Vascular Function

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Vascular function is regulated by many cell components, including endothelial cells (ECs), vascular smooth muscle cells (VSMCs), and adventitial tissues with inflammatory cells, autonomic nervous system, and vasa vasorum. The interactions among these cells/tissues are substantially involved in the vascular health and disease. All these cell components secrete several growth factors, cytokines/chemokines, and extracellular matrix, all of which contribute to vascular homeostasis. Among them, the growth factors secreted from VSMCs play important roles in the vascular remodeling process because they mediate various cellular responses. In addition, oxidative stress is one of the important stimuli that modulate VSMC function and proliferation. Many recent publications in *ATVB* have added further information on the roles of each cell component in the regulation of vascular function and diseases, including cytokines/chemokines, matrix metalloproteinases (MMPs), VSMC proliferation, and inflammation. Some publications have also provided a novel role of perivascular adipose tissues and perivascular stem cells that contribute to the development of vascular diseases. This article will focus on these recent publications in *ATVB*.

ECs for Vascular Function

ECs are exposed to blood flow, contributing to the maintenance of vessel structure and preservation of vascular functions. However, the effects of hemodynamic forces on cell signaling in the endothelium are still obscure. Several recent articles in *ATVB* addressed the role of ECs in the vascular function and mechanistic links to vascular diseases. Walshe et al[1] demonstrated that transforming growth factor-β (TGF-β) signaling mediates the protective effects of shear stress on ECs. They examined the potential role of TGF-β signaling in mediating the protective effects of shear stress on ECs. Finally, they concluded that shear stress induces TGF-β3 signaling and subsequent activation of Kruppel-like factor 2 and nitric oxide (NO), demonstrating a novel role for TGF-β3 in the maintenance of endothelial homeostasis in a hemodynamic environment.[1] This article provides a novel effect of shear stress on ECs in which induction of TGF-β3 expression leads to the activation of Kruppel-like factor 2 and NO signaling. Approaches designed to assess endothelial functions, as well as gene expressions in vivo, provide a novel finding in

the analyses of cardiovascular diseases. As Enkhjargal et al[2] have recently demonstrated, endothelial AMP-activated protein kinase mediates endothelium-dependent hyperpolarization responses and blood pressure regulation in mice. ECs are central to the initiation of vascular diseases, yet there has been limited success in studying their gene expressions in the arteries in vivo. To address this, Erbilgin et al[3] developed a novel method for determining the global transcriptional changes that occur in the mouse endothelium in response to atherogenic conditions and applied it to investigate inflammatory stimuli. They demonstrated that RNA can be isolated from mouse aortic ECs after in vivo and ex vivo treatments. In addition, they applied this method to identify a group of novel causative genes in vascular diseases. Choi et al[4] demonstrated that globotriaosylceramide accelerates endocytosis and lysosomal degradation of endothelial $K_{Ca}3.1$ via a clathrin-dependent process, leading to endothelial dysfunction in Fabry disease. In this study, the authors demonstrated that glycosphingolipid globotriaosylceramide modulates $K_{Ca}3.1$ expression in ECs via clathrin-dependent and early endosome antigen 1–enriched endosome-mediated lysosomal degradation. Specifically, inhibition of globotriaosylceramide –induced $K_{Ca}3.1$ degradation through clathrin knockdown suggested that the $K_{Ca}3.1$ protein is internalized by globotriaosylceramide via a clathrin-dependent process. On the basis of the study, the authors proposed a novel mechanism underlying globotriaosylceramide-mediated EC dysfunction, which is associated with suppression of endothelium-derived hyperpolarizing factors.[4,5]

This finding is particularly important in the clinical setting. H_2O_2 plays a crucial role as a signaling molecule at physiological low concentrations, which is one of the endothelium-dependent hyperpolarization factors that modulate vascular tone, especially in microvessels and in human coronary arteries. Thus, physiological levels of reactive oxygen species (ROS) levels are important for the regulation of EC functions. Although high levels of ROS induce vascular dysfunction, strictly controlled ROS formation mediates several important physiological vascular functions. However, it has long been awaited a plausible explanation and mechanisms for the biphasic effect of ROS on vascular function. A recent article in *ATVB* by Wood et al[6] demonstrated that eNOS in circulating erythrocytes also contributes to the regulation of systemic blood pressure and vascular homeostasis. Moreover, Ciccarelli et al[7] demonstrated that endothelial G-protein–coupled receptor kinase 2 removal induces endothelial dysfunction by increasing endothelial ROS production. Furthermore, Zippel et al[8] demonstrated that transforming growth factor-β-activated kinase 1 regulates redox balance in ECs by AMP-activated protein kinase α1, which acts as a metabolic master switch regulating several intracellular systems. In addition, Iso et al[9] clearly demonstrated that capillary endothelial fatty acid–binding protein 4/5 is required for fatty

acid transport into fatty acid–consuming tissues, including the heart, which controls the metabolism of energy substrates in fatty acid–consuming organs. All these recent reports focus on the crucial role of redox balance in the regulation of vascular function.

