

Activation of Renin-Angiotensin System in Hyperoxia-Exposed Lung Fibroblast
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Background: Angiotensin (Ang) II is a potential profibrotic mediator because it induces human lung fibroblast proliferation and stimulates collagen synthesis in human lung fibroblast. The role of renin-angiotensin system (RAS) in the pathophysiology of hyperoxia-induced pulmonary fibrosis is unclear. Objective: To establish an <i>in vitro</i> model of lung fibrosis induced by hyperoxia, to confirm that collagen up-regulation is mediated via activation of RAS, and to explore the role of RAS and its signaling pathways in hyperoxia-induced collagen expression. Design/Methods: Human lung fibroblast MRC-5 cell line was cultured in hyperoxic conditions by placing the cells in sealed glass chambers filled with 95% O₂-5% CO₂ at 37°C for up to 48 h. Renin, Ang II, Ang receptors, connective tissue growth factor (CTGF), collagen type I, and angiotensin-converting enzyme (ACE) expressions were measure by real time PCR and Western blot. Results: Hyperoxia increased Ang II, Ang type I receptor, CTGF, and collagen type I mRNA and protein expressions in a time-dependent manner. Hyperoxia significantly increased ACE expression while chymase expression was comparable between hyperoxia and control conditions. ACE, Ang II, and CTGF expressions are up-regulated at time points preceding the increased collagen production adding credence to the hypothesis that RAS plays a significant role in the pathogenesis of hyperoxia-induced collagen expression. Conclusions: The demonstration of a functional pathway to Ang II generation and hyperoxia-treated human lung fibroblasts are capable of producing and secreting renin and ACE represent strong evidence of a physiological role for RAS in hyperoxia-induced lung fibrosis. With an understanding of these signal transduction pathways, we can design therapeutic strategies to reduce hyperoxia-induced lung fibrosis.