106-09-29

Roles of MicroRNAs in Atherosclerosis and Neointimal Lesion Formation under Flow

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Abstract:

Atherosclerosis, a vascular pathology responsible for most cardiovascular-related morbidity and mortality, develops predictably in regions of the arterial tree in which wall shear stresses are generated by complex patterns of blood flow. It has been recognized that hemodynamic characteristics determine the location of lesions and contribute to the pathogenesis of atherosclerosis. The key cells involved in atherogenesis include vascular endothelial cells (ECs) and smooth muscle cells (SMCs). Recent evidence suggests that laminar blood flow in the straight part of the arterial tree and high shear stress modulate cellular signaling and EC function, and protect against atherogenesis. In contrast, disturbed flow in bifurcations of the arterial tree and the associated oscillatory low shear stress enhance leukocyte infiltration of the arterial wall and thus are atherogenic. However, little is known about the effect of disturbed flow on ECs, especially on their interactions with SMCs, whose phenotypic switching is significantly implicated in atherosclerosis and neointimal lesion formation. Our recent studies using microRNA (miR) assay, in vitro EC-SMC co-culture flow system, experimental animal models, and human specimens from patients with coronary artery disease (CAD) have identified several miRs to be involved in the formation and progression of atherosclerosis. Among these miRs, miR-146a and 10a play atheroprotective roles in ECs against atherogenesis induced by disturbed flow. MiR-451, by targeting Rab5a, inhibits vascular SMC proliferation and inflammation and suppresses injury-induced neointimal lesion formation. Our findings help the discovery of new target biomarkers and elucidation of functional mechanisms underlying atherosclerosis, thereby facilitating the development of new approaches for therapeutic interventions.

Jeng-Jiann Chiu, Ph.D.

Dr. Chiu received his Ph.D. degree in 1992 from National Cheng Kung University studying blood flow dynamics. He is currently the Distinguished Investigator in the Institute of Cellular and System Medicine in National Health Research Institutes (NHRI) in Taiwan. Dr. Chiu is an outstanding and international-renowned scientist specialized in interdisciplinary fields of mechanobiology, vascular biology, and bioengineering, with a breadth of knowledge and technologies in different areas. His major research interest is vascular biology in health and disease, especially the biochemical and molecular bases of mechanotransduction and functional regulation of vascular endothelial cells (ECs) and smooth muscular cells (SMCs), as well as EC-SMC interactions under different flow patterns. He has used a multidisciplinary, systems approach that includes nanotechnology, DNA microarrary, cell biophysics, and biomechanics to conduct ex vivo and in vivo investigations on the cardiovascular system. He has made seminal contributions to the understanding of the interplays between cellular/molecular and mechanical factors in modulating inflammation and atherogenesis, which are the two key pathophysiological changes of the vascular system underlying atherosclerosis. Most importantly, his research findings have significant implications to the uses of biotechnological and pharmacological approaches to treat clinical disorders such as myocardial infarction, stroke and intermittent claudication. He has received several prestigious research awards in Taiwan, such as Outstanding Research Award by National Science Council/Ministry of Science and Technology in 2006 to 2016.

106-10-06

Gut Microbes: Xenobiotic Detoxification and Antibiotic Resistance

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Abstract

The lecture will cover two topics of host-microbe interplays in the gut. One is related to xenobiotic detoxification. Xenobiotic metabolism, representing biochemical reactions to either inactive or facilitate the excretion of xenobiotics, mostly occurs in the liver. Glucuronidation is one of the major detoxification pathways. The enzyme UDP-glucuronosyltransferase catalyzes the conjugation of hydrophobic xenobiotics with glucuronic acid residues to increase their solubility. Once the resulting glucuronides enter the intestine, gut microbial β-D-glucuronidases (GUS) catalyzes the hydrolytic cleavage of glucuronic acid, to obtain an additional carbon source. Although, this is an example of host-microbial co-evolution, the gut bacterial GUS activity carries a deleterious consequence regenerating toxic xenobiotics in the gut. It is thus important to define the contribution of specific bacterial groups or species to the global gut microbiome GUS activity. Particularly the substrate preference of GUSs is necessary to understand their functional role in affecting human health and disease. Herein we dissected the relationship between the substrate specificities and structural information of gut bacterial GUSs, which helped to identify the major bacteria causing the xenobiotic toxicity. The development has also led to the successful development of potent enzyme inhibitors.

