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The vignette for V13N3 issue

Solution structure of the X4 protein encoded by the SARS coronavirus reveals an immunoglobulin-like fold and suggests a binding activity to integrin I domains

The etiologic agent of SARS, a novel coronavirus, has received intense interests due to the severe health and economical consequences of the disease [1]. One of the accessory proteins, X4, has little homology to known proteins and unclear function. To gain insights, this study conducted an analysis of its structure in solution using NMR spectroscopy [2]. The structure suggests significant similarity to the D1 domain of I-CAM1 and I-CAM2, thus arguing for binding activity for the αL integrin I domain of LFA-1. This information, which agrees with information based on a recent crystal structure [3], provides a potential insight into the function of this protein.

Impact of the anti-HBV drug PMEA (Adefovir) on the cytochrome P450-dependent drug metabolizing system

Many antiviral compounds have been developed that are currently used in the clinic, but drug toxicity remains a serious problem. PMEA (Adefovir) is an acyclic nucleoside phosphonate that is widely used in the clinic to inhibit the reverse transcriptase of hepatitis B virus (HBV) and human immunodeficiency virus type 1 (HIV-1). The interaction of PMEA with the cytochrome P450 (CYP)-dependent drug-metabolizing system was studied *in vivo* in rats by Zidek et al. [4]. Whereas no effect on the CYP mRNA and protein level was scored, the authors measured a shift from the active to the denatured CYP form and a concomitant reduction of CYP-mediated biotransformation of xenobiotics at high PMEA levels.

Coordinated expression and *in vivo* reactivity of signal-sensing phenotype in *Salmonella enterica* serovar Typhi under iron limitation, oxidative stress and anaerobic conditions

Coordinated expression of various genes encoding outer membrane proteins (OMPs) may be important for bacteria pathogens to overcome environmental stresses. In the current issue, Chanana et al. [5] compared the OMPs profiles using *Salmonella enterica* serovar Typhi grown under the iron-limited, oxidative stress as well as anaerobic conditions. A 69-kDa OMP was found to express with enhanced intensity under the selected stress conditions as compared to normal conditions. In addition, antibodies against the 69-kDa protein were detected in 85% of the sera from typhoid patients, suggesting the *in vivo* expression of this protein. Further characterization of the 69-kDa protein may lead to a better understanding of the host–microbe interactions.

Mutations on CaENO1 in *Candida albicans* inhibit cell growth in the presence of glucose

Enolase is a well-conserved key enzyme of glycolysis, the main metabolic pathway for sugar utilization [6]. Mutations in enolase block glycolysis, thus forcing the cell into alternative pathways for energy production [7]. Using the tetracycline-regulated promoter system, this study generated a special genetic strain of the fungal pathogen *Candida albicans* in which the single enolase gene was repressed in the presence of doxycycline [8]. Using this system it is shown that *C. albicans* is unable to grow in the presence of glucose when enolase expression is inhibited. It points out an opportunity to inhibit the growth of this pathogen in the blood stream by inhibiting enolase function.

Lipoprotein p37 from *Mycoplasma hyorhinis* inhibiting mammalian cell adhesion

Mycoplasmas have been documented as human pathogens for human respiratory or urogenital track diseases. Association of mycoplasma infection and human cancer has also been reported [9]. However, roles of mycoplasma infection in human cancer are still not known. One protein, p37 from *Mycoplasma hyorhinis* has been shown as a novel antigenic marker of human tumor regression [10]. A recent study suggests that p37 can induce invasiveness of human cancer cells [11]. Liu et al. [12] reported that overexpression of p37 can induce translocation of β-actin into nucleolus and down regulation of ICAM-1 expression. These results open a new direction of research to study involvement of mycoplasma infection in human cancer.

