107-3-9

IL-20 Antibody is a Potential Drug for Diseases

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Abstract:

Inflammation considered as a “silent killer.” has been a hot topic in biomedicine. Research indicates that long-term chronic inflammation is closely linked to important diseases such as cancer, diabetes, obesity and osteoporosis. Many studies also showed that as long as chronic inflammation can be suppressed, disease can be effectively inhibited. Interleukin-20 (IL-20) is a potent pro-inflammatory cytokine and involved in several diseases. We have developed the Interleukin-20 monoclonal antibody (7E) that specifically inhibits the biological functions of IL-20. My presentation will focus on how IL-20 participates in the following diseases, and that 7E can be used to treat the diseases in animal models:

(1) Osteoporosis: IL-20 is highly expressed in patients with osteoporosis. We discovered that IL-20 is involved in the differentiation of osteoclasts and 7E significantly enhanced bone density of the OVX-induced osteoporotic mice.

(2) Breast cancer and cancer-induced osteolysis: Our study found that breast cancer tissue highly expressed IL-20. 7E can effectively inhibit the growth of breast cancer, metastasis, and reduce the osteolysis in mice.

(3) Chemotherapy induced-neuropathic pain: Cancer patients after chemotherapy often develop neuropathic pain. Our study showed that IL-20 plays key role in the pathogenesis of paclitaxel -induced neuropathic pain and 7E effectively inhibits neuropathic pain in murine model.

(4) Liver Diseases: IL-20 is highly expressed in clinical sample of liver cirrhosis and hepatoma. In the mice model of liver injury, 7E significantly inhibits hepatic fibrosis, reduced ALT and AST and alleviate the liver injury.

107-3-16

Roles of Chemical Engineers in Metabolic and Tissue Engineering

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Abstract

CRISPR-Cas9 is a newly developed RNA-guided genome editing system that hinges on the Cas9 nuclease and the proper design of guide RNA (gRNA). CRISPR interference (CRISPRi) is another emerging technology employing catalytically inactive Cas9 and synthetic guide RNA for targeted gene repression. We have employed CRISPR technology to integrate DNA fragments as large as 10 kb into E. coli and have used this technique to integrate genes into the chromosome of cyanobacteria for the production of succinate. Further, we have employed CRISPRi to modulate the exogenous and endogenous gene expression in cyanobacteria to promote the succinate production. Recently, we have also exploited CRISPR and CRISPRi to integrate 1, 4-BDO synthetic pathways into E. coli for the production. Conversely, regenerative medicine requires coordinated functions of cells, materials and appropriate signaling. Recent years have witnessed the marriage of regenerative medicine and gene delivery by which various genes encoding anabolic/catabolic proteins or RNA therapeutics are delivered into cells to potentiate the tissue regeneration. We have employed viral vectors for genetic modification of mesenchymal stem cells derived from bone marrow or adipose tissue for tissue regeneration. In particular, we have extensively exploited baculovirus, an emerging nonpathogenic gene delivery vector, for the delivery of various anabolic genes and miRNA mimics/sponges to repair tissues. This presentation highlights the roles of chemical engineers in metabolic and tissue engineering.

107-3-23

Histone deacetylase 6-Selective Inhibitor Targeting Glioblastoma via Autophagy Inhibition and PD-L1 Blockade

