on immunopathology, cellular immunity, humoral immunity, and macrophages function. Liver weight was significantly increased in the mice exposed to BPA as dose-dependent manner. Hematological parameters including WBC were altered in the mice exposed to BPA. Decrease in CD3+ and CD4+CD8- cells among splenocytes as well as CD4+CD8- and CD4-CD8+ cells among thymocytes was resulted in the mice subacutely exposed to BPA. In addition to suppression of proliferation, IL-4 and IFN-γproduction of splenocytes was induced by exposure to high dose of BPA ex vivo or in vitro. Splenic IgM antibody forming response to SRBC and Serum levels of immunoglobulins were altered at the mice exposed to BPA in comparison with that of the control. In addition, BPA effected on the NO and TNF-α production ex vivo or in vitro, and decreased expression of B7-1 and B7-2 on macrophages. Overall our results suggest that BPA could affect the immune system of mice resulting in suppression of cellular immunity, humoral immunity, and peritoneal macrophages function.

Oral Presentations - Field C

[C1. Biochemistry] [C2. Microbiology] [C3. Cell Biology]

[OC-1] [04/18/2003 (Fri) 14:30 - 14:45 / Orchid]

Roles of MAPKs in H-ras-induced Invasion and Motility

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One of the most frequent defects in human cancer is the uncontrolled activation of the ras-signaling pathways. Elevated p21ras expression is associated with tumor aggressiveness in breast cancer including the extent of invasion into fat tissues, infiltration into lymphatic vessels and tumor recurrence. We demonstrate that H-ras, but not N-ras, upregulates matrix metalloproteinase (MMP)-2 expression and induces invasive phenotype in MCF10A human breast epithelial cells. We also show that H-ras-mediated invasiveness is significantly inhibited when the expression of MMP-2 is downregulated, using an oligodeoxyribonucleotide complementary to the MMP-2 mRNA, or when MMP-2 activity is blocked by its inhibitor, tissue inhibitors of matrix metalloproteinase-2 (TIMP-2). Our results show that the H-ras-induced invasive phenotype is associated more closely with the expression of MMP-2 in human breast epithelial cells. Since migration plays a crucial role in invasive, we examined motility of MCF10A cells transformed with H-ras or N-ras. We show that cell motility was increased by H-ras, but N-ras suggesting that H-ras-induced invasive phenotype may be mainly due to enhanced cell motility. We have investigated whether H-ras and N-ras differentially regulate ras effector pathways critical for cell motility and invasive phenotype. While neither H-ras nor N-ras activated JNK-1, both H-ras and N-ras effectively activated ERK-1/-2. Importantly, prominent activation of p38 was shown only in H-ras-activated cells but not in N-ras-activated MCF10A cells. Functional significance of H-ras-activated p38 in invasiveness and cell motility was evidenced by studies using SB203580, a chemical inhibitor of p38, and a dominant negative construct of p38. While inhibition of JNK-1 activity had no effect on H-ras-induced MCF10A cell invasion and motility, the inhibition of the ERK pathway using a chemical inhibitor PD98059 or dominant negative mutant of MEK-1, an activator of ERKs, significantly reduced H-ras-induced invasion and migration. We also provide evidence that p38 and, to a lesser degree, ERKs, are critical for H-ras-mediated upregulation of

MMP-2. In present study suggests that H-ras-induced activation of both p38 and ERK results in more invasive and motile phenotypes of human breast epithelial cells, whereas N-ras activation of ERKs is not sufficient for these phenotypic changes.

Oral Presentations - Field D

[D1. Medicinal Chemistry] [D2. Pharmacognosy] [D3. Oriental Medicine] [D4. Analytical Chemistry]

[OD-1] [04/18/2003 (Fri) 14:45 - 15:00 / Orchid]

ent-Kaurane Diterpenoids from *Croton tonkinensis* Inhibit LPS-induced Transcription Factor NF-κB Activation and NO Production

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Nuclear factor-κB (NF-κB) belongs to a group of homodimers and heterodimers of Rel/NF-κB proteins that bind to DNA target sites, where they directly regulate gene transcription. The activation of NF-κB has been shown to mediate inflammation and suppress apoptosis. Activated NF-κB has been found in various inflammatory diseases such as rheumatoid arthritis, atherosclerosis, asthma, inflammatory bowel disease, and *Helicobacter pylori*-associated gastritis and associated with cancer, cachexia, diabetes, euthyroid sick syndrome, and AIDS. With its apparent involvement in a variety of human diseases, NF-κB has been an attractive target in the discovery of anti-inflammatory and cancer chemopreventive drugs. *Croton tonkinensis* Gagnep. (Euphorbiaceae), commonly named in Vietnamese as "Kho sam Bac Bo", is a tropical shrub native to the Northern Vietnam. Its dried leaves have been used in Vietnamese traditional medicine to treat burn (boil), abscesses, impetigo, abdominal pain, dyspepsia, gastric and duodenal ulcers. Bioactivity-guided fractionation of MeOH extract from leaves of *C. tonkinensis* toward NF-κB inhibitory activity led to the isolation of four active *ent*-kaurane-type diterpenoids including two new *ent*-1β-acetoxy-7α,14β-dihydroxykaur-16-en-15-one and *ent*-18-acetoxy-7α,14β-dihydroxykaur-16-en-15-one together with two known *ent*-7α,14β-dihydroxykaur-16-en-15-one and *ent*-18-acetoxy-7α-hydroxykaur-16-en-5-one. These *ent*-kauranoids were demonstrated to strongly inhibit NF-κB activation in LPS-induced murine macrophage RAW264.7 at IC_{50} from 0.07 μM to 0.42 μM. Consistently, the *ent*-kauranoids markedly reduced LPS-stimulated NO production in a comparable concentration-dependent manner, thus appeared to inhibit iNOS gene expression by preventing the activation of NF-κB.

[OD-2] [04/18/2003 (Fri) 15:00 - 15:15 / Orchid]

Sensitive Determination of Alkylphenols, Chlorophenols, and Bisphenol A using GC/MS-SIM in Papers Materials

Kim Hyub[o] Kim Jin-Ho Kim Yong-Hwa