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The evolutionary continuum from lung development to homeostasis and repair

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Torday JS, Rehan VK. The evolutionary continuum from lung development to homeostasis and repair. *Am J Physiol Lung Cell Mol Physiol* 292: L608–L611, 2007. First published November 3, 2006; doi:10.1152/ajplung.00379.2006.—A functional, developmental, and comparative biological approach is probably the most effective way for arranging gene regulatory networks (GRNs) in their biological contexts. Evolutionary developmental biology allows comparison of GRNs during development across phyla. For lung evolution, the parathyroid hormone-related protein (PTHrP) GRN exemplifies a continuum from ontogeny to phylogeny, homeostasis, and repair. PTHrP signaling between the lung endoderm and mesoderm stimulates lipofibroblast differentiation by downregulating the myofibroblast Wnt signaling pathway and upregulating the protein kinase A-dependent cAMP signaling pathway, inducing the lipofibroblast phenotype. Leptin secreted by the lipofibroblast, in turn, binds to its receptor on the alveolar type II cell, stimulating surfactant synthesis to ensure alveolar homeostasis. Failure of the PTHrP/PTHrP receptor signaling mechanism causes transdifferentiation of lipofibroblasts to myofibroblasts, which are the hallmark for lung fibrosis. We have shown that by targeting peroxisome proliferator-activated receptor γ , the downstream target for lipofibroblast PTHrP signaling, we can prevent lung fibrosis. We speculate that the recapitulation of the myofibroblast phenotype during transdifferentiation is consistent with lung injury as lung evolution in reverse. Repair recapitulates ontogeny because it is programmed to express the cross talk between epithelium and mesoderm through evolution. This model demonstrates how epithelial-mesenchymal cross talk, when seen as a recapitulation of ontogeny and phylogeny (in both a forward and reverse direction), predicts novel, effective diagnostic and therapeutic targets.

Evo-Devo; alveoli; parathyroid hormone-related protein; peroxisome proliferator-activated receptor γ ; Wnt

PUBLICATION OF THE HUMAN GENOME has ushered in the “Golden Age” of biomedical research. But we lack an effective algorithm for arranging gene regulatory networks in a biological context (35), one which, like the periodic table of the elements, would predict the functions of genes, unlike interactomes that merely annotate gene and protein associations. Contemporary biology mirrors what happened in physics at the turn of the 20th century. We now have the genetic “elements” of the periodic table, and the Cambrian Burst is analogous to the Big Bang, so we should now consider the “initial conditions” for lung evolution and the “continuing strategy” for surviving the Permian extinction rather than continuing to reason backwards from phenotypes to genes (42). But we don’t have the biological analog of quantum mechanics. Statistical analysis of complex genomic databases, i.e., Systems Biology, will not achieve that goal because evolution did not occur by chance. Therefore, a functional genomic approach would seem like the most effective way of determining the first principles of physiology, and to do so across phyla as a developmental comparative

approach would be in keeping with the Evo-Devo approach now being used in evolutionary studies (13). Dobzhansky said that evolution is all of biology.

There has been a great renaissance in the field of evolutionary biology with the reemergence of developmental biology. By comparing gene regulatory networks across phyla and during development, the sequence of events by which structures and their functions evolved can be approximated. In a recent publication, we have shown how the lung may have evolved from the swim bladder of fish based on the parathyroid hormone-related protein (PTHrP) signaling pathway, a pathway necessary for both lung homeostasis and development. PTHrP signaling predicts the magnitude and direction of lung maturation (47) and may also predict the phylogenetic changes in the vertebrate lung, decreasing alveolar diameter (25–27), accompanied by the thinning (30) and strengthening (24) of the alveolar wall.

PTHrP is expressed throughout vertebrate phylogeny, beginning with its expression in the fish swim bladder as an adaptation to gravity; microgravity downregulates the expression of PTHrP by alveolar type II cells and by the bones of rats exposed to 0 g (54), suggesting that PTHrP signaling has evolved in adaptation to 1 g. PTHrP signaling is upregulated by stretching alveolar type II cells and interstitial fibroblasts (48), whereas overdistension downregulates PTHrP and PTHrP receptor expression (52), further suggesting an evolutionary adaptation. Both surfactant homeostasis and alveolar capillary perfusion are under PTHrP control, indicating that alveolarization and ventilation/perfusion matching may have evolved under the influence of PTHrP signaling.

