Land of hope and dreams

Selection of life science and translational medicine literature

by Marco Confalonieri

The lung comprises an extensive surface of epithelia constantly exposed to environmental insults. Maintaining the integrity of the alveolar epithelia is critical for lung function and gaseous exchange. So, regeneration and repair are usual healing process in the healthy lungs, but when these processes fail then pulmonary diseases can remain chronically. Regenerative medicine is a new biomedical field of research that focuses on the regeneration of lost or damaged tissues/organs and the restoration of normal organ function. This could give new hopes to treat chronic lung diseases with current no, or only supportive, treatment options. A number of diseases, including cancer, advanced chronic obstructive pulmonary disease (COPD), and congenital defects, require replacement or augmentation of respiratory system tissues and/or organs. However, current lung repair or replacement strategies are limited. Stimulating the regeneration of the patient's own tissue is an attractive alternative toward which the field of regenerative medicine is moving. Nevertheless, to have regenerative as a therapeutic in to the daily practice we firstly shoud better know the physiologic lung repair mechanism and which cells are involved in lung regeneration as progenitor cells. Differently from other tissue and organs, such as skin and the heart, the lungs are much less studied from the point of view of regenerative medicine. Two very recent articles focused on new aspects of pulmonary regeneration that could open interesting perspective for the knowledge on how to restore lung function after an injury respectively starting from adult stem cells (1), or human pluripotent stem cells (2). The first article, by Prof. Hogan et al., seems to give a convincing demonstration that type2 alveolar epithelial cells (AEC2s) function as alveolar progenitors and long-term stem cells in the adult lungs. This evidence comes from lineage-tracing experiments both during homeostasis and in a model of alveolar repair that allowed the Duke University's research group to visualize *in situ* clonal expansion of individual AEC2s. Hogan et al. studied also genetic modified mouse strain in order to identify the cell type that repairs the lung in response to bleomycin injury. They found also that club cells (previously called Clara cells) give rise to AEC2s after bleomycin injury.

The second article deals with regenerative pulmonary medicine from another point of view. Sarah Huang et al. showed a new method for directed differentiation of human pluripotent stem cells (hPSCs) into lung and airway epithelial cells. According to this method the pluripotent cells expressed markers of at least six types of lung and airway epithelial lineages and were particularly enriched in distal ATII cells capable of surfactant protein-B (SP-B) uptake and release. Furthermore, data from the Huang' study also confirm that the pathways Wnt, BMP4 (bone morphogenic protein 4) and retinoic acid are essential for efficient induction of lung progenitors from hPSCs.

1) Type 2 alveolar cells are stem cells in adult lung
Barkauskas CE, Cronce MJ, Rackley CR, Bowie EJ, Keene DR, Stripp BR, Randell SH, Noble PW, Hogan Brigid LM.
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Abstract
Gas exchange in the lung occurs within alveoli, air-filled sacs composed of type 2 and type 1 epithelial cells (AEC2s and AEC1s), capillaries, and various resident mesenchymal cells. Here, we use a combination of *in vivo* clonal lineage analysis, different injury/repair systems, and *in vitro* culture of purified cell populations to obtain new information about the contribution of AEC2s to alveolar maintenance and repair. Genetic lineage-tracing experiments showed that surfactant protein C-positive (SFTPC-positive) AEC2s self renew and differentiate over about a year, consistent with the population containing long-term alveolar stem cells. Moreover, if many AEC2s were specifically ablated, high-resolution imaging of intact lungs showed that individual survivors undergo rapid clonal expansion and daughter cell dispersal. Individual lineage-labeled AEC2s placed into 3D culture gave rise to self-renewing "alveolospheres," which contained both AEC2s and cells expressing multiple AEC1 markers, including HOPX, a new marker for AEC1s. Growth and differentiation of the alveolospheres occurred most readily when cocultured with primary PDGFRα^+ lung stromal cells. This population included lipofibroblasts that normally reside close to AEC2s and may therefore contribute to a stem cell niche in the murine lung. Results suggest that a similar dynamic exists between AEC2s and mesenchymal cells in the human lung.

2) Efficient generation of lung and airway epithelial cells from human pluripotent stem cells
Hogan SX L, Islam MN, O'Neill J, Hu Z, Yang Y-G, Chen Y-W, Mumau M, Green MD, Vunjak-Novakovic G, Bhattacharya J, Snoeck H-W.
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Abstract
The ability to generate lung and airway epithelial cells from human pluripotent stem cells (hPSCs) would have applications in regenerative medicine, modeling of lung disease, drug screening and studies of human lung development. We have established, based on developmental paradigms, a highly efficient method for directed differentiation of hPSCs into lung and airway

epithelial cells. Long-term differentiation of hPSCs *in vivo* and *in vitro* yielded basal, goblet, Clara, ciliated, type I and type II alveolar epithelial cells. The type II alveolar epithelial cells were capable of surfactant protein-B uptake and stimulated surfactant release, providing evidence of specific function. Inhibiting or removing retinoic acid, Wnt and BMP-agonists to signaling pathways critical for early lung development in the mouse-recapitulated defects in corresponding genetic mouse knockouts. As this protocol generates most cell types of the respiratory system, it may be useful for deriving patient-specific therapeutic cells.