APOPTOTIC AND IMMUNOLOGICAL MARKERS IN IDIOPATHIC PULMONARY FIBROSIS

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May 8th, 2012

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Idiopathic pulmonary fibrosis (IPF) is a rare and devastating lung disease of unknown aetiology. It is thought to be caused by repetitive damage to the epithelium and abnormal repair, resulting in fibrosis. Fibrosis is defined by an overgrowth of fibroblasts and extracellular matrix deposition which results in fatal respiratory dysfunction. IPF mainly occurs in elderly white males and has an average survival time of less than 4 years.

Currently, there is no simple test available to diagnose IPF. Clinical findings such as lung function tests and high resolution computed tomography (HRCT) are often considered sufficient, especially in typical cases of IPF. In other cases, lung biopsy will be needed. In many cases a bronchoalveolar lavage (BAL) will be performed in order to exclude other diagnoses.

The aim of this thesis was to find disease specific markers. In the search for molecular markers for diagnosis and prognosis, we focused especially on the immunological response to injury and on apoptosis, because of their emerging role in the pathogenesis of IPF. We hypothesized that the results might also contribute to new insights into the biological mechanisms involved in IPF.

Genetic variations in TP53 and CDKN1A, the genes encoding p53 and p21, were associated with susceptibility to IPF and progression of the disease, in our cohort of 77 IPF patients. P53 and p21 are vital cell cycle regulators that influence apoptosis,

cellular senescence and proliferation. Variations in these proteins could affect the damage and repair processes in the alveolar epithelium.

Damaged epithelium is thought to send out signals that activated the immune system. Many inflammatory cytokines are elevated in IPF patients but their exact role in the disease is unknown. We measured levels of MRP14 and YKL-40 in serum and BAL fluid of IPF patients and in closely related interstitial lung diseases. These proteins are thought to be produced by macrophages, neutrophils and epithelial cells and may represent chronic inflammation and fibrosis. Both MRP14 and YKL-40 were elevated in IPF patients and were highest in diseases that are hallmarked by fibrosis. YKL-40 was significantly associated with the prognosis in IPF patients.

We also performed a meta-analysis of genetic variations in IL1RN that were determined in 5 IPF cohorts with a total of 302 IPF patients and 879 healthy controls. The VNTR*2 haploblock was significantly associated with IPF susceptibility and resulted in lower levels of the cytokine IL-1Ra. IL-1Ra is an inhibitor of the pro-inflammatory and pro-fibrotic cytokine IL-1. Our results suggest that IL-1Ra plays a role in pathogenesis of IPF.

The findings in this thesis confirm that apoptosis and immune responses play a role in IPF susceptibility and progression. Our results suggest there may be a role for alternatively activated macrophages in the aetiology of IPF. These macrophages, also referred to as M2 macrophages, play a role in wound repair and fibrosis. They are thought to be elevated in IPF patients and may be associated with a poor prognosis. Further research is needed to identify the exact nature of the M2 macrophages and their role in IPF.