CYCLOOXYGENASE (COX-2) EXPRESSION AND NF-κB ACTIVATION IN HUMAN BREAST EPITHELIAL (MCF10A) CELLS

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Up-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 treatment of cancer as well as inflammation. As part of a program to evaluate the cancer chemopreventive potential of anti-inflammatory phytochemicals, we initially measured 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*-tetradecanoyl-phorbol-13-acetate (TPA) induced *cox-2* mRNA and COX-2 protein expression in time- and concentration-related manners. Hirsutanone from *Alnus hirsuta* 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-kappa B. In support of this notion, we found that the NF-kappa B inhibitor, pyrrolidine dithiocarbamate strongly suppressed the expression of COX-2 induced by TPA in MCF10A cells. Hirsutanone as well as curcumin attenuated the TPA-stimulated NF-kappa B activation, which was associated with inhibition of degradation of the inhibitory unit I-kappa B and subsequent translocation of the functionally active NF-kappa B subunit, p65. The luciferase reporter assay revealed that inactivation of NF-kappa B by hirsutanone led to blockade of its transcriptional activity. TPA treatment transiently induced the phosphorylation of p38 mitogen-activated protein kinase (MAPK) and extracellular signal-regulated kinases (ERK1 and ERK2) which are known to a play important role in inflammation. TPA-induced activation of p38 and ERK1/2 was substantially suppressed by curcumin treatment.

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Apoptotic Death in MDA-MB-231 Human Breast Cancer Cell Induced by Trichostatin A

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Trhichostatin A (TSA) is a Streptomyces product, which inhibits the enzyme activity of histone deacetylase. It is also known as an inducer of apoptosis on several human cancer cell lines. In this study, we investigated the mechanism of apoptosis process by TSA especially on MDA-MB-231 human breast carcinoma cells. The cytotoxicity of TSA on MDA-MB-231 cells was assessed by MTT assay. The cell viability was decreased dose-dependently and the IC 50 value was about 100 ng/ml after 24 h treatment with TSA. Morphological change and DNA ladder formation, the biochemical hallmark of apoptotic cell death, were observed after treatment of TSA in a concentration- dependent manner, which was accompanied with poly (ADP- ribose) polymerase cleavage and caspase-3 activation. TSA treatment up-regulated the expression of a cyclin-dependent kinase inhibitor p21(Waf1/Cip1) protein, a key regulatory protein of the cell cycle. We also observed down-regulation of Bcl-2 protein by TSA without alteration of Bax expression. These results demonstrated that TSA might inhibit cell growth and induce apoptosis on human breast carcinoma MDA-MB-231 cells.