MOLECULAR MECHANISMS OF EPITHELIAL-MESENCHYMAL TRANSITION IN IDIOPATHIC PILMONARY FIBROSIS

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INTRODUCTION - IPF

Idiopathic pulmonary fibrosis (IPF) is a disease that has an aggressive course and is usually fatal an average of 3 to 6 years after the onset of symptoms. Although the mechanisms underlying pulmonary fibrosis are not clearly understood, current evidence suggests that it is characterized by an excessive accumulation of extracellular matrix (ECM) and remodeling of the lung architecture (fig. 1). The ultimate effector cell in pulmonary fibrosis is the myofibroblast characterized by the presence of alpha-smooth muscle actin (α-SMA).

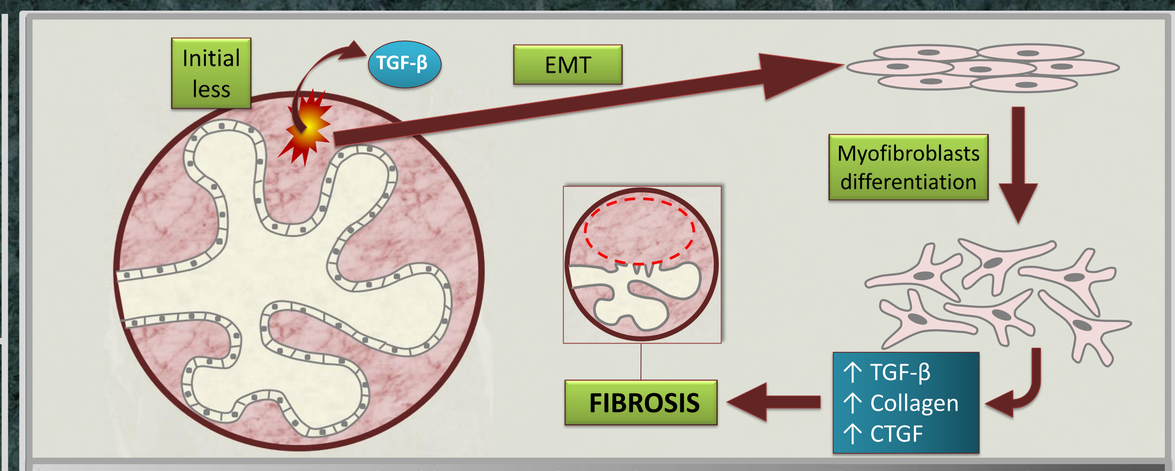

Figure 1. In response to injury, local latent TGF-β complexes are converted into active TGF-β and trigger the EMT resulting in the destruction of alveolar epithelium because increase myofibroblasts differentiation and EMC production.

EMT

The epithelial-mesenchymal transition (EMT) is one of the main processes involved in the development of fibrosis in IPF. In this process fully differentiated epithelial cells undergo transition to a mesenchymal phenotype giving rise to fibroblasts and myofibroblasts. The transforming growth factor (TGF-β) induces EMT in alveolar epithelial cells.

