JC virus causes the fatal demyelinating disease, progressive multifocalleukoencephalopathy under immunosuppressive states such as AIDS. During thepathogenesis of AIDS, HIV-infected microglia secret cytokines including interleukin-1 andtumor necrosis factor-α (TNF-α), which affect neuronal cells resulting in dysfunction of theCNS. We hypothesized that extracellular stimuli released from HIV-infected microglia mayreactivate JC virus by affecting neighboring oligodendrocytes. In the present study, wefound that PMA and interlukin-1β (IL-1β) dramatically increased JC virus transcription inglial cells. Site-directed mutagenesis and gel shift analyses revealed that PMA and IL-1βstrongly induced nuclear factor-1 (NF-1) binding to the JC virus enhancer region,increasing transcriptional activity of the viral early promoter. Additionally, wedemonstrated that protein kinase C (PKC) pathways were involved in the PMA/IL-1β-mediated up-regulation of the JC virus early promoter. These findings may represent one ofthe possible mechanisms for higher incidence of PML among AIDS patients.

[OC1-1] [2004-10-22 14:00 - 14:15 / Room 205]

Redox-sensitive Transcription Factors in Cellular Defence against Oxidative and Inflammatory Cell Death Induced by beta-Amyloid

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Oxidative stress induced by reactive oxygen species (ROS) has been considered as a major cause of cellular injuries in a variety of neurodegenerative disorders including Alzheimer's disease (AD). Rat pheochromocytoma (PC12) cells treated with beta-amyloid (Aβ), a neurotoxic peptide associated with senile plaques formed in the brains of patients with AD, exhibited increased intracellular accumulation of ROS and underwent apoptotic death. Resveratrol, an antioxidant present in grapes, attenuated Aβ-induced apoptosis and intracellular ROS accumulation. PC12 cells transfected with bcl-2 exhibited relatively high constitutive DNA binding and transcriptional activity of NF-κB, which were accompanied by the activation of ERK1/2 and Akt/protein kinase B. The ectopic expression of bcl-2 augmented cellular antioxidant capacity via upregulation of glutamylcysteine ligase (GCL) and catalase which was suppressed by NF-κB inhibitors. NF-E2-related factor 2 (Nrf2) plays a key role in regulating expression of antioxidant or phase II detoxifying genes. Transfection of PC12 cells with nrf2 rescued these cells from Aβ-induced apoptosis and intracellular ROS accumulation through upregulation of GCL. During Aβ-induced apoptosis in PC12 cells, expression of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) was elevated. Pretreatment with celecoxib, a selective COX-2 inhibitor or ergothioneine, a

naturally occurring thiol compound exhibiting peroxynitrite scavenging activities, ameliorated Aβ-induced induced PC12 cell death. Aβ treatment resulted in activation of NF-κB and AP-1, and NF-κB inhibitors and AP-1 antisense oligonucleotide decreased COX-2 and iNOS expression, respectively. Aβ induced rapid activation of ERK and p38 MAPK which are upstream of NF-κB and AP-1. Pharmacologic inhibition of both enzymes effectively suppressed Aβ-induced expression of COX-2 and iNOS.

[OD2-1] [2004-10-22 14:15 - 14:30 / Room 205]

Cytotoxic Constituents of a Marine Sponge Homaxinella sp.

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Marine sponges of the genus Homaxinella are reported to contain a variety of metabolites like cytotoxic bromopyrrole alkaloids, various sterols, and antimicrobial compounds. In our study on the cytotoxic compounds of a sponge Homaxinella sp., three new butenolides (1-3), a new cyclopentenone derivative (4), a known unsaturated alcohol (5), three new (6-8), and two known (9, 10) highly degraded sterols, four new 6-O-alkylated sterols (11-14), four known 5α,8α-epidioxy sterols (15-18), two new lysophosphatidylcholine derivatives (19, 20), and two new brominated fatty acids (21, 22), were isolated from the MeOH extract of the sponge, by bioactivity-guided fractionation. The highly degraded sterols (6-10) belong to the class incisterols, isolated from the marine sponge Dictyonella incisa, and are the first example of 4-hydroxy incisterols from any natural source. The gross structures of the compounds were elucidated by 1D and 2D NMR spectroscopic analyses and MS spectral data. The geometries of the double bonds in alkyl chains of 1-5 and 21, 22, and side chains of 6-18, were defined by comparison of ^{13}C NMR data of their allylic and diallylic carbons with those of model compounds and the coupling constants of the olefinic protons. The absolute configuration of the oxygenated substituents at α,β-unsaturated lactone and ketone moieties in butenolides, cyclopentenone derivative, and degraded sterols was defined by the comparison of the CD spectroscopic data and/or optical rotation values of the model compounds. The absolute configuration of the sterol side chains and nuclei was defined by comparison of NMR spectroscopic data with those of the model compounds.The isolated compounds were evaluated for cytotoxicity and showed marginal to significant activity against a panel of five human tumor cell lines. Of the compounds tested, cyclopentenone derivative (4) and degraded sterols (6-9) showed significant cytotoxicity against all of the cancer cell lines tested.