Rejuvenating old lungs: Ain't no tonic like a drop of retinoic

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One of the main challenges of experimental respiratory medicine today is the development of therapies that could support lung regeneration, leading to restoration of lung structure and function, in chronic lung diseases such as idiopathic pulmonary fibrosis (IPF). Current therapies such as pirfenidone and nintedanib slow down progression of the disease, but are insufficient to modify the underlying disease process to the extent that progression can be halted or that lung regeneration can be achieved.[1] Accordingly, new regenerative therapies will need to be developed guided by insights into the mechanistic underpinnings of defective alveolar regeneration. This challenge is on, not just for IPF, but also for other chronic diseases such as chronic obstructive pulmonary disease (COPD), and is complicated by the limited endogenous regenerative capacity of the ageing lung as the background against which these diseases often develop.

Retinoids are among the most widely studied classes of drugs with putative proregenerative capacity. Retinoic acid signals by binding to nuclear retinoic acid receptors which form heterodimeric complexes with retinoid X receptors to effect gene expression in a variety of cells. Both retinoic acid derivatives and retinoid X receptor ligands have been studied for their proregenerative effects, mostly in experimental models of COPD, and were found to enhance alveolar regeneration in the emphysematous lung.[2] Retinoic acid signalling also induces pulmonary microvascular angiogenesis, which may be deficient in COPD due to increased endothelial expression of CYP26A1 which degrades retinoic acid.[3] Furthermore, retinoic acid controls matrix deposition by lung fibroblasts, particularly elastin fibre formation[4] and was found to repress proliferation of fibroblasts of patients with IPF.[5]

Gokey *et al* describe new features of retinoic acid-induced mesenchymal–epithelial communication that are key in supporting neoalveolarisation. The authors describe strongly impaired neoalveolarisation and alveolar epithelial cell proliferation after partial pneumonectomy in aged mice.[6] Strikingly, their findings show that the ageing phenotype can be essentially reversed by pretreating mice with retinoic acid prior to the partial pneumonectomy. RNAseq data obtained from sorted fibroblasts and epithelial cells of these mice showed that ageing-induced gene expression signatures were enriched for apoptosis and inflammation pathways. Retinoic acid pretreatment normalised these effects in lung fibroblasts of aged mice, and in the epithelium, promoted gene expression reminiscent of a lung development signature. Crucially, the gene expression profiles predicted increased platelet-derived growth factor (PDGF)-A and reduced PDGF-BB signalling as upstream drivers of this effect, explaining both the distorted gene signature in the ageing lung after pneumonectomy and the normalisation of this effect following retinoic acid pretreatment. The involvement of PDGF-A was further demonstrated by using exogenous PDGF-A which restored the reduced alveolar organoid differentiation observed when using aged CD326+ epithelial cells in coculture with aged PDGF receptor A (PDGFRA)+ fibroblasts. These findings shed new light on the mechanisms of impaired neo-alveolarisation in the aged lung and show that deficient retinoic acid signalling in PDGFRA+ fibroblasts is key to this age-related change.

Probably one of the most striking implications from their work is the immensely dominant role of age-related changes in fibroblast function on epithelial regeneration. The authors suggest a shift from supportive matrix-secreting PDGFRA+ fibroblasts to PDGF-BB driven myofibroblasts associated with ageing to explain reduced neoalveolarisation in aged mice. Strikingly, AT1 differentiation of aged epithelial cells in vitro could be restored to the levels of young mice simply by using PDGFRA+ fibroblasts of young mice, or by using PDGFRA+ fibroblasts of retinoic acid pretreated aged mice. The same observations were made when using CD326+ epithelial cells from patients with lung fibrosis in coculture with mouse mesenchymal cells following similar pretreatments. This suggests that the lung regeneration defect in ageing and lung fibrosis is largely fibroblast intrinsic with considerable regenerative potential being maintained in the alveolar type II cell. Adding significance to these findings are their observations that non-fibrotic regions of IPF lung exhibit dramatic reductions in the numbers of matrix-producing PDGFRA+ fibroblasts when compared with aged matched donor lungs.

These findings raise the possibility that targeting the mesenchymal niche, for example, with retinoic acid, or by restoring PDGF-A signalling, may be effective in achieving lung repair in IPF. Thus, these new data touch on a larger unresolved research question, which is whether pharmacological activation of epithelial repair pathways or epithelial cell therapy is going to be effective in the microenvironment of a diseased lung which is not permissive for epithelial repair. Rather, the current data appear to advocate for a targeted approach to the fibroblast to unlock the repressive signals, which could allow for epithelial regeneration as a secondary effect, or could complement a potential epithelial-targeting regenerative therapy. This provocative hypothesis does need support from new in vivo studies that specifically target fibroblast function to interrogate subsequent effects on epithelial repair.

This study also raises interesting questions regarding the nature of fibroblast plasticity both in ageing and in diseased lung. To what extent do changes in fibroblast heterogeneity reflect stable changes in cell type (transdifferentiation) or the relative loss or expansion of distinct fibroblast populations? Or does this reflect shifts in cell state caused by altered local tissue microenvironment? Application of single-cell omics technologies will help to elucidate functionally relevant shifts in mesenchymal populations in the ageing lung, as has recently been shown for lung epithelium.[7] Moreover, while Gokey *et al* revealed loss of matrix-producing fibroblasts in non-fibrotic regions of IPF lung, it will be essential to similarly scrutinise regions of IPF lung where excessive and inappropriate matrix deposition predominates, which is the major driver of the pathology of restrictive lung disease.

Moving forward, targeting the correct cell populations precisely while minimising unwanted effects on other resident lung cell types will be an important prerequisite. For example, whereas retinoic acid might help to rejuvenate PDGFRA+ fibroblasts, retinoic acid represses growth of epithelial progenitors, while promoting their differentiation.[8] In

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view of these cell-specific roles of retinoic acid signalling, targeting retinoic acid to the PDGFRA+ fibroblast or exploring other means of specifically activating the PDGFRA+ fibroblast may open up new avenues for the regenerative pharmacological treatment of chronic lung diseases including IPF and COPD.

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