題名:Thrombin induces cyclooxygenase-2 expression via the ERK and NF-kB pathways in human lung fibroblasts

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摘要:There is growing evidence that increased expression of cyclooxygenase-2 (COX-2) in the lungs of patients is a key event in the pathogenesis of lung diseases. In this study, we investigated the involvement of the extracellular signal-regulated kinase (ERK), IκB kinase α/β (IKKα/β), and nuclear factor-κB (NF-κB) signaling pathways in thrombin-induced COX-2 expression in human lung fibroblasts (WI-38). Treatment of WI-38 cellswith thrombin caused increased COX-2 expression in a concentration- and time-dependent manner. Treatment of WI-38 cells with PD 98059 (2-[2-amino-3-methoxyphenyl]-4H-1-benzopyran-4-one, a MEK inhibitor) inhibited thrombininduced COX-2 expression and COX-2-luciferase activity. Stimulation of cells with thrombin caused an increase in ERK phosphorylation in a time-dependentmanner. In addition, treatment of WI-38 cells with Bay 117082, an IκB phosphorylation inhibitor, and pyrrolidine dithiocarbamate (PDTC), an NF-κB inhibitor, inhibited thrombininduced COX-2 expression. The thrombin-induced increase in COX-2-luciferase activity was also blocked by the dominant negative IκBα mutant (IκBαM). Treatment of WI-38 cells with thrombin induced IKKα/β and IκBα phosphorylation, IκBα degradation, and κB-luciferase

activity. The thrombin-mediated increases in IKKα/β phosphorylation and κB-luciferase activitywere inhibited by PD98059. Taken together, these results suggest that
the ERK-dependent IKKα/β/NF-κB signaling pathway plays an important role in thrombin-induced COX-2 expression in human lung fibroblasts.