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 veins. In addition, we developed an *in vivo* nanoimaging system to observe sarcomere contraction in the ventricles of small animals, such as rats and mice.

Research Activities

Analysis of characteristics of pulmonary veins
Pulmonary veins must differ in character from systemic veins because they carry blood with a high concentration of oxygen. However, the characteristics of pulmonary veins remain a mystery. We successfully established a novel, feasible rat model of pulmonary hypertension due to left heart disease by generating left atrium stenosis and are analyzing the effects of pulmonary congestion on the vascular structure and the function of pulmonary veins. In addition, we have generated the atrium-specific overexpression and deletion of pituitary homeobox 2c, a transcription factor that is specifically expressed in the pulmonary veins and the left atrium.

Molecular mechanism of closure of the DA
The DA is an essential artery that connects the main pulmonary artery and the descending aorta in the fetus. The DA closes immediately after birth in accordance with its smooth muscle contraction and vascular remodeling. We found that prostaglandin E_1 induces the secretion of the protein nephroblastoma overexpressed (NOV or CCN3) in rat DA smooth muscle cells and that this protein inhibits intimal cushion formation of the rat DA. We have also done the comprehensive analysis of the gene expression of the chicken DA and the aorta. These projects are in collaboration with Waseda University.

Regulation of endoplasmic reticulum stress on cardiac function
Endoplasmic reticulum (ER) stress is associated with cardiac function. We are interested in the regulation of the serine/threonine protein kinase/endoribonuclease inositol-requiring transmembrane kinase/endonuclease 1α (IRE1α) on ER stress in heart failure. in the sarcoplasmic reticulum. We found that IRE1α induced transient ER stress signaling and

conferred a protective effect against pressure overload–induced pathological remodeling in the heart. This project is a collaborative work with Professor Yibin Wang at the University of California, Los Angeles.

Regulation of cardiac metabolism
Cardiac metabolism plays an essential role in maintaining cardiac function. In the damaged heart, fatty acid (FA) oxidation is impaired and glycolysis is promoted. We examined the regulation of cardiac metabolism in a mouse model of cardiac injury due to the administration of monocrotaline. Metabolites in the tricarboxylic acid cycle were decreased and those in glycolysis were increased at 6 weeks. We found that pyruvate dehydrogenase activation is an early event to compensate for a subtle metabolic impairment from myocardial damage.

Pathophysiological mechanisms of overstretch–induced cardiac dysfunction
The mechanism of impaired cardiac function in a volume–overloaded heart is incompletely understood. We studied the effect of diastolic overstretch on cardiac function in isometrically contracting muscle prepared from rat right ventricular papillary muscles. We found that acute, severe overstretch of an isolated rat papillary muscle causes the inner collapse of mitochondria with the sarcomere structure being preserved. Therefore, we believe that abrupt disruption of the mitochondrial structure by acute diastolic overstretch might account for the mechanisms on pathogenesis of acute volume–overloaded heart failure.

Mechanism of sarcomere contraction in cardiac muscle
Sarcomeric contraction in cardiomyocytes serves as the basis for the heart's pump functions. Although sarcomeres play a pivotal role in the circulatory system, changes of myocardial sarcomere length 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–*Aequorea coerulescens* green fluorescent protein under this optics system, we analyzed physiological sarcomere dynamics in a single myofibril consisting of approximately 30 sarcomeres (i.e., with a near entire length) in a ventricular myocyte, simultaneously with hemodynamic variables (i.e., electrocardiography, left ventricular pressure, and a pressure volume loop). The findings were as follows. First, the sarcomere length values were 1.88 ± 0.29 μm in diastole and 1.66 ± 0.19 μm in systole, and the individual sarcomere length 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 an entire myofibril. Third, the correlation (R) between the dynamics of an individual sarcomere and that of an entire myofibril varied markedly, i.e., from −0.2 to 0.8, during 6 cardiac cycles. Fourth, sarcomeres that actively contributed to myofibrillar dynamics and those that did not coexisted at a similar ratio. These findings provides new insights for our understanding of cardiac function at the single–sarcomere level.

Publications

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