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CELECOXIB INHIBITS PHORBOL ESTER-INDUCED EXPRESSION OF CYCLOOXYGENASE-2 AND ACTIVATION OF ERK1/2 IN MOUSE SKIN *IN VIVO*

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There has been accumulating evidence for the association of inflammatory tissue damage with the process of cancer development. Cyclooxygenase (COX), an important enzyme involved in mediating the inflammation, catalyzes the formation of prostaglandins (PGs) from arachidonic acid. There are two isoforms of COX, designated as COX-1 and COX-2. COX-1 is a housekeeping enzyme which is constitutively expressed and is thought to be involved in maintaining physiological functions. In contrast, COX-2 can be induced rapidly and transiently by proinflammatory cytokines, endotoxins, growth factors, oncogenes and mitogens. Elevated levels of COX-2 have been found in cancers of breast, colon, and lung as compared with the surrounding normal tissues. Based on these findings, it is conceivable that targeted inhibition of abnormal up-regulation of COX-2 is one of the most broadly effective and promising approaches to cancer chemoprevention.

Celecoxib, a COX-2 selective inhibitor, has been reported to prevent experimentally induced colon, breast and skin carcinogenesis. Moreover, daily intake of celecoxib days resulted in significant reduction of polyps in patients with familial adenomatous polyposis. In the present study, we examined the effect of celecoxib on COX-2 induction in 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-treated mouse skin. When applied topically onto shaven backs of mice 30 min prior to TPA, celecoxib significantly inhibited expression of COX-2 protein and prostaglandin E_2 (PGE_2) production in a dose-related manner. To further elucidate the molecular mechanisms by which celecoxib regulates COX-2 protein expression and PGE_2 production, we have investigated its effect on activation of the upstream signaling enzyme extracelluar signal-regulated kinase (ERK) and transcription factors such

as NF-κB and activator protein-1 (AP-1) in mouse skin *in vivo*. Celecoxib inhibited both catalytic activity and phosphorylation of ERK1/2, while it slightly inhibited activation of NF-κB and AP-1 in mouse skin. These results suggest that celecoxib suppresses TPA-induced COX-2 expression in mouse skin by blocking activation of ERK and transcription factor(s) other than NF-κB and AP-1. This work was supported by the grant from Korea Research Foundation (F00299).