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

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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.