ABSTRACT

REGULATION OF ANGIOTENSINOGEN GENE EXPRESSION BY TRANSFORMING GROWTH FACTOR-BETA1 IN LUNG FIBROBLASTS

By

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Idiopathic Pulmonary Fibrosis (IPF) is a progressive and usually fatal lung disease leading to decreased lung volume with distorted architecture and thick walled airspaces. Local activation of renin angiotensin system (RAS) plays a key role in the fibrogenic response of the lung tissue. Several studies showed that the octapeptide angiotensin II (Ang II), the active peptide of RAS, plays an important role in alveolar epithelial cell apoptosis and hence contributes to fibrosis of the lung. Angiotensinogen (AGT) is the only known precursor to Ang II, while angiotensin converting enzyme-2 (ACE-2) acts on Ang II peptide to produce the opposing action heptapeptide angiotensin 1-7 (Ang 1-7).

In this study, expression of these two genes (AGT and ACE-2) is investigated in IPF with focus on AGT gene expression in human lung fibroblasts. Increased AGT gene expression is detected in the IPF lung tissue and found to co-localize to apoptotic alveolar epithelial cells and to myofibroblast foci, these are histologic features of IPF with myofibroblast foci an indicator of worsening of fibrosis. Myofibroblasts originate from fibroblasts under the influence of the profibrotic cytokine transforming growth factor-beta1 (TGF-β1). This transition from fibroblasts to myofibroblasts is found to be accompanied by an increase in AGT gene expression. In the study presented here, molecular mechanisms by which TGF-β1 induces AGT gene expression are investigated.

The data show that TGF-β1 stimulates AGT gene expression in human lung fibroblasts by increasing the binding of two transcription factors, JunD and hypoxia inducible factor (HIF)-1α, to an AGT promoter domain close to the transcription start site, suggesting a molecular mechanism linking hypoxia signaling and fibrogenic stimuli in the lungs. This TGF-β1 responsive domain in AGT promoter contains three single nucleotide polymorphisms (SNPs). These SNPs are shown here to alter transcription factor binding to AGT promoter in response to TGF-β1 in human lung fibroblasts. This suggests that AGT expression in response to TGF-β1 may be dependent on the individual's haplotype. On the other hand, gene expression of ACE-2, the Ang II degrading enzyme, is found to be down-regulated in IPF. Mechanisms for this down-regulation involve the ACE-2 product Ang 1-7 and the angiotensin receptor AT_1. This suggests impairment of balance between Ang II production and degradation in conditions promoting pulmonary fibrosis.

In conclusion, this study implies that the haplotype of the individual contributes to the imbalance between Ang II production and degradation by affecting AGT gene expression in response to the profibrotic factor TGF-β1.