PRIMARY ELEMENTS INVOLVED IN THE EMT DURING PULMONARY FIBROSIS

Growth Factors and others

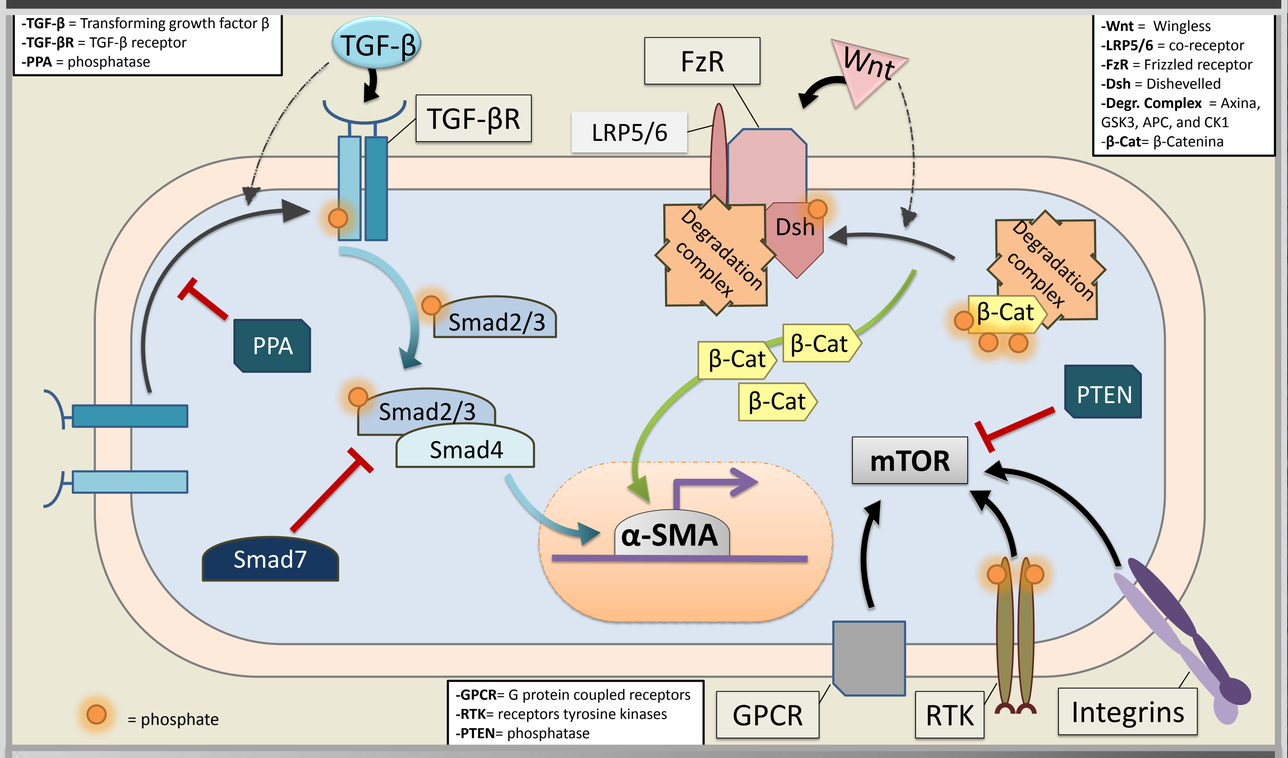

Figure 2. Receptors signaling and adhesion molecules involved in major fibrosis. The TGF-β and Wnt interact with their receptors and through Smad and β-Cat respectively increase the expression of genes such as α-SMA, collagen, CTGF and other, Smad7 and PPA inhibits this pathways. Moreover throught GPCR, TKR and integrins it activates mTOR which increase proliferation and decrease apoptosis, PTEN inhibit this pathways.

Epigenetic regulators and miRNAs

Most of these processes mainly affect suppressor factors or inducers of myofibroblasts. Among these are DNMT1, HDCA4 and miRNAs.

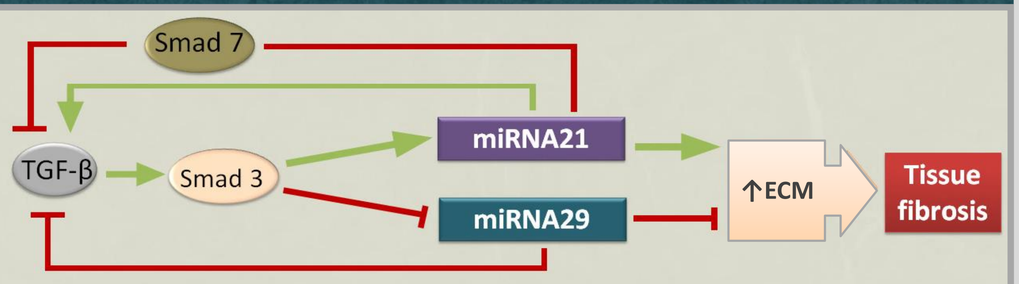

Figure 4. TGF-b activates Smad3 which directly triggers the transcription of miR-21, and then the evoked miR-21 affects the cellular availability of Smad7 via translational inhibition as a positive feedback to prolong the TGF-b/Smad3 signaling in order to facilitate the development of fibrosis in the affected tissue. Expression of miR-29 is negatively regulated by TGF-β/Smad3.