PTHrP is a highly evolutionarily conserved, stretch-regulated gene that is unusual among the paracrine growth factors that have been identified to mediate lung development because 1) the PTHrP knockout is stage specific and results in failed alveolarization, 2) unlike other such growth factors, PTHrP is expressed in the endoderm and binds to the mesoderm, and 3) only PTHrP has been shown to act pleiotropically to integrate surfactant synthesis and alveolar capillary perfusion, i.e., alveolar homeostasis. In contrast to this, others have focused on the importance of the epithelial-mesenchymal trophic unit (11) and on the importance of the fibroblasts of the “scaffold” that act as “sentinels” to regulate local inflammatory responses (5). However, PTHrP signaling from the epithelium to the mesoderm is highly significant. The earliest developmental signals emanate from the endoderm (14), and we have demonstrated the dependence of the fibroblast phenotype on epithelially derived PTHrP for development, homeostasis, and repair. All of these features of PTHrP biology justify its use as an archetype for our proposed model of lung evolution. We have schematized this integrated approach for lung developmental and comparative biology, homeostasis, and repair (Fig. 1).

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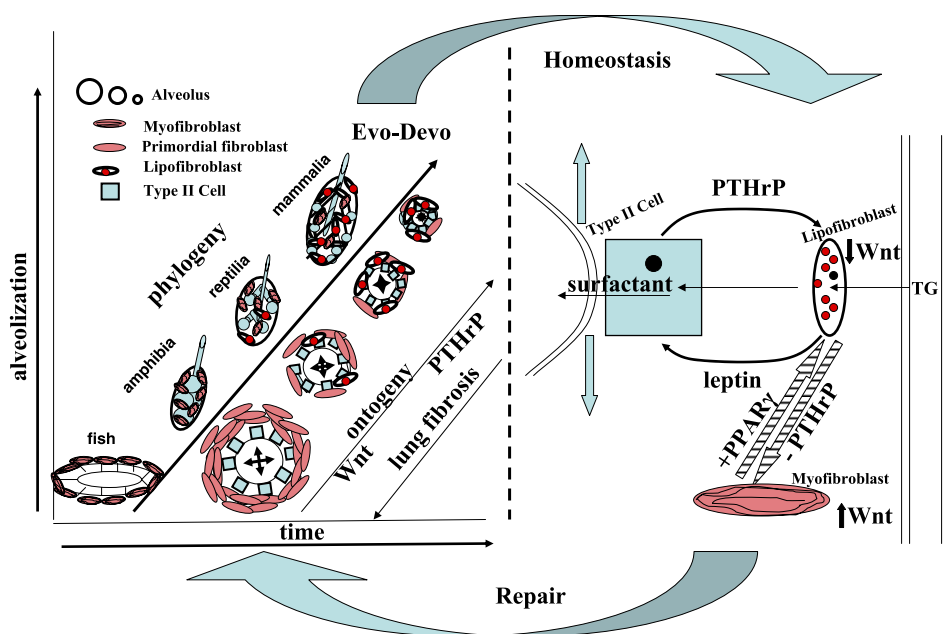


Fig. 1. Shown is a schematic of an integrated approach for lung developmental and comparative biology, homeostasis, and repair.

