Editorial

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Single Gene Expression as a Prognostic Marker in Idiopathic Interstitial Pneumonia?

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Idiopathic interstitial pneumonias (IIP) are a group of chronic interstitial lung diseases of unknown etiology characterized by progressive dyspnea, reduced lung volumes, and impaired gas exchange. Idiopathic pulmonary fibrosis (IPF) is the most common form of IIP and is histologically characterized by the pattern of usual interstitial pneumonia (UIP). Survival is very poor in UIP/IPF, with a mean rate of 2–3 years [1]. So far, no specific treatment has been available. Nonspecific interstitial pneumonia (NSIP), another frequent form of IIP, has a characteristic HRCT pattern and can be histologically characterized by a cellular or fibrotic form. Anti-inflammatory treatment is usually more beneficial in patients with NSIP compared to UIP/IPF, resulting in a better prognosis. Recent evidence suggests that both patterns, UIP and NSIP, can sometimes be documented in a subgroup of patients with IIP, however indicating a worse prognosis in the presence of UIP [2].

For optimal management of both patients with IPF or NSIP, reliable prognostic markers are important for clinicians in order to decide about optimal management. In patients with IPF, clinical (dyspnea index), physiological (changes of FVC, TLC, pO_2, desaturation during 6-min walk test), radiological (extent of reticulation and honey combing on HRCT) and histological markers (numbers of fibroblast foci) were suggested as possible markers of prognostic value, although their benefit and reliability are still under debate.

Although recent research in animal models of pulmonary fibrosis and patients with fibrotic lung diseases gave more insight into the cellular and molecular mechanisms of the development of pulmonary fibrosis, no biological markers of prognostic value are established in patients with UIP/IPF or NSIP. Growth factors and cytokines such as profibrotic TGF-β, CTGF, PDGF, IL-13 are, however, well recognized as crucial mediators in the development of fibrotic lung disease [3]. In this respect, it makes sense to speculate that profibrotic mediators may be potential candidates for biomarkers in IIP. In this issue of *Respiration*, Golec et al. [4] hypothesized that the levels of gene transcripts of selected growth factors and cytokines quantified by RT-PCR may correlate with physiological parameters and therefore serve as prognostic markers in patients with UIP and NSIP. They analyzed 179 sets of RT-PCR measurements in a total of 49 patients diagnosed with UIP, NSIP or both based on histology. As expected, transcripts of profibrotic TGF-β, CTGF and IL-13 were significantly upregulated in patients with fibrotic lung disease compared to controls. Moreover, transcription levels of TGF-β and IL-13 correlated with the decrease of two lung function parameters, vital capacity and total lung capacity. The authors conclude that transcription analysis of specific profibrotic genes (TGF-β, IL-13, CTGF) may be of prognostic value in patients with fibrotic lung disease.

Several studies were recently published that addressed the question whether gene expression patterns may be helpful as a diagnostic and/or prognostic marker of fibrotic lung diseases. For instance, Selman et al. [5] described distinct gene expression profiles between patients with IPF and hypersensitivity pneumonitis using microarray technology, studying over 40,000 gene clusters. Sel-

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man et al. also published data on a different gene expression pattern in patients with IPF that showed a short duration of symptoms with rapid progression compared to IPF patients with a slow clinical progression [6]. These data indicate that gene expression patterns indeed may give information about the clinical behavior and prognosis of patients with pulmonary fibrosis. Although the global systems approach may offer advantages over a 'reductionistic' approach focusing on a few selected gene transcripts in the diseased organ, the approach chosen by Golec et al. [4] studying selected single gene transcripts is interesting and will possibly even be more realistic in clinical practice.

The positive correlation of specific gene transcript levels of TGF-β and IL-13 to functional data is very promising, but needs further study. Since the data presented by Golec et al. are based on a retrospective study, a prospective evaluation of the values of gene transcription levels related to the clinical follow-up will be necessary in the future. Furthermore, 87% of the samples obtained from patients with UIP or NSIP were transbronchial biopsies. Due to the small sample size of this study, sampling errors cannot be ruled out and the amount of samples and the location of the biopsies in the injured and fibrotic lung need to be defined. Since the histological pattern in UIP is very heterogenous, the levels of gene transcripts may depend on the area where the biopsy was taken from. In this respect, further studies will be needed to set up an 'intrapulmonal local transcription profiling' in order to define the most appropriate location of sampling within the fibrotic lung. In this respect, differences were found in the levels of TGF-β transcripts in specimens obtained by video-assisted thoracoscopic surgery compared to specimens obtained by transbronchial biopsy. Further studies will also need to address the question to what extent the level of gene transcript corresponds to the level of protein expression in the lung since the biologically active protein will be more relevant in the development of the disease. Finally, clinical parameters need to be defined in more detail that will be correlated to gene or protein expression levels in the fibrotic lung. Clinical phenotyping of patients with IIP needs to be improved in order to achieve adequate correlation data with gene transcript levels. The change in (forced) vital capacity over 3–6 months is a well-accepted parameter for clinical follow-up of patients with fibrotic lung disease and an indicator of prognosis in UIP/IPF [7]. The positive correlation of gene transcript levels with vital capacity in this study is therefore promising. However, further clinically important parameters will need to be studied in the future, including time to disease worsening and survival. Finally, and probably most importantly, the patient numbers will need to be increased in future studies. Since IIP are relatively rare diseases, international collaborative projects within research networks as started in the US and recently in Europe will be crucial to further characterize the value of the assessment of specific gene transcripts in these complex lung diseases.

The determination of levels of transcripts of selected growth factors and cytokines may represent a novel approach to diagnose and manage patients with several lung diseases, including patients with IIP. Improvements in the identification and characterization of possible prognostic parameters will lead to an improvement in patient management. This study further supports the concept of gene transcription levels as prognostic markers in IIP. However, much more work needs to be done until the determination of specific gene transcript levels will find its way into clinical practice.

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