

[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 potentially involved in the melanogenic signaling cascade, and that S1P-induced ERK activation contributes to reduced melanin synthesis via MITF degradation.

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Induction of apoptosis and G₁ 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-dihydroxycyclopentanecarboxylic 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 G₁ 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.

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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