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Guest editorial: mutual relationship between vascular biology and hematology

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Vascular biology has rapidly progressed in a molecular level since the identification of growth factors regulating blood vessel formation in the mid-1990s. In contrast to hematology, in which cytokines involved in the development and proliferation of hematopoietic cells (HCs) were first identified and analyzed in the 1980s, vascular biology has a short history, as analysis of the mechanisms underlying blood vessel formation were started at the molecular level. Inhibitors of vascular endothelial growth factors (VEGFs) or their cognate receptors have, however, already entered clinical use in the treatment of cancer and retinopathy. Moreover, therapeutic angiogenesis by such methods as gene transfer, bone marrow cell injection, and cytokine administration has also entered clinical use. It is no exaggeration to say that translation from bench to bed side has proceeded extremely rapidly in vascular biology.

Recognition of the intimate interaction between hematopoiesis and blood vessel formation emerged from histological analyses showing that hematopoietic cells and vascular endothelial cells (ECs) originate from a common ancestor, known as the hemangioblast. However, several lines of evidence suggest that hematopoietic cells are derived from cells which have already committed to ECs, so-called hemogenic angioblasts, during embryogenesis. In the adult, however, bone marrow hematopoietic cells can differentiate into vascular cells, such as ECs and vascular smooth muscle-like cells. Clearly, these two populations follow complex developmental routes. Moreover, functionally, hematopoietic cells support angiogenesis as an accessory cell component, and, conversely, blood vessels provide a niche for the maintenance of the stemness of hematopoietic stem cells.

Clinically, bone marrow hematopoietic cell infusion therapy to induce angiogenesis for ischemic diseases, such as chronic lower extremity occlusive disease or ischemic heart disease, is one example of the utilization of the intimate interaction between hematopoiesis and vascular development. Usage of the hematopoiesis-related cytokine, G-CSF, in the mobilization of bone marrow hematopoietic stem/progenitor cells into peripheral blood to facilitate the recruitment of such cells to ischemic regions is one example of a strategy that brings together the fields of hematology and vascular biology.

In this PIH review series, a number of research approaches linking hematopoiesis and vascular biology are introduced. Dr. Beate Heissig overviews the mechanism of fibrinolysis for bone marrow cell mobilization associated with induction of angiogenesis, while Dr. Hideto Matsui discusses a strategy for the treatment of congenital coagulation defects using gene transfer into bone marrow endothelial progenitors. It is widely accepted that suppression of angiogenesis is a promising method for inhibiting tumor growth. By contrast, Dr. Yusuke Mizukami argues that induction of angiogenesis in tumor may also represent an effective alternative for tumor growth inhibition, as a means of providing routes of drug delivery. He introduces new blood vessel formation in tumor using bone marrow cells. Finally, the function of hematopoietic stem cells in the promotion of angiogenesis is reviewed, along with recent topics pointing to angiogenesis-related functions in cancer stem cells. The function of stem cells in promoting blood vessel formation may be closely associated with the formation of the vascular niche for stem cell maintenance, and, therefore, stem cells themselves may construct the foci needed to maintain their own stemness.

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It will be important to gain a better understanding of the precise molecular mechanisms behind blood vessel formation by stem cells, and to determine the vascular niche component if we are to develop effective strategies in both regeneration and cancer therapy.

Compared with research in hematology, in which extensive molecular analyses of lineage commitment from hematopoietic stem cells to well-differentiated mature hematopoietic cells have been performed, lineage analysis of the differentiation of vascular stem cells to mature ECs is yet to be addressed in vascular biology. While hematopoietic stem cells can be identified using a profile of surface molecules and isolated to analyze their differentiation, there are still no molecular markers of endothelial stem cells, and indeed, the endothelial stem cell itself has not been definitively identified. It is still unclear whether endothelial stem cells are present in the adult; however, as there are three different types of ECs during angiogenesis, they may still await identification. Tip cells are sprouted from pre-existing blood vessel in the initiation of angiogenesis and located in front of new vascular branch; however, these lack proliferative ability. Stalk cells situated behind the tip cells proliferate and induce the elongation of new branches. Finally, phalanx cells emerge, stabilize and mature into newly developed blood vessels. This heterogeneity of ECs suggests that there may be endothelial stem cells that produce different types of ECs. Vascular biology may grow even further once endothelial stem cells have been defined, and therapy for vascular diseases, including the suppression and induction of blood vessel formation, is improved.