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The vignette for V15 N1 issue

Aminoglycosides versus bacteria: a description of the action, resistance mechanism and nosocomial battleground

Aminoglycosides have been used as antibiotics since 1944; however, bacteria have developed selective and hardier resistance to the aminoglycosides. Aminoglycosides are aminocyclitols that kill bacteria by inhibiting protein synthesis by binding to 16S rRNA and disrupting the integrity of bacteria cell membrane. Bacteria acquire resistance mechanisms by: (a) inactivation of aminoglycosides by N-acetylation, adenylation or O-phosphorylation, (b) the reduction of intracellular concentration of aminoglycosides by changes in outer membrane permeability, decreased inner membrane transport, active efflux, drug trapping, (c) the alteration of 30S ribosomal subunit by mutation and (d) methylation of aminoglycoside binding site. This review [1] explores the molecular mechanism of aminoglycoside activity and resistance with an aim to minimize the spread of resistance.

Incorporation of Dengue virus replicon into virus-like particles by a cell line stably expressing precursor membrane and envelope proteins of dengue virus type 2

Dengue viruses containing a positive-sense, single-stranded 10-kb RNA genome belong to the genus Flavivirus in the family Flaviviridae. The four serotypes of Dengue viruses cause the most important arboviral disease in the tropical and subtropical areas. After Dengue virus infection, the patient may present a relatively mild disease, dengue fever, or develop the severe and potentially life-threatening diseases, Dengue hemorrhagic fever/dengue shock syndrome. Subgenomic replicons, which contain all the non-structural proteins required for amplifying themselves but lack some or all of the structural proteins, are useful tools to study viral replication in the absence of virion assembly and maturation [2]. Although subgenomic replicons of several flaviviruses have been recently reported to incorporate into virus-like particles (VLPs), no laboratory has demonstrated the generation of dengue VLPs by transducing dengue virus replicon or by using a complementation system to provide structural proteins in trans. Lai et al. [3] reported the generation of dengue VLPs capable of encapsidating homologous and heterologous replicons. Three steps are involved: (1) Establishment of a stable cell line producing RSPs of DENV2; (2) Construction of DENV2 subgenomic replicon and transfection of it into the stable cell line to generate DENV2 VLPs containing DENV2 replicon; and (3) Construction of DENV4 subgenomic replicon and transfection of it into the stable cell line to generate DENV2 VLPs containing DENV4 replicon. These VLPs can serve as a candidate for vaccine development in the future.

H. pylori infection can change the intensity of gastric Lewis antigen expressions differently between adults and children

Blood group binding adhesions expressed by H. pylori can selectively bind to the fucosylated Lewis antigens of human gastric epithelium and are believed to play an important role in inducing different severity of H. pylori infection. Here, Yang et al. characterized the expression of several gastric Lewis antigens and correlated them with H. pylori infection in stomach [4]. They found that the intensity of expression of Lewis antigens correlates with the H. pylori infection and the antigen expression is quite different between adults and children. Their findings facilitate our understanding of the pathogenesis of H. pylori infection

The role of amino acids T148 and R281 in human dihydrolipoamide dehydrogenase

Human dihydrolipoamide dehydrogenase (hE3) is a common component of α-ketoacid dehydrogenase complex. By multiple sequence alignment with other seventeen eukaryotic E3s, two amino acids, T148 and R281 were found to be potentially involved in catalytic function of the enzyme. By site-directed mutagenesis, the specific activities of

T148G, T148S, R281N and R281K were 76.4, 88.6, 12.55 and 11.9%, respectively that of E3, whereas the FAD content of these mutants were 71, 92, 96 and 93% that of wild type E3. The molecular mass analysis showed that these four mutant proteins form a dimer. Kinetic data demonstrated that Kcat of forward reaction of all mutants was affected, except for T148 mutant. This study [5] indicates that R281 is essential for E3 catalytic function but not T148.

A novel Phex mutation with defective glycosylation causes hypophosphatemia and rickets in mice

X-linked hypophosphatemic rickets (HYP) has characteristics of defective renal phosphate handling, vitamin D metabolism, and calcification of bone [6]. The primary defect in HYP has been shown as loss of function of a Zn-metalloendopeptidase called PHEX (Phosphate-regulating gene with Homologies to Endopeptidases on the X-chromosome) [7]. Using N-ethyl-N-nitrosourea (ENU)-induced mutagenesis in mouse to search for gene responsible for hypophosphatemia and rickets in mice, Xiong et al. [8] identified a novel Phex mutation with defective glycosylation. They further provided evidence to show that incompletely glycosylated PHEX protein was sequestered in the perinuclear region of cell and cannot be transported to the plasma membrane to exert its endopeptidase activity.

Association of angiotensin-converting enzyme (ACE) gene insertion-deletion polymorphism with spondylarthropathies

The spondyloarthropathies consist of a group of inflammatory joint diseases including ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis (ReA) and undifferentiated SpA. They are linked by shared characteristics that include a strong common genetic background. Genetic factors include major histocompatibility complex (MHC) genes such as HLA-B27 [9] and non-MHC genes such as IL-1 gene cluster [10]. Shehab et al. [11] examined and reported for the first time an association between ACE gene I/D polymorphism and inflammatory back pain (spondylarthropathies) in Kuwaiti Arabs. Whether such association is also held in other populations or ethnic groups deserves further investigation.

