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Title: Lineage differentiation of pulmonary alveolar fibroblasts

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Body: Alveolar fibroblasts are key cells to the process of alveolar septation as PDGFRα knock-out prevented alveolar myofibroblast differentiation and completely blocked secondary septa formation. Lipofibroblasts have been proposed to be essential for septation, peak in number during septation and regress significantly thereafter. Whether PDGFRα expressing precursors are deriving both lineages of fibroblasts is not known and transitions in between one or the other fibroblast type are unsolved. The aims of this work are to analyse the developmental fibroblast lineages, cell-cell transitions and ultimately the role of each cell type and the utility for regenerative septation in adulthood. To follow lineages, cre-reporter mice (mT/mG) expressing tomato fluorescent protein in the membrane of all cells, which switches to GFP upon cre-recombination, were crossed with constitutive PDGFRa-cre or conditional PDGFRa-creER mice. For identification of active PDGFRa expression, PDGFRα-GFP knock-in mice were used. Immunofluorescence staining revealed a co-expression of PDGFRα-GFP and αSMA in the bronchial compartment as well as in the alveolar space. The expression of ADRP co-localizes with the precursor marker in a subset of cells. The same pattern of expression could be observed in the constitutive PDGFRa-cre and the conditional PDGFRa-CreER mice. PDGFRα-GFP mice showed that PDGFRα-expressing precursor cells are differentiating into myo- as well as lipofibroblasts. The constitutive PDGFRa-cre mice revealed restriction of PDGFRα signalling to bronchial smooth muscle cells and alveolar fibroblasts in the lung. Lineage tracing with conditional PDGFRa-creER mice could confirm that postnatal PDGFRα cells derive lipofibroblasts and myofibroblasts.