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-\(\gamma\) 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-\(\alpha\)-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)-\(\alpha\) in ASM cells. They demonstrated that calcium-mobilizing agents functionally interact with TNF-\(\alpha\) 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 \(\alpha\)-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 \(\alpha\)-internexin and peripherin genes, in neurons or neuron-like cells participates differentially in axogenesis during embryonic development [15]. \(\alpha\)-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 \(\alpha\)-internexin and peripherin mRNA