PROGNOSTIC MARKERS FOR IDIOPATHIC PULMONARY FIBROSIS

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September 17th, 2013

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In this thesis the search for a prognostic biomarker in idiopathic pulmonary fibrosis (IPF) is described. IPF is a rapidly progressive interstitial lung disease with unknown aetiology. Treatment options remain disappointing and median survival varies between a few months to several years. Lung transplantation seems to be the only option for those who meet the criteria, but the waiting list mortality is high and the clinical course is highly variable. In order to predict prognosis in IPF patients, a biomarker which predicts the rate of progression would be helpful.

This thesis starts with an overview of molecular and non-molecular markers that can predict prognosis in IPF. The change in lung function parameters such as vital capacity (VC) or diffusion capacity (DLco) in 6 or 12 months is a robust determinant of prognosis, but since this requires a time interval, it can not be used as a predictor at first presentation. Promising in this context are the serological biomarkers, because they are non-invasive and may have additional value next to commonly used clinical parameters.

In each of the following chapters different potential serological biomarkers are described. First, the prognostic value of surfactant protein- D (SP-D) has been investigated. SP-D is synthesized by type II pneumocytes and occurs in serum mainly due to leakage through the lung parenchyma. Serum SP-D levels were significantly increased in IPF patients compared to controls and high serum SP-D levels were correlated with worse prognosis. In the next chapter, the role of endothelin-1 (ET-1) was evaluated. Increased serum levels of ET-1 were found, but remarkably decreased levels of ET-1 in BALf compared to healthy controls. This

unexpected finding led to the speculation that increased leakage through the damaged interstitium overrides the secretion of ET-1 by epithelial cells and macrophages. No clear explanation for this finding was found, so this finding requires further investigation.

Moreover, the susceptibility and disease modifying effects of genetic variations in the interleukin-1 (IL1)RN and IL1β gene in IPF, and the changed balance between IL-1Ra and IL-1β were described. As IL-1Ra inhibits the physiological activities of IL-1β by occupying the IL-1 receptor, we calculated the IL-1Ra/IL-1β ratio. A 3.5-fold decrease was observed in both serum and BALf of IPF patients compared to healthy controls, resulting in a relative shortage of IL-1Ra and thus a pro-inflammatory environment in IPF patients. In the IL1RN gene, one genetic variation was associated with both the susceptibility to IPF and reduced IL-1Ra/IL-1β ratios in BALf.

The last chapter evaluates the influence of SNPs in the CCL18 gene on CCL18 expression and survival. IPF patients demonstrated increased serum CCL18 levels. Both in IPF and healthy controls, genetic variation in the CCL18 gene significantly influenced CCL18 levels. Furthermore, high serum CCL18 levels correlated with decreased survival and patients carrying the CT genotype showed a significantly worse survival than patients with the TT genotype.

The thesis concludes by the recommendation that the above described biomarkers could help in estimating prognosis and clinical decision making in IPF patients.