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Editorial

Endothelial-to-mesenchymal transition contributes to the myofibroblast population in proliferative diabetic retinopathy

Ischemia-induced pathological growth of new blood vessels and expansion of extracellular matrix (ECM) in association with the outgrowth of fibrovascular epiretinal membranes at the vitreoretinal interface is the pathological hallmark in proliferative diabetic retinopathy (PDR), and often leads to catastrophic loss of vision due to vitreous hemorrhage and/or traction retinal detachment. Although the etiology of fibrotic disorders is quite diverse, and their pathogenesis is variable and dependent on the causative agent or initiating event, a common feature is the presence of large numbers of myofibroblasts and abnormal accumulation of ECM in the affected tissue(s). Myofibroblasts, the key cellular mediators of fibrosis, are contractile cells, characterized by the expression of α-smooth muscle actin (α-SMA), and their presence is a marker of progressive fibrosis. They have the capacity to produce several ECM components including collagen resulting in fibrosis.[1] In the epiretinal membranes from patients with PDR, inflammatory and fibrotic changes are characterized by the presence of inflammatory cells and α-SMA-expressing myofibroblasts in the stromal compartment.[2,3]

The origin(s) of myofibroblasts responsible for the exaggerated and uncontrolled production of ECM proteins in PDR epiretinal membranes has not been completely elucidated. Increasing evidence suggests that endothelial cells may undergo endothelial-to-mesenchymal transition (EndoMT) or endothelial-to-myofibroblast transition under physiological, as well as pathological circumstances.[4] During EndoMT, endothelial cells lose their adhesion and apical-basal polarity to form highly invasive migratory, spindle-shaped elongated mesenchymal cells. More importantly, biochemical changes accompany these distinct changes in cell polarity and morphology, including the decreased expression of endothelial markers, such as CD31, vascular endothelial (VE)-cadherin, and endothelial nitric oxide synthase (eNOS) and the acquisition of mesenchymal markers, such as α-SMA, fibroblast-specific protein-1 (FSP-1, also known as S100A4), calponin, and smooth muscle protein 22 α or transgelin.[4] The cells undergoing transition may contain both endothelial and mesenchymal properties.

Recently, we explored the hypothesis that EndoMT contributes to the myofibroblast population present in the epiretinal membranes from patients with PDR. We performed CD31/FSP-1 and CD31/α-SMA double-labeling to gain insights into possible EndoMT. We demonstrated for the first time that endothelial cells in epiretinal fibrovascular membranes from patients with PDR contribute to the emergence of fibroblasts/myofibroblasts via the process of EndoMT. We reported that some endothelial cells expressing CD31 co-express the fibroblast marker FSP-1 and the myofibroblast marker α-SMA.[5] The presence of $CD31^{+}/FSP\text{-}1^{+}$ and $CD31^{+}/\alpha\text{-}SMA^{+}$ cells indicates an intermediate stage of EndoMT.[6] Our observations suggest that EndoMT plays a role in creating fibroblasts and myofibroblasts responsible for fibrosis and progression of PDR. These findings also suggest that EndoMT contributes to the loss of endothelial cells in PDR epiretinal membranes and the spontaneous regression of new blood vessels in patients with end-stage PDR. Finally, we demonstrated that phenotypic changes take place in human retinal microvascular endothelial cells (HRMEC) following exposure to transforming growth factor-β1 and the proinflammatory cytokines interleukin-1β and tumor necrosis factor-α. In the stimulated cell cultures, endothelial cells changed morphology, down-regulated endothelial cell markers and upregulated mesenchymal/myofibroblast markers. These findings corroborate the hypothesis that EndoMT can contribute to the fibrotic process occurring during PDR.

A greater understanding of the molecular mechanisms involved in the EndoMT process and the subsequent pharmacological blockade of these pathways may represent a novel therapeutic approach to retard the progression of fibrosis associated with PDR.

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