Targeting Vascular Growth Factors in Cancer and Cardiovascular Diseases

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Many types of solid cancers induce growth of their own blood vessels, angiogenesis, by inducing vascular endothelial growth factor production. Although antibodies blocking vascular endothelial growth factors have been a success in the treatment of age-related macular degeneration in the eye, malignant tumors are often either refractory or acquire resistance to this treatment. A better knowledge of the major vascular growth factor signaling pathways should advance the efficacy of current combination therapies of cancer. We have discovered a wider family of vascular growth factors and expanded studies on the therapeutic potential of these factors to several human diseases.

The recent discovery of growth factors for lymphatic vessels has drastically changed our views on the organ-specific and plastic functions of lymphatic vasculature in physiological and disease processes. The growth of lymphatic vessels, lymphangiogenesis, is involved in a number of pathological processes including tissue inflammation and tumor dissemination, but is insufficient in patients suffering from lymphedema, characterized by chronic tissue edema and impaired immunity. A lymphangiogenic growth factor is currently in phase 2 clinical trial in human lymphedema. Various cancers produce lymphangiogenic growth factors that stimulate lymphatic growth and tumor metastasis to draining lymph nodes, but they can also boost cancer immunotherapy by enhancing the delivery of tumor antigens to lymph nodes for an effective launching of an anti-tumor immune response, for example in brain tumors. The recent discovery of an entire meningeal lymphatic vessel system has challenged the concept of brain immune privilege and shown lymphatic vessel involvement in neurodegenerative and neuroinflammatory diseases. Intestinal lacteal lymphatic vessels have shown unique properties for the control of dietary fat uptake and that could be targeted for the treatment of obesity. Furthermore, vessels with hybrid blood and lymphatic characteristics such as the Schlemm's canal in the eye could provide targets for the treatment of glaucoma.

Several attempts have also been made to stimulate vessel growth in tissue ischemia, in e.g. atherosclerosis, with limited success. One of the obstacles has been the property of angiogenic growth factors to increase vascular leakage, leading to tissue edema and subsequent inflammation, which can be counteracted by the angiopoietin growth factors. So far, angiogenic growth factors have not yet provided significant help for patients with cardiovascular disease, but a better understanding of their biology should facilitate therapeutics development. Impaired blood vessel growth has been implicated in adipose tissue dysfunction and the development of obesity-associated metabolic disorders. New experimental findings indicate that vascular growth factors can activate the thermogenic program in adipose tissue and even increase the basal metabolic rate, thus preventing diet-induced obesity and related metabolic complications.

As these examples show, vascular growth factors and their inhibitors possess potential for various applications in the treatment of human diseases. Furthermore, new technologies have revealed the great organ-specific heterogeneity of the vascular system, allowing a better tailoring of the vascular-based therapies for the benefit of patients.

Further reading: Aselli, G. De Lactibus, Sive Lacteis Venis. (Medioloni, Milan 1627). Apte RS, Chen DS, Ferrara N. VEGF in Signaling and Disease: Beyond Discovery and Development. Cell 176:1248, 2019. De Falco S, Gigante B, Persico MG. Structure and function of placental growth factor. Trends Cardiovasc Med. 12:241, 2002.