

level, which was completely abolished by pretreatment with catalase. However, this activation of ERK does not appear to be attributed to nuclear translocation of Smads, because nuclear translocation of Smads in response to TGF- β was not affected by inhibiting ERK signaling pathway, and also treatment with H₂O₂ alone did not cause the nuclear translocation of Smads. On the other hand, ERK inhibition caused the disruption of interaction between Smad3 and Sp1 induced by TGF- β , suggesting that ERK signaling pathway might be necessary for their interaction and essential for the TGF- β induction of p21^{WAF1/Cip1}. Taken together, these results suggest that H₂O₂-mediated ERK signaling pathway might be required for p21^{WAF1/Cip1} expression by TGF- β and play as a key determinant for interaction between Smads and Sp1 transcription factor.

[PC1-30] [2003-10-10 09:00 - 13:00 / Grand Ballroom Pre-function]

15-DEoxy-d^{12,14} Prostaglandin J₂ Rescues Pc12 Cells From Hydrogen Peroxide-induced Apoptosis Through Upregulation Of Heme Oxygenase-1

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Oxidative stress induced by reactive oxygen intermediates (ROIs) has been implicated in a variety of human diseases including cancer, diabetes, rheumatoid arthritis and neurodegenerative disorders. Hydrogen peroxide (H₂O₂), a representative ROI which is produced during the cellular redox process, can cause cell death via apoptosis and/or necrosis depending on its concentrations. 15-Deoxy-D^{12,14} prostaglandin J₂ (15d-PGJ₂), a dehydration product of prostaglandin D₂, has been reported to possess a number of biological activities such as anti-inflammatory, anticarcinogenic, and antioxidative properties. In this study, we have investigated the protective effect of 15d-PGJ₂ on H₂O₂-induced oxidative stress in rat pheochromocytoma (PC12) cells. H₂O₂ treatment caused oxidative PC12 cell death in a concentration dependent manner. PC12 cells treated with H₂O₂ exhibited apoptotic cell death as determined by morphological features, internucleosomal DNA fragmentation, cleavage of poly (ADP-ribose)polymerase, an increased Bax/Bcl-X_L ratio and decreased mitochondrial membrane potential, all of which were inhibited or restored by relatively low concentration of 15d-PGJ₂ pretreatment. In another experiment, PC12 cells treated with 15d-PGJ₂ exhibited transient activation of Akt/protein kinase B as well as extracellular signal-regulated kinase 1/2 and induction of heme oxygenase-1 (HO-1) expression and nuclear translocation of Nrf-2 as an adaptive response to oxidative insult. In conclusion, H₂O₂ caused apoptosis in PC12 cells by inducing oxidative stress, which was effectively protected by 15d-PGJ₂ through augmentation of the cellular antioxidant defence involving HO-1 and Nrf-2.

[PC1-31] [2003-10-10 09:00 - 13:00 / Grand Ballroom Pre-function]

Eupatilin, a Pharmacologically Active Flavone Derived from Artemisia Plants, Induces Cell Cycle Arrest in Ras-Transformed Human Mammary Epithelial Cells

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Extracts of *Artemisia asiatica* Nakai (Asteraceae) possess anti-inflammatory and anti-oxidative activities. Eupatilin (5,7-dihydroxy-3,4,6-tri-methoxy-flavone), one of the pharmacologically active ingredients derived from *Artemisia asiatica*, was shown to induce apoptosis in human promyelocytic leukemia (HL-60) cells (H.-J. Seo and Y.-J. Surh, *Mutat. Res.*, 496, 191-198, 2001). In the present study, we examined the cytostatic effects of eupatilin in H-ras-transformed human breast epithelial (MCF10A-ras) cells. Eupatilin inhibited the growth of MCF10A-ras cells in a concentration-dependent and time-related manner as determined by MTT reduction and [³H]thymidine incorporation assays. To determine whether the antiproliferative effects of eupatilin are mediated through dysruption of the cell cycle in MCF 10A-ras, DNA contents were analyzed by the flow cytometry. The area of the peak corresponding to a hypodiploid or apoptotic DNA content didn't change by eupatilin treatment. However, eupatilin (100 μ M) blocked the cell cycle progression in both G1/S and G2/M phase. Moreover, eupatilin inhibited the expression of Cdk2, Cdc2, cyclin B1 and cyclin D1, which are responsible for mediating