Rebuilding the lung: signals for a complex architectural task

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WHAT A REMARKABLE ORGAN THE human lung is! At the end of a deep breath, the vast majority of its volume (>80%) is air. More than half of the remaining volume (>10%) is blood. These two phases have to be separated strictly but also brought into close contact over a large surface to allow efficient gas exchange. However, what about those remaining <10% that serves this function: the “real” lung tissue?

Those few hundred grams of tissue consist of more than 40 cell types, originating from all 3 germ layers, and a sophisticated connective tissue network. Together they form an organ with a complex architecture optimized to serve its main function. The branching airway and vascular trees come in close proximity in the parenchymal region where gas exchange is facilitated by a minimized barrier thickness over a maximized surface area. This delicate parenchymal structure is stabilized by two factors: the surface tension modifying properties of the pulmonary surfactant system and the lung’s connective tissue “backbone.” A continuous network of connective tissue, consisting of collagenous and elastic fibers and the fibroblasts that produce them, forms a tensegrity structure in the lung (15). This network, however, appears as “focal” (as it is often described in cases of proliferation, e.g., in idiopathic pulmonary fibrosis, although it is actually a highly interconnected reticulum; Ref. 3) in thin histological sections, which underscores the importance of qualitative and quantitative three-dimensional information for proper characterization of lung structure in health and disease.

Mechanical signals that act within and on the lung are translated into biochemical signals that lead to effects at the cellular level, e.g., inducing secretion, tissue growth, or remodeling, which, in turn, affect lung mechanics (for review, see e.g., Ref. 16). One example specific to the lung is the stimulation of surfactant secretion by mechanical distension of surfactant-producing type II alveolar epithelial cells or their neighboring type I cells (reviewed in Ref. 5).

An interesting and relevant model to study the effects of mechanical forces on lung structure and function is compensatory lung growth following pneumonectomy. Moreover, compensatory lung growth is a paradigmatic example for the structural plasticity of the adult lung. Can the mechanical stimuli that induce compensatory lung growth after pneumonectomy, tissue expansion vs. microvascular perfusion, be dissected? A study by Ravikumar et al. (12) in this issue of the Journal of Applied Physiology elegantly demonstrates that this is possible. In adult dogs, the right lung was replaced by an inflated silicone prosthesis for 4 mo. Then, the prosthesis was either kept inflated or deflated for another 8 mo (long-term cohort). This study design was complemented by a short-term cohort with right pneumonectomy, prosthesis inflation for 1 mo, and immediate analysis either with or without deflation. This setting allowed the temporal separation of expansion- and perfusion-related stimuli for compensatory lung growth. A comprehensive quantitative analysis of lung structure was undertaken. Noninvasive chest imaging by high-resolution computed tomography was performed before and after pneumonectomy in the inflation and deflation groups. This was followed by post mortem morphometric analysis by light and electron microscopic stereology.

The prosthesis prevented mediastinal shift and lateral expansion of the left lung but allowed some caudal elongation. Capillary blood volume increased and microvascular congestion was noted at low inflation. This was accompanied by an increase in alveolar septal volume but not surface area. Subsequent deflation led to an immediate mediastinal shift and lateral expansion of the remaining left lung which, in the long-term cohort, further increased lung and alveolar septal tissue volume and surface area in comparison to the inflation group. These quantitative data demonstrate that lung tissue expansion and microvascular perfusion contribute nearly equally to postpneumonectomy lung growth.

As it is always the case with good studies and interesting results, further questions arise. One relates to the relevance of local microenvironmental differences. How heterogeneous are the remodeling processes and the relative contributions of tissue expansion and microvascular perfusion, e.g., when comparing central and subpleural regions? There is experimental evidence for nonuniform distribution of cellular responses to pneumonectomy (8) that needs to be explored further. From studies of postnatal development in rats, it is known that the gas-exchange region grows fastest at the periphery near the pleura (11), and recent data indicate a comparable pattern for postpneumonectomy growth (9, 17). However, postpneumonectomy lung growth is not a simple recapitulation of postnatal lung development (7). But are there “focal points” in the alveolar septal tissue network from where growth starts, and, if so, what makes them different? A further question, although not of direct relevance for overall functional capacity, however, of relevance for our mechanistic understanding, is to what extent growth occurs by enlargement of remaining alveoli or by formation of new alveoli. The latter process has been demonstrated previously in mice (6). A recent case study suggests that this may even be possible in humans. Based on apparent-diffusion-coefficient helium MRI data and a simple geometric model of acinar microstructure (which, however, may or may not sufficiently mimic the real structure under different conditions), an increase in alveolar number of 64% was reported in a 48-yr-old woman 15 yr after right-sided pneumonectomy (2). When considering the formation of new...
alveoli in the adult lung, the serial arrangement of alveoli along alveolar ducts and respiratory bronchioles also has to be taken into account (15). However, alveoli alone are not sufficient; compensatory growth of conducting airways and blood vessels has to match parenchymal growth. To study this, the combination of three-dimensional imaging datasets from whole lungs with alveolar resolution and stereology-based quantitation will most likely be required. At the moment, this can only be achieved with small sample sizes such as isolated fixed mouse lungs (e.g., Ref. 14).

The particular strengths of the study by Ravikumar et al. are the systemic approach that takes the complexity of the whole organ (and animal) level into account (“physiological” in the best sense, compare Ref. 13), the use of a large animal long-term in vivo model, a smart experimental intervention, and state of the art analytical methodology appropriate for the task. Together with physiological data published previously by the same group (4), this study once more underscores the structure-function correspondence in compensatory lung growth. However, the relevance of these studies extends beyond postpneumonectomy lung growth; they point to concepts for stimulating lung growth and regeneration in general, concepts that should be considered in the era of (stem) cell-based therapies (see e.g., Ref. 10). Here again, the lung is special. In contrast to other organs where one major cell type dominates in terms of the main function of the organ (e.g., cardiomyocytes in the heart and hepatocytes in the liver), many different cell types share this task in the lung, which poses particular challenges for lung regeneration.

There is a lot to learn from studies like the one by Ravikumar et al. (12). One major lesson often not appreciated appropriately is that “it takes more than cells to make a good lung” (see Ref. 15). Actually, the three Rs of lung health, repair, remodeling, and regeneration (1), require the three Cs, complexity, correlativity, and connectivity (15). This knowledge needs to be integrated into comprehensive concepts of lung growth and regeneration and its stimulation (e.g., “in vivo mechanical signal-based” therapeutic approaches). It is most likely not a single growth factor, not a single transcription factor, and not a single cell type that will suffice to rebuild an organ with an architecture as complex as that of the lung.

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