The Lefoulon Delalande Foundation honors the lymphatic vascular system

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The Lefoulon Delalande Foundation awarded its 2023 Scientific Grand Prize to Kari Alitalo from the University of Helsinki and the Wihuri Research Institute in Finland, and to Susan Quaggin from the Feinberg School of Medicine at Northwestern University in Chicago, USA. The 600 000-euro prize is awarded annually for researchers who significantly contributed to cardiovascular physiology, biology or medicine, and the 2023 edition was equally shared between the two laureates.

The 2023 Prize highlights the importance of the lymphatic vascular system in human health and disease. Lymphatic vasculature constitutes the draining arm of the cardiovascular system (Figure 1A). As blood pressure drives plasma fluid from circulating blood across capillaries into the body tissues, it bathes the tissues as interstitial fluid, carrying nutrients to the cells and collecting waste products, infectious agents, and damaged cells. Lymphatics are responsible for removing interstitial fluid along with macromolecules and immune cells from body tissues, and they also control lipid absorption in the gut. The mixture of fluids, lipids and waste products is called lymph once it is taken up by lymphatic capillaries in various tissues. Lymphatic capillaries take up lymph via specialized open junctions that facilitate entry. Lymphatic capillaries then coalesce into progressively larger and impermeable collecting vessels, which transport lymph back to the systemic circulation via large lymph ducts that merge with the subclavian veins (Figure 1A). Along the way, lymph passes through numerous lymph nodes, which filter out unwanted materials such as bacteria and damaged cells, hence lymphatics directly communicate with the immune system to fight infections (Figure 1A and B).[1-3]

Given the importance of a proper tissue drainage system, lymphatic dysfunction is intimately associated with diseases. Genetic defects that prevent lymphatic vessels from forming properly lead to lymphedema, which is a disabling and disfiguring condition associated with accumulation of protein-rich fluid and tissue swelling (Figure 1C). Lymphedema can also be acquired, notably in breast cancer patients upon surgical removal of lymph nodes. The lymph node removal is performed to prevent the metastatic spread of cancer cells, which also occurs through lymphatic vessels (Figure 1D). In addition to lymphedema and metastasis, recent research spearheaded by the laureates and other researchers, has implicated the lymphatic system in the pathogenesis of various diseases including obesity and metabolic disease, inflammation, hypertension, cardiovascular disease such as atherosclerosis and myocardial infarction, as well as glaucoma and neurodegeneration (Figure 1E).[1-3]

Kari Alitalo's work was instrumental in allowing research on lymphatic vessels to progress into a full-blown discipline that is now pursued by many laboratories around the world. His laboratory discovered the VEGFR3 tyrosine kinase growth factor receptor expressed on lymphatic vascular endothelial cells, demonstrating for the first time that growth of lymphatic vessels is regulated differently from that of arteries or veins.[4] He then discovered VEGF-C, which is the main ligand for VEGFR3 and the major lymphangiogenic growth factor known to date.[5] Kari's lab characterized the molecular interaction between VEGF-C and VEGFR3 biochemically and structurally, and used genetic ablation in mice to show that removal of one allele

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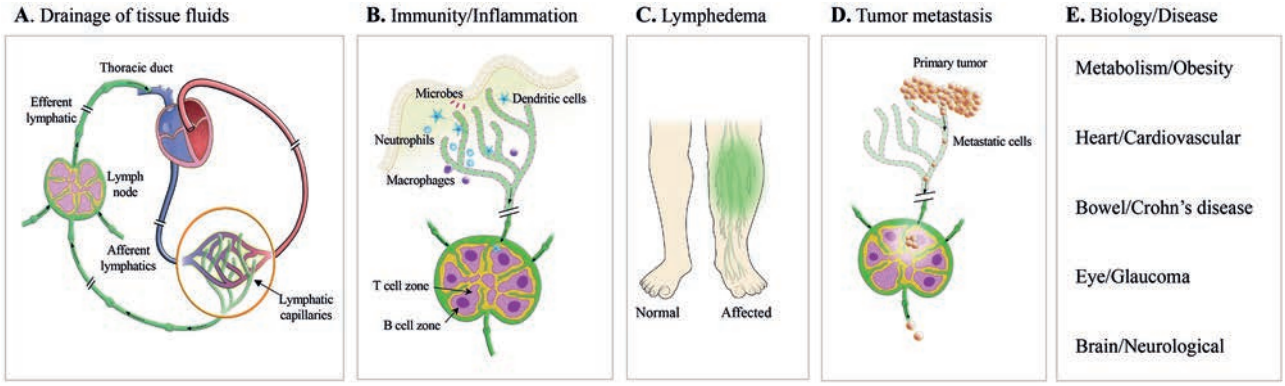

Figure 1. Lymphatic vasculature function. A) Lymphatics return extravasated capillary fluid to the circulation (arrows) via lymph nodes. B) They take up immune cells and control immunity and inflammation. C) Lymphatic dysfunction leads to lymphedema. D) Metastatic tumor cells spread via the lymphatics. E) New lymphatic biology in health and disease.

of *Vegf-c*, or removal of *Vegfr3* is lethal due to ablation of lymphatic vessel growth.[6] This enabled foundational studies to understand the functions of the lymphatic vascular system in health and disease.

In collaboration with geneticists and patient families, Kari's lab discovered human mutations in *VEGFR-3* that cause inherited lymphedema in patients.[7] The growth-promoting ability of VEGF-C was tested in phase 1 clinical trials to prevent secondary lymphedema in breast cancer patients that underwent surgical lymph node removal, with a successful reduction of arm volume.[8] Conversely, VEGF-C inhibitors can block experimental lymph node metastasis in mice and are tested clinically for their ability to block neovessel growth in blinding eye diseases.[9] These studies opened an active field of research that identified new biology associated with lymphatic vessels, which is much more important than previously thought. Dr. Alitalo notably discovered many of these new lymphatic functions, including the identification of a meningeal lymphatic drainage system that contributes to brain waste drainage and that has become an intense worldwide focus in neurological disease research.[3]

Susan Quaggin is the Charles Horace Mayo Professor of Medicine, Director of the Feinberg Cardiovascular Research Institute, and Chief of the Division of Nephrology at Northwestern University Feinberg School of Medicine. Work in her laboratory addresses microvascular damage in diabetic patients, which leads to kidney failure, blindness and nerve damage. She revealed endothelial growth factor signaling mechanisms required for the formation and integrity of the vasculature in the eye and in the kidney. Notably, her laboratory made mouse models carrying cell-type specific and temporally inducible inactivation of the TIE2 receptor, and its Angiopoietin1 (ANG1) ligand, to discover that these mutations specifically affect lymphatic drainage from the eye, leading to an increase in intraocular pressure, open-angle glaucoma and blindness.[10]

Next, with a team of clinicians and geneticists, they found that human mutations in ANG1 and TIE2 are found in several families with primary congenital glaucoma.[11] Quaggin showed that the mutations lead to a loss of function, with an autosomal dominant inheritance pattern, meaning that reduced ligand-receptor signaling in patients is sufficient to induce glaucoma disease. This observation holds true in patients and in mice,[12] and it provides strong rationale to give back the missing ANG1 protein in recombinant form as a treatment for these patients. Quaggin also showed that ANG1 additionally functions in the diabetic kidney vasculature to protect it from diabetic nephropathy, hence the ANG1 supplementation approach could be more widely relevant for diabetic nephropathy and microvascular diabetic complications. Susan Quaggin's work highlights the importance of the lymphatic system in regulating ocular fluid drainage in health and disease, and it exemplifies how basic science in lymphatic vascular biology can impact clinical practice.

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