Controversy as to the Source of H\textsubscript{2}O\textsubscript{2}/EDHF in Humans

Besides NOS, other endothelial enzymes, such as mitochondrial respiratory enzymes and NADPH oxidase, can generate superoxide anions and be at the origin of H\textsubscript{2}O\textsubscript{2}/EDHF production. In murine arteries, endothelial enzymes other than NOS do not appear to be involved in H\textsubscript{2}O\textsubscript{2}/EDHF responses. However, it has been reported that, in human coronary arteries, flow-induced endothelium-dependent dilation is associated with H\textsubscript{2}O\textsubscript{2}/EDHF generated by the mitochondrial respiratory chain-derived superoxide anions, whereas in the same human coronary arteries, bradykinin-induced endothelium-dependent dilation is linked to H\textsubscript{2}O\textsubscript{2} generated by NADPH oxidase-derived superoxide anions. Thus, the cellular and enzymatic sources of H\textsubscript{2}O\textsubscript{2}/EDHF in humans are still controversial, and this point remains to be clarified in future studies.

Functional Significance of H\textsubscript{2}O\textsubscript{2}/EDHF In Vivo

Shimokawa and colleagues have further examined the functional significance of H\textsubscript{2}O\textsubscript{2}/EDHF and revealed that H\textsubscript{2}O\textsubscript{2}/EDHF plays a crucial role in the regulation of coronary microcirculation (ie, coronary flow autoregulation, metabolic coronary vasodilatation, and cardiovascular protection against ischemia-reperfusion injury) in dogs in vivo.

Molecular Mechanisms for the Augmentation of H\textsubscript{2}O\textsubscript{2}/EDHF-Mediated Responses in Small Resistance Arteries

Although both H\textsubscript{2}O\textsubscript{2}/EDHF and NO are produced predominantly by the identical enzyme, NOS, it has remained to be clarified why the contribution of H\textsubscript{2}O\textsubscript{2}/EDHF and NO to vasodilatory effects is distinct in different sized blood vessels (ie, H\textsubscript{2}O\textsubscript{2}/EDHF-induced relaxation is augmented in small resistance arteries, whereas NO-induced relaxation is dominant in large conduit arteries). This mystery has now been solved. In this issue of the Journal, Shimokawa and colleagues present the molecular mechanisms for the augmentation of H\textsubscript{2}O\textsubscript{2}/EDHF-mediated responses in small resistance arteries in mice. First, they show that both vascular endothelial cells and vascular smooth muscle cells contribute to the augmentation of H\textsubscript{2}O\textsubscript{2}/EDHF-induced relaxation and hyperpolarization of small arteries. Second, they indicate that, at the endothelial level, Ca\textsuperscript{2+}/calmodulin-dependent protein kinase kinase β and cavelolin-1 are involved in the augmentation of H\textsubscript{2}O\textsubscript{2}/EDHF-induced relaxation and hyperpolarization of small arteries. Finally, they report that, at the vascular smooth muscle cell level, the sensitivity of exogenous H\textsubscript{2}O\textsubscript{2} to relaxation and hyperpolarization is enhanced in small arteries (murine mesenteric arteries) com-
pared with large arteries (murine aortas), in which protein kinase G1α is involved.

Crosstalk Among H₂O₂/EDHF, Bone Marrow, and Metabolic Functions

Shimokawa and colleagues recently reported the intriguing finding that bone marrow plays an essential role in the regulation of H₂O₂/EDHF-mediated responses in small resistance arteries. They proved that, in eNOS−/− mice, transplantation of normal bone marrow results in restoration of impaired H₂O₂/EDHF-mediated relaxation, and that both increased adiponectin production in adipose cells and enhanced nNOS expression in vascular endothelial cells are involved in this phenomenon. These results suggest the fascinating concept of crosstalk among H₂O₂/EDHF, bone marrow, and metabolic functions.

Conclusion

Since the discovery of H₂O₂ as an EDHF by Shimokawa and colleagues, EDHF research has been progressing rapidly. Although several factors have been proposed as EDHFs, it appears to be true that H₂O₂ is an EDHF at least in humans. The above-mentioned lines of evidence provide pivotal insights into the pathophysiological significance of EDHF in small resistance arteries. Because small resistance vessels play an important role in the regulation of coronary microcirculation, blood pressure, and tissue blood flow, it is hoped that novel EDHF-related therapeutic agents for the prevention and treatment of cardiovascular disease will be developed in the near future. Further studies are certainly needed to clarify whether the EDHF research results can be translated to human patients with cardiovascular disorders.

References