

Abstract

The lymphatic vasculature plays an essential role in draining tissue fluid, transporting fatty acids to the circulatory system as well as trafficking immune cells to and from the lymph nodes. Dysfunctional lymphatic vessels cause lymphoedema, while lymphatic vasculature surrounding a tumour may facilitate cancer metastasis. Interestingly, several lymphoedema syndromes are characterised by defects that affect vessels in specific tissues, yet organ-specific regulation of lymphatic development remains largely unexplored to date. This work addressed the function of the two major endothelial growth factor receptors, VEGFR2 and VEGFR3, as well as the VEGFR-activated PI3K pathway, during the development of dermal and mesenteric lymphatic vessels. With the use of novel transgenic mouse models, *Vegfr2*, *Vegfr3* and *p110 α* were deleted specifically in the lymphatic endothelium at different developmental stages. Analysis of dermal vasculature showed a critical role of VEGFR3 during embryonic lymphatic sprouting with a minor contribution of VEGFR2 to this process. Surprisingly, both VEGF receptors were dispensable for vessel sprouting postnatally, although vessel remodelling depended on VEGFR3. Contrary to the VEGFRs, deletion of *p110 α* revealed a requirement of PI3K signalling for the sprouting of dermal lymphatic vessels postnatally, but not during embryogenesis. Finally, examination of the transgenic mice with a combined haploinsufficiency for VEGFR3 and *p110 α* unveiled an organ-specific role of VEGFR3/PI3K signalling during initial stages of mesenteric lymphatic development. Lineage tracing analysis and loss-of-function studies provided evidence for a novel mechanism of lymphatic vessel formation from hematopoietic-derived progenitors. Better understanding of the mechanisms underlying the development of the lymphatic vessels holds a promise of finding a cure for diseases associated with the lymphatic system.