shown to inhibit experimental carcinogenesis and mutagenesis, but molecular mechanisms underlying its chemopreventive activities remain unclear. In the present work, we found that curcumin inhibited 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced expression of COX-2 in female ICR mouse skin when applied topically 30 min prior to TPA as determined by both immunoblot and immunohistochemical analyses. Multiple lines of evidence support the role of the eukaryotic transcription factor NF-κB in regulation of COX-2 expression. In agreement with this notion, the NF-κB inhibitor pyrrolidine dithiocarbamate suppressed not only NF-κB activation but also induction of COX-2 in mouse skin. Curcumin treatment attenuated TPA-stimulated epidermal NF-κB activation, which was associated with its blockade of degradation of the inhibitory protein IκBα and subsequent translocation of p65 subunit to nucleus. TPA treatment resulted in rapid activation via phosphorylation of extracellular signal-regulated protein kinase (ERK)1/2 and p38 mitogen-activated protein kinase (MAPK), which are upstream of NF-κB. The MEK1/2 inhibitor U0126 strongly inhibited NF-κB activation, while p38 MAPK inhibitor SB203580 failed to block TPA-induced NF-κB activation in mouse skin. Furthermore, U0126 blocked the TPA-induced IκBα phosphorylation by TPA, thereby blocking the nuclear translocation of NF-κB. Curcumin inhibited the catalytic activity of ERK1/2 in mouse skin. Taken together, suppression of COX-2 expression by inhibiting ERK activity and NF-κB activation may represent molecular mechanisms underlying previously reported anti-tumor promoting effects of this phytochemical in mouse skin tumorigenesis.

[PC1-18] [2003-10-10 09:00 - 13:00 / Grand Ballroom Pre-function]

p38 MAP kinase and Akt regulate Bax translocation from mitochondria during ceramide-mediated apoptosis

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Ceramide is an important lipid messenger involved in mediating a variety of cell functions including apoptosis. Previously, we have shown that ceramide induces Bax translocation which is associated with cytochrome c release from the mitochondria. In this study, we show that p38 MAP kinase is involved in ceramide-induced Bax translocation. In human leukemic cells, ceramide stimulated the phosphorylation of p38 MAP kinase. Preincubation of cells with SB203580, a specific inhibitor of p38 inhibited DNA fragmentation induced by cell-permeable ceramide. Protection from apoptosis by SB203580 inhibited activation of caspase-3 and translocation of Bax. Furthermore, expression of dominant negative mutant of p38 attenuated ceramide-induced Bax translocation and apoptosis, indicating that p38 activation is required for Bax-mediated apoptosis induced by ceramide. In respect to PI3 kinase pathway, expression of constitutively active Akt reduced cell death and Bax translocation. We also found that expression of dominant-negative p38 suppressed ceramide-induced Akt dephosphorylation, indicating crosstalk between the two signaling pathways. Our results show that both the p38 and Akt pathways are involved in ceramide-mediated apoptosis by regulating Bax translocation.

[PC1-19] [2003-10-10 09:00 - 13:00 / Grand Ballroom Pre-function]

Potent inhibition of human cytochrome P450 1 enzymes by SY-081

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Recently we have reported that various hydroxystilbenes show strong inhibition of human cytochrome P450 1 enzyme activities. A series of syntheic trans-stilbene derivatives were prepared and their inhibitory potentials were evaluated with the bacterial membrane of recombinant human cytochrome P450 1A1, 1A2 and 1B1 coexpressed with human NADPH-P450 reductase to find a new inhibitor of cytochrome P450 enzymes. Of the compounds tested, SY-081 exhibited a potent inhibition of human cytochrome P450 1B1 with an IC_{50} value of 2.6 nM. SY-081 also showed the inhibition of cytochrome P450 1A1 with IC_{50} value of 47.6 nM and cytochrome P450 1A2 with IC_{50} value of 116.6 nM. SY-081 showed 18-fold selectivity for cytochrome P450 1B1 over 1A1 and 45-fold selectivity for cytochrome P450 1B1 over 1A2. We also have investigated the inhibition kinetics of cytochrome