[PA1-1] [04/21/2000 (Fri) 10:30 - 11:30 / [1st Fl, Bldg 3]]

Differential Role of MAP Kinases in Antioxidant Response Element-mediated rGSTA2 Induction by t-BHQ

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The protective adaptive response to electrophiles and reactive oxygen species (ROS) is mediated with the activation of antioxidant response element (ARE) and subsequent induction of phase II detoxifying enzymes. The current study was designed to identify the mitogen-activated protein (MAP) kinase signaling pathways responsible for the induction of rGSTA2 by tert-butylhydroquinone (t-BHQ) and to study the role of phosphatidylinositol 3-kinase (PI3-kinase). c-Jun N-terminal kinase (JNK), extracellular signal-regulated kinase (ERK) and p38 MAP kinase all were activated in H4IIE hepatoma cell by t-BHQ treatment. The nuclear ARE complex was activated 1-6 h after t-BHQ treatment, as assessed by electrophoretic mobility shift assay. The rGSTA2 mRNA level was elevated by t-BHQ at 6-24 h, which led to the enzyme induction. Both nuclear ARE activation and increase in rGSTA2 mRNA was abolished by wortmannin or LY294002, PI3-kinase inhibitors. Curcumin a JNK inhibitor, completely inhibited both ARE activation and an increase in rGSTA2 mRNA. Conversely, either PD98059 or SB203580 enhanced the t-BHQ-induced increases in rGSTA2 mRNA and protein levels. These data provided evidence that JNK, p38 kinase and ERK differentially regulate the ARE-mediated rGSTA2 induction by t-BHQ and that PI3-kinase plays a crucial role in the expression of rGSTA2.

[PA1-2] [04/21/2000 (Fri) 10:30 - 11:30 / [1st Fl, Bldg 3]]

Fluorogenic HCV NS3 Protease Assay

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Hepatitis C Virus (HCV) is the etiologic agent of both parenterally transmitted and community acquired non-A, non-B hepatitis. One of the approaches to anti-HCV drug is the design and synthesis of specific small molecule compounds inhibiting the proteolytic processing of the HCV polyprotein. This proteolytic processing is catalyzed by a chymotrypsin-like serine protease, which is located in the N-terminal region of non-structural protein 3 (NS3). Over 2000 protease inhibitors were evaluated for their inhibitory activity on HCV NS3 protease through a fluorogenic assay based upon resonance energy transfer using recombinant NS3 protease. The cDNA of HCV NS3 (1-180) protease was cloned into expression vector. The fusion protein with the N-terminal six histidine was over-expressed in *Escherichia coli*. Through a high throughput screening program, YH3893 was identified as a potent inhibitor on NS3 protease having the competitive mode of action with respect to the substrate, NS5A/5B. This study was supported by a grant (CH1-3-12) from MOST.

[PA1-3] [04/21/2000 (Fri) 10:30 - 11:30 / [1st Fl, Bldg 3]]

in vitro Activities of Macrolides, Lincosamide, and Streptogramin B against Gram-positive bacteria

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The purpose of this study was to investigate the prevalence of antibiotics resistance macrolide, lincosamide, and streptogramin B antibiotics (MLS) in Gram-positive bacteria. The 1037 clinical isolates were provided by hospital laboratories in Seoul between May 1999 and January 2000. The determination of MICs(㎍/ml) was made by the agar dilution method recommended by the National Commit for Clinical Laboratory Standards(NCCLS) and the French Society for Microbiology (FMS).
S. aureus had erythromycin MICs between 0.125㎍/ml and 64㎍/ml and the resistant strains was 71% (MIC, 8 ㎍/ml) to this antibiotic.
The strains were also highly resistant (MIC 50/MIC90, 64㎍/ml) to clarithromycin, josamycin, azithromycin, and clindamycin, 70%, 64%, 72%, and 63% of the isolates were resistant to this antibiotics, respectively. But the strains were susceptible to pristinamycin (13% resistance). By NCCLS interpretive criteria, 59%, 61%, 43% 66%, 41% and 4% of Coagulase-negative staphylococci (CNS) clinical isolates were resistant to erythromycin, clarithromycin, josamycin, azithromycin, clindamycin and pristinamycin, respectively. Enterococci had 59%, 61%, 43%, 66%, 41%, and 4% resistance ratio to erythromycin, clarithromycin, josamycin, azithromycin, clindamycin and pristinamycin, respectively.
In this study Gram-positive bacteria in Seoul were resistant to Macrolide(erythromycin, clarithromycin, josamycin, azithromycin) and Lincosamide(clindamycin), but these bacteria were susceptible to Streptogramin B(pristinamycin).

[PA1-4] [04/21/2000 (Fri) 10:30 - 11:30 / [1st Fl, Bldg 3]]

In vitro Antibacterial Effect of YJA20379-8 on Helicobacter pylori

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We compared the susceptibility of Helicobacter pylori to two antiulcer agents, expressed as MICs and as bactericidal effectiveness in short (24 hours) time and long time (7 days) killing studies. MIC values of YJA20379-8 and omeprazole were about 6 mg/L and 31 mg/L respectively, for 10 strains of Helicobacter pylori. Long time-killing kinetic study demonstrated that YJA20379-8 produced decrease of viability within 1 day but omeprazole did not show bactericidal effect in the same drug concentration. Short time-killing kinetic study showed YJA20379-8 produced 2.9 log decrease in viability, but omeprazole slightly increased. As a results of MIC and time-kill data, a growth inhibitory effect of YJA20379-8 on Helicobacter pylori was observed and more potent than that of omeprazole.

[PA1-5] [04/21/2000 (Fri) 10:30 - 11:30 / [1st Fl, Bldg 3]]

5-FU inhibits the production of nitric oxide in stomach cancer cells

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Nitric oxide (NO) is synthesized in mammalian cells from the amino acid L-arginine by a family of enzymes, the nitric oxide synthases (NOS). This molecule plays a key role in many physiological as well as pathological processes, including inflammation and neoplasia. 5-fluorouracil (5-FUra), an antimetabolite effective against colon and gastric tumors, has been shown to suppress nitric oxide biosynthesis in colon carcinoma cell line, DLD-1. (Jin, Y., Heck, D.E., DeGeorge, G., Tian, Y., and Laskin, J.D. (1996) Cancer Res. 56, 1978). However, the exact mechanism how 5-Fura reduces NO production has not been known. In the present study, we characterized the effect of 5-Fura on NO