ECM-modulating proteins and physical factors

Lysyl oxidase (LOX) and fibronectin are matrix proteins that contributing to the development of fibrosis

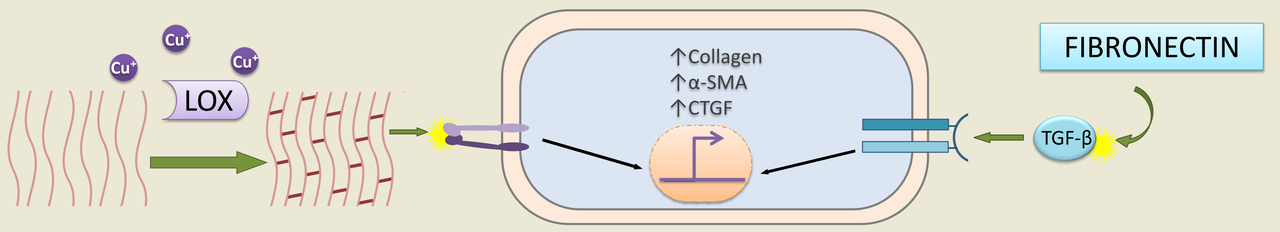

Figure 3. Fibronectin contain the extra domain A (EDA), an alternatively spliced form of the extracellular matrix protein fibronectin. In IPF, EDA-FN is deposited before collagens in regions of active fibrosis , which correlates with increased expression of TGF-β. Lysil oxidase (LOX) catalyzes formation of aldehydes from lysine residues in collagen and elastin precursors that results in cross-linking collagen and elastin.

TREATMENTS

At the moment, the available treatments can reduce the symptoms but not the progression of the disease. Some research treatments are follows

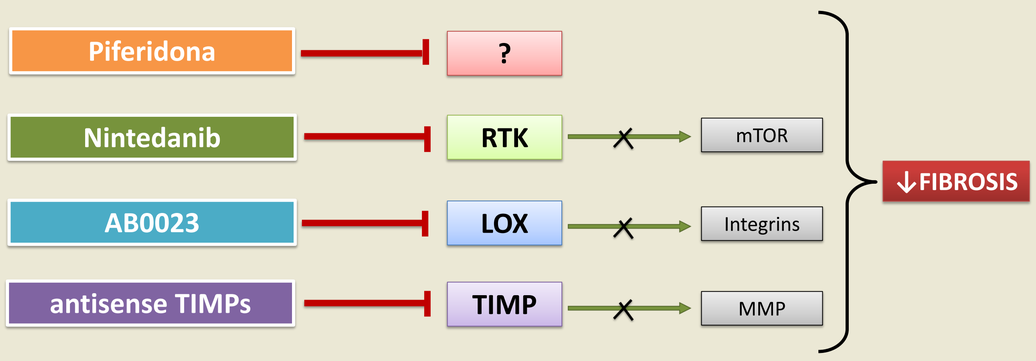

Figure 5. Nintedanib is an oral agent that simultaneously inhibits vascular endothelial growth factor receptors (VEGFR), platelet-derived growth factor receptors (PDGFR) and fibroblast growth factor receptors (FGFR). Piferidone reduced disease progression, but its target is unknown. LOXL2-specific monoclonal antibody AB0023 was efficacious in reducing disease in different models of fibrosis. TIMPs control MMP activities and, therefore, minimize matrix degradation. Antisense TIMP-1 cDNA was able to decrease endogenic TIMP-1 expression, increase MMPs activation and then restrain the proliferation of fibroblast cells and reduce the ECM components.

CONCLUSIONS

- It is possible that IPF develops as a consequence of abnormalities occurring in multiple biological pathways that affect inflammation and wound repair.
- Epigenetic studies IPF are relatively new and are providing data of great interest.
- Investigate markers improve early detection could benefit the efficiency of treatments.

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