Oxidized LDL and platelet aggregation

Oxidation of LDL may be one of the main factors involved in the initial development of atherosclerotic lesions [13]. Platelets interact with plasma lipoprotein as well as with arterial wall macrophages that play an important role in atherogenesis [14]. The intracellular mechanisms underlying oxidized low-density lipoprotein (oxLDL)-signaling pathways in platelets are not yet completely understood. In this study, oxLDL inhibited platelet aggregation in human platelet-rich plasma stimulated by agonists and decreased the fluorescence intensity of platelet membranes tagged with diphenylhexatriene. Rapid phosphorylation of a protein of M_r 47,000 (P47), a marker of protein kinase C activation, was markedly inhibited by oxLDL. In addition, oxLDL markedly increased levels of cyclic AMP and cyclic AMP-induced vasodilator-stimulated phosphoprotein (VASP) Ser157 phosphorylation. This study indicates that the antiplatelet activity of oxLDL may involve the following pathways. (a) oxLDL may initially induce conformational changes in platelet membranes, leading to inhibition of the activation of protein kinase C, followed by inhibition of P47 protein phosphorylation, and intracellular Ca^{2+} mobilization. (b) oxLDL also activates formation of cyclic AMP and cyclic AMP-induced VASP Ser157 phosphorylation, resulting in inhibition of the Na^+/H^+ exchanger; this leads to reduced intracellular Ca^{2+} mobilization, and ultimately to inhibition of platelet aggregation. This study further provides new insights concerning the effects of low concentrations of oxLDL on platelet aggregation [15].

Isolation of zebrafish BMP receptor-associated molecule 1

The bone morphogenetic proteins (BMP) signal pathway is activated through binding of BMP to type I and type II serine–threonine kinase receptors [16], and the BMP receptor IA interacts with a cytosolic protein, BRAM1 (BMP receptor-associated molecule 1). To date, two homologs of BRAM1 in *C. elegaus* (BRA-1 and BRA-2) have been identified, and BRA-1 negatively regulates TGF-β signaling by blocking physical interaction between the type 1 receptor and Smads [17]. Wu et al. [18] isolated zebrafish bram1, and found that BRAM1 directly interacts with the BMP receptors resulting in down-regulation of BMP signaling in cells.

The role of JWA, a novel signaling molecule, in retinoic acid-mediated induction of HL-60 cell differentiation

All-*trans* retinoic acid (ATRA) has been shown as a powerful differentiation-inducing agent *in vitro* and was developed as effective therapeutics against human acute promyelocytic leukemia (APL) [19]. One of the molecular mechanisms of ATRA's action is to induce downstream target genes of RAR and RXR. One novel gene JWA has been identified as a retinoic acid-induced and cytoskeleton-associated gene. JWA is also a potential environmental-responsive gene with increased expression in response to oxidative and heat-shock stresses [20]. Huang et al. [21] further examined the role of JWA in HL60 cell differentiation induced by ATRA. They found that JWA is not only a novel molecular marker for ATRA-induced HL-60 cell differentiation, but may also play an essential role in cell differentiation process.

A mouse prostate cancer model induced by Hedgehog overexpression

In prostate cancer, the activation of Hedgehog signaling was observed during advanced cancer

and metastasis [22]. A mouse prostate cancer model was produced by intra-prostate injection and eletroporation of a Hedgehog-overexpression vector to study whether Hedgehog overexpression can initiate prostate tumorigenesis [23]. Within 30 days, the manipulation caused lesions with characteristic prostate intraepithelial neoplasia or prostate cancer phenotypes. The tumorigenesis phenotypes were further confirmed by discontinuity of basal cell marker p63, mix-up of CK8-/CK-8 positive epithelial cells in stroma and absence of α-SMA positive fibro-muscular sheath. Therefore, in the present study, prostate cancer model induced by Hedgehog overexpression was established and could be useful for therapeutic approaches targeting at Hedgehog signaling pathway [24].

The conscious animal model of hemorrhagic shock

A number of animal models have been developed for simulating the end points of hemorrhagic shock. Methods used to control the hemorrhagic events include volume-controlled, pressure-controlled, and uncontrolled hemorrhage models [25]. Fixed pressure [26] and fixed volume models [27] of hemorrhage were developed and refined over the last century. An ideal experimental model of hemorrhagic shock should precipitate multiple organ dysfunctions and lead to multiple organ failure and late mortality [28]. In previous uncontrolled hemorrhagic shock animal models, the rate and the volume of blood loss could be adequately controlled and required prolonged anesthetic or a fasting state. The present study, by using a conscious, unrestrained and less stressed rat model, makes the control of blood loss more convenient and it could continuously monitor MAP and HR and collect blood samples for analysis for as long as 48 h. These results indicated that anesthetics significantly affected the physiology of experimental animals. Thus, the conscious, unrestrained and cumulative volume-controlled hemorrhagic shock model is a good experimental model to investigate physical phenomena without anesthetic interference [29].

