Bio-informational Pharmacology

1. Staffs and Students (April, 2009)

Professor	Tetsushi Furukawa, MD, PhD
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2. Purpose of Education

This laboratory focuses on understanding fundamental pathophysiological roles of ion channels and transporters in cardiovascular system. We employ multidisciplinary approach (patch-clamp, cell biology, optical recording, genetic analysis, and computational analysis) in order to seek novel regulatory mechanisms and modulatory molecules/compounds of ion channels and transporters in cardiac myocytes, vascular smooth muscle and endothelial cells, and circulating cells in vessels (monocytes and macrophages). Our ultimate goal is to discover novel diagnostic and therapeutic strategy for intractable and common cardiovascular diseases.

3. Research Subjects

1. Gender-specific medicine (GSM) for cardiac arrhythmias

Susceptibility of several diseases and responsibility to various drugs and therapy exhibit gender-difference, and cardiac arrhythmias and sudden cardiac death show unique gender difference. Using a series of experiments, we have recently proposed that non-genomic actions of sex hormones are novel regulatory system of cardiac ion channels and QT interval, which may, in part, explain the gender-difference in long QT-related cardiac arrhythmias. Currently, we study following specific projects;

a. Sex hormone receptors specific for non-genomic pathway
   Sex hormone receptor responsible for non-genomic pathway is currently a controversy topic. We try to identify and characterize sex hormone receptors specific for non-genomic pathway in cardiovascular system.
b. Spatial localization of molecules involved in non-genomic pathway
   Many signaling molecules participate in sex hormone non-genomic pathway, which are coordinated in a spatio-temporal dependent manner to execute non-genomic actions. We use a novel PLA (proximity ligation assay) method to characterize the spatial cordination of these molecules.

2. Pathogenesis of atrial fibrillation

Atrial fibrillation is the most frequent persistent arrhythmias, reaching more than 3.5 million patients in Japan. Associated cerebral infarction due to cardiogenic thrombosis (250,000 patients /year in Japan) causes reduced QOL and is one of the main causes of bedridden old people. Therefore, the establishment of protection and treatment of atrial fibrillation is warranted. Our current approaches are follows;

a. GWAS (genome-wide association study) in atrial fibrillation
   We carry out most extensive GWAS (genome-wide association study) in Japan to determine gene polymorphisms associated with atrial fibrillation. Our goal is to create a diagnostic algorithm for personalized medicine of atrial fibrillation.
b. Inflammatory and immunological mechanisms in atrial fibrillation
   Pathogenesis of many metabolic syndrome-related diseases, including atrial fibrillation, involves with chronic, mild inflammation, induced by interaction of many environmental and genetic risk. We examine environmental and genetic factors to cause recruitment of inflammatory cells (e.g. T lymphocytes, macrophages, mast cells) to atrial tissue.
c. Development of myocardial sleeve in the pulmonary vein
   Most atrial fibrillations are triggered by abnormal electrical activity in myocardial sleeve in the pulmonary vein, and isolation of pulmonary vein with catheter ablation technique becomes the most efficient therapy for atrial fibrillation. We study the transcriptional mechanism underlying development of myocardial sleeve in the pulmonary vein.

3. Pathogenesis of ventricular tachyarrhythmias and sudden cardiac death

Despite extensive effort by many researchers for years, ventricular tachycardia and fibrillation remain the main cause of sudden death, and the biggest challenge in arrhythmia research. Our laboratory takes following approaches;

a. Analysis of *NOS1AP* (NOS1 associated protein) KO mice

In recent GWAS performed in Western countries, *NOS1AP* is surprisingly the most closely related gene to sudden cardiac death. We analyzed *NOS1AP* KO mice to clarify the mechanism of association between *NOS1AP* and sudden cardiac death.

b. Brugada syndrome-like mouse model

Brugada syndrome is intractable familiar sudden death syndrome, which is frequently found in East Asia and is previously known as "pokkuri disease" in Japan. The lack of animal model hinders the understanding of pathogenesis of Brugada syndrome. In mice deficient of a Na^+ channel regulator with unique localization in the heart, we found phenotype closely related to human Brugada syndrome. We analyze this novel Brugada syndrome-like model mice, aiming to understand its pathogenesis and propose its protective and therapeutic strategy.

c. Novel disease category "auto-immune arrhythmia"

We have recently reported a case of ventricular arrhythmia caused by autoantibody against the cardiac ion channel, and propose a novel disease category "auto-immune arrhythmia". Our goal is to characterize "auto-immune arrhythmia", and estimate its prevalence.

