The lymphatic vascular system is a conduit for interstitial fluid extravasated from blood vessels and also plays important roles in maintaining immune responses, lipid uptake, and tissue homeostasis. In recent years, much attention has been given to lymphangiogenesis, a formation of new lymphatic vessels, because lymphangiogenesis has been shown to be involved in lymph node metastasis of tumors.1

The development of blood and lymphatic vascular systems is primarily regulated by vascular endothelial growth factor (VEGF) family members. This family consists of 5 members: VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placenta growth factor (PIGF). There are 3 members of VEGF receptor (VEGFR) tyrosine kinases: VEGFR1, VEGFR2, and VEGFR3. Members of the VEGF family show different affinities for these receptors. VEGFR1 is able to bind VEGF-A, VEGF-B, and PIGF. VEGFR2 is activated primarily by VEGF-A, but cleaved forms of VEGF-C and VEGF-D may also activate this receptor. VEGFR3 is activated by VEGF-C and VEGF-D. Vascular endothelial cells (ECs) express VEGFR1 and VEGFR2, whereas lymphatic ECs express VEGFR2 and VEGFR3 in the adult. The most important molecule in the VEGF family that controls angiogenesis is VEGF-A, and VEGFR2 is the major mediator of VEGF-A driven responses in vascular ECs. VEGFR1, on the other hand, has a higher affinity for VEGF-A but weaker tyrosine kinase activity. Thus, VEGFR1 on vascular ECs may act as a counter-regulator of VEGFR2. VEGFR1 is also expressed by monocytes/macrophages and hematopoietic stem cells, and in those cases, VEGFR1 transduces signal for the migration of those cells. Therefore, VEGFR1 has a dual function, acting in a positive or negative manner in different cell types or circumstances. The most important molecule in the VEGF family that controls lymphangiogenesis are VEGF-C and VEGF-D, and VEGFR3 is the major mediator of VEGF-C and VEGF-D driven responses in lymphatic ECs. However, VEGF-A may stimulate VEGFR2 on lymphatic ECs and induce lymphangiogenesis directly.2

The induction of VEGF-A is important for the initiation of angiogenesis. The principal trigger of angiogenesis is hypoxia, which induces the expression VEGF-A in various cell types. This induction in hypoxia is mediated by a transcription factor known as hypoxia-inducible factor 1 (HIF-1), a heterodimeric complex of HIF-1α and HIF-1β subunits, which binds to hypoxia responsive element (HRE) in the promoter of VEGF-A gene. Under normal oxygen tension, the expression of VEGF-A is suppressed by the product of a tumor suppressor gene known as the von Hippel Lindau (VHL) gene, which is involved in the degradation of HIF-1α through the ubiquitin proteasome system.2 Angiogenesis is normally associated with, or followed by, lymphangiogenesis, because defective lymphangiogenesis should cause tissue edema. However, little is known about the trigger of lymphangiogenesis. The aberrant expression of VEGF-C or VEGF-D and its correlation with lymph node metastasis was described in various tumors.1 Nevertheless, only a few studies have focused on the regulation of the expression of VEGF-C or VEGF-D. A transcription factor known as nuclear factor-kappa B (NF-κB) or an enzyme known as cyclooxygenase-2 (COX-2) is involved in the upregulation of VEGF-C in certain cancer cells.3–5

In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Murakami et al propose that the signal via VEGFR1 promotes angiogenesis in parallel with lymphangiogenesis through the recruitment of macrophages. To test the function of VEGFR1, they use K14 Vefg-A Tg mice, Vegfr1 tk−/− mice, and a double mutant of K14 Vefg-A Tg Vegfr1 tk−/− mice. K14 Vefg-A Tg Vegfr1 tk−/− mice show a significant decrease in angiogenesis and lymphangiogenesis in subcutaneous tissue where VEGF-A is overexpressed. To address the mechanism underlying this decrease of angiogenesis and lymphangiogenesis in K14 Vefg-A Tg Vegfr1 tk−/− mice, they focus on the recruitment of macrophages into subcutaneous tissue. VEGF-A augments the recruitment of macrophages through the activation of VEGFR1 on macrophages. This recruitment of macrophages is reduced in K14 Vefg-A Tg Vegfr1 tk−/− mice. Moreover, K14 Vefg-A Tg mice that receive bone marrow transplantation from Vegfr1 tk−/− mice show the reduction of macrophage recruitment as well as the decrease of angiogenesis and lymphangiogenesis. Thus, they conclude that VEGF-A stimulates mobilization and recruitment of macrophages from bone marrow through VEGFR1, and that is required for angiogenesis and lymphangiogenesis.

The role of macrophage recruitment in angiogenesis has been well documented.6 In addition, several recent articles described the involvement of macrophage recruitment in lymphangiogenesis as well. Schoppmann et al showed that, in certain human cancers, the density of lymphatic microvessels was significantly increased in peritumoral stroma, and that a subset of cells in peritumoral stroma, namely tumor-
associated macrophages (TAMs), expressed VEGF-C and VEGF-D. Their data indicated that the density of TAMs producing VEGF-C and VEGF-D correlated with peritumoral inflammatory reaction, peritumoral lymphangiogenesis, and frequency of lymph node metastasis.\textsuperscript{7,8} Cursiefen et al reported the relationship between VEGF-A stimulated lymphangiogenesis and macrophage recruitment in the suture-induced inflammatory corneal model of mice. Administration of VEGF Trap, a receptor-based fusion protein that neutralized VEGF-A but not VEGF-C or VEGF-D, completely inhibited both angiogenesis and lymphangiogenesis after corneal injury. Moreover, either systemic depletion of bone marrow–derived cells by irradiation or local depletion of macrophages in the cornea by clodronate liposome significantly inhibited angiogenesis and lymphangiogenesis in the cornea.\textsuperscript{9} Maruyama et al revealed that the decreased number of macrophages correlated with the reduced lymphangiogenesis in the diabetic skin wound healing model.\textsuperscript{10} These reports together with the present Murakami’s work point out the involvement of macrophage recruitment in lymphangiogenesis in certain conditions.

The scenario of angiogenesis and associating (or following) lymphangiogenesis may be as follows. The trigger of these phenomena should be the induction of VEGF-A. VEGF-A stimulates vascular ECs via VEGFR2 and that initiates angiogenesis. Simultaneously, VEGF-A induces the mobilization of bone marrow cells including monocytes via VEGFR1. Monocytes recruit to the area of angiogenesis, differentiate to macrophages, and produce both angiogenesis and lymphangiogenesis stimulators. Angiogenesis stimulators include VEGF-A, whereas lymphangiogenesis stimulators include VEGF-C and VEGF-D. Accordingly, VEGF-A from macrophages potentiates angiogenesis via VEGFR2 on vascular ECs, whereas VEGF-C and VEGF-D from macrophages induce lymphangiogenesis via VEGFR3 on lymphatic ECs. Of course, this scenario is drawn from data obtained by the models of pathological conditions. It is still unclear how physiological lymphangiogenesis is regulated. What cell type is the main source of VEGF-C and VEGF-D in the physiological condition? How is the expression of VEGF-C and VEGF-D regulated? Further studies are expected to resolve these questions.

Disclosures

None.

References

VEGFR1 for Lymphangiogenesis: An Alternative Signaling Pathway?

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