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Title: The role of NRF-2 and p38 MAPK on the function of human parenchymal fibroblasts

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Body: Oxidative stress and chronic inflammation are key processes in COPD. Damage to the alveolar epithelium signals to fibroblasts to implement the repair process. Dysregulation in this process can lead to alveolar destruction as seen in emphysema. Sulforaphane (SFN) activates NRF-2 and upregulates antioxidant genes. VX745 inhibits p38MAPK and plays a role in cytokine production. Both are targets for the treatment of COPD. We hypothesised that the compounds would modify the response of parenchymal fibroblasts suffering exogenous stress. Fibroblasts were grown from parenchymal explants. Confluent cells were serum starved for 24h, pre-treated with SFN & VX745 and stimulated with Cytomix (TNFα IFNγ IL-1β) +/- H_2O_2, IL-1 β, TNFα or TGFβ. IL-6 and IFNγ were detected in supernatant by ELISA. Collagen 1 & 3, Integrin β5 and β8 expression was quantitated by qPCR. Proliferation and apoptosis was assessed by BrdU incorporation and CaspACE3 assay. Cytomix+/- H2O2 induced IL-6 and IFNγ release into the supernatant. VX745 and SFN had no effect. IL-1β, TNFα and TGFβ induced IL-6. VX745 had a small inhibitory effect on all agonists but SFN was ineffective. Cytomix+/- H2O2 decreased collagen 1, 3 and Integrin β5 and β8 mRNA expression which was decreased further by SFN whereas VX745 exerted no effect. SFN inhibited proliferation and caused minor dose-dependent increase in apoptosis. VX745 limited proliferation and increased apoptosis at high doses. There was no difference in responses to p38 inhibition or NRF-2 activation from normal fibroblasts and fibroblasts from patients with COPD. Neither the p38 nor the NRF-2 pathways are likely to be targets for modifying fibroblast function in COPD. On behalf of COPDMAP consortium.