Oxidative stress causes vascular dysfunction, which is closely associated with vascular inflammation. Inflammation plays a crucial role in the regulation of endothelial functions and angiogenesis. A recent article in *ATVB* by Wagner et al[10] examined the capacity of toll-like receptor 2–blocking Abs to modulate angiogenic responses of ECs in vitro and in vivo. They identified a novel molecular mechanism linking toll-like receptor 2 to angiogenic processes that is independent from the activation of inflammatory cascades, further supporting the concept of a beneficial effect of toll-like receptor 2 inhibition for EC function in vascular disease.[10] Plasma levels of high-density lipoprotein (HDL) cholesterol are inversely associated with the risk of cardiovascular diseases. Multiple lines of evidence indicate that salutary effects of HDL on ECs include antioxidative, anti-inflammatory, antithrombotic, and proangiogenic effects. A recent article in *ATVB* by Tatematsu et al[11] reported that endothelial lipase acts on HDL to promote activation of $S1P_1$ (sphingosine-1-phosphate receptor 1). They also showed that endothelial lipase is a key player in facilitating the activation of HDL-dependent signals that lead to $S1P_1$ receptor activation, as well as Akt and eNOS phosphorylation.[11] These results provide new insights into the molecular mechanisms through which HDL, endothelial lipase, and their interaction could modulate angiogenesis and vascular function.[11]

VSMCs for Vascular Function

Oxidative stress plays a major role in the pathogenesis of vascular diseases. However, it remains to be elucidated which ROS promotes the development of vascular disease. A recent article in *ATVB* by Parastatidis et al[12] examined the effect of hydrogen peroxide (H_2O_2)–degrading enzyme catalase on the formation of aortic aneurysms. They showed that restoration of catalase activity in the vascular wall enhances aortic VSMC survival and prevents aneurysm formation primarily through modulation of MMP activity.[12] They concluded that altered H_2O_2 signaling as a consequence of decreased catalase activity in the vasculature could be an early insult that leads to aortic dilatation.[12]

About the role of ROS for the development of vascular diseases, Soe et al[13] also demonstrated that cyclophilin A plays a crucial role in the translocation of Nox enzymes, such as p47phox, which are known to contribute to VSMC proliferation and development of vascular diseases. Because ROS production by Nox enzymes activates other oxidase systems, cyclophilin A and Nox enzymes amplify ROS formation in a synergistic manner, leading to increased oxidative stress. Further knowledge of the role of cyclophilin A signaling on vascular cell components will contribute to the development of novel therapies for cardiovascular diseases. Rho-kinase is an important downstream effector of the small GTP-binding protein Rho and plays a crucial role in migration and proliferation of VSMCs. The RhoA/Rho-kinase pathway plays an important role in contraction, motility, and proliferation of

VSMCs, leading to the development of vascular diseases. The expression of Rho-kinase is accelerated by inflammatory stimuli, which upregulates nicotinamide adenine dinucleotide phosphate oxidase and further augments ROS formation. There are 2 isoforms of Rho-kinase, ROCK1 and ROCK2, and they have different functions. However, specific roles and functional differences between ROCK1 and ROCK2 remain to be elucidated in VSMCs. In a recent issue of *ATVB*, Shimizu et al[14] demonstrated that ROCK2 in VSMCs contributes to VSMC proliferation and pulmonary hypertension in mice and in humans. Furthermore, Ikeda et al[15] demonstrated that the Rho-kinase pathway (especially ROCK2) plays a crucial role in pressure-overload–induced right ventricular hypertrophy and dysfunction. Because secretion is regulated by Rho-kinase activity, the cyclophilin A/Rho-kinase pathway contributes to augmentation of oxidative stress and the development of cardiovascular diseases.

MMPs modulate extracellular matrix and regulates migration and proliferation of VSMCs. In a recent issue of *ATVB*, Xiao et al[16] demonstrated that MMP-8 promotes VSMC proliferation and neointima formation. In this study, the authors clearly demonstrated that MMP-8 enhances VSMC proliferation via an ADAM10, N-cadherin, and β-catenin–mediated pathway and plays an important role in neointima formation. Integrins also contribute to vascular morphogenesis through regulation of adhesion and assembly of the extracellular matrix. Turlo et al[17] showed an essential function of β1-integrin in the maintenance of vasomotor control and highlighted a critical role for β1-integrin in VSMC survival. Furthermore, Sutliff et al[18] demonstrated that Poldip2 knockdown reduces H_2O_2 production in vivo, leading to increases in extracellular matrix, greater vascular stiffness, and impaired agonist-mediated contraction. Abnormal proliferation and migration of VSMCs are critical events in the progression of several vascular diseases, where AMP-activated protein kinase plays a crucial role in cellular proliferation and migration. In a recent issue of *ATVB*, Song et al[19] demonstrated that deletion of AMP-activated protein kinase α2 causes aberrant VSMC migration with accelerated neointima formation in vivo. In the pathogenesis of pulmonary hypertension, MMP activation and VSMC proliferation/migration are substantially involved. Revuelta-López et al[20] showed a crucial role of low-density lipoprotein receptor–related protein 1–mediated Pyk2 phosphorylation on hypoxia-induced MMP-9 activation, VSMC migration, and hypoxia-induced pulmonary hypertension. Low-density lipoprotein receptor–related protein 1 is a large endocytic and signaling receptor that is abundant in VSMCs. Muratoglu et al[21] also suggested a critical role for low-density lipoprotein receptor–related protein 1 in maintaining the integrity of blood vessels by regulating protease activity, as well as matrix deposition by modulating HtrA1 and connective tissue growth factor. Xiao et al[22] demonstrated the potential therapeutic use of the soluble Jagged1 because it not only inhibits proliferation of pulmonary VSMCs but also restores VSMCs phenotype from the dedifferentiated to the differentiated state through interference with Notch-Herp2 signaling. Finally, Dalvi et al[23] showed that simultaneous exposure of pulmonary VSMCs to viral proteins and cocaine exacerbates

