Discovery of a new function of vascular endothelium has opened new horizons in the research field of vascular biology. Today, we cannot talk about vascular diseases without endothelial function. I am happy to have participated in the development of this field in those days.

In 1963, after graduating from the medical school at the University of Tokyo and finishing my internship, I entered the laboratory of Setsuro Ebashi who established the concept of calcium ion in intracellular signaling system, at the University of Tokyo. I started purification of \(\alpha\)-actinin in his laboratory, which was originally found by Ebashi. I demonstrated the existence of \(\alpha\)-actinin at the Z-line of striated muscle and elucidated the structure and function of the protein. Thus \(\alpha\)-actinin was established as a muscle protein. Furthermore, through the same line of experimentation, I also found M-protein. The development of muscle has been a unique type of myosin, which is different from adult myosin, and that those embryonic myosin (and also troponin) changed during the development of muscle in each muscle type. These results elicited the worldwide explosion of investigation into the isoform change of muscle protein, not only in develop-
ding factor. My young excellent colleagues Masashi Yanagisawa and Hiroki Kurihara started purification of this substance. From the beginning, we were joined by Katsutoshi Goto and Sadao Kimura. We quickly isolated an endotheli-
ium-derived contracting peptide and named it endothelin. The results were published in 1988. Successively, another young excellent student Takeshi Sakurai succeeded in the molecular cloning of the endothelin receptor, and Akihiro Inoue isolated the endothelin gene and found three isoforms.

Discovery of endothelium-derived nitric oxide, by Furchgott, and the following discovery of endothelin above mentioned, opened a new field in circulation research. It is now generally accepted that the vascular endothelial cells play a significant role in the regulation of multiple functions, including the modulation of vascular tone, coagulation state, cellular proliferate response, and leukocyte trafficking. A number of molecules identified in those days that mediate and/or affect these functions of endothelial cells facilitated the understanding of vascular physiology. The failure in these homeostatic functions is usually referred to as endothelial dysfunction, and it characterizes different pathological conditions, such as hypertension, atherosclerosis, diabetes, inflammation, and various classes of organ failure related to mal-circulation. The diversity of diseases related to endothelial dysfunction, in turn, indicates the importance of endothelium in physiological regulation.

The balance between endothelial vasoconstrictive and vasorelaxative factors seems to reflect well the state of endothelial cells, since the gene expression profile in endothelial cells shifts in a coordinated manner from a resting to dysfunctional state: antithrombotic to prothrombotic, anti-inflammatory to proinflammatory, growth inhibitory to growth promoting, and vasorelaxative to vasoconstrictive. An enormous number of studies on endothelium-derived nitric oxide and endothelin-1 support the idea that while these factors do not merely affect vascular tension, they also affect other parameters of blood vessels.

In the early 1990s, in the course of endothelin research, we became interested in the molecular mechanism of endothelial dysfunction, because expression of endothelin was enhanced in many kinds of vascular diseases, such as hypertension and atherosclerosis. Therefore, we set our next goal to the molecular identification of the factor that induces pathologi-
cal endothelial functions. Oxidized LDL (OxLDL) is one such factor that induces endothelial dysfunction, which seems to be related to both genetic and environmental factors. In addition, it has been observed that vascular endothelial cells internalize and degrade OxLDL through a putative receptor-mediated pathway but not macrophage scavenger receptors. Molecular cloning of this endothelial receptor looked like a fascinating project.

In my laboratory in 1995, Tatsuya Sawamura successfully identified the major endothelial receptor for OxLDL, a lectin-like oxidized LDL receptor, LOX-1. We published these results in 1997.2

LOX-1 is a type II membrane protein belonging to the C-type lectin family of molecules, which can act as a cell surface endocytosis receptor for OxLDL. Sequence and structure analysis of LOX-1 protein revealed that it did not resemble any known macrophage scavenger receptors. Interestingly, recent analyses of human LOX-1 gene suggested the association of LOX-1 gene polymorphism and coronary artery diseases.

After the discovery of LOX-1, we noticed that it might play a significant role in the generation of vascular diseases. To elucidate the clinical significance of LOX-1 quickly, as in the case of endothelin research, we expected collaboration with clinical investigators. We then asked Toru Kita, an expert in the field of atherosclerosis, for his help. Thus, Kita and his colleague Noriaki Kume joined us.

In vitro, the basal expression level of LOX-1 is low, but it can be induced by proinflammatory cytokines and vasoconstrictive factors, including angiotensin II and endothelin-1. OxLDL and oxidative stress also enhance the expression of LOX-1. Since enhanced LOX-1 expression is observed in the aorta of hypertensive rats in vitro, and in hyperlipidemia and diabetes-associated conditions in vivo, the additive or synergistic effects of the combination of inflammation, hyperlipidemia, hypertension, and diabetes in the regulation of LOX-1 expression were suggested.

Interaction of OxLDL with endothelial cells via LOX-1 generates superoxide anions, which accelerates the catabolism of nitric oxide and activates the NF-κB pathway. This quick response may lead to the progression of diseases in the implicated arteries.

Following the above rapid response to the binding of LOX-1 ligands, the changes in the gene expression profile in endothelial cells occur via transcription. Production of endothelin-1, AT1 receptor, angiotensin-converting enzyme, monocyte chemoattractant protein-1, and leukocyte adhesion molecules is all upregulated. These data support the fact that OxLDL interacting with endothelial cells via LOX-1 could induce multiple functional and phenotype changes relevant to “endothelial dysfunction.” In addition, LOX-1 binds to activated platelets and captures leukocytes to the vascular wall in inflammation.

At the beginning of the study of LOX-1, we intended to clarify the factor that induces endothelial dysfunction. However, we have noticed that LOX-1 itself has the property that mediates pathological function of endothelial cells. LOX-1, we believe, is a key molecule in the generation of endothelial dysfunction.3,4

Endothelial research has grown up with the development of cellular and molecular techniques. Now it has come back to clinical problems.

References
3. Chen M, Masaki T, Sawamura T. LOX-1, the receptor for oxidized low-density lipoprotein identified from endothelial cells: implications in endothelial dysfunction and atherosclerosis Pharmacol Ther. 2002;95; 89–100.

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