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Title: Endothelin-1 induced connective tissue growth factor expression in human lung fibroblasts by ETAR-dependent JNK/AP-1 pathway

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Body: Endothelin-1 (ET-1) acts as a key mediator of vasoconstriction and tissue repair. Overproduction of connective tissue growth factor (CTGF) underlies the development of lung fibrosis. However, little is known about the signaling pathway of CTGF expression caused by ET-1. We investigated the effect of ET-1 in CTGF expression in human lung fibroblasts by western blot, reporter gene assay and chromatin immunoprecipitation assay, etc. ET-1 caused concentration- and time-dependently increases in CTGF expression in primary normal adult human lung fibroblasts and human lung fibroblasts (WI-38). ET-1-induced CTGF expression was inhibited by BQ123 (ETAR antagonist), but not BQ788 (ETBR antagonist). Moreover, ET-1-induced CTGF expression was reduced by JNK inhibitor (SP600125), the dominant-negative mutants of JNK1/2 (JNK1/2 DN), and AP-1 inhibitor (curcumin). ET-1 induced phosphorylations of JNK and c-Jun in time-dependent manners. ET-1 induced the increase of AP-1 luciferase activity, and this effect was attenuated by SP600125. ET-1-indiced CTGF luciferase activity was predominately controlled by the sequence -747 to -408 bp upstream of the transcription start site on the human CTGF promoter. Furthermore, ET-1 caused the formation of AP-1-specific DNA-protein complex and the recruitment of c-Jun to the CTGF promoter. Moreover, we found that ET-1 induced α-smooth muscle actin (α-SMA) expression, which was inhibited by BQ123, SP600125, curcumin, and anti-CTGF antibody. These results suggest that ET-1 stimulates expressions of CTGF and α-SMA through ETAR/JNK/AP-1 signaling pathway, and CTGF is required for ET-1-induced α-SMA expression in human lung fibroblasts.