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**EFFECTS OF THE SOY ISOFLAVONE GENISTEIN ON COX-2  
EXPRESSION AND ACTIVATION OF ERK1/2 INDUCED BY  
PHORBOL ESTER AND TNF- $\alpha$  IN HUMAN BREAST EPITHELIAL  
CELL LINE (MCF10A)**

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Genistein has been shown to exert protective effects against chemically induced carcinogenesis in animals as well as malignant transformation in cultured cells, but molecular mechanisms of its chemopreventive or chemoprotective activities remain largely unresolved. In the present study, we have investigated the effects of genistein on induction of cyclooxygenase-2 (COX-2) that plays an important role in the pathophysiology of carcinogenesis as well as in cellular response to inflammatory stimuli. Treatment of cultured human breast epithelial cells (MCF10A) with 12-*O*-tetradecanoylphorbol-13-acetate (TPA) resulted in dose- and time-dependent increases in COX-2 expression and prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) production in these cells. MCF10A cells treated with genistein exhibited reduced levels of COX-2 and PGE<sub>2</sub>, which appeared to be attributable to suppression of the catalytic activity of COX-2 as well as its expression. There are multiple lines of evidence supporting that the expression of COX-2 is regulated by the eukaryotic transcription factor NF- $\kappa$ B. In agreement with this notion, pyrrolidine dithiocarbamate and *N*- $\alpha$ -*p*-tosyl-L-lysine chloromethylketone that are inhibitors of NF- $\kappa$ B significantly attenuated TPA-induced activation of COX-2 in MCF10A cells. Mitogen-activated protein kinases (MAPK), such as ERK1/2, are considered to be upstream signaling enzymes responsible for controlling NF- $\kappa$ B activation and subsequent induction of COX-2. Both TPA and TNF- $\alpha$  induced ERK1/2 activation in dose- and time-dependent manners. These effects were also inhibited by genistein. Above findings suggest that genistein attenuates COX-2 expression and PGE<sub>2</sub>

production via a mechanism that may involve the MAPK cascades in MCF10A cells. This work was supported by the grant (HMP-00-B-20800-0085) from the Ministry of Health and Welfare, Republic of Korea.