Macro- and microvascular disorders currently represent the principal causes of morbidity and mortality in patients with diseases involving the cardiovascular system, such as atherosclerosis, hypertension, stroke, and diabetes. Both metabolic and hormonal imbalances contribute to the pathogenesis of vascular disease, and disorder of the modulatory role of vascular cells may be a critical and initiating factor in the development of such diseases. In addition, the signaling pathways activated by vasoactive modulators may differ based on vessel type, cell type, stages of disease and gender. The complexity of intracellular signaling and interactions provide an exciting area of investigation for the pursuit of new pharmacological targets for the management of cardiovascular diseases such as atherosclerosis, hypertension, and diabetes. This Current Topics section is dedicated solely to developmental research into vasoactive modulators of vascular tone, as well as the regulation and alteration of cellular signaling that occurs in metabolic and cardiovascular diseases. Here we present three reviews and one article under the heading “Recent progress in the study of vasoactive modulators in metabolic and cardiovascular diseases” which describe the current understanding of the physiology of vasoactive modulators, as well as potential therapeutic strategies to overcome cardiovascular disease.

The three reviews and article have been written by leading scientists who are experts in their respective fields. The first review is “Progression of Time-Dependent Changes to the Mechanisms of Vasodilation by Protease-Activated Receptor 2 in Metabolic Syndrome” by Kagota and colleagues. Protease-activated receptor 2 (PAR2) is a G protein-coupled receptor activated either by serine proteases released from tissues or by synthetic peptide ligands administered pharmacologically. This research summarized recent findings from their studies of aging/chronic exposure to metabolic abnormalities associated with metabolic syndrome on the PAR2-mediated vasodilation in arteries of animal models of metabolic syndrome. Furthermore, they discussed the role of PAR2 and the implications of its age-related changes on circulatory function of the cardiovascular system in metabolic syndrome, along with its potential as a target for pharmaceutical development.

The second review is titled “Mammalian Target of Rapamycin (mTOR) as a Potential Therapeutic Target in Pathological Ocular Angiogenesis” by Nakahara et al. The abnormal growth of new blood vessels on the retina results in sight-threatening complications such as vitreous hemorrhage and tractional retinal detachment. Recent studies have demonstrated that inhibitors of mammalian targets of rapamycin display a narrow-spectrum effect on proliferating endothelial cells within the retinal vasculature. The researchers introduce the role of mTOR in physiological and pathological retinal angiogenesis and discuss the potential of targeting the mTOR pathway to treat ocular pathologic angiogenesis.

The third review is “New Insights into the Role of Basement Membrane-Derived Matricryptins in the Heart” by Okada et al. Matricryptin has been defined as a group of fragments cleaved from the extracellular matrix which contain matricryptic sites. Since most matricryptins have been clarified to be endogenous anti-angiogenic and anti-tumor factors, they are expected to be useful as a novel anti-tumor drug, and have thus been widely investigated. On the other hand, in the past ten years, several studies have demonstrated that the expression level of basement membrane-derived matricryptins changes in patients or experimental models of cardiac disease. Recently, Okada et al. and others have focused on some of these basement membrane-derived matricryptins, which are proposed to contribute to the regulation of cardiac remodeling through modulating the functions of cardiac cells. In this review article, they introduce and summarize those studies, and discuss the roles of matricryptins in cardiac diseases that lead to heart failure such as cardiac hypertrophy and myocardial infarction.

The fourth article is “Augmented Contractility to Noradrenaline in Femoral Arteries from the Otsuka Long-Evans Tokushima Fatty (OLETF) Rat, a Model of Type 2 Diabetes” studied by Kobayashi, Matsumoto et al. Vascular dysfunction often systematically occurs in type 2 diabetes; however, regarding type 2 diabetes, there is little evidence regarding the function of the femoral artery, which is the main artery to supply oxygenated blood to the lower limbs. Here, these researchers investigated whether the contractile response to noradrenaline in the femoral artery would increase in the type 2 diabetic male Otsuka Long-Evans Tokushima Fatty (OLETF) rat, which exhibits stable experimental and pathological characteristics resembling human type 2 diabetes at the chronic stage of disease. They found that noradrenaline-induced contractions increased in the femoral arteries in OLETF rats compared with age-matched control Long-Evans Tokushima Otsuka (LETO) rats, whereas serotonin-induced contractions were similar between these two animals. They also found that noradrenaline-induced contractions were enhanced by treatment with 1-NNA, a nitric oxide synthase inhibitor, and the between-group difference in contractions was eliminated by such treatment. Indomethacin, a non-selective cyclooxygenase inhibitor, reduced noradrenaline-induced contractions in both groups, although the contraction remained greater in the OLETF group versus LETO group. These results suggest that increased contractile responsiveness to noradrenaline is seen in the OLETF rat, and this may be attributable to the impaired suppressive effect of NO. Although further investigations should be required to determine the detailed molecular mechanisms and causative factor(s) underlying these augmented noradrenaline-induced contractions, the researchers believe that funding such research could significantly help in the management of peripheral arterial diseases associated with chronic type 2 diabetes.

Ischemic cardiovascular disease remains one of the leading causes of mortality in Japan and the world. In this Current Topics, we shall summarize recent progress in the development of vasoactive modulators on vascular tone, as well as their role in regulation and alterations in cellular signaling that occur in metabolic and cardiovascular disease. We believe that this review article will be of great benefit to readers interested in cardiovascular disease, vasoactive modulators and pharmacology.