Dietary organosurfur compounds including diallylsulfide, a component of garlic oil, have been shown to inhibit proliferation of tumar cells and suppress chemically-induced carcinogenesis in experimemtal animals. Since hepatocellular carcinoma is one of the most lethal malignancies and there is no effective preventive measure in this highly malignant disease to date, we wished to pursue the chemopreventive potential of the synthetic allylthiopyridazine derivatives (K compounds) on SK-Hep-1 hepatocarcinoma cells. Here, we report that the K compounds efficiently inhibited SK-Hep-1 cell proliferation through induction of apoptosis. Increased chain length at the 3-position of allylthiopyridazine ring improved potency of growth inhibition(3-propoxy>3-isopropoxy>3-ethoxy>3-methoxy>3-chloro derivatives).
Expression of the anti-apoptotic oncoprotein Bcl-2 was prominently decreased whereas the death-promoting Bax expression remained unchanged or slightly upregulated during the apoptosis precess in SK-Hep-1 cells treated with K compounds. We also provide evidence that the K compound-induced apoptosis involves cytochrome c release and caspase-3 activation. these resuls suggest that the allylthiopyridazine derivatives induce apoptosis in SK-Hep-1 hepatocarcinoma cells through a caspase-3-dependent mechanism, which may contribute to the chemopreventive function of these agents for hepatocellular carcinoma.

[PC1-4] [10/20/2000 (Fri) 15:30 - 16:30 / [Hall B]]

Study on the antiproliferative effects of apicidin derivative in tumor cell lines

Wang SY[O], Ahn SH, Lee HY[*], Hong SY[§], Han JW, Lee HW

Lab. of Biochemistry, College of Pharmacy, Sungkyunkwan University. College of Medicine, Konyang University *. College of Life Science and Natural Resources, Sungkyunkwan University §

Apicidin is a fungal metabolite shown to exhibit antiparasitic activity by the inhibition of histone deacetylase (HDAC). In this study, we evaluated apicidin derivative as a potential antiproliferative and detransforming agent. Treatment of HeLa cells with apicidin derivative resulted in morphological change, inhibition of HDAC *in vivo* and *in vitro* and cell cycle arrest at G_0/G_1 and G_2/M phase. Also, apicidin derivative showed a broad spectrum of antiproliferative activity against various cancer cell lines even though with differential sensitivity. In addition, apicidin derivative increased the expression of cyclin dependent kinase inhibitor, $p21^{WAF1/Cip1}$ and gelsolin which controls the length of actin stress fibers. Specially, the elevated levels of $p21^{WAF1/Cip1}$ led to decreased Rb phosphorylation. These results suggest that induction of histone hyperacetylation by apicidin derivative is responsible for the antiproliferative activity through selective induction of genes, which play important roles the cell cycle and cell mophology.

[PC1-5] [10/20/2000 (Fri) 15:30 - 16:30 / [Hall B]]

Alteration of antioxidant enzymes in response to oxidative stress and antioxidants

Kim JH[O], Kim AK

College of Pharmacy, Sookmyung Women's University

The induction of apoptosis by oxidative stress and the activity of antioxidant enzymes were investigated in SK-MEL-2 cells treated with hydrogen peroxide(H2O2). Cisplatin known to generate oxygen species was added to cells and the induction of apoptosis and the antioxidant enzyme activity were measured. The effects were compared with the results obtained H2O2 treated cells. After pretreatment with vitamin E and selenomethionine, SK-MEL-2 cells were exposed to H2O2 determine the effect of antioxidants on apoptosis. Also, H2O2 and cisplatin were concomitantly treated and the changes in apoptosis and the activity of antioxidant enzyme were investigated. The cell viability at 2.5mM H2O2 was declined gradually for 24 hrs and superoxide

dismutase(SOD) and glutathione peroxidase(GPX) activities increased in 3 hrs and then decreased or equaled in 6 hrs. The cell viability was declined and the antioxidant enzyme activities changed at 2.5 mM H2O2 and 50 uM cisplatin caused less alteration of the viability. Vitamin E and selenomethionine treated with 2.5 mM H2O2 were increased in the viability and changed in the antioxidant enzyme activities.

[PC1-6] [10/20/2000 (Fri) 15:30 - 16:30 / [Hall B]]

Inhibitory Effects on Several Human Carcinoma Cell Growth of Leuteinizing Hormone-Releasing Hormne Analogues, Leuprolide Acetate.

Seong Kon Seo°, Su-La Choi, Eun-Mi Kim and Pyung-Keun Myung

College of Pharmacy, Chungnam National University, Taejon 305-764, Korea.

Gonadotropin-releasing hormone (GnRH) has been shown to have an inhibitory effect on the growth of several hormone-dependent human tumors. LHRH binding sites and in vitro antiproliferative effects of LHRH analogues have been reported in human endometrial carcinoma cell. The effects of the LHRH agonist, leuprolide was studied on cell cytotoxicity, cell proliferation and cell death of the human endometrial cancer cell lines SNU-685 which was characterized in primary tumors of Korean patient and other cancer cell lines MCF-7, T24 and FB-13P. Antiproliferative effect on cells were determined by colorimetric methods, MTT and MTS/PMS assay. After 48 hr exposure to leuprolide acetate (1-300 μM), the proliferation of SNU-685 cell was reduced with a maximal decrease of about 20 % at 10 μM. Meanwhile, the proliferation of breast cancer cell line, MCF-7, urinary bladder cancer cell line, T24 or primary skin fibroblast, FB-13P cell was not affected significantly by leuprolide acetate.

[PC1-7] [10/20/2000 (Fri) 15:30 - 16:30 / [Hall B]]

Effect of p70 S6 kinase inhibitor on production of nitric oxide in RAW 264.7 cells

Jin HK°, Lee HY*, Hong SY§, Lee HW, Han JW

Lab. of Biochemistry, College of Pharmacy, Sungkyunkwan University. College of Medicine, Konyang University *. College of Life Science and Natural Resources, Sungkyunkwan University §

$p70^{S6K}$ plays an important role in the progression of cells from G_0/G_1 to S phase of the cell cycle by translational up-regulation of a family of mRNA transcripts that encode for components of the protein synthetic machinery. Rapamycin, $p70^{S6K}$ inhibitor, has been demonstrated to inhibit the production of nitric oxide (NO) induced by lipopolysaccharide (LPS) but not to reduce the expression of inducible nitric oxide synthase (iNOS), indicating that LPS-mediated NO production occurs via FKBP12-rapamycin-associated protein-dependent pathway by a mechanism probably involving posttranslational modification of iNOS. However, the relationship between LPS-induced NO production and $p70^{S6K}$ pathway is not completely understood. Here, we investigated the regulatory mechanism of iNOS expression by rapamycin. The activity of $p70^{S6K}$ was increased in RAW 264.7 cells treated with 1μg/ml LPS, and this increase was markedly attenuated by pretreatment of rapamycin. In parallel, rapamycin decreased NO production in LPS-stimulated RAW 264.7 cells. Furthermore, treatment with rapamycin led to a decrease in iNOS protein as well as mRNA expression levels. These results indicate that the inhibition of NO production by rapamycin might be mediated by the expression of iNOS regulated at transcriptional level, not the regulation of NOS activity through a posttranslational modification.

[PC1-8] [10/20/2000 (Fri) 15:30 - 16:30 / [Hall B]]