題名:Thrombin-Induced Connective Tissue Growth Factor Expression in Human Lung Fibroblasts Requires the ASK1/JNK/AP-1 Pathway

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摘要:Thrombin plays an important role in lung inflammatory diseases. Thrombin can induce connective tissue growth factor (CTGF) expression in lung fibroblasts. However, little is known about the signaling pathway in thrombin-induced CTGF expression. In this study, we investigated the role of apoptosis signal-regulating kinase 1 (ASK1) in thrombin-induced CTGF expression in human lung fibroblasts. Thrombin caused a concentration- and time-dependent increase in CTGF expression in WI-38 cells and primary lung fibroblasts. Thrombin-induced CTGF expression and CTGF-luciferase activity were inhibited by a protease-activated receptor 1 antagonist (SCH79797), the dominant-negative mutants (DNs) of ASK1 and JNK1/2, and an AP-1 inhibitor (curcumin). Thrombin caused ASK1 Ser(967) dephosphorylation, the dissociation of ASK1 and 14-3-3, and a subsequent increase in ASK1 activity. Thrombin induced increases in JNK phosphorylation and kinase activity, which were attenuated by ASK1DN. Furthermore, SCH79797 diminished the thrombin-induced ASK1 and JNK activities. Thrombin-induced CTGF-luciferase activity was predominately controlled by the sequence -747 to -184 bp upstream of the transcription start site of the human CTGF promoter and was attenuated by transfection with the deleted AP-1 binding site construct. Thrombin caused increases in c-Jun phosphorylation, the formation of an AP-1-specific DNA-protein complex, and the recruitment of c-Jun to the CTGF promoter. Furthermore, thrombin-mediated AP-1 activation was inhibited by ASK1DN, JNK1/2DN, and

SP600125. These results suggest for the first time that thrombin, acting through protease-activated receptor 1, activates the ASK1/JNK signaling pathway, which in turn initiates c-Jun/AP-1 activation and recruitment of c-Jun to the CTGF promoter and ultimately induces CTGF expression in human lung fibroblasts.