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# Commentary

## Lo, and the Niche Is Knit

### *Lysyl Oxidase Activity and Maintenance of Lung, Aorta, and Skin Integrity*

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Correct assembly or abnormal disassembly of the extracellular matrix is critical in the pathogenesis of many common diseases including pulmonary, skin, and cardiovascular disorders such as emphysema, cutis laxa (Ehlers-Danlos syndrome), and aortic aneurysms (Marfan syndrome). In this issue of *The American Journal of Pathology*, Mäki and colleagues[1] show that knockout mice deficient in lysyl oxidase (*Lox*) cannot correctly cross-link elastin or collagen and hence have major developmental problems in the lung as well as in the cardiovascular system and skin.[2,3] In addition, rupture of the membranous portion of the diaphragm forms a congenital hernia in some *Lox*-null embryos.

As Mäki and colleagues remark,[1] the phenotypic similarity between human LOX deficiency and other diseases that affect matrix assembly and disassembly is striking. Lathyrism, copper deficiency, and Menke's disease are all associated with decreased LOX activity. Moreover, the *Lox*-null mouse phenotype almost exactly overlaps with the null phenotype of the *Lox*-associated gene *Loxl1*, in which failure of elastogenesis leads to postpartum pelvic prolapse, as well as emphysema, cutis laxa, and aneurysms.[4]

In the lung, normal deposition and arrangement of elastin fibers is particularly important in the formation and maintenance of alveolar crests. For example, in young mice with the *Elastin*-null mutation,[5] alveolar crests fail to form. Similarly, in mice with the *Pdgf-a*-null mutation,[6] alveolar myofibroblasts fail to differentiate and produce elastin, preventing alveolar crest formation. In mice with the *Fgfr3/Fgfr4* double-null mutation,[7] excessive amounts of dysmorphic elastin are laid down, also disrupting the formation of alveolar crests. On the other end of the developmental spectrum, failure to protect elastin from proteolytic degradation in $\alpha$1-antitrypsin deficiency [Online Mendelian Inheritance in Man, OMIM (TM). Johns Hopkins University, Baltimore, MD. MIM no.: 107400. Date last edited: 3/14/2005. World Wide Web URL: *http://www.ncbi.nlm.nih.gov/omim/*], or from excessive destruction of elastin mediated by neutrophil elastase induced by chronic cigarette smoke exposure,[8] results in emphysema, a disease characterized by destruction of alveolar walls.

Elastic interdependence of the lung is an important concept in respiratory physiology, accounting for orderly elastic recoil of the lungs during passive expiration. At the alveolar level, elastic interdependence is mediated by the correct expression, cross-linking, and orientation of elastin and collagen fibers. This, as shown here in *The American Journal of Pathology*, depends on LOX activity.

Prenatally, the lung develops as a chloride secretion-driven, fluid-filled system with a net-positive hydraulic pressure imposed by constriction of the larynx. By contrast, the introduction of air by net-negative pressure and rapid drying of the alveolar surface mediated by the activation of active sodium pumping must occur immediately after birth. Moreover, because of the small size of individual alveoli and the inverse-fourth-power Laplace relationship between alveolar radius and surface tension, a functional balance between surfactant surface film, elastic interdependence, and elastic recoil is necessary to prevent collapse of the alveolar gas diffusion surface. Additionally, correct formation of alveolar crests requires remodeling of the alveolar microvasculature from a double to a single network, as well as correct modeling of the lymphatic vascular network.

Interference with any of the genes that function in these highly interdependent processes by null mutation or gain

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or loss of function results in a final common phenotype of neonatal lethal respiratory failure if the effect is severe or early onset emphysema if it is somewhat milder. For example, null mutation of *Smad3,* which is a key receptor-activated co-Smad in the transforming growth factor-$\beta$ signaling pathway, results initially in a rather subtle failure of correct organization of the matrix, which in turn is an antecedent of the subsequent, early onset pulmonary emphysema.[9] This early onset emphysema in *Smad3*-null mutants is also associated with activation of excessive matrix metalloproteinase activity. Thus, correct organization of the matrix during alveolarization may protect against subsequent proteolytic degradation and deterioration of the matrix as well as eventual loss of functional alveolar gas diffusion surface. We have also recently found that exposure to side stream smoke profoundly exacerbates and accelerates alveolar destruction in young *Smad3*-null mice (unpublished results). This provides further support for the concept that failure of correct matrix organization may predispose to certain serious degenerative diseases; conversely, correct matrix organization may be protective against these same degenerative diseases.

Failure of the correct establishment or maintenance of a functional matrix niche for alveolar epithelial progenitor cells is another idea that may have relevance to understanding the *Lox*-null phenotype. This idea is not entirely new,[10] but is worth revisiting because of the increasing interest in the potential feasibility of adult, fetal, and embryonic stem or progenitor cell therapy for respiratory failure due to insufficient alveolar surface area.[11] One way of interpreting the *Lox*-null phenotype, as well as the other matrix-deficient phenotypes mentioned above, is that dysplastic and/or degraded matrix cannot provide the necessary structural niche and/or environmental cues needed for peripheral airway stem/progenitor cells to assume and/or repair the correct cell lineage phenotype. The hope is that exogenous cells will contain the required information to restore the absent or damaged niche matrix and hence provide a permissive environment for tissue repair and regeneration to take place. But will they? Or can they be engineered to do so or encouraged to do so with appropriate growth factors? It will be important to answer these questions.

Lastly, the *Lox*-null phenotype described by Mäki and colleagues[1] not only adversely affects lung integrity, but also the pressure-bearing characteristics of aorta and skin. Thus, how well the niche is knit likely determines not only how well stem and progenitor cells function but also the micromechanical properties of some very important tissues.

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