Pathophysiology of IPF overview

Evidence suggests that interstitial pulmonary fibrosis (IPF) results from abnormal alveolar repair responses to repetitive micro-injury leading to uncontrolled fibrosis.\(^1\)

The current model for the pathogenesis of IPF consists of three core stages: initial and repeat epithelial injury, abnormal repair response and progression of tissue damage and fibrotic lung changes.\(^2\)\(^-\)\(^4\)

**Stage 1: Injury**

After injury, the normal alveolar epithelium initiates a repair response to restore barrier integrity.

1. Injury of alveolar epithelial cells
2. Initiation of normal repair mechanisms
3. Release of profibrotic mediators into the alveolar lumen
4. Extracellular matrix production, fibroblast recruitment/proliferation and wound clot formation

**Stage 2: Abnormal repair response**

1. Abnormal re-epithelialisation
2. Influx and proliferation of fibroblasts and emergence of myofibroblasts
3. Imbalance of anti- and profibrotic mediators promotes the progressive formation of fibrotic tissue
4. Characteristic thickening of alveolar walls, the loss of normal lung architecture and formation of honeycomb cysts

**Stage 3: Progression**

Deposition of extracellular matrix leads to the progression of tissue damage and fibrotic lung changes.

1. Myofibroblasts agglomerate into areas known as fibroblastic foci
2. Connective tissue matrix begins to accumulate and fibrosis becomes established
3. The basement epithelial membrane is irreversibly lost, and gas exchange between the alveoli and surrounding pulmonary capillaries is permanently disrupted
Mediators driving initiation and progression of fibrosis in IPF

TGF-β receptors and TGF-β signalling are both present in fibroblastic foci in IPF; it has been linked to multiple pathological activities in IPF.

Conversely, while inflammation was previously believed to have a role in IPF pathogenesis, research has found little evidence of this and points to the current models of repetitive micro-injury and incomplete healing leading to fibrosis.
References