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ANNOUNCEMENT

Biomedical vignette

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Hepatitis B viral factors and clinical outcomes of chronic hepatitis B

Human hepatitis B virus (HBV), a hepatotropic and non-cytopathic DNA virus, causes acute hepatitis. Patients with persistent HBV infection are at a high risk of developing chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC). The natural history of persistent HBV infection has four dynamic phases, immune tolerance phase with positive HBeAg and very high viral load, immune clearance phase with seroconversion of HBeAg to anti-HBe and reduced viral load, low replication phase with positive anti-HBe and low viral load, and reactivation phase with negative HBeAg and high viral load [1]. In the review by Lin and Kao [2], evidence showing that high viral load, genotype C, basal core promoter mutation and pre-S deletion are associated with liver disease progression and HCC development in patients with persistent HBV infection is discussed.

Gender dimorphism of tumor growth

Tumor growth has a complex relationship with the host's immune and endocrine systems [3]. From the study of a murine model of a transplantable T-cell lymphoma of spontaneous origin designated as Dalton's lymphoma (DL), it had been reported that DL growth is associated with thymus regulation, modulation of macrophage activation, humoral and T cell-mediated immune responses [4]. Gupta and Sing [5] in this issue studied if a gender-dependent differential induction of tumor cell apoptosis is responsible for the manifestation of gender dimorphism in DL growth. They found that male hormone androgen and female estrogen could differentially modulate tumor cell proliferation and apoptosis through alteration in the expression of cell death regulating genes: p53 and CAD. DL cells obtained from male mice showed a higher expression of proapoptotic proteins: CAD and p53. Furthermore, these gonal hormones also induced tumor cells to produce tumor growth regulating proteins including VEGF, FGF-β, INF-γ and IL-2. Androgen-treated DL cells expressed more INF-γ, whereas estrogen-treated cells elaborated more TGF-β and IL-2. These results demonstrated that the progressive growth of a T cell lymphoma displays gender dimorphism in a differential rate of tumor cell growth and in the expression of proteins regulating tumor growth and cell death.

DNMT1 mediates mutant p53-determined $p16^{ink4A}$ expression

Mutations in the p53 gene are frequently observed in human tumors, and inheritance of mutated p53 gene predisposes patients to genomic instability and subsequent tumor development [6]. Previous study suggested that DNA (cytosine-5) methyltransferase 1 (DNMT1) level is elevated in p53-null cells, whereas its expression is low in wild-type p53 cells but is increased dramatically in response to p53-dependent DNA damage signaling [7]. Guo et al. [8] therefore compared the expression levels of DNMT and $p16^{ink4A}$ in TK6 cells expressing wild type p53 and WTK1 cells expressing a mutant form of p53. Lower level of $p16^{ink4A}$ protein was detected in WTK1 cells than in TK6 cells, which was accompanied by DNMT1 gene expression as well as hypermethylation of the $p16^{ink4A}$ promoter. Furthermore, loss of suppression function of

mutant p53 to DNMT1 in WTK1 was caused by the attenuation of its binding ability to the DNMT1 promoter. These results indicate that the mutant p53 loses its ability to suppress DNMT1 expression, and thus enhances methylation level of the $p16^{ink4A}$ promoter and subsequently down-regulates $p16^{ink4A}$ protein.

Ca^{2+} binding protein-1 inhibits Ca^{2+} currents and exocytosis in bovine chromaffin cells

Recently, a group of calcium-binding proteins (CaBP1 ~ 5) with structures similar to that of calmodulin (CaM) has been described [9]. CaBP1 was found to have two alternatively spliced variants, L- and S-CaBP1 [10]. It has been shown to modulate the activity of various calcium channels through its binding to the C-terminal CaM-binding domain or to the IQ domain [11]. In this communication, Chen et al. [12] reports that CaBP1 inhibits stimulation-induced calcium current in cultured neurons, suggesting that CaBP1 plays an important role in modulating the stimulation-coupled activation of calcium channels. These findings are significant and may shed light on the function of CaBP1 in modulating Ca^{2+} currents and neurotransmitter release in excitable cells.

Cholestin attenuates homocysteine-induced inflammatory reactions in endothelial cells

Homocysteines (HCY) is a sulfhydryl amino acid metabolite of methionine, and elevated HCY level in the plasma has been recognized as a major risk factor in cardiovascular diseases [13]. Cholestin is a dietary supplement related to red yeast rice that has been reported to have lipid-lowering effects and has been considered beneficial in subjects with hyperlipidemia [14]. Lin et al. [15] studied the effects of cholestin on the expression of adhesion molecules and activation of redox-sensitive transcription factor NF-κB by HCY-treated human endothelial cells. Cholestin attenuated HCY-induced expression of VCAM and HCY-activated transcription factor NF-κB. Cholestin also inhibited the reactive oxygen species generation in HYC-treated cells. These results support the notion that cholestin may have potential implications in clinical atherosclerosis disease.

Mistletoe lectin enhances NO production in macrophages

Mistletoe lectin has become a subject of interest due to its marked biological activities including its cytotoxicity and immunomodulatory effects [16]. It consists of two units, an A chain and a B chain, linked by a disulfide bond, and the disulfide bridge between the A and B chains is necessary for maintaining the cytotoxicity of the lectin [17]. Kang et al. [18] studied the effect of Korean mistletoe lectin (KML-IIU) on nitric oxide (NO) production in murine macrophage cells in order to delineate its immunomodulatory effect. Treatment of cells with subchains of the KML-IIU, which have lower toxicity, enhanced NO production by cells in the presence of a suboptimal concentration of INF-γ through the induction of iNOS gene expression. These results demonstrated that the subchains of KML-IIU induce NO production in murine macrophages via activation of iNOS expression, suggesting that the KML-IIU subunits may be used as an immunomodulator to enhance the effector functions of innate immune cells.

