題名:Involvement of Ras/Raf-1/p44/42 MAPK in YC-1-induced cyclooxygenase-2 expression in human pulmonary epithelial cells

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摘要:Our previous study demonstrated that 3-(5'-hydroxymethyl-2'-furyl)-1-benzylindazole (YC-1) might activate the soluble guanylate cyclase (sGC)/cGMP/protein kinase G (PKG) pathway to induce cyclooxygenase-2 (COX-2) expression in human pulmonary epithelial cells (A549). In this study, we further investigated the role of Raf-1 in YC-1-induced nuclear factor-kappaB (NF-kappaB) activation and COX-2 expression in A549 cells. YC-1-induced COX-2 expression was attenuated by a Raf-1 inhibitor (GW 5074) in a concentration-dependent manner. Treatment of A549 cells with YC-1 or 8-bromo-cGMP, a cell-permeable cGMP analogue, induced Raf-1 Ser338 phosphorylation in a time-dependent manner. YC-1-mediated Raf-1 activation was inhibited by an sGC inhibitor (ODQ), a PKG inhibitor (KT-5823), a Ras inhibitor (manumycin A), a dominant negative Ras mutant (RasN17), a protein kinase C-alpha (PKC-alpha) inhibitor (Ro 32-0432), and a phosphoinositide-3-OH-kinase (PI3K) inhibitor (LY 294002). Pretreatment of A549 cells with either manumycin A or GW 5074 attenuated YC-1-induced p44/42 MAPK activation. The YC-1-mediated increase in IKKalpha/beta activation and kappaB-luciferase activity were attenuated by GW 5074, a MAPK/ERK kinase (MEK) inhibitor (PD 98059), and an ERK2 inhibitor (AG 126). Furthermore, YC-1-induced COX-2 promoter activity was also inhibited by GW 5074, PD 98059, and AG 126. These results indicate that YC-1 might activate the sGC/cGMP/PKG pathway to elicit Ras/Raf-1/p44/42 MAPK

activation, which in turn induces IKKalpha/beta and NF-kappaB activation, and ultimately causes COX-2 expression in A549 cells. Moreover, PKC-alpha and PI3K signal might be involved in YC-1-induced Raf-1 activation.