AIMS

- Understanding the pathomechanism of IPF
- Apprehend the change of paradgigm if IPF pathogenesis from predominant inflammation to impaired wound repair in IPF
- Understanding the pathomechanism of granulomatous disease potentially leading to fibrosis

SUMMARY

Idiopathic pulmonary fibrosis (IPF) was considered longtime a defect in immune response. Over years patients were treated with triple immunosuppression. A model of impaired wound repair has replaced this paradigm. More importantly, the PANTHER study comparing azathioprine, prednisone and N-acetylcysteine against placebo revealed that mortality under this treatment was increased. Understanding the exact pathomechanism of disease is crucial in order to develop treatment strategies. Tremendous progress has been made in understanding the mechanisms of pathogenesis of IPF. On the microscopic level a distinct histopathological pattern is observed in IPF. The typical heterogeneous distribution of fibrotic areas with fibroblast accumulation (so-called fibroblasts foci) is called usual interstitial pneumonia (UIP), which is not exclusively found in IPF, but also other fibrotic lung diseases (e.g. rheumatoid arthritis).

On the cellular level, initial injury by undetermined agents (so-called hit e.g. by gastric reflux, environmental substances, smoking, infection) induces epithelial cell apoptosis. Apoptosis of epithelial cells leads to interrupted alveolar structures and prompt vascular leak. Fibrin is released and accumulates in the alveolar space. The coagulation cascades are activated. Released cytokines and activated coagulation induce further wound repair mechanisms, which are exaggerated in lungs of IPF patients possibly due to genetic differences and/or multiple hits. Fibroblasts are main player of wound repair, covering the epithelial defect. Fibroblasts transform into myofibroblasts and group into so-called fibroblast foci, the hallmark of UIP pattern. Myofibroblasts produce extracellular matrix, which further stimulates fibrosis progression. They are also resistant towards apoptosis in contrast to epithelial cells undergoing apoptosis. This phenomena has been called apoptosis paradox. These and
other mechanisms lead to accumulation of fibrotic tissue instead of alveolar structure and can ultimately end in respiratory failure due to impaired gas exchange possibilities.

Understanding the underlying mechanisms has lead to the development of different anti-fibrotic medications, which are now being recognized as effective treatment for this devastating disease.

Other pulmonary lung diseases can lead to pulmonary fibrosis. Granulomatous disease like sarcoidosis may ultimately present with advanced lung fibrosis. Histopathological hallmark of sarcoidosis are non-caseating granuloma, which can infiltrate multiple organs. On the mechanistic level, impaired T cell response is involved in sarcoidosis development. Continuous production of cytokines is responsible for an exaggerated activation of the immune system. Treatment of sarcoidosis differs from fibrotic disease like IPF, as suppression of the immune system remains the main approach for sarcoidosis patients. If end stage fibrosis in sarcoidosis responds to antifibrotic treatments needs to be determined.

REFERENCES