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Abstract

Histone deacetylase 6 (HDAC6) has considered as a target for drug development to treat cancer due to its major contribution in cell homeostasis, cell proliferation and metastasis. A serial of compounds has been synthesized in this laboratory and was found to be selective against HDAC6. Glioblastoma is the most fatal type of primary brain cancer, and current treatments for glioblastoma are insufficient. HDAC6 is overexpressed in glioblastoma, and siRNA-mediated knockdown of HDAC6 inhibits glioma cell proliferation. We find a high-selective HDAC6 inhibitor, J22352, which has PROTAC-like property resulted in both p62 accumulation and proteasomal degradation, leading to proteolysis of aberrantly overexpressed HDAC6 in glioblastoma. The consequences of decreased HDAC6 expression in response to J22352 were decreased cell migration, increased autophagic cancer cell death and significant tumor growth inhibition. Further studies on molecular and cellular level demonstrated that a novel HDAC6 inhibitor, J22352, can inhibit autophagic flux and lead to elevated metabolic stress result in autophagic cancer cell death. Surprisingly, we observed that this selective HDAC6 inhibitor can also reduce the immunosuppression of PD-L1, further lead to the T cells activation to against glioblastoma. J22352 induced inhibition of autophagy and immune response act in a synergistic manner to amplify its anticancer activity, resulting in preferential killing of cancer cells in vitro and in vivo. Most importantly, these results lend some facts to support that selective HDAC6 inhibitors have two major functions in anticancer actions through autophagy inhibition and recruiting the immune response to against glioblastoma. The cytotoxic activity and mechanism of action of these compounds will be presented.

107-3-30

IL-1 Signal in Epileptogenesis and Epilepsy-Induced Sleep Disruption

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Abstract

Epilepsy is one of the common neurological disorders that affect people of all ages and is often associated with sleep disorders, but the interaction between sleep and epilepsy is still not clear. Interleukin-1 beta (IL-1β) is a sleep regulatory substance (SRS) and participates in many pathological disorders, such as epilepsy and Parkinson's disease. Our studies have demonstrated that seizure occurred at different zeitgeber times (ZTs) alter sleep differently and IL-1 mediates the sleep alteration induced by the ZT13 epilepsy. Therefore, we investigate the role of IL-1 signaling and the consequence of NMDA receptor activation in epileptogenesis and epilepsy-induced sleep disruptions. In this study, the spontaneously generalized seizures were induced by intraperitoneal injection of pentylenetetrazol (PTZ). Sleep-wake activity and seizure threshold were determined in both the wildtype and IL-1R1 knockout (KO) mice. We found that the occurrence of spontaneous seizure was higher in the wildtype treated with PTZ than that in the IL-1R1 KO mice treated with PTZ. Furthermore, non-rapid eye movement (NREM) sleep was decreased in wildtype mice treated with PTZ, but it was not altered in IL-1R1 KO mice. The expression of NR1 and NR2B subunit proteins and the tyrosine phosphorylation of NR2B (at Tyr1472) in the hippocampus and the hypothalamus were significantly lower in the IL-1R1 KO mice when comparing to those in the wildtype mice. In contrast, the expression of NR1 and the phosphorylated-NR2B in the frontal cortex were significantly higher in the IL-1R1 KO mice treated with PTZ when comparing to those in the wildtype mice. We further demonstrated that phosphorylation of NR2B is mediated by the Src kinase in the IL-1 signaling cascade, while the increased expression of NR1 and NR2B subunits is regulated by the activation of NF-B. These findings suggest that the epileptogenesis and sleep alteration are attributed to the up-regulation of NMDA receptors, which is mediated by the IL-1 signal.

