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ROLES OF PGE_2 AND 15-DEOXY-$D^{12,14}$ PROSTAGLANDIN J_2 IN ET-18-O-CH_3-INDUCED INFLAMMATORY CELL DEATH

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Cyclooxygenase-2 (COX-2) is an inducible enzyme expressed in response to a variety of cytokines and other proinflammatory stimuli. It has been known that aberrant up-regulation of COX-2 is associated with resistance to apoptosis. Contrary to the above notion, treatment of MCF10A-ras cells with the anti-tumor agent ET-18- O-CH $_3$ caused increased expression of COX-2 and its mRNA transcript, while inducing apoptosis as revealed by proteolytic cleavage of poly(ADP-ribose)polymerase, caspase-3 activation, and positive TUNEL staining. To determine whether the ET-18- O-CH_3 -induced apoptosis is associated with up-regulation of COX-2 expression, the selective COX-2 inhibitor celecoxib was used. Celecoxib treatment attenuated ET-18- O-CH_3 -induced apoptosis as well as COX-2 expression and PGE_2 production, suggesting that induction of COX-2 by ET-18-O-CH_3 is causally linked to the induction of apoptosis. In another study, PGE_2 and 15-deoxy-$D^{12,14}$ prostaglandin J_2 (15d-PGJ_2) induced apoptosis in MCF10A-ras cells. ET-18-O-CH_3 induced expression of EP2 receptor and peroxisome proliferator-activated receptor γ (PPAR γ). GW9662, an antagonist of PPAR γ, suppressed the ET-18-O-CH_3-induced COX-2 expression. These findings suggest that ET-18-O-CH_3 induces COX-2 expression through interaction with PPAR γ that PGE_2 and 15d-PGJ_2 accumulated as a consequence of COX-2 up-regulation may mediate apoptosis in ET-18-O-CH_3-treated MCF10A-ras cells.

Keyword : COX-2, Apoptosis, MCF10A-ras