The other interplay is relevant to cholesteryl glucosides in *Helicobacter pylori*. H. pylori is the main cause of various gastric diseases. It is known that the bacterium does not have the biosynthetic machinery to produce cholesterol. After hijacking cholesterol from the host, *H. pylori* modifies it into different forms of cholesteryl glucosides. We recently developed a specific metabolite-tagging method for the purpose of rapid identification, quantitative analysis and structural characterization. The development, the resulting analysis and the collected evidence have led to the findings that the bacteria employ cholesterol glucosides to enhance the lipid rafts clustering and the subsequent adhesion. We also identified and characterized the corresponding biosynthetic enzyme. Most interestingly, the enzyme was identified to be a new target of therapeutic intervention for antibiotic resistance.

106-10-13

Centriole, Centrosome in Health and Disease

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Abstract

Centrioles are microtubule-based cylinders that form centrosomes, which are the major microtubule organizing centers of animal cells, and are vital for many cellular and developmental processes. Primary microcephaly (MCPH) is an autosomal recessive congenital disorder characterized by smaller brain size with mild to severe mental retardation. Currently, at least twelve MCPH genes have been identified. Interestingly, most MCPH gene-encoding proteins are located at the centriole/centrosome and the roles of these MCPH proteins are incompletely understood. We previously showed that overexpression of STIL/MCPH7 induces centriole amplification (EMBO J 2011), excess CPAP/MCPH6 induces extra-long centrioles (Nat Cell Biol 2009), and phosphorylation of CPAP by Aurora-A kinase could cohere PCM proteins and maintain spindle pole integrity during mitosis (Cell Report 2016). Interestingly, CEP135/MCPH8 could directly interact with SAS6 and CPAP, and serve as a linker protein that connect the cartwheel to the outer microtubules for centriole duplication (EMBO J 2013). We also demonstrate that the interaction between CEP120 and CPAP (J Cell Biol 2013), and CEP295 and microtubules (J Cell Sci 2016) are required for centriole assembly. Here, we uncover a novel role for another microcephaly protein RTTN in centriole duplication and its action mechanism (Nat Commun 2017). Our studies demonstrate that the N-terminal domain of RTTN directly interacts with STIL and acts downstream of STIL-mediated centriole assembly. Interestingly, depletion of RTTN or complete loss of RTTN does not affect the initial step of procentriole assembly, instead, it inhibits the recruitment of later-born centriolar proteins POC5 and POC1B to the distal half centrioles. To assess the function of disease-associated RTTN mutations, we replaced endogenous RTTN with wild-type or missense mutants of RTTN-GFP transgenes. We found that a mutation of RTTN (A578P) that causes MCPH in humans shows a low affinity for STIL binding and inhibits centriole duplication. This suggests that the STIL-RTTN interaction is critical for assembly of a full-length centriole, and that dysfunction of this interaction may cause MCPH in humans. Together, we provide a molecular model to delineate a pathway of how four microcephaly proteins (CPAP, STIL, CEP135, RTTN) participate in centriole duplication. The significance and role of centriole/centrosome in cancer and primary

microcephaly will be discussed.

106-10-20

Co-activation of CLEC5A and TLR2 is Critical for NET Formation-Implication in Autoimmune Diseases

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Abstract

Thrombocytopenia is a critical factor to predict the onset of dengue hemorrhagic fever. CLEC5A (also known as MDL-1) and CLEC2 are Syk-coupled myeloid C-type lectins receptors (Syk-CLRs) expressed in macrophages/neutrophils and platelets, respectively. We have shown that dengue virus (DV) activates NALP3 inflammasome and induces proinflammatory cytokines from macrophages via CLEC5A (BLOOD 2013), and blockade of CLEC5A is able to attenuate DV-induced hemorrhaging shock and lethality (Nature 2008), bone erosion (J. Mol, Med. 2016). We further found that DV activate platelets via CLEC2, and DV-activated platelet-derived microparticles (DV-PMPs) induced 'neutrophil extracellular trap' (NET) formation and proinflammatory cytokine release via co-stimulation of CLEC5A and TLR2. Recently, we also showed bacteria also induce NETs via CLEC5A and TLR2 (Nature Communications, in press). This observation suggests CLEC5A and TLR2 are co-activated by both endogenous and exogenous PAMPs and lead to bone erosion and NET formation, and may be implicated for the treatment of autoimmune diseases attributed to aberrant NET formation.

