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CELECOXB (CELEBREX) INHIBITS PHORBOL ESTER-INDUCED COX-2 EXPRESSION AND PGE_2 PRODUCTION IN MOUSE SKIN: AP-1 AND C/EBP AS POSSIBLE MOLECULAR TARGETS

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Cyclooxygenase (COX), an important enzyme involved in mediating the inflammation, catalyzes the rate-limiting step in the formation of prostaglandins from arachidonic acid. There are two isoforms of COX, designated as COX-1 and COX-2. While COX-1 is constitutively expressed in most tissues, COX-2 can be induced transiently by proinflammatory cytokines, endotoxins, growth factors, oncogenes, UV and mitogens. Elevated levels of COX-2 have been observed 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 inappropriate or abnormal up-regulation of COX-2 is one of the most broadly effective and promising approaches to cancer chemoprevention.

Celecoxib, a selective COX-2 inhibitor, has been reported to prevent experimentally induced colon, breast and skin carcinogenesis. Moreover, daily intake of celecoxib 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. Topical application of 0.1, 1.0, or 10 μmole celecoxib onto shaven backs of female ICR mice (6 to 7 wk of age) 30 min prior to 10 nmole TPA inhibited expression of COX-2 protein and subsequent production of prostaglandin E_2 in a dose-related manner. Under the same experimental conditions, the levels of the constitutive enzyme COX-1 remained unchanged. To further elucidate the molecular mechanisms by which celecoxib suppresses COX-2 expression and PGE_2 production, we have investigated its effects on activations of the upstream mitogen-activated protein kinases (MAPKs) and transcription factors in mouse skin. Celecoxib inhibited activation of AP-1 and C/EBP transcription factors in a dose dependent manner. Furthermore, celecoxib inhibited both catalytic activity and phosphorylation of ERK1/2. These results suggest that celecoxib

suppresses TPA-induced COX-2 expression in mouse skin by blocking activation of ERK, which appears to be mediated by transcription factor(s) such ad AP-1 and C/EBP.

keyword : Celecoxib, Cyclooxygenase-2, Transcription factors, Mouse skin