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Biomedical Vignette

In the current issue:

Characterization of HPV-16 E6 DNA vaccines employing intracellular targeting and intercellular spreading strategies

Cervical cancer is a leading cause of cancer-related death in women. More than 99% of invasive cervical cancers contain human papillomavirus (HPV) and E6/E7 HPV oncoproteins are consistently expressed and are responsible for the malignant transformation of HPV-associated cancer cells [1]. E6 and E7 are therefore ideal targets for the development of therapeutic HPV vaccines. Using intracellular targeting strategies (CRT, LAMP-1, HSP70) as well as the intercellular spreading strategy (VP22), Peng et al. [2] report enhanced E6-specific CTL response in vaccinated mice and potent antitumor effects against TC-1 tumor cells. Thus, intracellular targeting and intercellular spreading strategies that have previously been shown to enhance E7 DNA vaccine potency also enhanced E6 DNA vaccine potency. These results have strong implications on the therapy of cervical cancers.

Molecular basis of the selection of HIV-1 reverse transcriptase mutant T215Y revealed

Mutations at codon 215 of HIV-1 reverse transcriptase (RT) have been known to confer resistance to nucleoside analogs through ATP-dependent phosphorolysis. In this issue, Yahi and coworkers [3] showed that the T215Y mutant was preferentially selected over T215F during the HAART. The authors carried out molecular modeling studies of ATP–RT complexes. These studies showed that the aromatic side chain of Y (tyrosine) stacked much better than that of F (phenylalanine) with the adenine ring of ATP. An additional mutation L210W, which was often co-selected with the T215Y, further stabilized the stacking interaction. This study thus provides a molecular basis accounting for the selection of T215Y mutant of HIV RT.

Characterization of neutralizing monoclonal antibodies recognizing a 15-residues epitope on the spike protein HR2 region of severe acute respiratory syndrome coronavirus (SARS-CoV)

The severe outbreak of Severe Acute Respiratory Syndrome (SARS) in Asia and Canada has been linked to a new coronavirus, SARS-CoV [4]. Its infection in Taiwan has claimed 346 cases and 37 deaths. The vaccine development against SARS-CoV is urgent. The spike protein, S, of coronavirus is responsible for binding to viral receptor on the surface of host cells, which makes it a target for generating the neutralizing antibody. Lai et al. [5] reported that monoclonal antibodies which recognized a fifteen-residue peptide from amino acid 1143–1157 effectively neutralized the infection of Vero E6 cells by SARS-CoV in a dose-dependent manner. This fifteen-residue peptide locates to the second heptad repeat (HR2) region of the S protein, which may be a good target for vaccine development against SARS-CoV.

Functional assay of HLA A2-restricted epitope variant of latent membrane protein 1 (LMP-1) of Epstein-Barr virus in nasopharyngeal carcinoma of southern China and Taiwan

Human leukocyte antigen (HLA) A2 was consistently associated with increased risk for nasopharyngeal carcinoma (NPC) in Chinese populations. Lin et al. [6] have previously reported that an Epstein-Barr virus strain carrying an HLA A2-restricted CTL epitope variant of LMP-1 is prevalent in NPC in southern China and Taiwan. In the current study, Lin et al. found that the LMP-1-specific HLA-A2 restricted CTL peptide variant prevalent in NPC bound to HLA-A2 molecules less efficiently than prototype CTL

peptide. Furthermore, the LMP-1 peptide-specific CTL lysed EBV-infected B cells expressing HLA-A2, whereas the CTL peptide variant abrogated CTL recognition and IFN-γ response [7]. These results suggest that EBV isolates from NPC in southern China and Taiwan are dominated by HLA-A2-restricted "epitope-loss variants" of LMP-1, allowing the virus to resist recognition and contributing to the prevalence of NPC in these populations.