Knockdown of zebrafish $Na_v1.6$ sodium channel impairs embryonic locomotor activities

The voltage-gated Na + channel is the key regulator of neuronal excitability. The mutation leading to inactivation of the Scn8a Na + channel-subunit gene, which encodes $Na_v1.6$ protein, is responsible for motor endplate disease of mouse [12]. The developmental roles of scn8a has been examined in zebrafish using antisense morpholinos to knock down $Na_v1.6a$ protein [13]. The results show that voltage-gated Na + channels play cell-autonomous and non-cell-autonomous roles during neuronal development. Similar approach was performed by Chen et al. [14] and they demonstrated that the function of $Na_v1.6$ sodium channels is essential for the normal early embryonic locomotor activities.

Identification of c-Fos as a mitotic phosphoprotein: regulation of c-Fos by Aurora-A

The activation of the transcription factors such as c-Fos or c-Jun family members is one of the earliest nuclear events induced by growth factors. Intensive studies have been done to elaborate the role of c-Fos in cell cycle Go/G1 transition [15]. Little is known about whether c-Fos also plays any regulatory role in cell cycle G2/M transition. Increased c-Fos/AP-1 at G1/S has been shown to directly transactivate the wee1 kinase gene to halt mitotic cell division by phosphorylating and inhibiting cdc2 activity [16]. Yu et al. [17] searched for putative substrate for Aurora-A kinase and found that c-Fos may be phosphorylated by Aurora-A kinase during mitosis. This observation will open a new direction to investigate a novel role of c-Fos in G2/M transition of cell cycle progression.

IGF-1 enhances the efficacy of MSCs transplantation

Mesenchymal stem cells (MSCs) have been considered to be one of the potential cell sources for cellular cardiomyoplasty because of their multipotency and immunomodulatory properties [18].

A recent report also revealed that IGF-1 increased the expression of CXCR4 protein in vitro and this effect can be attenuated by IGF-1 neutralizing antibody [19]. However, little is known about the effect of pretreatment of MSCs with IGF-1 on the efficacy of cell transplantation therapy. Results of this study demonstrated that IGF-1 treatment has time-dependent and dose-dependent effects on CXCR4 expression in MSCs in vitro, and IGF-1 improves the efficacy of MSCs transplantation in a rat model of myocardial infarction mainly via enhancement of the number of cells attracted into the infarcted heart. These findings provide a novel stem cell therapeutic intervention against ischemic heart disease [20].

Endostatin gene therapy enhances the efficacy of paclitaxel to suppress breast cancers and metastases in mice

The field of cancer therapy is moving towards multimodality therapy. Here, Li et al. reported combination of antiangiogenic therapy using naked DNA encoding endostatin with chemotherapy using paclitaxel in a preclinical breast cancer model [21]. They demonstrated that the combination therapy generated significantly better therapeutic antitumor effects by inducing apoptosis of tumor cells and anti-angiogenesis, resulting in the control of metastasis to the lung and liver as compared to monotherapy. Their results have a significant potential for future clinical translation.

Chemopreventive effect of plant-derived glycoprotein on colitis-mediated colorectal cancer in A/J mice

Oral intake of the glycoprotein isolated from Ulmus davidiana Nakai (UDN) with a Mw 116-kDa significantly reduced the incidence and multiplicity of colorectal tumor in mice induced by 1.2-dimethyldrazine and dextran sodium sulfate. The abnormal levels of lactate dehydrogenase, thiobarituric reactive substrates and nitric oxide were significantly suppressed. Meanwhile, the levels of PCNA, iNOS and COX-2 were reduced, and DNA-binding activities of NFKβ and AP-1 in mouse colonic tissue was decreased. By RT-PCR assay, the UDN glycoprotein inhibited the expression of TNF-α and IL-6 mRNA in mice. Collectively, this study [22] showed that UDN glycoprotein has chemopreventive activity via modulation of inflammation-related factors responsible for colitis-mediated CRC in A/J mice.

Inhibition of associative long-term depression by activation of β-adrenergic receptors in rat hippocampal CA1 synapses

Long-term depression (LTD), a phenomenon of use-dependent change in synaptic efficacy, is a widely accepted model for the cellular and molecular mechanisms that underlie synaptic changes during learning and memory. In addition to homosynaptic LTD which is induced in the nerve cells following prolonged low-frequency stimulation [23], associative LTD can be induced when stimulation of the presynaptic fibers occurs simultaneously in conjunction with postsynaptic spiking preceded by 20–100 ms [24]. This spike-timing-dependent neural plasticity has been described in many CNS synapses, although the underlying mechanisms for induction are not clear. In this issue, Lin et al. [25] reported that in hippocampal CA1 synapses, associative LTD could be induced by a weak Schaffer collateral input paired with an independent strong input at a paired-pulse interval of less than 100 ms. Associative LTD induced by this pairing protocols was heterosynaptic, NMDA receptor-dependent and required activation of calcineurine. The PKA-MAPK/ERK kinase signal cascade following activation of the β-adrenergic receptors, on the other hand, inhibited this phenomenon. The author and his colleagues have previously reported [26] that endogenous noradrenergic system is involved in the induction of homosynaptic long-term potentiation (LTP) in the CA1 synapses. Together these results provide cellular mechanisms on modulation of cortical plasticity by LTP and associative LTD upon activation of brain noradrenergic system.

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