Ultraviolet B (UVB) is known to induce apoptosis in human melanocytes. Here we show the cytoprotective effect of sphingosine-1-phosphate (S1P) against UVB-induced apoptosis. We also show that UVB-induced apoptosis of melanocytes is mediated by caspase-3 activation and poly(ADP-ribose) polymerase (PARP) cleavage, and that S1P prevents apoptosis by inhibiting this apoptotic pathway. We further investigated three major subfamilies of mitogen-activated protein (MAP) kinases and the Akt pathway after UVB irradiation. UVB gradually activated c-Jun N-terminal kinase (JNK) and p38 MAP kinase, while extracellular signal-regulated protein kinase (ERK) was inactivated transiently, but the Akt pathway was not affected. Blocking of the p38 pathway using SB203580 promoted cell survival and inhibited the activation of caspase-3 and PARP cleavage. These results suggest that p38 activation may play an important role in the UVB-induced apoptosis of human melanocytes. To explain this cytoprotective effect, we next examined whether S1P could inhibit UVB-induced JNK and p38 activation. However, S1P was not found to have any influence on UVB-induced JNK or p38 activation. In contrast, S1P clearly stimulated the phosphorylation of ERK, and the specific inhibition of the ERK pathway using PD98059 abolished the cytoprotective effect of S1P. Based on these results, we conclude that the activation of p38 MAP kinase plays an important role in UVB-induced apoptosis, and that S1P may show its cytoprotective effect through ERK activation in human melanocytes.

[PA1-54] [2003-10-10 14:00 - 17:30 / Grand Ballroom Pre-function]

Lysophosphatidic acid Inhibits Melanocyte Proliferation via Cell Cycle Arrest

Kim Dong-Seok°, Park Seo-Hyoung, Kim Sung-Eun, Sohn Uy-Dong, Park Kyoung-Chan
Research Division for Human Life Sciences, Seoul National University, Department of Dermatology, Seoul National University College of Medicine, Department of Pharmacology, College of Pharmacy, Chung-Ang University

Lysophosphatidic acid (LPA) is a well-known mitogen in various cell types. However, we were surprised to find that LPA inhibits melanocyte proliferation. Thus, we further investigated the possible signaling pathways involved in melanocyte growth inhibition. We first examined the regulation of the three major subfamilies of mitogen-activated protein (MAP) kinases and of the Akt pathway by LPA. The activations of extracellular signal-regulated protein kinase (ERK) and c-Jun N-terminal kinase (JNK) were observed in concert with the inhibition of melanocyte proliferation by LPA, whereas p38 MAP kinase and Akt were not influenced by LPA. However, the specific inhibition of the ERK or JNK pathways by PD98059 or D-JNKI1, respectively, did not restore the antiproliferative effect. We next examined changes in the expression of cell cycle related proteins. LPA decreased cyclin D_1 and cyclin D_2 level but increased $p21^{WAF1/CIP1}$ (p21) and $p27^{KIP1}$ (p27) levels, which are known inhibitors of cyclin-dependent kinase. Our results suggest that LPA induces cell cycle arrest by regulating the expressions of cell cycle related proteins.

[PA1-55] [2003-10-10 14:00 - 17:30 / Grand Ballroom Pre-function]

Induction of Apoptosis in Chinese Hamster Lung Cells by NOCF via Caspase-dependent Bax expression and Cytochorme c release.

BangWool Lee°, SeonHee Oh, ByungHoon Lee
College of Pharmacy, Wonkwang University

Carbofuran(CF) is one the most widely used carbamate pesticides in the world applied for insect and nematode control. Due to its widespred use in agriculture and households. contaminaion of food, water, and air has become serious, and consequently adverse health effects are inevitable in humans, animals, wildlife and fish, it has reported that CF alone or in combination with other carbamate insecticides influences the level of reproductive and metabolic hormones such as thyroxine and corticosterone, and results in impairment of endocrine. immun behavioral functions. we investigated the effects of NOCF on the Chinese hamster lung fibroblast(CHL) induction of apoptosis. The treatment CHL cells with NOCF caused activation of caspase-3,8,9 protease. NOCF did affect the expression of proapoptotic protein bax and bid did cause a release of mitochondria cytochrome c into cytosol. A broad-spectrum caspase inhibitor and a caspase 8-specific inhibitor completely blocked NOCF-induced activation of caspase 3 and cell death. These findings and data showing the early release of cytochrome c,