SPECIAL LECTURES

LUNCHEON LECTURES

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SL 1

Myofilament Dysfunction in Heart Failure

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Heart failure is characterized by a progressive decline in pump function. A decline in cellular contractile function has been shown to be at the basis of this syndrome. The mechanisms underlying myocyte dysfunction are incompletely understood, which hampers the development of novel therapeutic strategies to combat morbidity and mortality. Numerous studies have shown that cardiac cellular calcium homeostasis is disturbed in both human and experimental heart failure, and this may be responsible for the reduction in contractile function of the cardiac myocyte. However, the function of the cardiac contractile apparatus has, until recently, received far less attention. Here we show that myofilament function is depressed in human and experimental heart failure. Moreover, depressed contractile protein function is not caused by altered protein isoform expression, but rather due to post-translational modifications, most likely maladapted contractile protein phosphorylation, in particular the troponins, myosin regulatory light chain, and myosin binding protein C. Our results show that contractile protein phosphorylation is an important (negative) regulator of cardiac myocyte contractile function and a potential target for therapeutic interventions. No COI.

SL 2

Circadian rhythms, molecular clock and skeletal muscle; why muscles need to keep time

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Disruption of circadian rhythms in humans and genetic models of circadian disruption in rodents have implicated a fundamental role for circadian rhythms in systems health including links to metabolic and cardiovascular diseases. These models also exhibit skeletal muscle weakness and altered metabolism. Here we show that disruption of the molecular clock in adult skeletal muscle is sufficient to disrupt maintenance of muscle function and phenotype as well as skeletal and cardiovascular homeostasis. Targeted deletion of the molecular clock gene, Bmal1 (iMSBmal1-/-) in skeletal muscle caused pathological changes including reductions in specific tension, altered gait, a shift toward a more oxidative fiber type, and muscle fibrosis. Surprisingly, the iMSBmal1-/- mice exhibited pathological changes in bone and cartilage along with cardiac hypertrophy and elevated blood pressure. We found that the Renin Angiotensin System (RAS) was altered with loss of muscle Bmal1 with increased expression of angiotensinogen and other RAS components in liver and skeletal muscle consistent with elevated blood pressure, changes in the skeletal system and muscle fibrosis. These findings highlight the critical function of the molecular clock in skeletal muscle and uncover the fundamental role that skeletal muscle, an organ system comprising approximately 40 percent total body mass, impacts systemic health. No COI.

SL 3

Novel aspects of the autoregulation of blood flow: from isolated vessels to human

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Supply of the brain can be achieved only if the blood volume and consequently intracranial pressure is tightly controlled. Thus a very effective autoregulation must be present, which is an important feature of the cerebral circulation. This issue has been investigated by several previous studies and it was logically assumed that autoregulation of CBF is somehow coupled to changes in hemodynamic forces, such as pressure and shear stress.

Pressure sensitive vasomotor response: For many years, autoregulation of CBF has been primarily explained by the pressure-induced myogenic mechanism of cerebral vessels: the inherent property of vascular smooth muscle to dilate to a decrease and to constrict to an increase in intraluminal pressure. There are two critical downstream mechanisms are activated by increases in wall stress: Ca^{2+}-dependent and –independent, RhoA/Rho kinase pathway, sensitizing actin-myosin proteins to Ca^{2+}, leading to the constriction.

Flow sensitive vasomotor response: Only very recently, it was shown in certain cerebral vessels, such as the middle cerebral artery a flow sensitive mechanism also exists. In contrast to peripheral arterial vessels, in the presence of constant pressure increases in flow elicit constrictions in this type of vessels. The constrictions are mediated by 20-HETE (20-hydroxieicosatetraenoic acid, a constrictor metabolite of arachidonic acid synthesized by cytochrome P450 hydroxylases) and reactive oxygen species (ROS).

On the basis of above, it is plausible that in the cerebral vascular network, during increases in systemic blood pressure when both pressure and flow changes (for example during exercise) the flow-constriction is superimposed on the pressure-constriction resulting substantial constrictions of arterial vessels providing a relatively stable level of blood flow. These mechanisms are present in vivo protecting the capillaries from pressure and flow overload and the blood brain barrier (BBB). No COI.

SL 4

The role of prostaglandin E_2 in gastric mucosal inflammation and the significance of dysregulation of degradation pathway of prostaglandin E_2 in gastric carcinogenesis

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Prostaglandin E_2 (PGs), which are synthesized by cyclooxygenase (COX) fromarachidonic acid liberated from membrane phospholipids, havea variety of biological effects. In physiological condition, PGE_2 is produced by COX-1, which is regularly expressed late-limiting enzyme for synthesis of PGs to maintain gastric mucosal integrity and wound healing. PG is also produced by COX-2, an inducible isoform by inflammatory stimuli, mainly Helicobacter plyori infection in the stomach. Our previous study shows that PGE_2 exert anti-inflammatory effect against Helicobacter plyori infection-induced proinflammatory responses in the stomach, which may suppress initial event of gastric carcinogenesis such as progression of cell turnover of gastric glands. However, as inflammatory change in gastric mucosa progresses, PGE_2 promotes carcinogenic effect such as promotion of cell proliferation and tumor angiogenesis. Accumulating clinical and experimental evidence establish the involvement of PGE_2 in a variety of cancer in the gastrointestinal tract. Although tissue levels of PGE_2 stem from relative rates of biosynthesis and degradation, most of previous studies about gastrointestinal carcinogenesis have extensively focused on production system of PGE_2, especially COX-2. In addition, recent studies indicate that degradation pathway of PGE_2 which includes PG transporter and 15-hydroxyprostaglandin dehydrogenase (15-PGDH) have tumor suppressor property. Our recent studies showed that both PGT and 15-PGDH is arethe prognostic factor for poor survival of gastric adenocarcinoma patients who underwent gastrectomy. Our studies demonstrate that reduced expression of PGT and 15-PGDH in gastric carcinogenesis is associated with tumor cell proliferation and tumor angiogenesis. Thus, our studies suggest that themaintenance andrestorationof regulation system of PGE_2 could be a key for prevention of gastric carcinogenesis. No COI.

