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# ET-18-O-$CH_3$ INDUCED APOPTOSIS IN H-RAS TRANSFORMED HUMAN BREAST EPITHELIAL CELLS THROUGH UP-REGULATION OF CYCLOOXYGENASE-2

Hye-Kyung Na and Young-Joon Surh

College of Pharmacy, Seoul National University, Seoul 151-742, Korea

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-$CH_3$ , 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 $E_2$ ($PGE_2$). The apoptotic effect of ET-18-O-$CH_3$ involved intracellular accumulation of reactive oxygen species. Treatment of MCF10A-ras cells with the selective COX-2 inhibitor celecoxib (50 $\mu$M) attenuated ET-18-O-$CH_3$ -induced apoptosis as well as COX-2 expression and production of $PGE_2$ , suggesting that unusual expression of COX-2 by ET-18-O-$CH_3$ is causatively implicated in the induction of apoptosis. ET-18-O-$CH_3$ inhibited activation of both Akt/protein kinase B and transcription factor NF-$\kappa$B that are involved in cell survival pathways. ET-18-O-$CH_3$ also inhibited activation of ERK1/2 and p38. ET-18-O-$CH_3$ -induced inactivation of these protein kinases and NF-$\kappa$B 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-CH3