Inhibitory effects of isoquinoline alkaloids on proinflammatory cytokines of tumor necrosis factor(TNF-α), interleukine-1β(IL-1β), interleukine-5(IL-5) have been estimated. Among 11 kinds of isoquinoline alkaloids (tetrahydopapaverine, salsolinol, berberine, coralyne chloride, hydrastine, laudanosine, pamatine chloride, noscapine, papaverine, ethaverine, and tetrahydropapaveroline) tested, 9 samples exhibited inhibitory effects on the IL-5 bioactivity with an IC50 value of 7.5 uM by tetrahydropapaverine, 3.5uM by salsoline, 0.9 uM by berberine, 0.3 uM by coralyne chloride, 24 uM by laudanosine, 15.8 uM by pamatine chloride, 1.4 uM by papaverine, 1.4 uM by ethaverine, and 1.6 uM by tetrahydropapaveroline. However, the compounds have no inhibitory effects on TNF-α and IL-1β bioactivities. Experiments to know effects on IL-3, IL-4 and IL-6 are in progress.

[PC1-11] [10/19/2001 (Fri) 09:00 - 12:00 / Hall D]

Celastrol, a quinone methide triperpenoid, suppresses NF-kB Activation by inhibiting phosphorylation of IkBa

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Celastrol, a quinone methide triterpenoid, was isolated as a NF-kB inhibitor from Celastrus orbiculatus by activity-guided fractionation. This compound dose-dependently inhibited the induced NF-kB reporter gene expression and DNA-binding activity of NF-kB in different cell lines by various stimuli without affecting DNA-binding activity of AP-1 transcription factor. Preincubation of celastrol completely blocked the induced degradation and phosphorylation of IkBa protein by LPS, TNF-a, or PMA. Moreover, celastrol suppressed the induced NF-kB activation by overexpression of NEKK-1, NIK, or IKK-a, but not by p65, suggesting that celastrol suppressed the induced NF-kB activation by preventing phosphorylation of IkB, possibly through inhibiting kinase activity of IkB kinase complex. To verify that celastrol is a NF-kB inhibitor, we investigated its effect on some NF-kB target genes expressions. Celastrol prevented not only LPS-induced mRNA expression of iNOS and TNF-a, but also TNF-a induced expression of Bfl-1/A1, a prosurvival bcl-2 homologue. Consistent with these results, this compound significantly suppressed the production of NO and TNF-a in LPS-stimulated RAW264.7 cells, and increased the cytotoxicity of TNF-a in HT-1080 cells. Taken together, this study extends our understanding on the molecular mechanisms underlying the antiinflammatory activities of celastrol and celastrol-containing extracts that are used in traditional oriental medicine. Furthermore, celastrol could be an interesting lead compound for the modulation of NF-kB-dependent pathological conditions such as inflammatory diseases and cancer.

[PC1-12] [10/19/2001 (Fri) 09:00 - 12:00 / Hall D]

Mechanism of Cinnanaldehyde induced-apoptosis in human leukemia HL-60 cells

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In the previous report, we found that cinnamaldehyde, isolated from the stem bark of Cinnamomum cassia, induced cytotoxicity and apoptosis. These effects were completely prevented by pretreatment with antioxidant N-acetyl-L-cystein (NAC). Cinnamaldehyde activated various caspases, such as caspase-3, caspase-8 and caspase-9 activities, and induced the release of cytochrome-c from mitochondria into the cytosol. Bid, a death agonist member of the Bcl-2 family, was processed following exposure of cells to cinnamalehyde. These data suggest that cinnamaldehyde induced apoptosis of HL-

60 cells through activation of caspase in conjunction with cytochrome c release induced by a processed product of Bid. Now we are further investigating the relationship with the mitochondrial potential, ROS and Fas expression.

[PC1-13] [10/19/2001 (Fri) 09:00 - 12:00 / Hall D]

Intermedeol-Induced Apoptosis Involved Fas/Fas-L and cytochrome c dependent pathway in Human Leukemic cell HL-60

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We previously demonstrated that Intermedeol, a sesqueterpene isolated from Ligularia Fischery var., had a antitumor activity by induction of cell differentiation and apoptosis in HL-60. In this study, we examined signaling pathways implicated in Intermedeol up-regulation of Fas receptor expression and caspase 8 activation of Intermedeol. Bid is processed after Fas ligation and thus might activate the mitochondrial-dependent apoptotic cascade. Activated Bid preceded the release of cytochrome c without mitochondrial permeability transition. Cytochrome c release led to the activation of caspase 9 and downstream death effector, caspase 3. These finding suggest that Intermedeol induced cytochrome c-dependent apoptosis through Fas/Fas-L pathway.

[PC1-14] [10/19/2001 (Fri) 09:00 - 12:00 / Hall D]

Requirement for JNK activation in costunolide-induced apoptosis

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Costunolide is an active compound isolated from the root of Saussurea lappa Clarks, a Chinese medicinal herb, and considered as a therapeutic candidate for various types of cancers. In this study, we investigate the effects of costunolide on the induction of apoptosis in human leukemia cells and its putative pathways of action. Using diphenylamine and Hoechest apoptosis analysis, costunolide caused apoptosis of U-937 cells in a concentration- and time-dependent manner. Since costunolide-induced apoptosis was completely prevented in Bcl-2 overexpressed cells, these apoptosis was associated with Bcl-2, Furthermore, we demonstrated a requirement for c-Jun N-terminal Kinase, a member of the mitogen-activated protein kinase family in mediating cosunolide-induced apoptosis of human leukemia U-937 cells. JNK activation by costunolide contributed to apoptosis because transdominant-negative JNK significantly blocked costunolide-induced cell death. These findings cause the possibility that the JNK activation by costunolide can inhibit the Bcl-2 activity by phosphorylation.

[PC1-15] [10/19/2001 (Fri) 09:00 - 12:00 / Hall D]

Studies on the Growth-Inhibitory Effects of Pini Resina and Sodium Chloride against Oral Bacteria

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There has been considerable interest in the use of antimicrobial agents including a number of antiseptics, antibiotics and some natural products, as additives of some oral hygienic products for the purpose of treatment and/or prevention of periodontal disease.