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INHIBITORY EFFECTS OF CURCUMIN ON PHORBOL ESTER-INDUCED ACTIVATION OF p38 MAP KINASE AND SUBSEQUENT INDUCTION OF CYCLOOXYGENASE-2 IN MOUSE SKIN

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Curcumin, a yellow coloring ingredient of turmeric (*Curcuma longa* L., Zingiberaceae), has been shown to inhibit experimental carcinogenesis and mutagenesis, but molecular mechanisms underlying its chemopreventive activities remain unclear. In the present work, we have assessed the effects of curcumin on 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced expression of cyclooxygenase-2 (COX-2) in mouse skin. When topically applied onto shaven backs of female ICR mice 30 min prior to TPA, curcumin significantly inhibited expression of COX-2 protein and its mRNA in a dose-related manner. Multiple lines of evidence support the role of the eukaryotic transcription factor NF-κB in regulation of COX-2. In agreement with this notion, the NF-κB inhibitor pyrrolidine dithiocarbamate suppressed not only NF-κB activation but also induction of COX-2 in mouse skin. Curcumin treatment attenuated TPA-stimulated epidermal NF-κB activation, which was associated with its blockade of degradation of the inhibitory protein IκB-α and subsequent translocation of p65 subunit to nucleus. TPA treatment resulted in rapid activation via phosphorylation of ERK1/2 and p38 mitogen-activated protein kinases, upstream of NF-κB. SB203580 and U0126, selective inhibitors of p38 MAPK and MEK1/2, respectively attenuated TPA-induced expression of COX-2. Curcumin inhibited activation of p38 MAP kinase while it did not influence the phosphorylation of ERK1/2 in mouse skin. In addition, curcumin inhibited both catalytic activities of p38 MAP kinase and ERK1/2. Supported by the Korea Research Foundation Grant (# F00299).