107-4-13

Resolution of Inflammation in Primary Immunodeficiency by Regulatory T Cells

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Abstract

Emerging evidence indicates that primary immunodeficiency syndromes are attributed to mutations in immune receptor/signaling with inflammation triggered by selective infection. X-linked lymphoproliferative syndrome type-2 (XLP-2) is a primary immunodeficiency disease linked to mutation of X-linked inhibitor of apoptosis protein (XIAP), with molecular mechanism incompletely understood. We found that XIAP-deficiency selectively impaired BCL10-mediated innate responses to dectin-1 ligands, but did not affect responses to various Toll-like receptor (TLR) agonists. Consequently, Xiap-/- mice became highly vulnerable upon Candida albicans infection. The compromised early innate responses led to persistent presence of C. albicans and inflammatory cytokines in Xiap-/- mice, resulting in death with excess inflammation. In addition, we found that mouse Xiap-/- regulatory T cells (Tregs) and human XIAP-deficient Tregs were defective in their suppressive function. We linked the Xiap-/- Tregs defect partly to decreased SOCS1 expression. XIAP binds SOCS1 and promotes SOCS1 stabilization. We observed a reduced Foxp3 stability in Xiap-/- Tregs. Additionally, Xiap-/- Tregs were prone to secreting IFN- and IL-17. Re-introduction of SOCS1 restored the function and stability of Xiap-/- Tregs. We also demonstrated that transfer of wild-type (WT) Tregs partly rescued Xiap-/- mice from infection-induced lethality. Therefore, XIAP-intact Tregs restore the ability of Xiap-/- mice to respond to infection and infection-induced inflammation, indicating that Tregs could be used to treat primary immunodeficiency. Furthermore, inflammation-induced reprogramming of Xiap-/- Tregs could be prevented by blockade of the IL-6 receptor (IL-6R), and a combination of anti-IL-6R and Xiap-/- Treg cells confers survival to inflammatory infection in Xiap-/- mice. These results demonstrate that XLP-2 can be corrected by combinatory treatment of autologous Tregs and anti-IL-6R, bypassing the necessity to transduce XIAP into Tregs. Our data also suggests the therapeutic feasibility of combining Treg cells and anti-IL-6R for the treatment of primary immunodeficiency diseases.

107-4-20

Glycan-Binding Proteins in Inflammation and Immunity

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Abstract

Glycan-binding proteins (GBPs) function by recognizing glycans on the cell surfaces and extracellular matrices. Currently, C-type lectins (such as selectins), C-type lectin receptors (Clec), Siglecs, and galectins have gained more attention. These proteins have been shown to be involved in inflammation and immunity, as well as many other physiological processes and pathogenesis of a variety of diseases. Importantly, many of them have been identified as biomarkers of diseases and therapeutic targets.

Galectins are a family of -galactoside-binding proteins, which differ from other glycan-binding proteins by not having a classical signal sequence and thus not being synthesized through the ER-Golgi pathway to be exocytosed. They are in fact present in the cytosol and can be translocated to the nucleus, although they can be secreted through an as yet undefined mechanism and exist in the extracellular space. Extracellularly, galectins can bind to and engage cell-surface glycans, thereby affecting a variety of cellular processes. However, importantly, they can function intracellularly in a glycan-independent fashion. A number of galectins have been shown to play a role in various immune and inflammatory responses. A key challenge is the determination of whether they function extracellularly or intracellularly in an organism.

Galectins can bind to cytosolic glycans presented as a danger signal when cells are infected by intracellular microbes. For example, galectin-3 accumulates around Listeria monocytogenes that had escaped from phagosomes through binding to host glycans on the membrane of ruptured phagosomes that initially contain the bacteria. Moreover, through this mechanism, galectin-3 suppresses autophagy induced by Listeria infection.

107-5-4

A Novel Regulation of DNA Repair in Neurons: the Complex of DISC1, GSK3β, and TRAX

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Abstract

Mental disorders affect millions of people around the world, and account for a significant proportion of medical burden. Although tremendous efforts have been devoted to the development of therapeutic treatments for mental disorders in the past decade, many important mechanistic details remained elusive. Elevated oxidative stress that results in oxidative DNA damage and insufficient repair of DNA damage may cause abnormal neurotransmission and compromise neuronal survival, and aggravate the development of psychotic disorders. We recently reports that inhibition of GSK3β, by either agonists of the A2A adenosine receptor (A2AR) or inhibitors of GSK3β, enhances DNA repair activity via regulating the TRAX/DISC1/GSK3β (TDG) complex. Activation of A2AR leads to dissociation of the TRAX/DISC1/GSK3β complex (TDG complex). This is of great interest because TRAX plays a critical role in detecting DNA damage by directly interacting with ATM to trigger DNA repair machinery. Dissociation of the TDG complex facilitates the release of TRAX from the TDG complex and allows TRAX entering the nucleus to facilitate DNA repair and subsequently enhance neuronal survival. Collectively, the TDG complex might serve as a potential therapeutic target for the development of novel treatments for diseases with defects in DNA repair.

