VPH NoE Study Group 2009

Alveolar Epithelial Cell Injury and Repair in Fibrotic Lung Disease

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Health Condition

Pulmonary fibrosis (PF) is a devastating illness involving exaggerated lung scarring; with no efficacious therapy to modify its natural progressive clinical course. An estimated two-thirds of patients die within 2 to 4 years of diagnosis. Donated healthy lung transplants are used to replace fibrosed lungs, but need for transplants far outweighs available supply. Stem cell research currently offers tremendous promise for effective treatment of PF. However, clinical efficacy of stem cell–based strategies could be hampered by extracellular fibrotic factors driving disease processes at the target site. W*e hypothesise that PF-related abundance of profibrogenic factors such as Connective Tissue Growth Factor (CTGF) and Transforming Growth Factor (TGFβ1) drives progenitor alveolar epithelial cells (AEC) away from terminal differentiation conducive to local alveolar tissue regeneration; towards effector fibroblast/myofibroblast development.* This fundamental question needs addressing; it has implications for stem cell therapy in repair of fibrosed lungs. As there are no animal models that fully capture PF-disease processes, information obtained from well-designed mathematical models could be critical for development of strategies that would beneficially enhance stem cell engraftment in *in vivo* implants.

Pulmonary Fibrogenesis. Marked disruption in AEC integrity is the hallmark of PF; reflecting an *in vivo* example of abnormal wound repair, possibly due to inappropriate epithelial-mesenchymal signalling and aberrant lung stem cell differentiation. Presumed sequential microinjury/ies (as yet undefined) provoke marked disruption in AEC integrity with diverse hyperplastic / metaplastic phenotypes *in situ*. Adjacent, are distinct 'fibroblastic foci' of actively proliferating and secreting fibroblasts/ myofibroblasts, with aberrant collagen synthesis and exaggerated ECM deposition. Pulmonary stem cells, whether resident niches or recruited to the lung, have a capability for both epithelial and mesenchymal lineage potential. It remains unclear why progenitor cells fail to regenerate alveolar epithelial tissue in PF, and whether this is due to inappropriate terminal cell differentiation or apoptosis. In respect of the former, possibilities include: (i) aberrant epithelial-mesenchymal transdifferentiation to restore epithelial cell - fibroblast balance; (ii) fibroblast/ myofibroblast development from a reservoir of resident tissue-specific precursors; (iii) fibroblast phenotypes arising from progenitor cells. All are plausible mechanisms and may co-exist; their presence regulated by the particular pathogenic stage of the local milieu. A further compounding factor could be age-related; specifically PF is a condition that commonly afflicts those in middle age and upwards. Thus it is possible that age and above-described disease processes both affect the lung tissue environment, such that alveolar epithelium is unable to adequately repair and/or regenerate. Such events could have significant implications for stem cell-engraftment strategies in PF.

Study Group We are particularly interested in addressing the above gaps in knowledge using a mathematical model that captures relevant key cellular and pathogenic processes in PF to address the following issues :

1. Determine degrees of effect, if any, of profibrogenic factor abundance within the target milieu on AEC differentiation and consequently on local alveolar tissue regeneration; against a bias towards effector fibroblast/myofibroblast development.
2. Evaluate, if possible, superimposed effects of ageing on above endogenous AEC eventual phenotype.
3. Explore novel approaches to PF treatment aimed at manipulating local milieus so as to collectively reduce local profibrotic burden and reverse autologous AEC dysfunction or refresh target alveolar epithelium using pre-treated exogenous AEC progenitors

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