Antimuscarinic actions of antihistamines on the heart

The newest antihistamines, desloratadine, fexofenadine and cetirizine, are metabolites of the older antihistamines, loratadine, terfenadine and hydroxyzine [30]. All these compounds are selective H1-histamine receptor antagonists. The newer agents also cause less drowsiness than first-generation antihistamines (e.g., diphenhydramine) [31]. In addition, the newest compounds do not interact with HERG channels in the heart to cause a prolonged QT syndrome as did terfenadine, the parent compound of fexofenadine [32]. Another potential interaction of antihistamines with cardiac function is at receptors involved in modifying heart rate and contraction. The first-generation compounds were known to be competitive inhibitors of muscarinic receptors [33] and caused tachycardia by impairing vagal tone on the heart and xerostomia by inhibiting muscarinic stimulation of salivary function. In this report the authors examined the interaction of antihistamines with muscarinic receptor-induced reduction of cardiac function in a working rat heart model using a Langendorff apparatus.

Thalidomide and hepatic fibrosis

Liver fibrosis is characterized by an excessive deposition of extracellular matrix (ECM) proteins and can ultimately lead to cirrhosis and organ failure [34]. Activation of hepatic stellate cells (HSCs) has been implicated in the pathogenesis of liver fibrosis [35]. Both *in vitro* and *in vivo* studies suggest a critical role of NFκB in the activation of HSCs and an anti-TNF-α strategy to be potentially beneficial for treating liver fibrosis. Thalidomide has been therapeutically used for intractable diseases with pathogenesis involving TNF-α, including graft versus host disease, rheumatic arthritis, sarcoidosis, Crohn's disease, and ulcerative colitis [36]. The present study was therefore undertaken to investigate firstly the anti-fibrogenic effects of thalidomide, using *in vitro* assays in HSCs, and secondly conduct a therapeutic study in another rat model of hepatic fibrosis induced by dimethylnitrosamine. Thalidomide inhibited NFκB transcriptional activity induced by TNF-α in HSC-T6 cell in a concentration-dependent manner. In addition, thalidomide also suppressed TGF-β1-induced α-SMA expression and collagen deposition in HSC-T6 cells. *In vivo*, thalidomide significantly reduced fibrosis scores of livers and hepatic collagen contents induced by DMN.

Furthermore, real-time PCR analysis indicated that hepatic mRNA expressions of TGF-β1, α-SMA, collagen 1α2,TNF- and iNOS genes were attenuated by thalidomide treatment. In conclusion, results showed that thalidomide inhibited activation of HSC-T6 cells by TNF-α and ameliorated liver fibrosis in DMN-intoxicated rats [37].

Breast cancer risk associated with genotypic polymorphism of the genes involved in the estrogen-receptor-signaling pathway: a multigenic study on cancer susceptibility

Estrogen exposure and family history are the two major factors associated with breast cancer risk. Estrogen receptor ß sequence variants (SNP) have been reported to have synergistic effects with endogenous estrogen exposure on breast cancer risk in Chinese population [38]. Similar observation on the polymorphisms of ER-α gene has been shown to correlate with various aspects of breast cancer especially for breast cancer lymph node metastasis in Taiwan [39]. Yu et al. [40] further examined whether breast tumorigenesis was linked to genotypes of candidate genes in the ER signal transduction pathway. They observed interesting association between the ER-MTA3-Snail-E-Cad pathway and the risk of breast cancer development.

Loss of viability during freeze–thaw of intact and adherent human embryonic stem cells with conventional slow-cooling protocols is predominantly due to apoptosis rather than cellular necrosis

One of the major challenges in the application of hES (human embryonic stem) cells in clinical therapy and basic scientific research is to develop efficient cryopreservation protocols. The survival rate of hES cells is lower than 5% by conventional slow-cooling protocols using 10% (v/v) DMSO as standard cryoprotectant [41–43]. In the present study [44], the authors surprisingly found that more than 98% of hES cells was viable immediately after the post-thawing washing as demonstrated by trypan blue exclusion test. If the hES cells were incubated at 4 °C for 90 min, more than 90% of cells was viable while incubated at 37 °C for 90 min, 30% of cells was viable. The hES cells death was caused by apoptosis but not necrosis as demonstrated by terminal deoxynucleotidyl transferase (TdT)-mediated dUTP nick-end-labeling (TUNEL) assay and the up-regulation of caspase-3. How to reduce the apoptosis remains to be further investigated [44].

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