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Roles of ERK1/2 and p38 Mitogen-Activated Protein Kinases in Phorbol Ester-induced NF-κB Activation and COX-2 Expression in the Human Breast Epithelial Cell Line (MCF10A)

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Inappropriate up-regulation of cyclooxygenase-2 (COX-2) has been implicated for pathogenesis of various types of human cancer. COX-2 expression is known to be regulated by the eukaryotic transcription factor NF-κB. In an attempt to link the NF-κB activation and COX-2 induction, we have examined the kinetics of phorbol ester-induced activation of NF-κB and COX-2 expression in the immortalized human breast epithelial cell line (MCF10A). Treatment of MCF10A cells with 60 nM TPA resulted in rapid induction of NF-κB in 10 min with maximal activation observed at 30 min. Increased DNA binding of NF-κB was accompanied by enhancement of its transcriptional activity as determined by the luciferase reporter gene assay. Under the same experimental conditions, COX-2 mRNA expression peaked at 2 h and 4 h, respectively. TPA caused an increases in the production of PGE_2. Treatment of cells with the NF-κB inhibitor pyrrolidine dithiocarbamate (PDTC) resulted in significant suppression of TPA-induced COX-2 expression. TPA induced activation of ERK1/2 and p38 mitogen-activated protein kinases (MAPK) via phosphorylation. PD 98059 (ERK inhibitor) and SB 203580 (p38 MAPK inhibitor) not only suppressed the phosphorylation of the corresponding kinases, but also down-regulated the COX-2 expression. Furthermore, TPA-induced COX-2 induction as well as NF-κB activation was blocked in MCF10A cells transfected with a vector containing dominant negative mutant ERK1/2 or p38 MAPK. In another study, we assessed the NF-κB activation and COX-2 induction in MCF10A cells bearing activated H-*ras* oncogene, but we found no distinct up-regulation of COX-2 via NF-κB activation, compared with parental cell line. Collectively, these findings suggest that Ras mutation alone is not sufficient to induce COX-2 expression in MCF10A cells, and activation of other pathways including p38 MAPK may be required for up-regulation of NF-κB and subsequent induction of COX-2 in these cells.