YC-1-induced cyclooxygenase-2 expression is mediated by cGMP-dependent activations of Ras, phosphoinositide-3-OH-kinase, Akt, and nuclear factor-kB in human pulmonary epithelial cells

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摘要

Abstract

We demonstrated previously that 3-(5'-hydroxymethyl-2'-furyl)-1-benzylindazole (YC-1), an activator of soluble guanylate cyclase (sGC), induces cyclooxygenase-2 (COX-2) expression via cGMP- and p44/42 mitogen-activated protein kinase-dependent pathways in human pulmonary epithelial A549 cells. In this study, we explore the role of Ras, phosphoinositide-3-OH-kinase (PI3K), Akt, and transcription factor nuclear factor-kappaB (NF-kappaB) in YC-1-induced COX-2 expression in A549 cells. A Ras inhibitor (manumycin A), a PI3K inhibitor (wortmannin), an Akt inhibitor (1l-6-Hydroxymethyl-chiro-inositol2-[(R)-2-O-methyl-3-O-octadecylcarbonate]), and an NF-kappaB inhibitor [pyrrolidine dithiocarbamate (PDTC)] all reduced YC-1-induced COX-2 expression. The YC-1-induced increase in COX activity was also blocked by manumycin A, wortmannin, PDTC, and the dominant-negative mutants for Ras (RasN17), Akt (Akt DN), and IkappaBalpha (IkappaBalphaM). The YC-1-induced increase in Ras activity was inhibited by an sGC inhibitor [1H-(1,2,4)oxadiazolo[4,3-a]quinozalin-1-one (ODQ)], a protein kinase G (PKG) inhibitor [1-oxo-9.12-epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-l][1,6]benzodiazocine-10-carboxylic acid methyl ester (KT-5823)], and manumycin A.

YC-1-induced Akt activation was also inhibited by ODQ, KT-5823, manumycin A, and wortmannin. YC-1 caused the formation of an NF-kappaB-specific DNA-protein complex and an increase in kappaB-luciferase activity. YC-1-induced kappaB-luciferase activity was inhibited by ODQ, KT-5823, manumycin A, wortmannin, an Akt inhibitor, PDTC, RasN17, Akt DN, and IkappaBalphaM. Likewise, YC-1-induced IKKalpha/beta activation was inhibited by ODQ, KT-5823, manumycin A, wortmannin, and an Akt inhibitor. Furthermore, YC-1-induced COX-2 promoter activity was inhibited by manumycin A, RasN17, Akt DN, PDTC, and IkappaBalphaM. Taken together, these results indicate that YC-1 might activate the sGC/cGMP/PKG pathway to induce Ras and PI3K/Akt activation, which in turn initiates IKKalpha/beta and NF-kappaB activation and finally induces COX-2 expression in A549 cells.