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Title: Murine lung airway fibroblasts drive fibrosis through STAT4 signaling after cigarette smoke exposure

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Body: Cigarette smoke-induced emphysema and small airway remodeling (SAR) are the anatomic bases of chronic obstructive lung disease (COPD), but the pathogenesis of these changes is unclear and current treatments for COPD are minimally effective. We exposed wild type (WT) and STAT4-/- mice to cigarette smoke for 6 months and found that STAT4-/- mice are protected against smoke-induced small airway remodeling but not emphysema. Unexpectedly, we observed that STAT4 is expressed in cultured murine wild type (WT) lung parenchyma-derived and airway-derived fibroblasts, but to a much greater extent in the latter. The same phenomenon was seen in cultured human parenchymal and airway fibroblasts. WT airway fibroblasts proliferated faster than STAT4-/- airway fibroblasts, whereas there was no difference between strains for parenchymal fibroblasts. IL-12 is up-regulated in human and mouse lungs after smoke exposure, and treatment with IL-12 caused phosphorylation of STAT4 in WT airway fibroblasts. Exposure of WT airway, but not parenchymal, fibroblasts to IL-12 caused increased expression of collagen 1α1 and TGFβ, factors involved in SAR, whereas STAT4-/- fibroblasts were unresponsive to IL-12. STAT4 thus controls proliferation and matrix production in airway but not parenchymal fibroblasts, and smoke-induced IL-12 can drive small airway remodeling via STAT4 signaling. These findings suggest that treatment with clinically available anti IL-12p40 drugs might provide a new completely approach to preventing SAR in cigarette smokers.