106-10-27

Image-Based Measurement and Biomechanical Analysis of Natural and Prosthetic Joints during Activities

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Abstract

The mobility and stability of human joints are controlled by a complex interaction between the articular surfaces and the surrounding connective tissues, including ligaments and muscles. Study of the kinematic and force interactions between these force-bearing structures during multi-joint functional tasks is helpful for a better understanding of the etiology of relevant diseases, and for planning and evaluating subsequent treatments such as ligament reconstruction, total joint replacements and rehabilitation. Skin marker-based stereophotogrammetry has been widely used to measure inter-segmental motions of human movement, both for research and clinical purposes. However, the detailed motions of the articular surfaces and the surrounding connective tissues cannot be measured. In order to bridge the gap, there has been a growing interest in developing medical image-based approaches for measuring the kinematics and subsequent biomechanical analysis of the joints during activities. In this presentation, a brief review of these developments will be given. In particular, the development of a digitally reconstructed radiograph (DRR)-based 3D fluoroscopy method and its application to the study of a series of natural and prosthetic joints will be described. The 3D fluoroscopy method has also been integrated with a skin marker-based motion capture system and forceplates for the simultaneous measurement of the detailed motion of the knee joint and its coordination with other joints within the limb during multi-joint weight-bearing tasks, such as cycling. With 3D mathematical and finite element modeling, the accurate in vivo skeletal motion data of the knee provide a good opportunity for a more comprehensive subject-specific analysis of the articular contacts and ligaments of the joint during functional activities. Because of the hazards of ionizing radiation involved in fluoroscopy-based methods, the development of a new slice-to-volume registration method using FLASH MRI for the real-time measurement of joint kinematics in vivo will also be described.

106-11-03

Hypoxia-Mediated DUSP2 Downregulation Drives Cancer Stemness and Drug Resistance

蔡少正(Tsai, Shaw-Jenq) 司長

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Abstract

Hypoxia is a common pathophysiological feature of various diseases including cancer. Clinical investigation reveals that elevation of hypoxia-inducible factor-1α (HIF-1α) makes tumor cells more resistant to chemotherapy and increases the likelihood of metastasis and poor outcome. However, the mechanisms underlying the chemoresistance of hypoxic cancer cells remain largely unexplored. Our recent studies discovered that the expression of dual specificity phosphatase-2 (DUSP2), a nuclear phosphatase, was negatively regulated by HIF-1-dependent hypoxic stress. Reduced expression of DUSP2 leads to prolonged activation of ERK and thus increases transcription of numerous genes involved in angiogenesis, cell survival, cancer stemness, and drug response. In contrast, forced expression of DUSP2 or treatment with novel histone deacetylase inhibitors ameliorates hypoxia-induced cancer stemness and malignancy. Taken together, these data demonstrate that cancer cells evolve multiple processes to overcome the detrimental effect of low oxygen stress and DUSP2 serves as the key hub to control these processes. Targeting DUSP2 proves to be effective in developing more efficacious treatment regimens for cancer therapy.

106-11-10

Telomere Dysfunction Triggers Multiple Events to Solve Proliferation Problem

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Abstract

The replication of telomeres requires optimal timing and specific mechanisms for initiation and termination. In yeast, the initiation involves in combined actions of kinases on Cdc13 to promote telomerase recruitment at the late S phase. However, how cells terminate the function of telomerase at G2/M is still elusive. Here we show that PP2A phosphatase and Aurora kinase coordinately inhibit the function of telomerase. Pph22 phosphatase and Ipl1 kinase dephosphorylates and phosphorylates, respectively, the telomerase recruitment domain of Cdc13 to inhibit telomerase recruitment at G2/M phase. While Pph22 removes Tel1/Mec1-mediated Cdc13 phosphorylation to reduce Cdc13-Est1 interaction, Ipl1-dependent Cdc13 phosphorylation elicits an Est1/TLC1 dissociation. Failure of these regulations prevents telomerase from departing telomeres, causing perturbed telomere lengthening and prolonged M phase. Together our results demonstrate that differential and additive actions of PP2A phosphatase and Aurora kinase on Cdc13 limit telomerase action by removing active telomerase from telomeres at G2/M phase.

