Transforming growth factor-beta1 stimulates heme oxygenase-1 expression via the PI3K/Akt and NF-kappaB pathways in human lung epithelial cells.

許銘仁

Lin CC;Chiang LL;Lin CH;Shih CH;Liao YT;Hsu MJ;Chen BC

摘要

Abstract

A previous report showed that transforming growth factor-β1 (TGF-β1) can induce heme oxygenase-1 (HO-1) expression, attenuate cellular injury, and maintain tissue homeostasis. In this study, we investigated the involvement of phosphoinositide-3-OH-kinase (PI3K)/Akt and the nuclear factor-κB (NF-κB) signaling pathway in TGF-β1-induced HO-1 expression in human lung epithelial cells (A549). Treatment of A549 cells with TGF-β1 caused HO-1 to be expressed in a concentration- and time-dependent manner. Treatment of A549 cells with LY 294002 (2-(4-morpholinyl)-8-phenyl-4H-1-benzopyran-4-one, a PI3K inhibitor), an Akt inhibitor, and the dominant negative mutant of Akt (Akt DN) inhibited TGF-β1-induced HO-1 expression and HO-1-luciferase activity. Stimulation of cells with TGF-β1 caused an increase in Akt phosphorylation in a time-dependent manner, which was inhibited by wortmannin and LY 294002 (PI3K inhibitors). In addition, treatment of A549 cells with Bay 117082 ((E)-3-[4-methylphenylsulfonyl]-2-propenenitrile, an IκB phosphorylation inhibitor), pyrrolidine dithiocarbamate (PDTC, an NF-κB inhibitor), and the dominant negative mutant of IκBα (IκBαM) inhibited TGF-β1-induced HO-1 expression and HO-1-luciferase activity. Treatment of A549 cells with TGF-β1-induced IκB kinase α/β (IKKα/β) phosphorylation, IκBα phosphorylation, IκBα degradation, p65 Ser536 phosphorylation, and κB-luciferase activity. The TGF-β1-mediated increases in IKKα/β phosphorylation, p65 Ser536 phosphorylation, and κBluciferase activity were inhibited by LY 294002, an Akt inhibitor, and Akt DN. Taken together, these results suggest that the PI3K/Akt dependent IKKα/β/NF-κB signaling pathway plays an important role in TGF-β1-induced HO-1 expression in A549 cells.