Molecular Mechanisms Underlying Chemopreventive Activities of Selected Phytochemicals: Down Regulation of Cyclooxygenase-2 via Suppression of NF-kappa B

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배경 A wide variety of phenolic substances derived from edible plants possess substantial antioxidative and anti-inflammatory properties, which can contribute to their chemopreventive or chemoprotective potential. Since inflammation is closely linked to tumor promotion, substances with potent anti-inflammatory activities are anticipated to exert chemopreventive effects on carcinogenesis, particularly in the promotion stage. In the present study, we have investigated the effects of selected dietary and medicinal phytochemicals on phorbol ester-induced expression of cyclooxygenase-2 (Cox-2), an important enzyme that mediates inflammatory processes. Recent studies have demonstrated that eukaryotic transcription factor NF-kappa B is involved in regulation of Cox-2 expression. Multiple lines of evidence indicate that extracellular-regulated protein kinase (ERK1/2) and p38 mitogen-activated protein kinase (MAPK) are key elements of the intracellular signaling cascades responsible for NF-kappa B activation in response to a wide array of external stimuli. In an attempt to elucidate the molecular mechanisms underlying chemopreventive activities of anti-inflammatory phytochemicals, their effects on the activation of NF-kappa B and the aforementioned upstream signaling enzymes were also assessed.

방법 The Cox-2 protein and mRNA levels were determined by Western blot and Northern blot analysis, respectively. The NF-kappa B DNA binding was assessed by electrophoretic mobility shift assay using the gamma-32P-labeled 22-bp double-strand oligonucleotides containing the NF-kappa B consensus motif. Activation of ERK1/2 and p38 MAPK was determined by using the antibodies that can specifically detect their phosphorylated forms. Kinase assays were also conducted in parallel.

결과 Curcumin inhibits TPA-induced expression of COX-2 in mouse skin in vivo and also in the cultured human breast epithelial cell line through blockade of the eukaryotic transcription factor NF-kappa B. Curcumin also inhibited the activation of p38 MAPK. Capsaicin, a principal pungent principle of red pepper, also suppressed TPA-induced activation of NF-kappa B and AP-1 transcription factors in mouse skin. [6]-Gingerol, a major pungent principle in ginger, exhibits anti-tumor promoting activities as revealed by inhibition of phorbol ester-induced ornithine decarboxylase activity, TNF-alpha production, and papilloma production in mouse skin.

결론 These findings suggest that anti-inflammatory and antioxidative phenolic substances present in edible plants exert their anti-tumor promoting effects via intracellular signaling cascades that involve NF-kappa B.