SL 5

Evolutionary and comparative cognitive neurobiology of human and non-human primates

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Human evolution has involved a continuous process of addition of new kinds of cognitive capacity, including those relating to manufacture and use of tools and to the establishment of linguistic faculties. The dramatic expansion of their brains that accompanied additions of new functional areas would have supported such continuous evolution. Extended brain functions would have driven rapid and drastic changes in the ecological niche of human ancestors, which in turn demanded further brain resources to adapt to it. In this way, humans have constructed a novel niche in each of the ecological, cognitive and neural domains, whose interactions accelerated their individual evolution through a process – namely, "Triadic Niche Construction". Thus emerged human intelligence should be structured to comprise a part of dynamic patterns of holistic terrestrial ecosystem. The primate brain's functional characteristics seem to play a key role in this triadic interaction. We advance a speculative argument about the origins of its neurobiological mechanisms, as an extension with wider scope of the evolutionary principles of adaptive function in the nervous system of the non-human primates. Neurobiological mechanisms to acquire novel tool-use skills in non-human primates would shed light on such properties of human intelligence developed through the course of evolutionary processes. No COI.

SL 6

Systems Biology of Aquaporin-2 Regulation in Kidney Collecting Duct

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Vasopressin regulates water transport in the renal collecting duct epithelium in part by increasing abundance of the AQP2 water channel protein. We are using quantitative proteomics (LC-MS/MS) and transcriptomics to identify how vasopressin regulates gene expression in collecting duct cells. We used dynamic SILAC (LC-MS/MS) to quantify the effect of vasopressin on the steady-state translation and degradation rates of each protein in cultured mouse mpkCCD cells. Of the 4403 proteins quantified, vasopressin significantly altered protein half-life of <20 proteins. This included AQP2, whose protein half-life increased from 10 to 14 hrs. Many more proteins showed increases in translation rate including AQP2 (10 fold increase). Simultaneous global measurements of protein abundances (standard SILAC quantification) and transcript abundances (Affymetrix expression arrays) revealed that as many as 35% of proteins that undergo a change in abundance in response to vasopressin had no corresponding change in mRNA (despite sufficient statistical power), pointing to the possibility of extensive translational regulation. AQP2, however, showed an increase in mRNA roughly proportional to the measured increase in translation. A change in mRNA abundance could be due to a change in transcription rate or mRNA degradation rate. To begin to address the former, we carried out simultaneous RNA-seq and ChIP-seq profiling for RNA Polymerase II (Pol-II). These experiments showed a 6-fold increase in Pol-II binding to the Aqp2 gene with an accompanying 18-fold increase in mRNA. The increases for Aqp2 outstripped the vasopressin-induced changes in all other genes, pointing to a highly selective transcriptional network triggered by vasopressin signaling. No COI.

LUNCHEON LECTURE

Luncheon lecture 1

NSAIDs/aspirin enteropathy: From bench to bedside

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Small bowel injury caused by indomethacin in animals had been reported in 1960s. This phenomenon, however, has been ignored for 40 years in a clinical field until capsule endoscopy was available. NSIADs and/or low-dose aspirin are widely used for patients with chronic arthritis and/or ischemic vascular diseases respectively and now we have a lot of publications regarding NSAID-enteropathy. We have shown in the animal model that indomethacin increases gram-negative bacilli, stimulates proinflammatory cytokines, and neutrophil infiltration in the mucosa of small bowel. The enteropathy was inhibited by antibiotics specific for gram-negative bacilli, antibodies against TNFα and IL-1β, and antiserum against neutrophils. These results may indicate that gram-negative bacilli over-grown translocates through the mucosa weaken due to the insufficiency of prostaglandins, then the inflammatory system is stimulated, which triggers the injury. The inflammatory activation and injury were attenuated in TLR-4 knockout mice, whereas they were enhanced by treatment with TLR-4 ligands such as LPS and HMGB1, indicating the TLR-4-dependent pathway may play a key role. Therefore, this pathway may be the target of drug development for the prevention and treatment of NSAID-enteropathy. Recently we have found that the NLRP3 inflammasome/IL-1β axis could be another target. To prevent or treat NSAID-enteropathy, several small studies have done with available drugs and substances and have shown that misoprostol, a prostaglandin derivative, rebamipide, a mucoprotective drug which may affect intestinal microbiota, and probiotics may be promising. Further clinical studies are needed with possible drugs to inhibit the TLR-4-dependent pathway or the NLRP3 inflammasome/IL-1β axis. This study is supported by Otsuka Pharmaceutical Co., Ltd., which provided rebamipide and its placebo used.