[PA1-38] [2003-10-10 14:00 - 17:30 / Grand Ballroom Pre-function]

The Role of Sphingosine-1-phosphate in Melanogenesis

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This study shows that sphingosine-1-phosphate (S1P) significantly inhibits melanin synthesis in a concentration-dependent manner, and that the activity of tyrosinase was also reduced in S1P-treated cells. In contrast, a specific extracellular signal-regulated protein kinase (ERK) pathway inhibitor, PD98059 increased tyrosinase activity and melanin production, and PD98059 restored the reduced tyrosinase activity and pigmentation induced by S1P. We also found that S1P induces the sustained activation of ERK and the subsequent degradation of microphthalmia-associated transcription factor (MITF), which plays a key role in melanogenesis. Thus, we further studied the relationship between the ERK pathway and melanin synthesis. PD98059 was found to prevent the MITF phosphorylation and degradation induced by S1P and to abrogate reduced tyrosinase and tyrosinase-related protein 1 (TRP1) production by S1P. These results indicate that the ERK pathway is potently involved in the melanogenic signaling cascade, and that S1P-induced ERK activation contributes to reduced melanin synthesis via MITF degradation.

[PA1-39] [2003-10-10 14:00 - 17:30 / Grand Ballroom Pre-function]

Induction of apoptosis and G_1 arrest by LJ-331, a novel nucleoside analog,in human leukemia HL-60 cells

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In a continuous effort to develop novel anticancer agents we newly synthesized and evaluated the antitumor activity of nucleoside analogues. One analogue, 4-[2-Chlor-6-(3-iodo-benzylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentanecarboxylic acid methylamide (LJ-331), has been shown to exert a potent inhibition of human cancer cell growth in vitro including human lung (A549), stomach (SNU-638) and leukemia (HL-60) cancer cells. Following mechanism of action study revealed that LJ-331 induces cell cycle arrest at the G_1 phase in HL-60 cells and evokes apoptotic phenomena such as an increase in DNA ladder intensity and chromatin condensation by a dose- and time-dependent manner. LJ-331 also activated the caspase-3 activity in HL-60. This result suggests that the growth inhibition of human cancer cells by LJ-331 might be related to the cell cycle arrest and induction of apoptosis.

[PA1-40] [2003-10-10 14:00 - 17:30 / Grand Ballroom Pre-function]

Effects of E-4031 on hERG channel currents expressed in CHO cells in an accordance with temperature

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The most commonly proposed mechanism for QT interval prolongation(LQT) by pharmaceuticals is inhibition of the rapid delayed rectifier potassium channel (I_{Kr}). The LQT potency of pharmaceuticals can be effectively evaluated by examining the effect on hERG channels expressed in CHO cells, known to be equal to I_{Kr}. But, It was known that hERG channels according to increase the bath temperature have several changes, including a marked increase in the amplitude of the outward and tail currents, and acceleration of the rates of activation, recovery from inactivation, and deactivation. Therefore, we need to examine that the blockade of hERG channels by pharmaceuticals was changed in an accordance with temperature. We have investigated the effect of E-4031, which block selectively on hERG channels, on hERG currents at various temperatures. Concentration-response

relations for E-4031 of hERG channel block were obtained in the concentrations between 1, 10 and 100 nM. At 26°C(room temperature), 1, 10 and 100 nM E-4031 decreased hERG currents by 17, 36 and 99% respectively. IC_{50} was 14.18 nM. At 30°C(middle temperature), 1, 10 and 100 nM E-4031 decreased hERG currents by 13, 28 and 67% respectively. IC_{50} was, 6.55 nM. At 35°C(physiological temperature), 1, 10 and 100 nM E-4031 decreased hERG currents by 21, 43 and 99% respectively. IC_{50} was 9.98 nM. It may be concluded that the effect of E-4031 on hERG currents was temperature-independent.

[PA1-41] [2003-10-10 14:00 - 17:30 / Grand Ballroom Pre-function]

Studies of the functional roles of DRY motif in dopamine D2 and D3 receptors

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Asparate-arginine-tyrosine (DRY) motif is highly conserved among GPCRs, and the alternation of this motif has been reported to exist naturally and involved with various diseases that involves constitutive activation or desensitization of receptor. To understand the interaction between G protein and β-arrestin more systemically, we produced the DHY mutants for the D2R and D3R. The introduction of R to H mutation in DRY motif caused differential effects on the characteristics of D2R and D3R: for both receptors receptor-effector coupling and agonist-induced translocation of b arrestins were disrupted; for D2R agonist-induced receptor phosphorylation and receptor sequestration were blocked; the subcellular localization was not changed for D2R but more receptors were observed intracellularly for D3R; the ligand binding properties of D2R were not changed but the affinity for the antagonists was slightly increased for D3R.

[PA1-42] [2003-10-10 14:00 - 17:30 / Grand Ballroom Pre-function]

Induction of cell cycle arrest and apoptosis by an indirubin analog, a CDK inhibitor, in human lung cancer cells

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Cyclin-dependent kinases (CDKs) regulate the cell division cycle, apoptosis, transcription and differentiation. Inhibition of CDK is a promising target in development of anti-cancer agents. An indirubin analog (AGM011), a CDK inhibitor, is a synthetic compound that inhibits human cancer cell growth in vitro. AGM011 showed a potent cytotoxicity in cultured human cancer cell lines (IC_{50}= 5.43 μM for A549, human lung cancer cell; IC_{50}= 1.21 μM for SNU-638, human stomach cancer cell; IC_{50}= 25.49 μM for Col2, human colon cancer cell; IC_{50}= 5.87 μM for HT1080, human fibrosarcoma cell; IC_{50}= 9.23 μM for HL-60, human leukemia cell). Prompted by the potent cytotoxicity, additional action mechanism studies were performed with cultured A549 human lung cancer cells. Using flow cytometric analysis, AGM011 showed G2/M phase cell cycle arrest and induction of apoptosis in a concentration- and time-dependent manner with characterizing apoptotic features under microscopic observation and DNA fragmentation by agarose gel electrophoresis. These results indicate that AGM011 induces the cell cycle arrest and apoptosis against human cancer cells. Therefore, it might be developed as an effective anti-cancer agent.

[PA1-43] [2003-10-10 14:00 - 17:30 / Grand Ballroom Pre-function]

Chronic administration of quercetin in rats causes the suppression of glutathione metabolism

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The present study was performed to investigate the effects of chronic administration of quercetin on lipid