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Title: PAR-2 agonists induce TGF-β and EMT leading to lung fibrosis

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Body: Rationale: The idiopathic interstitial pneumonias (IIPs) are characterized by variable degrees of pulmonary inflammation and fibrosis. However, the pathogenetic mechanisms leading to these responses remain unclear. Epithelial-to-mesenchymal transition (EMT) may play a role as a central process of pulmonary fibrosis. Transforming growth factor (TGF)-β is known to induce the transformation of fibroblasts to myofibroblasts and EMT of epithelium, which may contribute to lung fibrosis. Recently, protease activated receptor (PAR)-2, a G-protein-coupled receptor activated by serine proteases such as trypsin and tryptase has been recognized as a key molecule in inflammation and fibrosis. We hypothesized that activation of PAR-2 induces TGF-β expression and EMT which are associated with lung fibrosis. Methods: Cultured human lung epithelial cells (Calu-3) were exposed to trypsin or a specific activating peptide, PAR-2AP. Secreted TGF-β was measured using ELISA. E-cadherin and vimentin were assessed by Western blot. Results: The functional PAR-2 was expressed on Calu-3, lung epithelial cells. Activation of PAR-2 by trypsin or PAR-2AP induced TGF-β secretion with time-dependent manner. Cleavage of E-cadherin and induction of vimentin expression were seen by PAR-2 activation. This correlated with ERK activation. Conclusion: Activation of PAR-2 induces TGF-β secretion and features of EMT of lung epithelial cells leading to lung fibrosis. PAR-2 may be a key molecule driving lung fibrosis.