Phorbol-12-myristate-13-acetate up-regulates cyclooxygenase-2 expression in human pulmonary epithelial cells via Ras, Raf-1, ERK, and NF-kB, but not p38 MAPK, pathways

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Abstract

In this study, we investigated the signaling pathway involved in cyclooxygenase-2 (COX-2) expression and prostaglandin E2 (PGE2) release by phorbol 12-myristate 13-acetate (PMA), a protein kinase C (PKC) activator, in human pulmonary epithelial cells (A549). PMA-induced COX-2 expression was attenuated by PKC inhibitors (Go 6976 and Ro 31-8220), a Ras inhibitor (manumycin A), a Raf-1 inhibitor (GW 5074), a MEK inhibitor (PD 098059), and an NF-KB inhibitor (PDTC), but not by a tyrosine kinase inhibitor (genistein) or a p38 MAPK inhibitor (SB 203580). PMA also caused the activation of Ras, Raf-1, and ERK½. PMA-induced activation of Ras and Raf-1 was inhibited by Ro 31-8220 and manumycin A. PMA-mediated activation of ERK½ was inhibited by Ro 31-8220, manumycin A, GW 5074, and PD 098059. Stimulation of cells with PMA caused IκBα phosphorylation, IκBα degradation, and the formation of a NF-κB-specific DNA-protein complex. The PMA-mediated increase in KB-luciferase activity was inhibited by Ro 31-8220, manumycin A, GW5074, PD 098059, and PDTC. Taken together, these results indicate that PMA might activate PKC to elicit activation of the Ras/Raf-1/ERK½ pathway, which in turn initiates NF-KB activation, and finally induces COX-2 expression and PGE2 release in A549 cells.