downregulation of bone morphogenetic protein receptor. Taken together, these studies in the recent issues of *ATVB* have substantially contributed to the progress of our understanding on the important roles of VSMCs in the development of vascular diseases.

Adventitial Tissues and Inflammatory Cells for Vascular Function

Cross talk between cells in the blood vessel wall is crucial for vascular homeostasis and diseases. EC dysfunction leads to the expression of adhesion molecules for inflammatory cells, which promotes the development of vascular diseases. The adhesion and migration of inflammatory cells produce an oxidizing environment, which is critical for the progression of vascular diseases. The accumulating inflammatory cells produce abundant ROS and secrete inflammatory cytokines and growth factors, all of which contribute to EC dysfunction and VSMC proliferation.[24] In a recent issue of *ATVB*, Karper et al[25] identified a crucial role of toll-like receptor accessory molecule RP105 on circulating inflammatory cells in atherosclerotic plaque formation. In addition, Shiomi et al[26] demonstrated that coronary vasospasm could trigger coronary plaque injury and acute ischemic myocardial damage in Watanabe heritable hypercholesterolemic rabbits. Furthermore, Callegari et al[27] demonstrated that osteoprotegerin derived from the bone marrow block the progression of vascular calcification.[27] About the pathogenesis of aneurysms, Marinkovic et al[28] performed an interesting study to limit aneurysm growth by inhibition of inflammation and reducing EC activation with immunosuppressive drug azathioprine. They showed that azathioprine has an anti-inflammatory effect in ECs and inhibits Rac1 and c-Jun-terminal-N-kinase activation, which may explain its protective role in the development of aneurysm formation and severity.[28] The N-terminal lectin-like domain of thrombomodulin is known to have an anti-inflammatory function. The recent study by Lin et al[29] provided a mechanism showing that recombinant thrombomodulin domain 1 can inhibit inflammation by binding to its carbohydrate ligand Le(y). However, peroxisome peroxisome proliferator-activated receptor (PPAR)-γ coactivator 1α is an important mediator of mitochondrial biogenesis and function. Because dysfunctional mitochondria are involved in the pathogenesis of vascular disease, Kröller-Schön et al[30] examined the effects of peroxisome PPAR-γ coactivator 1α deficiency during chronic angiotensin II treatment in vivo. Peroxisome PPAR-γ coactivator 1α deletion caused vascular dysfunction and inflammation during chronic angiotensin II infusion by increasing mitochondrial ROS production.[30] Furthermore, the findings by Doyon et al[31] provided new insights into the molecular mechanism of the pathological role of angiotensin II and assist in identifying the beneficial effects of IκB kinase-β inhibition for the treatment of cardiovascular diseases. Finally, perivascular adipose tissue wraps blood vessels and modulates vasoreactivity by secretion of vasoactive molecules. Mammalian target of rapamycin complex 2 has been shown to control inflammation and is expressed in adipose tissue. Bhattacharya et al[32] identified mammalian target of rapamycin complex 2 as a critical regulator of perivascular adipose tissue–directed protection of normal vascular tone. They concluded that modulation of mammalian target of rapamycin complex 2 activity in adipose tissue is a potential therapeutic approach for inflammation-related vascular damage.[32]

Summary

In summary, the interactions among ECs, VSMCs, adventitial tissues, and inflammatory cells regulate vascular functions and diseases. As reviewed in this highlights, recent publications in *ATVB* have significantly contributed to our understanding on the roles of each vascular cell component for vascular functions in health and disease. These studies have demonstrated the novel mechanistic roles of secreted factors, as well as intracellular signaling for endothelial homeostasis, VSMC proliferation, and inflammatory cell migration. Indeed, we are getting closer to the understanding of fundamental vascular functions and causative cell signaling pathways, all of which should be useful for the development of novel therapeutic strategies in cardiovascular medicine.

Disclosures

H. Shimokawa is a consultant of Asahi Kasei Pharma. K. Satoh reports no conflicts.

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