Ontogeny and Homeostasis

Stimulation of PTHrP and its receptor by alveolar wall distension coordinately increases surfactant production (48) and alveolar capillary blood flow, referred to as ventilation/perfusion (V/Q) matching. V/Q matching is the net result of the evolutionary integration of cell/molecular interactions by which the lung and pulmonary vasculature have functionally adapted to the progressive increase in metabolic demand for oxygen (25–27). The structural adaptation for gas exchange is threefold: 1) the decrease in alveolar diameter (7), 2) the thinning of the alveolar wall (30), and 3) the maximal increase in total surface area (6, 59). These structural adaptations could have resulted from the phylogenetic amplification of the PTHrP signaling pathway. PTHrP signaling through its receptor is coordinately stimulated by stretching the alveolar parenchyma (48). Binding of PTHrP to its receptor activates the cAMP-dependent protein kinase A signaling pathway (40). Stimulation of this signaling pathway results in the differentiation of the alveolar interstitial lipofibroblast, characterized by increased expression of adipocyte differentiation related protein (ADRP) and leptin. ADRP is necessary for the trafficking of substrate for surfactant production (43), and leptin stimulates the differentiation of the alveolar type II cell (50). PTHrP affects the cellular composition of the alveolar interstitium in at least three ways: 1) it inhibits fibroblast growth (28) and stimulates apoptosis (36), causing septal thinning, 2) stimulation of epithelial type II cell differentiation by leptin (50) can inhibit epithelial cell growth (36), and 3) leptin may upregulate type IV collagen synthesis (60), reinforcing the alveolar wall (24).

Ontogeny and Phylogeny

Primordial lung endoderm and mesoderm differentiate into over 40 different cell types. We know a great deal about growth factor signaling that determines these processes and the downstream signals that alter nuclear read-out. And because a great deal of effort has been put into understanding the conse-

quences of preterm birth, we also know how these mechanisms lead to homeostasis, or fail to do so, in which case the phenotype for chronic lung disease informs us of the mechanism of lung fibrosis.

Embryonic lung development is subdivided into branching morphogenesis and alveolarization, the latter being plastic (58). Deleting the PTHrP gene results in failed alveolarization (41), inferring relevance of PTHrP to lung evolution, since alveolarization is the mechanism for vertebrate lung evolution (23, 25). Because PTHrP and its receptor are highly conserved (9) and stretch regulated (48, 53), linking the endoderm and mesoderm to the vasculature (19), we are compelled to investigate its overall role in lung phylogeny and evolution.

The combined effects of 1–3 in the previous section would lead to natural selection for progressive, concomitant decreases in both alveolar diameter and alveolar wall thickness through ontogeny (33) and phylogeny (7, 23, 30), increasing the surface area-to-volume ratio of the lung. PTHrP turns off myofibroblast differentiation by inhibiting Gli (20), the first molecular step in the mesodermal Wntless/int (Wnt) pathway, and by inactivating β -catenin (15), followed by activation of LEF-1/TCP, C/EBP α , and peroxisome proliferator-activated receptor γ (PPAR γ). The downstream targets for PPAR γ are adipogenic regulatory genes such as ADRP and leptin. PTHrP induces the lipofibroblast phenotype, first described by Vaccaro and Brody (55). This cell type is expressed in the lungs of a wide variety of species (31), including both newborn and adult humans (37). They are found next to type II cells in the alveolar interstitium (12) and are characterized by neutral lipid inclusions wrapped in ADRP, which mediates the uptake and trafficking of lipid from the lipofibroblast to the type II cell for surfactant phospholipid synthesis (43, 46) and protects the alveolar acinus against oxidant injury (51). The concomitant inhibitory effect of PTHrP on both fibroblast and type II cell growth, in combination with PTHrP augmentation of surfactant production, would have the net effect of distending and “stenting” the thinning alveolar wall, synergizing with the upregulation of PTHrP and physiologically stabilizing

what otherwise would result in an unstable structure that would collapse (34).

Myofibroblast Transdifferentiation as Evolution in Reverse

Lung development prepares the fetus for birth and physiological homeostasis (21). Surfactant production in particular is crucial for effective gas exchange (2). Based on this functional linkage between lung development and homeostasis, we have generated data demonstrating that the underlying mechanisms of repair may recapitulate ontogeny. If lung fibroblasts are deprived of PTHrP, their structure changes (52). First, the PTHrP receptor is downregulated, as are its downstream targets ADRP and leptin: the decline in the lipofibroblast phenotype is mirrored by the gain of the myofibroblast phenotype, characteristic of fibrosis.

