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Mini Review

Role of Endothelial to Mesenchymal Transition in Pulmonary Fibrosis

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1. Review

Idiopathic pulmonary fibrosis (IPF) is a progressive, chronic interstitial lung disease characterized by increased extracellular matrix deposition. Repetitive alveolar epithelial injury triggers the early development of fibrosis [1]. A growing body of evidence suggests that IPF is an epithelial-driven disease in which an aberrantly activated lung epithelium produces mediators of fibroblast migration, proliferation, and differentiation into active myofibroblasts. These myofibroblasts secrete excessive amounts of extracellular matrix (ECM) that subsequently remodel the lung architecture [2].The imbalance between profibrotic and antifibrotic mediators that leads to chronic fibroblast proliferation is created by epithelial cell dysfunction and aberrant mesenchymal cross-talk. Under pathogenic conditions, both epithelial and endothelial cells undergo a transition to their mesenchymal phenotypes. These processes are known as epithelial-to-mesenchymal transition (EMT) and endothelial-to-mesenchymal transition (EndoMT), respectively [3]. EMT and EndoMT processes lead to the accumulation of collagen-producing myofibroblasts that contribute to the overall pathogenesis of fibrotic disease. In other words, these processes create a pro-fibrotic environment [4,5].

The accumulation of activated fibroblasts and myofibroblasts leads to extracellular matrix deposition, which causes progressive lung remodeling and architectural distortion. Pro-fibrotic mediators such as TGFβ1, platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and tumor necrosis factor alpha (TNF-α) are involved in these processes. These mediators may also activate endothelial cells by modulating EndoMT crosstalk. This may contribute to the pulmonary vascular remodeling that is a feature of IPF and pulmonary hypertension (PH) pathogenesis.

Arterial wall thickening in IPF patients and increased expression of the mesenchymal biomarkers S100A4 and vimentin suggest that active EndoMT contributes to vascular remodeling [6]. EndoMT is a process in which endothelial cells undergo a phenotypic transformation into myofibroblasts. This process is induced by TGFβ-dependent and TGFβ-independent mechanisms. Stimulation with transforming growth factor-β (TGFβ), bone morphogenic protein (BMP) [7,8], Notch ligands, inflammatory stress, and hypoxia induce the expression of transcription factors such as Twist1, Slug, and Snail, resulting in EndoMT [9]. Other signaling pathways such as Wnt, Sonic Hedgehog (SHh), and NOTCH also follow their own distinct pathways to undergo EndoMT [10,11].

During endothelial transition, endothelial markers such as VE-cadherin, platelet endothelial cell adhesion molecule (PECAM)-1, Tie1 and Tie2 are repressed and mesenchymal markers such as S100A4, vimentin, α-smooth muscle actin (α-SMA), fibronectin, collagen 1 and 3 are upregulated [12]. The resulting phenotypic transformation of endothelial cells into myofibroblasts is largely responsible for the fibrotic process observed in IPF. In mice, endothelial overexpression of HSPB1 was sufficient to inhibit pulmonary fibrosis by blocking EndoMT. Knockdown of HSPB1 in human pulmonary

endothelial cells accelerated the onset of the fibrotic phenotype after treatment with TGFβ or other cytokines associated with pulmonary fibrosis, suggesting that HSPB1 preserves endothelial cell identity [13].

Conflicts of Interest:
The authors declare no conflict of interest.

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