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.