*Forum Minireview***New Molecular Mechanisms for Cardiovascular Disease:
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Cardiovascular disease is the most critical cause of morbidity and mortality in developed countries (1). The major cardiovascular diseases, such as coronary artery disease, myocardial infarction, congestive heart failure, and common congenital heart disease, are caused by the interaction between genetic predisposing mechanisms and environmental factors (2, 3). The elucidation of the molecular mechanisms of cardiovascular disease is a critical initial step in developing improved methods of drug screening and therapy. This Forum Minireview contains the proceedings of the symposium at the 83rd Annual Meeting of The Japanese Pharmacological Society held on March 16, 2010. The aim of this symposium was to discuss recent findings about the new molecular mechanisms for cardiovascular disease. This review series represents four topics about the blood flow sensing mechanism in vascular endothelial cells, functional deficiency of endothelium associated with ageing, genetic remodeling in heart failure, and cardiac cell-volume regulation.

Endothelial cells lining blood vessels have a variety of functions and play a critical role in the homeostasis of the circulatory system. It has become clear that biomechanical forces generated by blood flow regulate endothelial cell functions (4, 5). Yamamoto and Ando show that shear-induced activation of P2X4 requires endogenously released ATP and that shear stress induced cultured endothelial cells to release ATP, which was mediated by cell-surface ATP synthase in caveolae (6). P2X4^{-/-} mice do not exhibit normal endothelial cell responses to blood

flow. Furthermore, no adaptive vascular remodeling is observed in the P2X4^{-/-} mice. Thus, P2X4-mediated shear stress mechanotransduction plays an important role in vascular homeostasis, including the control of blood pressure and vascular remodeling (7).

The endothelium regulates vascular tone via release of endothelium-derived relaxing factors (8). The mesenteric vascular bed produces vascular resistance to develop blood pressure and regulate tissue blood flow that plays an important role in maintenance of systemic blood pressure (9). Jin et al. use a pharmacological method to investigate the role of the vascular endothelium in the regulation of α_1 -adrenoceptor agonist-induced vasoconstriction in rat mesenteric vascular beds (10). Their results suggest that EDHF (endothelium-derived hyperpolarizing factor) mainly counteracts continuous vasoconstriction induced by methoxamine in the mesenteric resistance arteries of the rat and this endothelial regulation of agonist-induced vasoconstriction markedly decreases with age (11).

Genetic remodeling contributes to the progression of heart failure by affecting myocardial cellular function and survival. In the search of transcriptional regulation of cardiac gene expression, Kuwahara and Nakao show transcriptional pathways involved in pathological cardiac remodeling. The transcriptional repressor NRSF (neuron-restrictive silencer factor) regulates expression of multiple fetal cardiac genes through the activity of HDACs (histone deacetylases) (12). Inhibition of NRSF in the heart results in cardiac dysfunction and sudden arrhythmic death. In the pathological calcineurin – NFAT (nuclear factor of activated T-cells) signaling pathway, TRPC6 is a key component of a Ca²⁺-dependent regulatory loop. Indeed, inhibition of TRPC significantly ameliorates this pathological process in a mouse model

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of cardiac hypertrophy (13). Moreover, they show that MRTF-A (myocardin-related transcription factor-A) mediates prohypertrophic signaling by linking the small GTPase Rho-actin dynamics signaling pathway to cardiac gene transcription. Collectively, their studies have revealed the transcriptional network involved in the development of cardiac dysfunction and potential therapeutic targets for the treatment of heart failure (14).

Cardiac hypertrophy is an increase in the muscle volume of the ventricle due to the enlargement of cardiac cells. In cardiac cells, one of the essential factors for cell-volume regulation is the volume-regulated anion channel (15). However, the relationship between cardiac hypertrophy and cell-volume regulation is not clear. Yamamoto et al. show that the impairment of volume-regulated anion current is exhibited in ventricular cells from mice with cardiac hypertrophy induced by transverse aortic constriction (16). Similar results are observed in caveolin-3-deficient mice, which develop cardiac hypertrophy without pressure overload. Their results suggest that the volume-regulated anion channel will be a new target for protection from the development of cardiac hypertrophy (17).

We hope that this Forum Minireview will provide the readers with clues to solve the puzzle of the molecular mechanisms for cardiovascular disease and to design new diagnostic and therapeutic strategies.

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