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Stem cells, aging and pulmonary vascular remodelling

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Epidemiological observations indicate idiopathic pulmonary fibrosis (IPF) as an aging-associated disease (1), whereby telomere dysfunction and other genetic defects, together with exposure to environmental noxae lead to lung epithelial stem cells exhaustion and accelerated parenchymal senescence (2). Interestingly, the studies of Auerbach and colleagues have shown that aging, with exposure to tobacco smoke as a co-factor, is associated with progressive abnormalities of pulmonary vessels (3). Diffuse thickening of the small and medium size pulmonary arteries with intimal thickening, smooth muscle cell (SMC) hypertrophy and/or hyperplasia and deposition of extracellular matrix is also a feature of IPF (4). Diffuse vascular remodelling and pulmonary hypertension have been found in 30 to 40% of IPF patients at the time of diagnosis, with higher rates in advanced disease and associated increased mortality (5-7).

A number of observations point to the concomitancy of bronchiolo-alveolar and vascular abnormalities in IPF, including anastomotic communications between the pulmonary and bronchial circulation, small vessel vasculitis and increased capillary and venule density in the least affected lung areas (8-11). These findings suggest that pathological vascular and fibrotic remodelling, similar to changes accompanying tumour progression (12), relate to the same pathogenetic mechanisms, with the majority of SMCs acquiring a de-differentiated or "synthetic" phenotype, with the expression of stem cell antigens (13). Observations in humans and data from animal models suggest that circulating stem/reparative cells play a significant role in lung parenchymal post-injury repair. Similarly, circulating inflammatory and bone marrow-derived stem cells contribute to vascular remodelling. In a rat model of hypoxia, stem cell depletion is followed by marked vascular reduction of adventitial thickening and an almost complete inhibition of extracellular matrix deposition (14, 15). C-kit$^+$ and VEGFR-1$^+$ progenitor cells accumulate in the vasa vasorum during pulmonary hypertension but are also present in the thickened intima of aged donor vessels (13, 16). VEGFR-1 expression mediates monocyte-macrophage recruitment and favours vessel lumen increase and stabilization and counteracts pathological angiogenesis stimulated from PlGF-mutated variants that do not bind VEGFR-1 (17). It seems extremely likely that the age-related changes in bioavailability and properties of both circulating stem and resident progenitor cells contribute to the acceleration of adverse vascular remodelling and the consequent parenchymal senescence occurring in IPF. The use of senescence-accelerated mice in the bleomycin-induced model of pulmonary

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fibrosis has allowed to demonstrate that the ability of bone marrow-derived cells to modulate lung injury repair is key to the development of usual interstitial pneumonia-type lung fibrosis (18). Silica-induced alveolar injury has been recently employed as alternative murine model of lung fibrosis. As this model has been used to test the efficacy of stem cell therapy for the amelioration of lung fibrosis, it is amenable to investigate molecular mechanisms of pulmonary vascular remodelling and new stem cell-based and pharmacological therapeutic strategies aimed to counteract accelerated lung senescence (19, 20).

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