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We have previously reported that activation of K^+-Cl^--cotransport (KCC) by N-ethylmaleimide (NEM) induces apoptosis through generation of reactive oxygen species (ROS) in HepG2 human hepatoblastoma cells. In this study we investigated the possible role of phospholipase A_2 (PLA_2)-arachidonic acid (AA) signals in the mechanism of the NEM actions. In these experiments we used arachidonyl trifluoromethylketone ($AACOCF_3$), bromoenol lactone (BEL) and *p*-bromophenacyl bromide (BPB) as inhibitors of the calcium-dependent cytosolic PLA_2 ($cPLA_2$), the calcium-independent PLA_2 ($iPLA_2$) and the secretory PLA_2 ($sPLA_2$), respectively. BEL significantly inhibited the NEM-induced KCC activation, ROS production and apoptosis, whereas $AACOCF_3$ and BPB did not. NEM increased AA liberation in a dose-dependent manner, which was markedly prevented only by BEL. The NEM-induced actions (KCC activation, ROS generation and apoptosis) were not significantly altered by treatment with indomethacin and nordihydroguaiaretic acid (NDGA), selective inhibitors of cyclooxygenase (COX) and lipoxygenase (LOX), respectively. Treatment with AA or 5, 8, 11, 14-eicosatetraynoic acid (ETYA), a non-metabolizable analogue of AA, markedly activated the KCC, produced ROS and induced apoptosis. Collectively, these results suggest that AA liberated through activation of $iPLA_2$ may mediate the NEM-induced ROS generation, KCC activation, and apoptosis induction in HepG2 cells.

[PA1-6] [10/18/2002 (Fri) 09:30 - 12:30 / Hall C]

Inhibitory effect of 2-amino-3-ethoxycarbonyl-1-methyl pyrolo (3,2-b) naphtho-4,9-dione on tumor cell invasion in human fibrosarcoma cells by downregulating matrix metalloproteinase-2 and 9

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Matrix metalloproteinases (MMPs) play an important role in tumor invasion and metastasis by matrix degradation. To analyze the effect of 2-amino-3-ethoxycarbonyl-1-methyl pyrolo (3,2-b) naphtho-4,9-dione (compound 1) on the invasion or metastasis of cancer cells the expression of matrix metalloproteases (MMPs) was investigateded in human fibrosarcoma HT1080 cells by RT-PCR or gelatin zymographic methods. As a result, compound 1 decreased the expression of MMP-2 and 9, but increased the expression of a tissue inhibitor of metalloproteinase-1 (TIMP-1). In addition, compound 1 inhibited cancer cell migration and colony formation. These results suggest that compound 1 might be inhibiting tumor cell invasion and metastasis by suppression of MMPs and elevation of TIMP-1 production in tumor cells, and thus compound 1 could be a lead candidate for developing anti-metastatic or anti-invasive agent against cancer cell growth. (This work was supported in part by Korea research FoundationGrant, KRF-2001-005-F00023).

[PA1-7] [10/18/2002 (Fri) 09:30 - 12:30 / Hall C]

High-Throughput Screening for Novel Inhibitors of Protein-Tyrosine Phosphatase-1B

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Protein-tyrosine phosphatases (PTPs) constitute a family of receptor-like and cytoplasmic enzymes, which catalyze the dephosphorylation of phosphotyrosine residues in a variety of receptors and