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The generation of lung progenitors from human embryonic stem cells

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Directed differentiation of human pluripotent stem cells into midgut and hindgut endoderm derivatives has been successfully established. The generation of anterior foregut lineages (trachea, lung and pharyngeal organs) proved more challenging, however. Previously, we showed that dual inhibition of transforming growth factor-β and bone morphogenic protein signaling in definitive endoderm resulted in a specification of anterior foregut endoderm. Here, we further pursued differentiation into cells of the respiratory system. By modifying the anteriorization protocol, we increased the efficiency of the generation airway-committed cells to 60%. We next devised conditions that specify proximal vs. distal fates, which yielded cultures where >90% of the cells expressed markers of lung and airway cells, including p63 airway basal cells, $CC10^+$ Clara cells, $mucin5AC^+$ $mucin2^+$ goblet cells, acetylated-α $tubulin^+$ ciliated cells, and $SP\text{-}B^+$ putative alveolar cells. Subsequent culture in Matrigel yielded spherical structures lined by $p63^+$ cells that are consistent with tracheospheres obtained from postnatal tracheal basal cells. After seeding onto slices of decellularized lung matrices, the cells lined up along the matrix. Further differentiation and spatial organization of the cells in this model is currently investigated. We conclude that we achieved, for the first time, highly efficient differentiation of hES cells into most lineages of respiratory cells with minimal contamination from other lineages. Importantly, this strategy does not require enrichment of cells committed to a respiratory fate based on reporter gene expression. This work is a major step towards regenerative medicine for lung disease using decellularized human lung matrices seeded with hiPS-derived respiratory cell populations.

Biography

Snoeck obtained his MD and PhD at the University of Antwerp, Belgium. He has held a faculty position at the Mount Sinai School of Medicine since 1998, and is currently faculty at the Columbia Center for Translational Immunology in New York.

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