Alternative 5′UTRs of a stress-responsive protein dPrx 1 mRNA differentially regulate translation efficiency in steady-state and oxidative-stressed cells

The 5′-untranslated region (UTR) of an mRNA often regulates translation efficiency of the mRNA. This phenomenon is further illustrated by Chen et al. [8] in this issue studying the regulation of expression of the peroxiredoxin (Prx) gene family. This protein family responds to reactive oxygen species (ROS), but how their expression is regulated by oxidative stress is not clear. Chen et al. found that the 5′UTR of the Prx 1 mRNA exists in two alternative forms. One form enhances translation in steady-state cells, whereas the other stimulates translation in cells under oxidative stress. This observation provides a novel form of posttranslational regulation of cellular genes.

Transcriptional regulation of the rat Mrp3 gene promoter by the specificity protein (Sp) family members and CCAAT/enhancer binding proteins

Human multidrug resistance-associated protein (MRP3) is located on the basolateral membrane of hepatocytes. Its expression is upregulated in the liver of patients with the Dubin-Johnson syndrome [9]. Tzeng et al. [10] studied the regulatory mechanism of rat mrp3 gene in rat liver cell lines. Their results demonstrated that the cooperation between C/EBP and Sp1/Sp3 transcription factors through −157 to −106 region regulated the promoter activity of rat mrp3 gene. Although the transcription synergy between C/EBP and Sp1 proteins was also shown in CYP2D5 and IL-10 genes, the detailed regulatory mechanism in the synergy between C/EBP and Sp1 in mrp3 gene is different from the previous mechanism found in CYP2D5 and IL-10 genes.

G-protein-coupled receptor agonists differentially regulate basal or tumor necrosis factor-α-stimulated activation of interleukin-6 and RANTES in human airway smooth muscle cells

Thapsigargin (Tg), a calcium-mobilizing agent, has been previously used to study the role of intracellular calcium in the regulation of cytokine-induced intercellular adhesion molecule (ICAM)-1 expression in human airway smooth muscle (ASM) cells [11, 12]. Here Huang et al. [13] study how Tg and other calcium-mobilizing agents affect the expression of pro-inflammatory genes in response to tumor necrosis factor (TNF)-α in ASM cells. They demonstrated that calcium-mobilizing agents functionally interact with TNF-α to differentially regulate pro-inflammatory gene expression in human ASM cells, possibly by involving Tg-sensitive intracellular calcium stores. Their study provides a better understanding of how calcium-mobilizing agents affect the functional activity of ASM cells.

The expression of α-internexin and peripherin in the developing mouse pineal gland

The mature mammalian pineal gland contains pinealocytes, interstitial glial cells, perivascular macrophages, neurons and peptidergic neuron-like cells. The neurons in the pineal gland are parasympathetic in nature, and the neuron-like cells exert a paracrine regulatory function on the pinealocytes [14]. Expression of the neuronal intermediate filaments (IF) genes, including α-internexin and peripherin genes, in neurons or neuron-like cells participates differentially in axogenesis during embryonic development [15]. α-Internexin is widely expressed during development and throughout adulthood in the central nervous system (CNS), whereas peripherin is predominantly found in the adult peripheral nervous system (PNS). Very limited information, however, is available on the expression patterns of these two proteins in pineal gland during development. By comparison of the temporal profiles in the expression of α-internexin and peripherin mRNA

or protein, Ko et al. [16] demonstrated that both molecules were readily detected immediately after birth, peaked on the postnatal day 7 (P7), rapidly declined at p14, and reached their adult levels at P21. α-Internexin mRNA and protein were expressed in soma and nerve processes in developing as well as adult mouse pineal gland. Fewer peripherin-immunoreactive or RNA-expressing cells or nerve processes were identified in the pineal gland during development. These observations indicate that some cells in the developing mouse pineal gland may differentiate into neurons and neuron-like cells that express both α-internexin and peripherin only after birth. These cells may possess dual properties of CNS and PNS neurons.