During the process of fetal lung development, the mesodermal fibroblasts are characterized by Wnt/ β -catenin signaling that determines the splanchnic mesodermal fibroblast (44). We have shown that during alveolarization, the formation of lung fluid upregulates the PTHrP signaling pathway in the endoderm, causing the downregulation of the Wnt/ β -catenin pathway (49), leading to the differentiation of the lipofibroblast. These cells dominate the alveolar acinus during fetal lung development but are highly apoptotic in the postnatal lung (3), giving rise to the alveolar septa (1). Central to this paracrine determination of the mesodermal cell types is the failure of the fibroblasts to terminally differentiate (17).

Phylogenetically, the swim bladder and frog lung interstitium are characterized by myofibroblasts; lipofibroblasts don't appear until reptiles and mammals (24–27). The recapitulation of myofibroblasts during lung injury is consistent with the similarities between lung ontogeny and phylogeny and with the molecular mechanisms of fibroblast transdifferentiation described above, and may, therefore, represent lung evolution in reverse.

A wide variety of factors can inhibit the normal paracrine induction of the lipofibroblast and promote myofibroblast proliferation and fibrosis, including prematurity, barotrauma, oxotrauma, nicotine, and infection. In all of these instances, injury of the epithelial type II cell can cause downregulation of PTHrP (29), causing the mesodermal fibroblasts to default to the myofibroblast phenotype (52). Myofibroblasts cannot promote the growth and differentiation of the alveolar type II cell for alveolarization (52) and produce angiotensin II, which further damages the type II cell population (57).

The PTHrP receptor is present on the alveolar epithelial fibroblasts (22). Stretching of the alveolus by fluid or air upregulates both PTHrP ligand (53) and PTHrP receptor activity (48), promoting surfactant production by the type II cell, and lipofibroblast neutral lipid uptake, protecting them against oxidant injury (51). PTHrP receptor binding stimulates cAMP-dependent protein kinase A expression, which determines the lipofibroblast phenotype. Treatment of the transdifferentiating myofibroblast either in vitro (52) or in vivo (39) with PPAR γ agonists blocks the transdifferentiation of the myofibroblast, preventing fibrotic injury (39).

The Roles of PPAR γ in Ontogeny and Repair

PTHrP induces lipofibroblast differentiation via the protein kinase A pathway, which blocks Wnt signaling by inhibiting both Gli and GSK 3 β , and upregulates the lipofibroblast

phenotype, PTHrP receptor, ADRP, leptin, triglyceride uptake, by stimulating PPAR γ expression (39, 52).

On the basis of the minimalist idea that development culminates in homeostasis, disruption of homeostasis may lead back to developmental motifs (10). This occurs in various lung diseases (4, 8, 16, 56), and by focusing on the continuum from development to homeostasis, we can select treatments that are more consistent with promoting cellular reintegration than stopping inflammation. For example, bronchopulmonary dysplasia can be induced by overdistingending an otherwise healthy but immature newborn baboon lung (8). Changing the homeostatic balance of the alveolus by knocking out surfactant protein genes B, C, and D leads to alveolar remodeling that is either grossly flawed (B) or less than optimal (C, D) physiologically. Interfering with cell-cell signaling blocks lung development (18), usually resulting in parenchymal simplification. Conversely, replacing missing developmental elements can reestablish lung development (44), homeostasis (45), and structure (30).

Repair recapitulates ontogeny because it is programmed to express the cross talk between epithelium and mesoderm through evolution (47). This model is based on three key principles: 1) the cross talk between epithelium and mesoderm is necessary for homeostasis, 2) damage to the epithelium impedes the cross talk, leading to loss of homeostasis and readaptation through myofibroblast proliferation, and 3) normal physiology will either be reestablished or cell/tissue remodeling/alterd lung function may occur, and/or fibrosis will persist, leading to chronic lung disease. The cell-molecular injury affecting epithelial-mesenchymal cross talk recapitulates ontogeny (in reverse), providing effective diagnostic and therapeutic targets.

GRANTS

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