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Induction of Heme Oxygenase-1 By 15-Deoxy-Delta12,14-Prostaglandin J2 Is Mediated Through Activation of Transcription Factor Nrf2 in Mcf-7 Cells.

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Peroxisome proliferator-activated receptor gamma (PPAR-gamma), a member of the nuclear hormone receptor superfamily, is involved in the suppression of growth of several types of tumors such as liposarcoma, cancers of breast, prostate, and colon, possibly through induction of cell cycle arrest and/or apoptosis. 15-Deoxy- Delta12,14-prostaglandin J2 (15d-PGJ2), the natural PPAR-gamma ligand, displays a potent anti-inflammatory effect at high concentrations through direct inhibition of nuclear factor (NF)-kappa B activation. However, recent data indicate that cyclopentenone PGs have cytoprotective effect at low concentrations in several cell lines, but the molecular mechanisms of such protection are still unclear. In this study, we investigated the effects of 15d-PGJ2 on the viability of estrogen receptor (ER)-positive human breast cancer cell lines, MCF-7 cells. Treatment of MCF-7 cells with 15d-PGJ2 resulted in a dose- and time-dependent increase in the expression and activity of heme oxygenase-1 (HO-1), that plays a key role in cytoprotection against oxidative insult. Reverse transcription-polymerase chain reaction (RT-PCR) revealed that the expression of ho-1 mRNA was induced by 15d-PGJ2 in a dose-dependent manner. 15d-PGJ2 induced phosphorylation of Akt/PKB in a time- and concentration-dependent manner. Up-regulation of HO-1 by 15d-PGJ2 was suppressed in cells pretreated with the phosphatidyl inositol-3 kinase (PI-3k) inhibitor LY294002. Furthermore, 15d-PGJ2 stimulated the expression of Nrf2 in a time-dependent manner, leading to increased Nrf2 binding to the resident ho-1 antioxidant response element (ARE). These findings suggest that induction of HO-1 expression by 15d-PGJ2 is mediated by the transcription factor Nrf2, which might be implicated in the resistance of human breast cancer cells against oxidative stress induced by redox-cycling anticancer drugs.

Keyword : 15d-PGJ2, PI-3K/Akt pathway, HO-1, Nrf2, MCF-7 cells