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PLENARY SESSION 1
LYMPHATICS IN HEALTH AND DISEASE

LYMPHANGIOGENESIS IN HEALTH AND DISEASE

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Despite the intensive research on the lymphangiogenic VEGF-C/VEGFR-3 signaling pathway in the last two decades, new and unexpected findings do not cease to be made. Diseases that involve the lymphatic system have helped to uncover mechanisms of its normal functioning and development.

A recent example of new basic knowledge that resulted from the investigation of a human disease is Hennekam lymphangiectasia-lymphedema syndrome (OMIM 235510). It is an autosomal recessive condition, which can co-segregate with mutations in the collagen- and calcium-binding EGF domains 1 (*CCBE1*) or the protocadherin Fat 4 (*FAT4*) gene.

Both CCBE1 and the lymphangiogenic vascular endothelial growth factor C (VEGF-C) are necessary for the early lymphatic development, namely for the budding and migration of endothelial cells from the cardinal vein (CV) and for the formation of the early lymphatic structures. These processes fail in embryos deficient of either Ccbe1 or Vegfc. In Vegfc-deficient embryos pro-spective lymphatic endothelial cells fail to sprout from the CV, whereas in Ccbe1-deficient embryos, the sprouting is abnormal and does not result in the formation of discrete lymphatic structures.

The similar phenotypes of Ccbe- and Vegfc-deficient embryos result from the interaction of CCBE1 with the VEGF-C growth factor signaling pathway, which is critical in embryonic and adult lymphangiogenesis. VEGF-C is synthesized as an inactive proprotein and needs to be processed by at least two distinct proteases to become fully active. The presence of CCBE1 promotes VEGF-C by two independent mechanisms. The C-terminal domain of CCBE1 boosts VEGF-C function via increased ADAMTS3-mediated proteolytic activation of VEGF-C, while the N-terminal domain of CCBE1 concentrates pro-VEGF-C on endothelial cell-surfaces, where it can be activated in situ by cell-surface associated proteases. Both mechanisms lead to increased VEGFR-3 signaling and increased lymphangiogenesis.

These results show that CCBE1 is integral to lymphangiogenesis by increasing the levels of active VEGF-C at the endothelial cell surface. Because some forms of lymphedema appear to be treatable by increasing the amount of VEGFR-3 signaling, the first clinical trials designed around a pro-lymphangiogenic concept use VEGF-C. The goal in these trials is to enhance the integration of lymph nodes into the lymphatic vasculature after autologous transfer to treat postmastectomy lymphedema. On the other hand, VEGF-C-induced lymphangiogenesis enhances tumor metastasis and VEGF-C-induced tumor angiogenesis in several mouse models. Blocking VEGF-C might be for these reasons an attractive adjuvant treatment to supplement current cancer treatment regimens that include anti-angiogenic drugs. The right balance between pro- and anti-lymphangiogenic stimuli might therefore differ between individuals and CCBE1 is an attractive drug target to adjust pro- and anti-lymphangiogenic stimuli by tuning the rate of VEGF-C activation.

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