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Commentary

Advances in the Molecular Mechanisms of Pancreatic Fibrosis and Therapeutic Implications

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DESCRIPTION

Pancreatic fibrosis is a hallmark of several chronic pancreatic disorders, most notably Chronic Pancreatitis (CP) and Pancreatic Ductal Adenocarcinoma (PDAC). Characterized by the excessive deposition of Extracellular Matrix (ECM) proteins, fibrosis leads to irreversible architectural distortion, exocrine and endocrine dysfunction, and significant morbidity. In recent years, our understanding of the molecular mechanisms driving pancreatic fibrosis has expanded significantly, offering new insights into potential therapeutic strategies that target the fibrotic process at the cellular and molecular levels.

At the core of pancreatic fibrosis is the activation of Pancreatic Stellate Cells (PSCs), which are normally quiescent cells residing in the periacinar space. Upon exposure to injurious stimuli such as alcohol, oxidative stress, cytokines, or ductal obstruction, PSCs transform into myofibroblast-like cells. These activated PSCs express Alpha-Smooth Muscle Actin (α-SMA) and secrete large amounts of ECM components, including Collagen Type I and Fibronectin, thereby contributing to tissue fibrosis. A complex network of signaling pathways regulates PSC activation, with Transforming Growth Factor-Beta (TGF-β), Platelet-Derived Growth Factor (PDGF), and Tumor Necrosis Factor-Alpha (TNF-α) playing pivotal roles.

One of the most critical mediators in this process is TGF-β, which promotes fibrogenesis by activating the SMAD signaling pathway. Upon binding to its receptor, TGF-β triggers the phosphorylation of SMAD2 and SMAD3, which then form a complex with SMAD4 and translocate to the nucleus to regulate the transcription of pro-fibrotic genes. Inhibitors of TGF-β signaling, including SMAD pathway blockers and neutralizing antibodies, are currently under investigation for their anti-fibrotic potential.

Recent studies have also highlighted the importance of oxidative stress and mitochondrial dysfunction in promoting PSC activation. Reactive Oxygen Species (ROS), generated during chronic inflammation, can directly stimulate PSCs and amplify pro-inflammatory signaling cascades such as the Nuclear Factor Kappa B (NF-κB) pathway. Therapeutic strategies aimed at reducing oxidative stress-such as antioxidants and mitochondrial protective agents-have shown promising results in preclinical models.

Another significant development is the role of microRNAs (miRNAs) in regulating fibrogenic signaling. Several miRNAs, including MiR-21, MiR-29, and MiR-199, have been implicated in PSC activation and ECM production. For instance, MiR-21 promotes fibrosis by targeting SMAD7, an inhibitory SMAD protein, thereby enhancing TGF-β signaling. On the other hand, MiR-29 has been shown to suppress collagen synthesis and may serve as a therapeutic candidate for fibrosis attenuation. Modulation of these miRNAs through mimics or inhibitors is an emerging therapeutic approach currently being explored in experimental studies.

The crosstalk between inflammatory cells and PSCs further complicates the fibrotic landscape. Macrophages, especially the M2 subtype, and T cells secrete cytokines such as Interleukin-6 (IL-6) and Interleukin-10 (IL-10), which enhance PSC activation and sustain the fibrogenic response. Blocking this inflammatory feedback loop using cytokine antagonists or immune-modulating agents holds promise as a strategy to limit fibrosis progression.

Importantly, fibrosis is now recognized not merely as a consequence of chronic pancreatic injury, but as an active contributor to disease progression, particularly in PDAC. The dense desmoplastic stroma formed by PSCs in PDAC acts as a physical and biochemical barrier, impairing drug delivery and promoting tumor growth and immune evasion. Consequently, anti-fibrotic therapies are being studied not only for their role in preventing CP progression but also as adjuvants in cancer therapy. Agents such as Hedgehog pathway inhibitors, Angiotensin II receptor blockers, and TGF-β antagonists are currently under various stages of clinical and preclinical evaluation.

CONCLUSION

The molecular mechanisms underpinning pancreatic fibrosis are becoming increasingly well-defined, unveiling a range of potential therapeutic targets. Central to this process is the

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activation of PSCs, modulated by a network of cytokines, oxidative stress, miRNAs, and immune cells. Targeting these molecular drivers holds the promise of not only halting fibrosis but also improving clinical outcomes in CP and enhancing the efficacy of cancer therapies in PDAC. Continued translational research and clinical trials are essential to bring these experimental approaches into mainstream clinical practice.