apoptosis is still unclear. In the present study, we determined if p38 MAP kinase was involved in ceramide-induced cell death. Treatment with SB203580, a p38 MAP kinase inhibitor, protected HL-60 cells from ceramide-induced cell death, which is in accordance with phosphorylation of p38 MAP kinase induced by ceramide. Ceramide elevated caspase-3 and -9 activities and induced translocation of Bax from cytosol to mitochondria. Treatment with SB203580 diminished caspase-3 and -9 induction and blocked Bax translocation induced by ceramide. These results demonstrate that p38 MAP kinase may play an important role in ceramide-mediated cell death in HL-60 cells.

[PC3-8] [10/19/2001 (Fri) 09:00 - 12:00 / Hall D]

Activation of hypoxia-inducible factor-1a in hepatocarcinogenesis by Hepatitis B virus X protein

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Hepatitis B viruse x (HBx) protein has been directly involved in development of hepatocellular carcinoma (HCC), highly vascularized solid tumors. However, the molecular function of HBx remains controversial. We previously reported that HBx increases the expression of vascular endothelial growth factor (VEGF) mRNA in HBx-expressed cells lead to stimulate angiogenesis in vivo mouse Matrigel plug assay. It is well known that hypoxia-inducible factor-1a (HIF-1a) is major regulator of VEGF expression under hypoxia. Herein, We examined the expression of HIF-1a in the liver of transgenic mice expressing the HBx gene. HBx and HIF-1a proteins are highly expressed in the HBx-transgenic liver, in contrast, these proteins are rare or no expressed in normal liver. Also, VEGF protein is highly expressed in HBx-transgenic liver. HBx induces HIF-1a and VEGF protein level in HEK 293 cells in normoxic condition. We further show that HBx blocks the ubiquitination of HIF-1a in normoxia mediated by down-regulation of p53. Our results suggest that HBx induce expression of HIF-1a in the HBV-infected liver and then stimulates angiogenesis, result in development of HCC.

[PC3-9] [10/19/2001 (Fri) 09:00 - 12:00 / Hall D]

Determination of interaction between a novel biotinylated biocompatible polymer and a hepatoma cell line (HePG2)

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Nanoparticles can be delivered to specific sites in the body by size-dependent passive targeting or by active targeting using receptor-mediated interactions. For developing a potential liver cancer targeting system, we attempted to design a receptor-mediated delivery system using biotinylated pullulan acetate (PA/biotin 500). The interactions between the RITC-labeled nanoparticles [pullulan acetate (PA) and PA/biotin 500] and HepG2 cells were quantified by a microplate fluorescence reader and flowcytometer. PA/biotin 500 showed stronger adsorption to HepG2 cells than PA. We investigated the changes of fluorescence intensity as a function of concentration and cultivation time of PA and PA/biotin 500. The fluorescence intensity of HepG2 cells linearly increased with the concentration of PA and PA/biotin 500. The cultivation time of HepG2 cells for the time also affected the fluorescence intensity in similar way. To clarify the specific interaction between RITC-labeled nanoparticles and HepG2 cells, we attempted to use confocal laser microscopy. HepG2 cells were strongly luminated by specific interactions with PA/biotin 500 while the luminescence of PA was a little observed. Therefore, It is suggested that the PA/biotin 500 has a specific interaction with HepG2 cells by ligand-receptor recognition. In conclusion, PA/biotin 500 is a potential drug delivery system for the treatment of liver cancer. The carrier may induce the immunological enhancement activity in the body and attach to hepatoma cell (HepG2) by ligand-

receptor mediated interaction.

[PC3-10] [10/19/2001 (Fri) 09:00 - 12:00 / Hall D]

Development of blood-brain barrier by oxygen-regulated novel genes

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The blood-brain barrier (BBB) is known as a highly selective barrier between the blood and the central nervous system and essential for the maintenance of the neural microenvironment. Since the oxygen tention during the development of vascular systems and the importance of astrocytes in differentiation of BBB have been suggested, we investigated the differentiation factors of BBB regulated by oxygen in astrocytes.
We used the Representational Difference Analysis (RDA) to clone mRNA fragments differentially expressed in hypoxic versus reoxygenated astrocytes and cloned several mRNAs upregulated by reoxygenation. We confirmed that clone R1 is increased at 30min of reoxygenation and clone R2 is highly increased at 3 h of reoxygenation by Northern and Western blotting. In [3H]sucrose permeability assay, clone R2 strongly enhanced the barrier function of ECV 304 cells. The conditioned media of clone R2 transfected astrocytes upregulated the expression of occludin and clone R2 also redistribute the localization of occludin in coculture system. Moreover, the conditioned media of clone R2 inhibited the neovasculization in vivo CAM assay. Clone R2 also decreased the expression of vascular endothelial growth factor/ vascular permeability factor.
Taken all together, we suggest that astrocytes activated by reoxygenation regulate the maturation and development of the BBB.

Poster Presentations - Field D1. Medicinal Chemistry

[PD1-1] [10/19/2001 (Fri) 14:00 - 17:00 / Hall D]

Synthesis and Biological Activities of Benzo[b]quinolin[2,3-d]thiophen-6,11-diones via Palladium-catalyzed Reaction of 5,8-Quinolinediones with Arylmercaptane

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The benzo[b]naphtho[2,3-d]furan-6,11-diones 1 have received attention due to their potential biological activities. We designed and synthesized benzo[b]quinolin[2,3-d]thiophen-6,11-diones 2, as a bioisostere of the compound 1. Reactions of 6,7-dichloro-5,8-quinolinedione 3 and arylmercaptanes in DMF at RT and a catalytic amount of palladium acetate gave compounds of benzo[b]quinolin[2,3-d] thiophen-6,11-dione derivatives 2 in good to high yields. The compound 3 were tested for in vitro antifungal activities against pathogenic fungi. Most of the tested compounds exhibited antifungal activities against Candida species and Aspergillus niger.

[PD1-2] [10/19/2001 (Fri) 14:00 - 17:00 / Hall D]