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[6]-Gingerol Inhibits Phorbol Ester-Induce d Expression of Cyclooxygenase-2 in Mouse Skin: p38 MAPK and p65/RelA as Possible Molecular Targets

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Ginger (*Zingiber officinale* Roscoe, Zingiberaceae) has a wide array of pharmacologic effects. Our previous studies have demonstrated that [6]-gingerol, a major pungent ingredient of ginger, inhibits mouse skin tumor promotion and anchorage-independent growth of cultured mouse epidermal cells stimulated with epidermal growth factor. In this study, we have investigated the molecular mechanisms underlying chemopreventive effects of [6]-gingerol on mouse skin carcinogenesis. Cyclooxygenase-2 (COX-2), a key enzyme in the formation of prostaglandins, has been recognized as a molecular target of many chemopreventive as well as anti-inflammatory agents. The murine COX-2 promoter contains several transcriptional elements, particularly those involved in regulating inflammatory processes. One of the essential transcription factors responsible for COX-2 induction is NF-kappa B. Topical application of [6]-gingerol inhibited the COX-2 expression through suppression of NF-kappa B activation in phorbol ester-treated mouse skin. [6]-Gingerol, through down-regulation of p38 MAPK, abrogated the DNA binding activity of NF-kappa B by blocking phosphorylation of p65/RelA at the Ser 536 residue. These findings suggest that [6]-gingerol exerts an anti-tumor promotional activity through inhibition of the p38 MAPK-NF-kappa B siganling cascade in mouse skin.