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Resveratrol Inhibits TPA-induced Expression of COX-2 and Activation of Signaling Molecules in Mouse Skin

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Multiple lines of evidence suggest that inflammation is causally linked to carcinogenesis. Inappropriate up-regulation of cyclooxygenase (COX)-2 has been implicated in malignant transformation of cells. Resveratrol, a phytoallexin present in grapes and red wine, has been reported to inhibit chemically-induced carcinogenesis in mouse skin. The present study was aimed at investigating the effect of resveratrol on 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced COX-2 expression in mouse skin and underlying molecular mechanisms. Dorsal skin of female ICR mice was treated with resveratrol 30 min prior to topical application of TPA. Skin tissue homogenates were subjected to western blot analysis, the eletrophoretic mobility shift assay, and in vitro kinase assay to examine the effects of resveratrol on TPA-induced expression of COX-2, and the activation of transcription factors and upstream kinases in mouse skin, respectively. Topical application of resveratrol inhibited TPA-induced COX-2 expression in mouse skin. Resveratrol pretreatment resulted in a decrease in the phosphorylation of extracellular signal-regulated protein kinase (ERK) as well as the catalytic activity of ERK and p38 MAP kinase. In addition, resveratrol prevented TPA-induced DNA binding of activator protein-1 (AP-1) and nuclear factor-κB (NF-κB). Resvetarol also blocked TPA-induced phosphorylation and degradation of IκBα as well as attenuated phosphorylation and nuclear translocation of p65. A kinetic study revealed that TPA caused a significant increase in IκB kinase (IKK)-β activity after 30 min of topical application to mouse skin. Pretreatment with resveratrol attenuated TPA-induced IKK-β activity. Resveratrol suppressed TPA-induced COX-2 expression in mouse skin, which appears to be mediated by blocking the activation of NF-κB and AP-1, and upstream kinases such as ERK, p38 MAP kinase and IKK-β, lending mechanistic support to the previously reported anti-tumor promoting effect of this dietary phytochemical.

Keyword : Mouse skin, Cyclooxygenase-2, Resveratrol, AP-1, NF-κB, IKK-β, MAPK