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COMMENTARY

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Antifibrotic Agents Targeting Non TGF-B Pathways: Inhibitors of PI3K/Akt and MMP Activators

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About the Study

Excessive deposition of Extra Cellular Matrix (ECM) components causes fibrosis, a pathological condition that affects normal tissue structure and function. Numerous chronic illnesses, such as renal fibrosis, pulmonary fibrosis, and liver cirrhosis, develop as a result of this process. Among the various signaling pathways implicated, Transforming Growth Factor-beta (TGF-β) signaling and extracellular matrix remodeling play important roles. TGF-β is a multifunctional cytokine that regulates cell growth, differentiation, and ECM production. It is produced by various cell types, including fibroblasts, epithelial cells, and immune cells. TGF-β is a major source of ECM accumulation and tissue scarring. TGF-β exerts its effects by binding to specific cell surface receptors, TGF-β type I and type II receptors (TGF-βRI and TGF-βRII). Upon ligand binding, TGF-βRII phosphorylates and activates TGF-βRI, which in turn phosphorylates receptor-Regulated Smads (R-Smads), specifically Smad2 and Smad3. These phosphorylated Smads form a complex with Smad4, which translocates to the nucleus to regulate the transcription of target genes involved in fibrosis, such as those encoding ECM proteins (e.g., collagen and fibronectin), Connective Tissue Growth Factor (CTGF), and Plasminogen Activator Inhibitor-1 (PAI-1).

Beyond the canonical Smad-dependent pathway, TGF-β also activates several non-Smad signaling pathways, including the Mitogen-Activated Protein Kinase (MAPK) pathways (ERK, JNK, and p38 MAPK), Phospho Inositide 3-Kinase (PI3K)/ protein kinase B (Akt) pathway, and Rho-like Guanosine Triphos Phatase (GTPase) signaling pathways. These non-Smad pathways can modulate cellular responses to TGF-β and contribute to fibrotic processes. For example, the PI3K/Akt pathway has been implicated in TGF-β-induced fibroblast proliferation and survival, while the Rho-like GTPase pathway regulates cytoskeletal dynamics and fibroblast motility, further contributing to ECM deposition and tissue remodeling.

Extracellular matrix remodeling is a dynamic process involving the synthesis, degradation, and modification of ECM components. ECM formation results from an imbalance between ECM production and the breakdown in fibrosis. The primary cellular mediators involved in ECM remodeling are myofibroblasts, a highly elastic and ECM-producing subtype of fibroblasts. The primary cause of the overproduction of collagen and other components of the ECM in fibrotic tissues is myofibroblasts, which are identified by the expression of alpha-Smooth Muscle Actin (α-SMA). Several factors contribute to the activation of fibroblasts to myofibroblasts, including mechanical stress, inflammatory cytokines, and growth factors like TGF-β. The persistence of myofibroblasts in fibrotic tissues is a key feature of chronic fibrosis and is associated with ongoing ECM production and tissue contraction. The involvement of Matrix Metallo Proteinases (MMPs) and Tissue Inhibitors of Metallo Proteinases (TIMPs), which are MMPs' inhibitors, is an important factor in extracellular matrix remodeling. A family of enzymes known as MMPs breaks down different components of the extracellular matrix, whereas TIMPs prevent MMP activity. In fibrotic conditions, there is often an imbalance between MMPs and TIMPs, preferring ECM accumulation. For instance, TGF-β upregulate the expression of TIMPs while down regulating MMP expression, advancing the use of ECM deposition. The fibrotic process is also influenced by interactions between different cell types, including fibroblasts, epithelial cells, endothelial cells, and immune cells. For instance, TGF-β and other cytokines generated

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by injured hepatocytes and invading immune cells activate Hepatic Stellate Cells (HSCs) in liver fibrosis. Activated HSCs transform into myofibroblasts-like cells, producing large amounts of ECM proteins and contributing to liver scarring. Similarly, in pulmonary fibrosis, alveolar epithelial cells undergo Epithelial-to-Mesenchymal Transition (EMT) in response to TGF-β, increasing the number of myofibroblasts in the body and making fibrosis worse.

Immune cells, such as macrophages and T cells also play important roles in the development and progression of fibrosis Macrophages exhibit a variety of phenotypes, such as the pro-fibrotic M2 and pro-inflammatory M1 phenotypes. M2 macrophages secrete TGF-β and other profibrotic factors, advancing fibroblast activation and ECM production. T cells, particularly regulatory T cells (Tregs), can modulate the fibrotic response by influencing the activity of other immune cells and fibroblasts through cytokine secretion and direct cell-cell interactions. In addition to cellular mechanisms, various molecular factors and signaling pathways are involved in fibrosis. For example, Connective Tissue Growth Factor (CTGF) is a downstream mediator of TGF-β signaling and plays an important role in ECM production and fibroblast proliferation. Other growth factors, such as Platelet-Derived Growth Factor (PDGF) and Fibroblast Growth Factor (FGF), also contribute to fibroblast activation and ECM synthesis.