highway 271, Tyler, TX 75708 (e-mail: barry.starcher@uthct.edu).
deposition are not met, septation does not occur, or is at least altered. One might expect that fragile or incomplete alveoli would occur, but this is not the case. Perhaps the myofibroblast-derived elastase that Bland et al. describes is more important than we realize. Even when present in lower levels, it may constantly contribute to remodeling abnormal elastic fibers and may prevent septation and extension of the alveolarization process when elastin assembly is flawed.

REFERENCES