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## ET-18-O-CH<sub>3</sub> INDUCED APOPTOSIS IN H-RAS TRANSFORMED HUMAN BREAST EPITHELIAL CELLS THROUGH UP-REGULATION OF CYCLOOXYGENASE-2

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Cyclooxygenase-2 (COX-2) is an inducible enzyme expressed in response to a variety of cytokines. The presence of oncogenic ras has been associated with sustained induction of COX-2, which confers resistance to apoptosis. Contrary to the above notion, we found that MCF10A-ras cells treated with an anti-tumor agent, ET-18-O-CH<sub>3</sub>, underwent apoptosis as revealed by proteolytic cleavage of poly(ADP-ribose)polymerase, pro-caspase 3 activity, and TUNEL staining, while the same treatment caused an increased expression of COX-2 as well as the elevated production of prostaglandin E<sub>2</sub> (PGE<sub>2</sub>). The apoptotic effect of ET-18-O-CH<sub>3</sub> involved intracellular accumulation of reactive oxygen species. Treatment of MCF10A-ras cells with the selective COX-2 inhibitor celecoxib (50 μM) attenuated ET-18-O-CH<sub>3</sub>-induced apoptosis as well as COX-2 expression and production of PGE<sub>2</sub>, suggesting that unusual expression of COX-2 by ET-18-O-CH<sub>3</sub> is causatively implicated in the induction of apoptosis. ET-18-O-CH<sub>3</sub> inhibited activation of both Akt/protein kinase B and transcription factor NF-κB that are involved in cell survival pathways. ET-18-O-CH<sub>3</sub> also inhibited activation of ERK1/2 and p38. ET-18-O-CH<sub>3</sub>-induced inactivation of these protein kinases and NF-κB was attenuated by celecoxib. Taken together, the above findings suggest that COX-2 up-regulation does not necessarily confer the resistance to apoptosis in ras-transformed cells, but may rather sensitize these cells to apoptotic death. This work was supported by the grant (01-PJ1-PG1-01CH05-0001) from the Ministry of Health and Welfare, Republic of Korea.

keyword : Cyclooxygenase-2, Apoptosis, ET-18-O-CH<sub>3</sub>