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Title: Aberrant expression and activity of histone deacetylases in idiopathic pulmonary fibrosis (IPF)

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Body: Introduction: Histone deacetylases (HDACs) are enzymes that remove acetyl groups from lysine residues on histones, resulting in epigenetic repression of gene transcription. HDACs can also catalyze deacetylation of many non-histone proteins, such as the tumor suppressor p53. HDACs thus pivotally control gene expression and cellular signaling. Here, we describe for the first time an expression analysis of Class-I, Class-II and Class-III-HDACs in lungs from patients with sporadic IPF (n=18) and organ donors (n=10). Methods: Peripheral lung tissue was analyzed by RT-PCR, immunoblotting and immunohistochemistry (IHC). Results: Compared to donors, protein-levels of Class-I-HDACs (HDAC1,2,3 and 8) and of the Class-III-HDAC Sirtuin1 were significantly elevated in IPF lungs. By means of IHC, strong induction and nuclear expression of HDACs 1-3 and Sirtuin1 was observed in myofibroblasts of fibroblast foci (FF) and in abnormal bronchiolar basal cells at sites of aberrant re-epithelialization in IPF lungs, but not in donors. Similarly, induced cytoplasmic expression of Class-II-HDACs: 4,5,7,9,10 could be encountered in FF and basal cells in IPF. Importantly, type-II cells of IPF-lungs did not reveal notable expression of Class-I/-II/-III-HDACs, possibly due to ER stress in this cell type. Conclusions: We suggest that fibroblast-myofibroblast differentiation and the apoptosis-resistant phenotype of myofibroblasts are mediated due to enhanced expression and action of Class-I/-II-HDACs, and Sirtuin1. Aberrant overexpression of HDACs in basal cells of IPF lungs may cause the exaggerated, proliferative character of this cell type in IPF and thus govern the process of bronchiolization in this disease.