107-5-11

Deconstructing Psychophysiology of Chronic Pain

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Abstract

Chronic pain disorders are accompanied by central amplification, which results in comorbid symptoms including anxiety- and depression-like behavior. Although the amygdala is thought as a key node of the neural circuits mediating emotional behavior, it also serves a major receiver of purely nociceptive signals. However, the circuit mechanisms by which the amygdala contributes to the pain-associated anxiety and depression has remained unclear. Here, we investigated central sensitization of neural circuitry in mouse models of chronic pain, including fibromyalgia-like pain and neuropathic pain. We found that the phosphorylated ERK (pERK) level increased in the lateral subdivision of central amygdala (CeL) of mice with the development of chronic pain. To address the role of the CeL in chronic pain, we attempted to manipulate CeL neurons using a chemogenetic approach. Selective expression of designer receptors exclusively activated by designer drugs (DREADDs) was achieved by injecting a virus encoding Cre-dependent Inhibitory DREADDs (i.e., hM4Di receptor) into a somatostatin (SOM)-Cre driver, a mouse line specifically expressing Cre recombinase in a major population of the CeL. We hypothesized that silencing of SOM+ neurons in the CeL, which may activate CeL output neurons (i.e., SOM- neuron) and thereby suppresses the CeM projecting neurons and reduces mechanical sensitivity and chronic pain-related emotional behavior. Consistent with this hypothesis, we found that chemogenetic silencing of SOM+ neurons in the CeL reduced mechanical allodynia, anxiety- and depression-like behaviors and increased sociability.

107-5-18

Precision Medicine: how to make it happen in Taiwan

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Abstract

Precision medicine takes individual variability and disease mechanism into account in the prevention, diagnosis, and treatment of diseases. To practice precision medicine, it is necessary to collect comprehensive information that defines a person (from genetic background, to environmental exposure, to lifestyles, etc.) and the diseases (from defective gene function, to structural protein abnormalities, to metabolic derangement, etc.). When individual information is interpreted against population norms and disease characteristics are informed by deep biological knowledge, the best strategies can be formulated to prevent or treat diseases defined by molecular mechanisms rather than by symptoms alone.

Taiwan, with its advanced health care system and a relatively homogeneous population, is perfectly suited to implement precision medicine. By defining the common genetic background of the population, one can obtain comprehensive genetic profiles of individuals by imputation when they are genotyped with a low cost, population-specific single nucleotide polymorphism (SNP) array. The genetic information can then be incorporated into one's medical record and used to prevent adverse reactions to medications, predict susceptibility to common diseases, and select effective therapies for the individual.

There are societal and technical challenges, however, for precision medicine to be successful. Besides the acceptance of precision medicine by the population, other near-term obstacles include cost of building population references, creating a database of genetic variability, deepening our biological knowledge, and developing sound data mining methods.

With inter-disciplinary efforts and support from all the stakeholders, Taiwan can bring precision medicine to the clinic in the near future.

107-5-25

Metabolic Reprogramming in Mitochondrial Diseases and in Stem Cell Differentiation and iPSCs Formation

