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Title: Regulation and localization of the telomerase enzyme-complex and the shelterin-telosom-complex in sporadic idiopathic pulmonary fibrosis (IPF)

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Body: Introduction: IPF is an adult-onset, lethal lung disease of unknown etiology. Reports linking telomerase mutations to familial IPF suggest that reduced telomerase activity and telomere shortening are key factors in disease pathogenesis. Accelerated telomere shortening is also observed in sporadic IPF in the absence of gene mutations. We therefore aimed to analyze the expression of the Telomerase-[TERT,TERC,DKC1,NOP10,NHP2] and the Shelterin-complex [TERF1/-2,POT1,TIN2,PTOP,RAP1] in lungs from sporadic IPF-patients (n=30) and organ donors (n=12). Methods: Lung tissue was analyzed by RT-PCR, immunoblotting and immunohistochemistry (IHC). Results: Gene expression analysis for TERT and the telomerase RNA-component TERC by RT-PCR indicated a significant downregulation in IPF-lungs. Surprisingly, we could not detect any protein expression of Telomerase- and Shelterin-components in type-II cells of IPF- and donor lungs using conventional IHC. Instead, we observed a strong TERT expression in a subset of Clara-cells (CC10-positive) in IPF- and donor lungs, and expression of POT1 (protection of telomeres1) was exclusively localized in a subset of TERT-negative Clara-cells in both categories. The other Shelterin-members revealed strong expression in fibroblast foci and in basal cells at sites of aberrant bronchiolar proliferation. Conclusion: We suggest that the robust expression of TERT in CC10-positive cells of IPF- and donor lungs might indicate a cell population with stem cell characteristics. Due to the reduced expression of TERT and TERC in IPF lungs, we conclude that the regenerative capacity of TERT-positive Clara cells is impaired in IPF.