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Helenalin, a cell-permeable pseudoguainolide sesquiterpene lactone, is a potent anti-inflammatory agent that inhibits NF-κB DNA binding activity by selectively alkylating the p65 subunit of NF-κB. Transcription factors such as NF-κB provide powerful target of drugs to use in the treatment of cancer. Human promyelocytic leukemia HL-60 cells are differentiated into monocytic or granulocytic lineage when treated with 1,25-dihydroxyvitamin D_3 [1,25-$(OH)_2D_3$] or all-trans-retinoic acid (ATRA), respectively. In this study, we investigated the effect of helenalin on the differentiation of HL-60 leukemia cells. Helenalin by itself induced HL-60 cell differentiation via inhibition of NF-κB activity in a concentration-dependent manner, and also markedly increased the degree of HL-60 cell differentiation when simultaneously combined with low doses of either 1,25-$(OH)_2D_3$ or ATRA. Flow cytometric analysis indicated that helenalin induced HL-60 cell differentiation into granulocytes, and stimulated 1,25-$(OH)_2D_3$- and ATRA-induced differentiation into monocytes/macrophages and granulocytes, respectively. Moreover, PKC and ERK inhibitors inhibited HL-60 cell differentiation enhanced by helenalin, while PI3-K and p38 MAPK inhibitors did not. These results indicated that helenalin induced and enhanced HL-60 cell differentiation via the inhibition of NF-κB activity and activation of PKC and ERK pathways.

[PC3-9] [2003-10-10 09:00 - 13:00 / Grand Ballroom Pre-function]

Up-regulation of Cyclin A-Cdk2 activity is associated with depolarization of mitochondrial membrane potential during apoptosis of human hepatoma SK-HEP1 cells induced by treatment with panaxadiol

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Here we show that panaxadiol, a ginseng saponin with a dammarane skeleton, induces acute apoptotic cell death in human hepatoma SK-HEP-1 cells as evidenced by analysis of DNA fragmentation, caspase activation, and changes in cell morphology. The kinetic study showed that panaxadiol-induced apoptosis is associated with depolarization of mitochondrial membrane potential and cytochrome c release. Sequential activations of caspases-9, and -3, or –7, but not of caspase 8 coincide well in a time dependent manner with mitochondrial membrane depolarization and cytochrome c release from mitochondria during apoptosis of SK-HEP-1 cells induced by treatment with panaxadiol. To further investigate the molecular mechanisms underlying the panaxadiol-induced apoptosis of the cells, we examined whether activities of Cyclin-dependent protein kinases, Cdk2 and Cdc2 are up-regulated during apoptosis of the cells by immune-complex kinase assay. Cdk2 kinase activity, but not the Cdc2 kinase activity is markedly up-regulated and the time-dependent up-regulation correlates well with the mitochondria membrane depolarization and cytochrome c release. In the presence of olomoucine or roscovitine, specific Cdks inhibitors, the depolarization of mitochondrial membrane potential and apoptotic progression are equally and effectively prevented in panxadiol-treated SK-HEP-1 cells. These results indicated that the induction of apoptosis in human hepatoma cells treated with panaxadiol requires the up-regulation of Cdk2 kinase activity that is functionally associated with depolarization of mitochondrial membrane potential and accordingly apoptosis progression.

[PC3-10] [2003-10-10 09:00 - 13:00 / Grand Ballroom Pre-function]

Monitoring the Expression Profiles of Doxorubicin-Resistant Acute Myelocytic Leukemia Cells by DNA Microarray Analysis

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Anticancer drug resistance occasionally occurs in malignant hematologic diseases such as acute myelocytic leukemia (AML) treated with chemotherapy and is a major problem to complete remission. Malignant cells primarily induce intrinsic resistance to treatment of anticancer drug, but gradually obtain acquired resistance to cytotoxic activities of chemotherapy. In this study, we monitored the expression profiles of doxorubicin resistance-