Acetaldehyde-induced interleukin-1β and tumor necrosis factor-α production is inhibited by berberine through nuclear factor-κB signaling pathway in HepG2 cells

Acetaldehyde is a highly reactive metabolite of alcohol and is responsible for much of the toxicity associated with excess ethanol. Previous study has shown that acetaldehyde did not induce oxidative stress, but still activated NF-κB and AP-1 in HepG2 cells [17]. Acetaldehyde has also been shown to induce TNFα and to activate p38 and ERK1/2; the latter in turn activates NF-κB in rat Kupffer cells [18]. Hsiang et al. [19] demostrated that acetaldehyde stimulated IL-1β and TNF-α production in HepG2 cells by regulating NF-κB signaling pathway. Furthermore, they showed that a major component of a Chinese medicinal herb, berberine, abolished acetaldehyde-induced NF-κB activity and cytokine production in HepG2 cells. This result opens a new avenue to explore the potential of Chinese medicinal herb to treat alcohol-induced liver diseases in the future.

Epigenetic activation of α4, $2 and β6 integrins involved in cell migration in trichostatin A-treated Hep3B cells

Histone deacetylase (HDAC) inhibitors have been shown to exert diverse biological activities including induction of cell growth arrest, apoptosis and differentiation [20]. The effect of the HDAC inhibitor, trichostatin A (TSA), on cell growth and gene expression have also been examined in several cultured human hepatoma cell lines [21]. TSA not only inhibited cell growth in all cell lines examined, but also upregulated the expression of a few genes, including integrin. Lin et al. [22] examined the effect of TSA on the expression of integrin family members in human hepatoma cells. They found that six integrins were specifically up or down regulated by TSA. The TSA up-regulated integrins contribute to TSA-induced cell migration activity. This study provides a new clue to explore therapeutic application of TSA on human hepatoma.

Lack of an association between candidate gene loci and idiopathic generalized epilepsy in Kuwaiti Arab children

Idiopathic generalized epilepsies (IGEs) are the most common types of epilepsy in childhood and adolescence. It is known that genetic predisposition plays a major role in the etiology of IGEs [23]. Previously, it has been shown that there is a strong association between IGE and certain candidate genes e.g., acetylcholine receptor gene, sodium channel gene and cystatin B gene among Caucasian populations [23, 24]. In this communication, the authors reported a lack of association between IGE and these genes in Kuwaiti Arab children [25]. These findings are quite significant and highlight the importance of undertaking genetic association studies in different populations and ethnic groups before a gene or locus is established as the major contributor to genetic susceptibility for a complex disorder such as epilepsy.

Non-linear cancer classification using a modified radial basis function classification algorithm

Improvements in cancer classification are central to advances in cancer treatment. Rapid development of microarray technology and cancer classification algorithms makes it possible to more accurately classify cancers. In the current issue, Wang and Huang [26] propose a modified radial basis function classification algorithm for non-linear cancer classification. This algorithm can be used to perform non-linear cancer classification based on gene expression profiles and applied to

two microarray data sets involving various human tumor classes: (1) normal versus colon tumor; (2) acute myeloid leukemia versus acute lymphoblastic leukemia. They demonstrated the accuracy and stability of their algorithm by comparing it with other cancer classification algorithms.

Warburg effect and vascular smooth muscle cells

Warburg effect has been observed in several different tumor cell lines [27]. In malignant cells, enhanced glycolysis has been shown to correlate with cellular proliferation and disease progression [28]. Various epidemiological, animal and molecular studies indicate that glucose metabolism plays a critical role in vascular reactivity and disease [29]. In this issue, Werk et al. [30] investigated glycolysis and its regulatory mechanism in proliferating VSMC in order to further elucidate the role of glucose metabolism in the proliferation of VSMC which is significantly elevated in atherogenesis [28, 29]. Results demonstrated that platelet derived growth factor (PDGF)-induced proliferation of VSMC significantly stimulated glucose flux through glycolysis. Further analysis of flux:metabolite co-responses revealed that anaerobic glycolytic flux is controlled at different sites of gycolysis in proliferating VSMC, consistent with the concept of multi-site modulation. These findings indicate that regulation of glycolytic flux in proliferating VSMC differs from the traditional concepts of metabolic control of the Emden–Meyerhof pathway [30].

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