Moreover, upon environmental changes, proliferating cells delay cell cycle to prevent further damage accumulation. Cip1 is a CDK associated protein. However, the function and regulation of Cip1 are still poorly understood. Here we demonstrate that Cip1 expression is co-regulated by the cell cycle-mediated transcriptional factor Mcm1 and the stress-mediated transcriptional factors Msn2/4. Overexpression of Cip1 arrests cell cycle through inhibition of all Cdk1-G1 cyclin complexes at G1 stage, and the stress-activated protein kinase dependent phosphorylation of Cip1 T65, T69, and T73 strengthens the Cip1and Cdk1-G1 cyclin complexes interaction. Cip1 accumulation mainly targets Cdk1-Cln3 complex to prevent Whi5 phosphorylation and inhibit early G1 progression. Under osmotic stress, Cip1 expression triggers transient G1 delay which plays a functionally redundant role with another hyperosmolar activated CKI, Sic1. These findings indicate that Cip1 functions similar to mammalian p21 as a stress induced CDK inhibitor to decelerate cell cycle through all G1 cyclins to cope with environmental stresses.

106-11-24

Biosignatures of Pain in Small Fiber Degeneration of Diabetic Neuropathy

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Abstract

Diabetic neuropathy is the most prevalent etiology of peripheral nerve degeneration disorders. Patients with diabetic neuropathy have various neuropathic manifestations including (1) negative symptoms (loss-of-function), such as insensitivity to thermal stimuli and (2) positive symptoms (gain-of-function), e.g. neuropathic pain to innocuous stimuli. These are attributed to degeneration of small-diameter nociceptive nerve, small fiber neuropathy. The objective diagnosis of small fiber neuropathy with pathologic evidence was a challenge to neurologists. We hence developed skin biopsy to examine the degeneration of nociceptive nerves. This approach has become the standard diagnostic method for negative symptoms of small fiber neuropathy. To explore the signatures of positive symptoms, we set up contact heat evoked potential coupled with functional MRI. These examinations provide physiological and imaging signatures of neuropathic pain in diabetes. Furthermore these observations demonstrate maladaptive brain plasticity underlying mechanisms of nerve degeneration-induced neuropathic pain.

106-12-01

The Roles of Rab37-Mediated Exocytosis in Tumorigenesis

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Abstract

Rab small GTPases are master regulators of membrane trafficking and guide vesicle targeting. Our lab previously identified Rab37 as a novel metastasis suppressor Rab that functions through the tissue inhibitor of metalloproteinase 1 (TIMP1)-MMP9 pathway in lung cancer (Nat Commun 2014). We also show that thrombospondin-1 (TSP1), a secreted glycoprotein that inhibits angiogenesis, is another cargo of Rab37 (Clin Cancer Res 2017). Notably, secreted frizzled-related protein 1 (SFRP1) was identified as a putative cargo by our Rab37-mediated secretomic analysis. SFRP1 is known to be an extracellular antagonist of the Wnt signaling pathway, which is critical for cancer stemness. We reveal a novel component of the vesicular exocytic machinery mediated by Rab37 small GTPases in anti-stemness in cancer cells, xenograft and clinical models. Mechanistically, Rab37-mediated SFRP1 secretion inhibits Wnt signaling pathway and cancer stemness properties. Clinically, concordantly low expression of Rab37 and SFRP1 in tumor specimens correlated with high expression of Oct4 stemness marker and the worse clinical outcome of lung cancer patients. Targeting these Rab37-mediated exocytosis pathways for therapeutic value to treat lung cancer will be discussed in my talk.

Keywords: Rab37, exocytosis, metastasis, angiogenesis, stemness, lung cancer

106-12-08

Andrographolide and its Derivatives as Anticancer Agents through a Novel Hsp90-Dependent Mechanism

