Department of Cell Physiology

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General Summary

The aim of research in our laboratory is to understand the regulatory mechanism of the cardiovascular system. In particular, we are interested in the development of the cardiovascular system, the mechanics of sarcomere contraction, Ca^{2+} homeostasis in the cardiac sarcoplasmic reticulum, and the pathophysiology of cardiac fibrosis and pulmonary hypertension. We established an experimental system to investigate small fetal arteries, such as the rat fetal ductus arteriosus (DA) and pulmonary vein. In addition, we developed an *in vivo* nanoimaging system to observe sarcomere contraction in the ventricles of small animals, such as rat and mouse.

Research Activities

Establishment of the rat model of pulmonary hypertension due to left heart disease
Pulmonary hypertension due to left heart disease (PH-LHD) is the most frequent cause of pulmonary hypertension (PH). Although pulmonary artery hypertension has been intensively investigated, PH-LHD remains unclear because of the lack of an appropriate PH-LHD animal model. We successfully established a novel, feasible rat model of PH-LHD by generating left atrium stenosis. Using this novel PH-LHD rat model, we found that TGF-β and endothelin-1 were significantly increased in the lung of PH-LHD.

Molecular mechanism of closure of the DA
The DA is an essential artery that connects the main pulmonary artery and the descending aorta in fetus. The DA closes immediately after birth in accordance with its smooth muscle contraction and vascular remodeling. We are investigating the effect of long-term use of prostaglandin E_1 on DA structure and function using human DA samples. This project is a collaborative work with Hyogo Prefectural Kobe Children's Hospital.

Regulation of sarcoplasmic reticulum ATPase activity
We are interested in regulation of the sarcoplasmic reticulum Ca^{2+}-ATPase and Ca^{2+} homeostasis in the sarcoplasmic reticulum. We found that a sarcolemma membrane targeted protein phosphatase, PP2Ce, is a specific and potent phospholamban (PLN) phosphatase. PP2Ce expression was elevated in failing human heart and induced acutely at protein level by β-adrenergic stimulation or oxidative stress in cardiomyocytes. We think that PP2Ce is a new regulator for cardiac function and pathogenesis. This project is a collaborative work with Professor Yibin Wang at UCLA.

Regulation of cardiac metabolism
Cardiac metabolism plays an essential role in maintaining cardiac function. Vitamin B1 (VitB1, thiamine) deficiency causes Beriberi, which is characterized by peripheral sensory and motor neuropathy, and congestive heart failure. Dr. Kenehiro Takaki who founded Jikei University, eliminated Beriberi from the Imperial Japanese Navy by improving dietary habit (thiamine supplementation). We found that pretreatment with VitB1 preserved cardiac function in ischemic-reperfusion injury. We are now investigating the microstructural changes using electron microscope and the metabolic changes using Mass spectrometer.

Pathophysiological mechanisms of overstretch-induced cardiac dysfunction
The mechanism of reactive fibrosis in volume overloaded heart is incompletely understood. We studied the effect of diastolic overstretch on induction of cardiac fibrosis in isometrically contracting muscle preparation from rat right ventricular papillary muscles. We stretched papillary muscle to 10 to 15% over stretch for 4 hours with tension measurement, then compared with non over stretched samples. Immediately after length, active tension decreased to ≦50% of the initial tension. The expression levels of fibrosis related factors (CTGF and PC-3) in over stretched samples were significantly higher than those in non over stretch. These results suggest that overstretch significantly reduced tension, and induce fibrotic transition.

Mechanism of sarcomere contraction in cardiac muscle
Sarcomeric contraction in cardiomyocytes serves as the basis for the hearts pump functions. Although sarcomeres play a pivotal role in the circulatory system, myocardial sarcomere length (SL) changes have not been systematically investigated *in vivo*. Here we developed a high-speed (100 frames per second), high-resolution (20 nm) spinning disc confocal-imaging system for the beating mouse heart *in vivo*. Via expression of α-actinin-AcGFP under this optics system, we analyzed physiological sarcomere dynamics in a single myofibril consisting of ～30 sarcomeres (i.e., with a near entire length) in a ventricular myocyte, simultaneous with hemodynamic parameters (i.e., ECG, LVP and PV loop). The findings were as follows: First, the SL values were 1.88±0.29 and 1.66±0.19 μm, respectively, in diastole and systole, and the individual SL values varied markedly during the cardiac cycle even in the same myofibril. Second, the dynamic behavior of each sarcomere was not always synchronized with that of a whole myofibril. Third, the correlation (R) between the dynamics of an individual sarcomere and that of a whole myofibril varied markedly, i.e., from −0.2 to 0.8, during six cardiac cycles. Fourth, sarcomeres that made an active contribution to myofibrillar dynamics and those that did not coexisted at a similar ratio. These findings will give new insights in our understanding of cardiac functions at the single sarcomere level.

Publications

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