P-34

EFFECTS OF NATURALLY OCCURRING DIARYHEPTANOIDS ON CYCLOOXYGENASE-2 EXPRESSION AND NF-κB ACTIVATION IN HUMAN BREAST EPITHELIAL CELLS

Jung-Hwan Kim and Young-Joon Surh

College of Pharmacy, Seoul National University, Seoul 151-742, Korea

Abnormal regulation of the inducible form of cyclooxygenase (COX-2) has been often observed in various types of cancerous and transformed cells. Recently, targeted inhibition of COX-2 is recognized as one of the promising strategies for the prevention or treatment of cancer as well as inflammation, As part of a program to evaluate the cancer chemopreventive potential of anti-inflammatory phytochemicals, we initially determined the COX-2 inhibitory activity of some naturally occurring diarylheptanoids structurally related to curcumin. Treatment of human breast epithelial (MCF10A) cells with the tumor promoter, 12-*O*-tetradecanoylphorbol-13-acetate (TPA) induced *cox*-2 mRNA and COX-2 protein expression in time-and concentration-related manners. Hirsutanone from *Alnus hirsute* var. sibirica and curcumin present in turmeric (*Curcuma longa* L.) inhibited TPA-induced COX-2 expression at both transcriptional and post-transcriptional levels. There is some evidence that expression of COX-2 is regulated by the eukaryotic transcription factor NF-κB. In support of this notion, We found that the NF-κB inhibitor, pyrrolidine dithiocarbamate strongly suppressed the expression of COX-2 induced by TPA in MCF10A cells. Hirsutanone treatment also attenuated the TPA-stimulated NF-κB activation, which was associated with inhibition of degradation of the inhibitory unit I-kB and subsequent translocation of functionally active NF-κB subunit, p65. The luciferase reporter gene assay revealed that inactivation of NF-κB by hirsutanone led to blockade of its transcriptional activity. TPA treatment also resulted in rapid induction of such mitogen-activated protein kinases (MAPK) as ERK1/2 and p38. Addition of PD985059 and SB203580 which are inhibitors of ERK1/2 activity and p38 MAPK, respectively suppressed TPA-induced expression of

COX-2 in MCF10A cells. Furthermore, MCF10A cells expressing dominant negative p38 or ERK1/2 exhibited much lower levels of COX-2 after stimulation with TPA. This study was supported by the grant from the Korea Research Foundation (F00299).