Natural Products Research Institute Seoul National University, Seoul 110-460, *College of Veterinary Medicine, Seoul National University, Suwon 441-744

Estrogens are potent mitogens in a number of target tissue including the mammary gland where they play a pivotal role in the development and progression of mammary carcinoma. Many endocrine disruptors (EDs) show the estrogenic effect. As the effects of EDs are reported to be main causes of hormone-related cancers such as breast cancer among women, we studied the effects of EDs using mouse mammary gland organ culture (MMOC) model. Also, the expression of estrogen receptor and p53 in the preneoplastic lesion was measured by using the flow cytometry. The research on more parameters related to the breast cancer will help in proving the mechanism of preneoplastic lesion by EDs. Moreover, it will help develop the antiestrogenic agent to inhibit the EDs activity.

[PC1-40] [10/20/2000 (Fri) 15:30 - 16:30 / [Hall B]]

Effects of PCBs on human mast cell line HMC-1.

Kwon OK°, Moon TC, Chang HW

College of Pharmacy, Yeungnam University, Gyongsan 712-749, Korea

Polychlorinated biphenyls (PCBs) are widely spread environmental contaminants consisting of chemical mixtures containing many of the 209 possible congeners. The potential immunomodulatory properties of PCBs have been the subject of extensive experimental investigations. The available evidence indicates that the immune system is a target for PCBs and is perhaps one of the most sensitive indicators for adverse PCB induced health effects.
Mast cells are the primary effector cells of immediate hypersensitivity reactions in humans and their numbers are increased in a broad spectrum of pathologic conditions.
We have examined effects of PCBs on human mast cell line HMC-1. In this study, expressions of xenobiotic responsive genes were analyzed to examine their molecular mechanisms in 2,2',4,4',5,5'-hexachlorobiphenyl (2,2',4,4',5,5'-hexaCB)-treated HMC-1. Reverse transcriptase-polymerase chain reaction (RT-PCR) and immunoblot analysis were performed to detect altered expressions of genes associated with 2,2',4,4',5,5'-hexaCB responses. The RT-PCR analysis showed that interleukin-6 (IL-6) and cyclooxygenase-2 (COX-2) genes were well expressed. Whereas interleukin-1β (IL-1β) and interleukin-4 (IL-4) did not expressed. In case of tumor necrosis factor-α (TNF-α) and aromatic hydrocarbon receptor (AhR), gene expressions were decreased by dose dose- and time-dependent manner. However transcription levels of AhR nuclear translocator (ARNT) were not changed.

[PC1-41] [10/20/2000 (Fri) 15:30 - 16:30 / [Hall B]]

Molecular Mechanism of Dioxin-induced Endocrine Disruption through Induction of Oxidative Estrogen Metabolism

Hurh Yeon-Jin°[1], Cho Myung-Haing[2] and Surh Young-Joon[1]

[1]College of Pharmacy, Seoul National University, Seoul 151-742, [2]College of Veterinary Medicine, Seoul National University, Suwon 441-744

2,3,7,8-Tetrachlorodibenzo-para-dioxin (TCDD; dioxin), the prototype agonist of the aromatic hydrocarbon (Ah) receptor, has a marked effect on estrogen metabolism in MCF10A cells by induction of human cytochrome P1A1(CYP1A1) and P450 1B1 (CYP1B1), which are responsible for hydroxylation of 17beta-estradiol (E_2) at C-2 and C-4 positions, respectively. The resulting catechol estragens, 2-hydroxyestradiol ($2OHE_2$) and 4-hydroxyestradiol ($4OHE_2$) have been

proposed to undergo redox cycling that could lead to the generation of reactive oxygen species (ROS) that would subsequently cause oxidative damage to DNA associated with hormonal carcinogenesis. The effects of TCDD on expression of CYP1A1 and CYP1B1 were measured by Western Blot analysis in human breast epithelial MCF10A cells. DNA strand breaks induced by $2OHE_2$ and $4OHE_2$ and in the presence of Cu(II) were assured by the conversion of supercoiled phage ΦX-174 DNA into open circular one. Furthermore, in MCF10A cells these catechol estrogens showed cytotoxic and antiproliferative effects. $2OHE_2$ induced intracellular accumulation of ROS in MCF10A cells as assessed by DCF-DA staining. MCF10A cells treated with $2OHE_2$ underwent apoptotic death as determined by morphological features, positive in situ terminal nick end-labeling (TUNEL) and poly(ADP-ribose)polymerase (PARP) cleavage. Concomitant with the apoptosis, $2OHE_2$ activated the c-Jun N-terminal protein kinase (JNK) pathway via phosphorylation and induced JNK expression. $4OHE_2$ increased DNA binding activity of nuclear factor-kappaB (NF-kappaB), but not of activator protein-1 (AP-1). In another experiment expression of cyclooxygenase-2, one of the target genes regulated by NF-kappaB, was induced by $4OHE_2$. In addition, $4OHE_2$ induced the activation of extracellular-signal regulated protein kinase (ERK) and p38 MAPK.

[PC1-42] [10/20/2000 (Fri) 15:30 - 16:30 / [Hall B]]

Activation of p38 mitogen-activated protein kinase in H-ras MCF10A cells: Possible role in H-ras-induced invasive phenotype

Lee Eun-Jung , Kim Mi-Sung ,Moon Aree

College of Pharmacy, Duksung Women's University, Seoul 132-714

One of the most frequent defects in human cancer is the uncontrolled activation of the ras-signaling pathways. We have previously shown that H-ras, but not N-ras, induces an invasiveness in human breast epithelial cells (MCF10A), while both H-ras and N-ras induce transformed phenotype. Since migration plays a crucial role in invasion, we examined motility of MCF10A cells transformed with H-ras or N-ras. Here, we show that cell motility was greatly increased by H-ras, but not N-ras, suggesting that H-ras-induced invasive phenotype may be mainly due to enhanced cell motility. It has been recently shown that p38, a member of the mitogen activated protein (MAP) kinase family, is important for cell migration. We wished to investigate the functional role of p38 MAP kinase in H-ras-induced invasive phenotype. We show that p38 is prominently activated in H-ras MCF10A cells comparing to the parental MCF10A cells or N-ras MCF10A cells, while no significant difference was found in the activation of stress-activated protein kinase-1/c-Jun N-terminal protein kinase (SAPK-1/JNK). Extracellular signal-regulated protein kinase (ERK)-1,2 were activated in both H-ras and N-ras MCF10A cells. These results suggest a possible involvement of p38 in H-ras-induced invasiveness/motility. Effect of a specific p38 inhibitor, SB203580, on the H-ras-mediated invasion is currently being investigated.

[PC1-43] [10/20/2000 (Fri) 15:30 - 16:30 / [Hall B]]

Expression of novel human angiotensin II/vasapressin like like gene during coculture of BMMC with swiss3T3 fibroblast

Moon TC, Yanoshita R, Murakami M, Kudo I, Chang HW

College of Pharamcy, yeungnam University

Mast cells have been regarded as one of the most important effector cells in IgE-dependent allergic response. There are at least two distinct population of rodent mast cells. One is connective mast cells (CTMC) and the other is mucosal mast cells (MMC). CTMC contain heparin