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The Novel Phospholipase C Activator, *m*-3M3FBS, Induces Apoptosis in Tumor Cells through Caspase Activation, Down-regulation of XIAP and Intracellular Calcium Signaling

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We investigated the effect of the novel phospholipase C activator, *m*-3M3FBS, on the apoptosis of human renal Caki cancer cells. Treatment with *m*-3M3FBS induced apoptosis of Caki cells, which was accompanied by accumulation of sub-G1 phase and DNA fragmentation. We found that induction of apoptosis is a common response of several cancer cell types to *m*-3M3FBS treatment. Overexpression of Bcl-2 and c-FLIPs fails to block *m*-3M3FBS-induced apoptosis. However, ectopic expression of XIAP partly inhibits *m*-3M3FBS-mediated apoptosis in Caki cells. *m*-3M3FBS-induced apoptosis appeared to involve the down-regulation of anti-apoptotic XIAP and caspase activation. *m*-3M3FBS also induced the expression of a potential proapoptotic gene, C/EBP homologous protein (CHOP), however, suppression of CHOP expression by small interfering RNA did not abrogate the *m*-3M3FBS-induced apoptosis. In addition, inhibition of PLC or chelation of intracellular calcium prevented *m*-3M3FBS-mediated apoptosis in Caki cells, suggesting that the involvement of PLC pathway and intracellular calcium signaling on the apoptosis in *m*-3M3FBS-treated Caki cells. Collectively, our present results suggest that *m*-3M3FBS-induced apoptosis in Caki cells may result from the activation of caspase, down-regulation of XIAP and intracellular Ca2+ release pathway and that *m*-3M3FBStreatment might overcome the anti-apoptotic effect of Bcl-2 or c-FLIPs in cancer cells. This work was supported by the Korea Science & Engineering Foundation (KOSEF) through the MRC at Keimyung University (R13-2002-028-03001-0), R01-2005-000-10786-0 and Korea Research Foundation grant KRF-2005-070-C00100.

Key words: *m*-3M3FBS, apoptosis, calcium, PLC

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Sulforaphane Suppresses Lipopolysaccharide-induced Cyclooxygenase-2 (COX-2) Expression through the Modulation of Multiple Targets in COX-2 Gene Promoter

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Sulforaphane is a natural, biologically active compound extracted from cruciferous vegetables such as broccoli and cabbage.It possesses potent anti-inflammation and anti-cancer properties. The mechanism by which sulforaphanesuppresses COX-2 expression remains poorly understood. In the present report, we investigated the effect of sulforaphaneon the expression of COX-2 in lipopolysaccharide (LPS)-activated Raw 264.7 cells. Sulforaphane significantly suppressed the LPS-induced COX-2 protein and mRNA expression in a dose-dependent manner. The ability of sulforaphaneto suppress the expression of the COX-2 was investigated using luciferase reporters controlled by various *cis*-elements in COX-2 promoter region. Electrophoretic mobility shift assay (EMSA) verified that NF-kB, C/EBP, CREB and AP-1 were identified as responsible for the sulforaphane-mediated COX-2 down-regulation. In addition, we demonstrated the signal transduction pathway of mitogen-activated protein kinase (MAP kinase) in LPS-induced COX-2 expression. Taken together, these results demonstrate that sulforaphane effectively suppressed the LPS-induced COX-2 protein via modulation of multiple core promoter elements (NF-kB, C/EBP, CREB and AP-1) in the COX-2 transcriptional regulation. These results will provide new insights into the anti-inflammatory and anti-carcinogenic properties of sulforaphane. This work was supported by the Korea Science & Engineering Foundation (KOSEF) through the MRC at Keimyung University (R13-2002-028-03001-0), R01-2005-000-10786-0

Key words: Sulforaphane Cyclooxygenase-2, promoter macrophage, lipopolysaccharide