P450 1A1, 1A2, or 1B1 by SY-081. The modes of inhibition by SY-081 were mixed-type for all three cytochrome P450 1 enzymes. The K_i values of SY-081 for P450 1A1, 1A2, or 1B1 inhibition were 15.1, 29.6, or 1.4 nM, respectively. Effect of preincubation with NADPH on inhibition of cytochrome P450 1A1, 1A2, 1B1 by SY-081 was determined. Taken together, the data suggest that SY-081 is a new potently selective inhibitor of cytochrome P450 1B1 and understanding of the detailed mechanism of SY-081 action will be helpful to elucidate how cytochrome P450 1B1 is involved in the metabolism of procarcinogens such as benzo[a]pyrene or DMBA.

[PC1-20] [2003-10-10 09:00 - 13:00 / Grand Ballroom Pre-function]

Induction of cell death by 2,4,3',5'-tetramethoxystilbene in human acute promyelocytic leukemia (HL-60) cells and its mechanism.

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We have previously shown that 2,4,3',5'-tetramethoxystilbene (TMS), a synthetic trans-stilbene analogue, is one of the most potently selective inhibitor of human cytochrome P450 1B1 in vitro and in vivo. In the present studies, the apoptotic effects of TMS were investigated in HL-60 cells. The effects of TMS on the proliferation of HL-60 cells were determined with MTT assay. TMS exhibited cytotoxicity with an IC_{50} value of 37 nM. Cotreatment with TMS and etoposide, a well-known anticancer drug significantly enhanced the cytotoxicity. We have investigated the detailed mechanism of cell death by TMS. We have determined that the cytotoxic effect of TMS was due to the induction of apoptosis, which was confirmed by Annexin V staining, poly(ADP-ribose) polymerase (PARP) cleavage, and cytochrome c release. TMS also induced DNA fragmentation in a dose-dependent manner. Taken together, we suggest that the apoptosis-inducing activity and inhibitory activity of cytochrome P450 1B1 of TMS make this compound be useful for anticancer strategies of hormone-mediated carcinogenesis.

[PC1-21] [2003-10-10 09:00 - 13:00 / Grand Ballroom Pre-function]

Inhibitory mechanism of cyclohexylimminobenzoxathiol LYR-64 compound on LPS-induced NO production

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Nitric oxide (NO) is known to work as an important signaling molecule involved in regulating a wide range of biological activities in the neuronal, vascular, and immune system. NO and its metabolites mediate a number of host defence functions and are also implicated in the pathogenesis of tissue damage associated with inflammation. Cyclohexylimminobenzoxathiol LYR-64 compound inhibited LPS-induced NO production in murine macrophages Raw264.7 with an IC50 value of 0.7 uM with 95.9% inhibition at 3 uM, 63.5% at 1 uM and 30.2% at 1 uM. Moreover, iNOS mRNA and its protein expressions were abrogated by the cyclohexylimminobenzoxathiol LYR-64 compound in LPS-stimulated Raw264.7 cells. To further investigate the mechanism responsible for the inhibition of iNOS gene expression by cyclohexylimminobenzoxathiol LYR-64 compound, we examined the effect of the compound on NF-kB signaling. We found that cyclohexylimminobenzoxathiol LYR-64 compound inhibited NF-kB DNA binding activity as well as nuclear translocation, but did not inhibit IkB degradation.

[PC1-22] [2003-10-10 09:00 - 13:00 / Grand Ballroom Pre-function]

Inhibitory effects of [6]-gingerol on phorbol ester-induced cox-2 expression in mouse skin: p38 mapk and p65/rela as possible molecular targets

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[6]-Gingerol, a major pungent ingredient of ginger (Zingiber officinale Roscoe, Zingiberaceae) has a wide array of pharmacologic effects. Our previous studies have demonstrated that [6]-gingerol inhibits mouse skin tumor promotion and anchorage-independent growth of cultured mouse epidermal cells stimulated with epidermal growth factor. In this study, we have investigated the molecular mechanisms underlying anti-tumor promoting effects of [6]- gingerol on mouse skin carcinogenesis. Cyclooxygenase-2 (COX-2), a key enzyme in the prostaglandin biosynthesis, has been recognized as a molecular target for many chemopreventive as well as anti-inflammatory agents. The murine COX-2 promoter harbours several transcriptional elements, particularly those involved in regulating inflammatory processes. One of the essential transcription factors responsible for COX-2 induction is NF-κB. Topical application of phorbol ester-induced COX-2 expression in both mouse skin in vivo and non-trnasfromed murine keratinocytes (Pam212) in culutre. [6]-Gingerol treatment prior to topical application of phorbol ester inhibited the COX-2 expression through suppression of NF-κB activation in mouse skin. [6]-Gingerol, through possible down-regulation of p38 MAPK, abrogated the DNA binding activity and transcriptonal activity of NF-κB by blocking phosphorylation of p65/RelA at the Ser 536 residue. These findings suggest that [6]-gingerol exerts an anti-tumor promotional activity through inhibition of the p38 MAPK-NF-κB signaling cascade in mouse skin.

[PC1-23] [2003-10-10 09:00 - 13:00 / Grand Ballroom Pre-function]

Apicidin-induced gelsolin expression via Sp1 sites is mediated by PKC signaling

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Gelsolin, a actin binding protein, has been demonstrated to be involved in controlling cell morphology, motility, signaling, and apoptosis. It's expression is frequently downregulated in cervix cancer and several types of different human cancers indicating the role of gesolin in suppression of tumorigenicity. Apicidin, a novel histone deacetylase inhibitor, has been shown to cause growth arrest and morphological change of cancer cells, resulting from the alternation of protein expression, such as $p21^{WAF1/Cip1}$ and gelsolin. However, the molecular mechanism of apicidin induction of gelsolin remains to be elucidated. In this study, we investigated the molecular mechanism of gelsolin expression by apicidin. Treatment of HeLa cells with mithramycin, which has been demonstrated to inhibit the binding of Sp1 family transcription factors to genes containing G+C-rich promoters, led to the downregulation of gelsolin expression by apicidin indicating that Sp1 family transcription factors might mediate apicidin induction of gelsolin. In addition, inhibitor study using different types of well known specific kinase inhibitors revealed that apicidin induction of gelsolin expression was inhibited by PKC inhibitor calphostin C but not by other kinase inhibitors. similarly, PKCe dominant-negative mutant also decreased the level of gelsolin protein induced by apicidin. In summary, Sp1 transcription factors is responsible for apicidin induction of gelsolin and this transcriptional activation might be mediated by protein kinase C.

[PC1-24] [2003-10-10 09:00 - 13:00 / Grand Ballroom Pre-function]

Characterization of Acharan Sulfate Binding Proteins in Murine Lewis Lung Carcinoma Cell

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We have focused on various biological activities of acharan sulfate (AS) isolated from the giant African snail Achatina fulica. In a previous study, AS showed antiangiogenic and immunomodulating activity. We also investigated antitumor activity of AS. In vitro AS had no cytotoxicity within 0 to 200 ug/ml in tumor cells such as Lewis lung carcinoma(LLC) , KM1214 (human colon cancer cell) and Caki-1 (human kidney cancer cell) by both MTT and SRB assay. In vivo AS was used to treat C57BL/6 mice bearing LLC by subscutaneous injection. On day 21st, tumor tissues were removed and weighed. The tumor growth was inhibited by 37% at