4. Use of iPS cells for arrhythmia research

Traditional arrhythmia researches have been performed in cardiomyocytes of species other than human, or in cultured cells, in which human ion channel genes have been heterologously expressed. The milieu different from human cardiac myocytes (especially the lack of excitation-contraction coupling machinery) is the huge limitation for arrhythmia research. Cardiomyocytes differentiated from human iPS cells could overcome this critical limitation, and would bring marked advance in arrhythmias researches. We take following 2 approaches;

a. Establishment of iPS cells from LQT patients

We try to establish and characterize iPS cell-derived cardiomyocytes from human fibroblasts obtained from congenital LQT patients.

b. Drug screening system using human iPS cells-derived cardiomyocytes

New drugs are developed in a research consisted of ①discovery of a lead compound→②pre-clinical study in animals→③clinical study. Because of cardiac toxicity in human, many candidates compounds advanced to clinical trials fail to pass, which is because of the lack of assay system in human tissues in pre-clinical study step. Cardiomyocytes derived from human iPS cells could provide a assay system in human tissues in pre-clinical study step, and facilitate new drug discovery and prevent unexpected drug side effects.

4. Publications List

Original Article

1. Yang PC, Kurokawa J, Furukawa T, Clancy CE. (2010) Acute effects of sex steroid hormones on susceptibility to cardiac arrhythmias: A Simulation Study. ***PLoS Comput Biol*** 6, in press.
2. Kaihara A, Sunami A, Kurokawa J, Furukawa T. (2009) A genetically encoded bioluminescent indicator for the sodium channel activity in living cells. ***J Am Chem Soc,*** 131, 41388-4189.
3. Kakusaka S, Asayama M, Kaihara A, Sasano T, Suzuki T, Kurokawa J, Furukawa T. (2009) A receptor-independent effect of estrone sulfate on the hERG channel. J Pharmacol Sci, 109, 152-156.
4. Asada K, Kurokawa J, Furukawa T. (2009) Redox- and calmodulin-dependent S-nitrosylation of the KCNQ1 channel. ***J Biol Chem,*** 284, 6014-6020.
5. Kurokawa J, Bankston JR, Kaihara A, Chen L, Furukawa T & Kass RS. (2009) KCNE variants reveal a critical role of the beta subunit carboxyl terminus in PKA-dependent regulation of the I_{Ks} potassium channel. ***Channels,*** 3, 16-24.
6. Sasano T, Kelemen K, Greener ID, Donahue JK. (2009) Ventricular tachycardia from the healed myocardial infarction scar: validation of an animal model and utility of gene therapy. ***Heart Rhythm*** 6, S91-7.
7. Lautamaki R, Schuleri KH, Sasano T, Javadi MS, Youssef A, Merrill J, Nekolla SG, Abraham MR, Lardo AC, Bengel FM. (2009) Integration of Infarct Size, Tissue Perfusion and Metabolism by Hybrid Cardiac PET-CT – Evaluation in a Porcine Model of Myocardial Infarction. ***Circulation Cardiovascular Imaging*** 2, 299-305.
8. Johnston PV, Sasano T (contributed equally), Mills K, Evers R, Lee ST, Smith RR, Lardo AC, Steenbergen C, Gerstenblith G, Lange R, Marbán E. (2009) Engraftment, differentiation and functional benefits of autologous cardiosphere-derived cells in porcine ischemic cardiomyopathy. ***Circulation*** 120, 1075-83.