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, metabolomic changes in the diseased heart, 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 a high-precision analyzing system to measure the temperatures of cells.

Research Activities

Analysis of characteristics of pulmonary veins
Pulmonary veins must have a character that differs from that of systemic veins due to containing a high concentration of oxygen in blood. However, the characteristics of pulmonary veins remain a mystery. We have generated the atrium-specific overexpression of paired-like homeodomain transcription factor 2 (Pitx2c), a transcription factor that is specifically expressed in the pulmonary veins and the left atrium. We found that the transgenic mice exhibited sinus node dysfunction using a telemetric electrocardiographic analysis system.

Molecular mechanism of closure of the DA
The DA is an essential artery that connects the main pulmonary artery and the descending aorta in a fetus. The DA closes immediately after birth in accordance with its smooth muscle contraction and vascular remodeling. We found that a new chemical compound EP4 antagonist, RQ-15986 (renamed from CJ-042794), selectively contracted the DA when we measured the isometric tension of rat DA in the presence of RQ-15986. In addition, we investigated the effect of gentamicin on DA closure. We found that standard-dose gentamicin did not increase the risk of DA patency in rat neonates. Furthermore, we examined the transcriptional profiles of chick DA, which anatomically differs from mammal DA. A DNA microarray analysis revealed newly identified genes in the chicken pulmonary artery-sided DA. Subsequent pathway analysis with the Database for Annotation, Visualization and Integrated Discovery (DAVID) Bioinformatics Resources revealed that the pulmonary artery-sided DA showed enhanced expression of the genes involved in melanogenesis and tyrosine metabolism, suggesting that tyrosinase and the related genes play an important role in the proper differentiation of neural crest-derived cells during vascular remodeling in the chick DA. These projects are a collaborative work with Waseda University.

Regulation of cardiac metabolism

Cardiac metabolism plays an essential role in maintaining cardiac function. Fatty acid oxidation is impaired and glycolysis is promoted in the damaged heart. We used 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 one of the earliest events 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 an isometrically contracting muscle preparation from rat right ventricular papillary muscles. We found that acute severe overstretch of an isolated rat papillary muscle caused inner mitochondrial collapsing with preserved sarcomere structure. We are now checking these phenomena in in-vivo experiments using a pulmonary banding model.

Mechanism of sarcomere contraction in cardiac muscle

Sarcomeres are activated via thin filament structural changes (i.e., from the "off" state to the "on" state) in response to a release of Ca^{2+} from the sarcoplasmic reticulum. This process involves chemical reactions that are highly dependent on ambient temperature. We investigated the effects of rapid heating by focused infrared laser irradiation on the sliding of thin filaments reconstituted with human α-tropomyosin and bovine ventricular troponin in an in-vitro motility assay. We performed high-precision analyses measuring temperature by the fluorescence intensity of rhodamine-phalloidin-labeled F-actin coupled with a fluorescent thermosensor sheet containing the temperature-sensitive dye europium (III) thenoyltrifluoroacetonate trihydrate. This approach enabled a shift in temperature from 25°C to∼46°C within 0.2 second. We found that in the absence of Ca^{2+} and the presence of ATP, infrared laser irradiation elicits sliding movements of reconstituted thin filaments with a sliding velocity that increases as a function of temperature. The heating-induced acceleration of thin filament sliding likewise occurs in the presence of Ca^{2+} and ATP; however, the temperature dependence is more than twofold less pronounced. These findings might indicate that in the mammalian heart, the "on-off" equilibrium of the cardiac thin filament state is partially shifted toward the "on" state in diastole at physiological body temperature, enabling rapid and efficient myocardial dynamics in systole.

Publications

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Reviews and Books

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