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Abstract

Andrographolide is the major constituent of Andrographis paniculata, a medicinal plant which has been used as folk medicine in Asia. My laboratory recently found that andrographolide could induce cleavage of heat shock protein 90 (Hsp90), degradation of Hsp90 client proteins and apoptosis in cancer cells (Biochemical Pharmacology, 2014, 87: 229-242), suggesting a novel anticancer mechanism of andrographolide via Hsp90 inhibition. Hsp90 is a crucial molecular chaperone that maintains protein stability of its clients, and several hallmark oncoproteins (ex: Bcr-abl, EGFR, HER2) which served as clinical drug targets are also known Hsp90 client proteins. Therefore, targeting Hsp90 to destabilize oncogenic client proteins has long been considered as a promising anticancer strategy. We thus further explored the anti-cancer mechanism and potential therapeutic application of Hsp90 inhibition mediated by andrographolide. We found andrographolide could directly bind to Hsp90 protein and reduced the interaction between Hsp90 and its client proteins. In addition, a fluorescent bioactive andrographolide-based chemical probe was created for studying the action mechanism of andrographolide (PLOS one, 2016; 11: e0152770). Moreover, two synthetic andrographolide derivatives exhibiting superior anticancer activity than andrographolide were also developed. Although chronic myeloid leukemia (CML) is clinically treatable with imatinib through inhibiting the kinase activity of Bcr-Abl oncoprotein, the increasing imatinib resistance caused by T315I missense mutation of Bcr-Abl (Bcr-AblT315I) becomes a clinical issue for CML patients. Our recent results indicate that andrographolide and its derivatives are able to induce apoptosis, differentiation and mitosis-arrest of imatinib-resistant CML cells by decreasing Bcr-AblT315I oncoprotein in an Hsp90-dependent manner. Notably, andrographolide derivatives delayed growth of imatinib-resistant CML cells in vivo without causing toxicity. Currently, we are exploring the therapeutic application of andrographolide and its derivatives on solid tumors via targeting other known Hsp90 clients including EGFR and oncogenic p53 missense mutant proteins.

106-12-15

Orexin-Initiated Endocannabinoid Signaling in Stress-Induced Analgesia, Stress-Induced Drug Craving and Acupuncture Analgesia

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Abstract

The orexin system consists of orexin A and B (also named hypocretin 1 and 2) and two Gq protein coupled receptors (GqPCRs), OX1 and OX2. Orexins have been implicated in arousal, feeding, reward and pain regulations. We have previously revealed a novel analgesic mechanism of orexins, i.e., orexin A can induce analgesia via activating OX1Rs, a GqPCR family, to generate 2-arachidonoylglycerol (2-AG) via an enzymatic cascade mediated by phospholipase C (PLC) and diacylglycerol lipase (DAGL). 2-AG, an endocannabinoid, then produces retrograde inhibition of GABA release (disinhibition) via CB1Rs in the ventrolateral periaqueductal gray (vlPAG), a midbrain region crucial for initiating descending pain inhibition. 1 We further explored the physiological significance of this orexin-induced disinhibition mechanism, i.e. when endogenous orexins can be released and produce disinhibition via this OX1R- PLC-DAGL-2-AG-CB1R cascade. Interestingly, we found that this orexin-initiated endocannabinoid-mediated disinhibition mechanism in the vlPAG can contribute to stress-induced analgesia, 2 and acupuncture-induced analgesia. Importantly, this mechanism also exists in the ventral tegmental area and contributes to stress-induced cocaine seeking.3

1.Ho YC, Lee HJ, Tung LW, Liao YY, Fu SY, Teng SF, Liao HT, Mackie K and Chiou LC (2011) Activation of orexin 1 receptors in the periaqueductal gray of male rats leads to antinociception via retrograde endocannabinoid (2-arachidonoylglycerol)-induced disinhibition. J Neurosci 31:14600-14610.

2.Lee HJ, Chang LY, Ho YC, Teng SF, Hwang LL, Mackie K and Chiou LC (2016). Stress induces analgesia via orexin 1 receptor-initiated endocannabinoid/CB1 signaling in the mouse periaqueductal gray. Neuropharmacology 105:577-586.

3.Tung LW, Lu GL, Lee YH, Yu L, Lee HJ, Leishman E, Bradshaw H, Hwang LL, Hung MS, Mackie K, Zimmer A and Chiou LC (2016) Orexins contribute to restraint stress-induced cocaine relapse by endocannabinoid-mediated disinhibition of dopaminergic neurons. Nature Communications 7:12199.

106-12-22

A Novel Nutrient Sensor that Mediates the Longevity Response to Dietary Restriction