Human uridine-cytidine kinase phosphorylation of ribavirin: a convenient method for activation of ribavirin for conjugation to proteins

Ribavirin is a nucleoside analog that has been used as an antiviral for some viruses. The most widespread application is to combine it with interferon alpha for the treatment of chronic hepatitis C [19]. Although the combination therapy is effective for hepatitis C, ribavirin can induce hemolytic anemia that may necessitate dose reduction or even discontinuation of the therapy [20]. Selective delivery of ribavirin to hepatocytes would be desirable to enhance its antiviral activity and meanwhile decrease the systemic side effects. In this issue, Jukic et al. [21] showed in vitro evidence that human uridine-cytidine kinase 1 recognizes ribavirin and phosphorylates it. They were able to conjugate ribavirin monophosphate to asialoorosomucoid molecule, a natural high-affinity ligand for asialoglycoprotein receptors. The conjugate may be useful for liver-specific targeting.

Characterization of cocaine-elicited cell vacuolation: the involvement of calcium/calmodulin in organelle deregulation

Cocaine has been known to affect morphology or functions of intracellular apparatus, including disruption of function and morphology of mitochondria [22], as well as to induce cell vacuolation in animals, isolated organs and cultured cell systems [23]. It has been proposed that cellular vacuolation is associated with cell injury or cytotoxicity [24]. However, the exact mechanism of cocaine-induced vacuolation has not been elucidated. In this issue, Yu et al. [25] reported that calcium influx and calmodulin were required for the initiation of cocaine-induced vacuole formation. These findings are quite significant and may provide clues for therapeutic intervention of cocaine-induced cytotoxicity.

Hypercalcemia and lung injury

Pulmonary edema (PE) or acute respiratory distress syndrome (ARDS) can be induced by a variety of disorders. This serious clinical condition usually results in fatal outcome [26, 27]. Thus, the purpose of this study was to determine whether calcium loading can produce lung injury in conscious rats and isolated perfused rat lungs. Results demonstrated that elevation of calcium concentration in conscious rats caused systemic hypotension and bradycardia accompanying sympathetic inhibition and parasympathetic activation. It also increased the plasma nitrate/nitrite, hydroxyl radical, proinflammatory cytokines, and procalcitonin levels as well as the iNOS activity in lung tissue. Severe pulmonary edema occurred. Both calcitonin and L-Nil attenuated these changes. The present study suggested that the pathogenesis of hypercalcemia-induced PE may be mediated by NO production following the activation of iNOS and the release of proinflammatory cytokines [28].

Quinazoline-based α1 adrenoceptor antagonists and occlusion-reperfusion injury

Quinazoline-based compounds such as prazosin and its congeners including doxazosin, bunazosin, and terazosin are widely used as antihypertensive agents. However, there were many clinical observations showing that using these agents may result in higher risk of cardiovascular accidents in recent years [29]. This study compared the effects of four α1-adrenoceptor antagonists, prazosin, doxazosin, bunazosin, and terazosin on occlusion-reperfusion injury in a Langendorff-perfused rat model. Results demonstrated that prazocin and doxazocin apparently increased infarct size, and CK-MB and LDH activities after 2 hrs reperfusion. In contrast, bunazocin decreased infarct size and those biochemical indicators of cellular damage as compared to control hearts. Although infarct size after reperfusion was differently changed by these four α1-adrenoceptor antagonists, TUNEL-positive nuclei and caspase-3 protein expressions of all the groups were not significantly different. We supposed that the different effects of these four agents on infarct size came from the difference in necrosis rather than apoptosis [30].

A novel synthetic oleanolic acid derivative (CPU-II2) attenuates liver fibrosis in mice through regulating the function of hepatic stellate cells

This study [31] reported that a novel synthetic oleanolic acid derivative with nitrate, CPU-112, alleviated CCl4-induced hepatic fibrosis in mice with a decrease in hepatic hydroxyproline content and histological changes. CPU also attenuated the mRNA expression of α-smooth muscle actin and tissue inhibitor of metalloproteinase type 1 (TIMP-1). However, CPU-112 did not affect the survival of HSC-T6 cells but decreased the expression of procollagen-α1 through drown-regulation of the phosphorylation of P38 MAPK.

Androgen receptor gene polymorphism may affect the risk of urothelial carcinoma

The incidence of human urothelial carcinoma (UC) is three times higher in males than in females [32]. Several studies have implicated the involvement of androgen in spontaneous and chemical-induced bladder tumor development in rats [33]. However, the role of androgen and androgen receptor (AR) in the development of human UC has been less well studied. The length polymorphism of the CAG triplet repeat coding for a polyglutamine (PolyGln) of AR has been shown to associate with endocrine or neurological disorders [34]. Liu et al. [35] examined the association of smoking and the length polymorphism of CAG and GGN repeat of AR in UC cases and age and sex-matched controls. They found that among the medium-dose cigarette smokers, those who had 23 CAG and shorter GGN (<22) repeats had a higher risk than those with longer CAG and GGN. This observation opens up a new direction to study interaction of genetic factor and smoking in the development of human UC.

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