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Abstract

Mitochondrial DNA (mtDNA) mutations are an important cause of mitochondrial diseases, for which there is no effective treatment due to complex pathophysiology. Accumulating evidence has suggested that mitochondrial dysfunction-elicited overproduction of reactive oxygen species (ROS) plays a vital role in the pathogenesis of mitochondrial diseases, and that the expression levels of several clusters of genes are altered in response to the elevated oxidative stress. We reported that glycolysis in affected cells with mitochondrial dysfunction is upregulated by AMP-activated protein kinase (AMPK), and such an adaptive response of metabolic reprogramming plays an important role in the pathophysiology of mitochondrial diseases. Adaptive responses via AMPK–PFK2, AMPK–FOXO3a, AMPK–PGC-1α, and AMPK–mTOR signaling pathways, respectively are modulated for the survival of human cells under oxidative stress induced by mitochondrial dysfunction. Elucidation of the adaptive mechanisms involved in AMPK activation cascades has led us to better understand the crosstalk between mitochondria and the nucleus in affected cells from patients with mitochondrial diseases. In another line of research, we first demonstrated that mitochondrial biogenesis and respiratory function and antioxidant enzymes are upregulated during osteogenic and adipogenic differentiation of human stem cells. By contrast, mitochondrial biogenesis and function are down-regulated in the process of generation of induced pluripotent cells (iPSCs) from somatic cells. iPSCs rely on glycolysis rather than oxidative phosphorylation as a major supply of energy. Mitochondria-rich neurons, myocytes, and cardiomyocytes are most affected cells in the patients with mitochondrial dysfunction, which can be differentiated from fibroblasts-derived iPSCs. Generating these cells from iPSCs derived from skin fibroblasts of patients with mitochondrial diseases will provide a cell model to study the pathogenic mechanism of mtDNA mutations and serves as a platform for screening of drugs to treat patients with mitochondrial diseases.

107-6-1

New Service Model of Chronic Diseases Based on the Cyber-physical System

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Abstract

Industry 4.0 is the current trend of automation in manufacturing business. The key technology underlying the industry 4.0 is the cyber-physical system, which integrates Internet of things, cloud computing, and cognitive computing. In terms of medical service, the cyber-physical system also provides an opportunity to the automation that most ancient business facing major challenges in recent years.

With the growing of the aging population, the hospitals are now crowded with peoples with various kinds of diseases. With the latest technology of the cyber-physical system, a majority part of the chronic patients is possible to be diagnosed and even treated at home without having to visit the hospitals. With the backgrounds of medicine and computer engineering, Dr. Kuo will share the experiences in remote examination of cardiovascular diseases and sleep disorders, and will discuss the possible service models of these chronic diseases based on the cyber-physical system.

107-6-15

Functional Genomics on Hepatocellular Carcinogenesis

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林口長庚紀念醫院胃腸肝膽科

Abstract

It is unclear how proliferating cells elicit suppression on cell proliferation and how cancer cells evade this growth suppression. Using a loss-of-function screening of the human kinome and phosphatome to identify genes suppressing tumor initiation in human hepatocellular carcinoma (HCC), we identified 19 genes and characterised one of the top scoring tumor suppressor candidate, Protein Tyrosine Phosphatase Receptor type F (PTPRF). We found that PTPRF was induced during cell proliferation by cell-cell contact. Ectopic expression of wild-type PTPRF, but not the phosphatase-inactive mutant, suppressed cell proliferation and colony formation in soft-agar assays. In contrast, PTPRF silencing led to cell hyperproliferation, enhanced tumor colony formation in soft-agar, and increased xenograft tumor growth in nude mice. Mechanistically, PTPRF silencing showed aberrant ERK-dependent signaling including the phosphorylation/stabilization of MYC through the direct activation of SRC and suppression of PP2A. This PTPRF-mediated growth suppression during cell proliferation functioned independently of the Hippo-Yap pathway. Clinically, PTPRF was downregulated in 42% HCC (37/89), 67% gastric cancer (27/40), and 100% colorectal cancer (40/40). PTPRF upregulation was found in 24% HCC (21/89) and associated with better clinical outcomes. Conclusion: A novel PTPRF-mediated growth suppression pathway was identified via a functional genomics screening in human hepatoma cells. Induction of PTPRF by cell-cell contact during cell proliferation quenched the activated ERK-dependent proliferation signaling to prevent cell hyperproliferation and tumor initiation. PTPRF downregulation in HCC facilitated tumor development. Our findings have shed light on how cancer cells can evade growth suppression and open a new avenue for future development of anticancer therapies.