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Abstract

Dietary restriction (DR) slows aging and extends lifespan in a wide range of species. However, how animals sense dietary changes and modulate its cellular defensive and metabolic responses to improve survival remains largely unclear. Recently, we have demonstrated that sams-1, the C. elegans homolog of Sadenosylmethionine synthetase (SAMS/MAT), to be a key mediator of the DRinduced lifespan extension. SAMS-1 catalyzes the biosynthesis of S-adenosyl methionine (SAM), which serves as a universal methyl group donor for numerous biochemical reactions. RNAi knock-down of sams-1 produces phenotypes that are similar to the dietary restricted animals, such as extended lifespan, smaller body size, and reduced fecundity. Over-expression of sams-1 makes worms insensitive to dietary changes and eliminates the lifespan effects of either DR or over-feeding. Moreover, feeding worms with SAM is sufficient to rescue the lifespan phenotype of sams-1 KO mutants and DR animals. Intriguingly, we found that SAMS-1 acts in the intestine to cell non-autonomously regulate longevity and aging. In response to dietary changes, intestinal SAMS-1 moves out of nucleus, where it normally accumulated. Most importantly, this re-distribution of SAMS-1 in the intestinal cells is required for its role in the longevity regulation and is tightly regulated via an AMPK-dependent phosphorylation. Together, our findings suggest that DR might influence the rate of aging by affecting the sub-cellular distribution of SAMS-1 activity and consequently the local SAM levels. SAM is required in the majority of biological methylations, including the methylations of RNAs, DNAs, lipids, and various proteins. A genetic screen of ~109 predicted SAM-dependent methyltransferases done in our lab suggests that the reduction of RNA methylation, histone methylation, and PC synthesis may be responsible for the longevity phenotypes observed in sams-1 mutants.

106-12-29

Transketolase Regulates Dynamic Switch of Glucose Metabolism to Control Breast Cancer Cell Metastasis via α-KG Signaling Pathway

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Abstract

Metabolic reprogramming including glucose metabolism is associated with progression of tumor growth. To identify the important players in such reprogramming, we employed 4T1/BALB/c syngeneic model to compare tumors of varying sizes. We identified the glycolytic enzyme transketolase (TKT) to be upregulated in the bigger tumors. We found TKT expression levels were the highest in lymph node metastases compared with primary tumor and normal tissues of patients. The higher levels of TKT expression had poor overall survival. Reduced TKT attenuated cancer cell growth and metastatic behaviors by in vitro and in vivo assays. Depletion of TKT elevated the expression of α-KG, which was able to inhibit cancer cell growth and metastasis. Reduced TKT or addition of α-KG switched glucose metabolism from glycolysis to TCA cycle through the regulation of enzymes involved in those pathways. These results suggest that TKT-mediated α-KG signaling pathway may be exploited for anti-metastasis therapy in breast cancer.

Our study for the first time demonstrates that TKT regulates the switch of glucose metabolism between glycolysis and TCA cycle through α-KG signaling pathway, thereby controlling breast cancer cell growth and metastasis. Overall, our findings reveal novel metabolic regulation and new therapeutic targets for metastatic breast cancer.

107-1-5

Unraveling Autoimmune Diabetes by Using Genetically Modified Mouse Models: from Mechanism Dissection to Clinical Application

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Abstract

Insulin-dependent diabetes mellitus (IDDM) is a T cell-mediated autoimmune disease. To delineate the protective roles of some immune modulatory molecules, such as soluble decoy receptor 3 (DcR3), cytotoxic T lymphocyte antigen 4 (CTLA4), program death ligand 1 and 2 (PD-L1 and 2), heme oxygenase 1 (HO-1), and chemokine receptor D6 in the autoimmune process and to search for potential preventive and/or therapeutic targets in this disease, we have generated (a) insulin promoter (pIns)-sDcR3 transgenic non-obese diabetic (NOD) mice, (b) pIns-single chain anti-CTLA4 transgenic NOD mice, (c) pIns-single chain anti-4-1BB transgenic NOD mice, (d) pIns-PD-L1 transgenic NOD mice, (e) pIns-HO-1 transgenic NOD mice, and (f) pIns-D6 transgenic NOD mice and demonstrated their immunomodulatory potential and underlying mechanisms. Meanwhile, to explore the modulatory potential of interleukin-12, 23 and 27 on autoimmune diabetes, we have generated following transgenic, knockout and knockdown NOD mice: (1) Th1 and Th2 doubly transgenic (2) IL-12 knockout (3) IL-23 knockdown (4) IL-27 knockdown NOD mice. Our results revealed that 20% IL-12-deficient NOD mice still developed autoimmune diabetes, the diabetic incidence of IL-23 knockdown NOD mice is lower than that of control littermates, and the number and percentage of Th1 cells are dramatically decreased and Th17 cells are increased in IL-27 knockdown mice, indicating a differential role of IL-12 cytokine family in modulating Th1 and Th17 cell development during autoimmune diabetogenic process. Making full use of these unique mouse strains, we are quantitatively and qualitatively investigating the immunopathogenic mechanisms of autoimmune diabetes and providing valuable information for the development of novel immunotherapies.