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Elucidating organ-specific mechanisms of development and disease within the lymphatic vasculature

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Research area:

Vascular Biology

Brief description

The project investigates mechanisms of lymphatic vascular development in different organs and provides insight into tissue-specific functional specialization and disease manifestation within the vasculature. We focus on characterizing organ-specific endothelial progenitor cells using genetic mouse models, microscopy and single-cell transcriptomics.

Aim

This project aims to investigate differences in the formation of the lymphatic vasculature in different organs, which may underlie organ-specific manifestation of lymphatic dysfunction in disease. The focus is on uncovering organ-specific origin(s) and identity of lymphatic endothelial progenitor cells.

Background

Lymphatic vasculature is critical for tissue fluid homeostasis and immune surveillance, and has recently been shown to play an active role in many important physiological processes and common diseases such as autoimmune diseases and cancer. Pathological lymphatic diseases, for which there are generally no effective treatments, mostly affect specific tissues, yet organ-specific properties and functions of the vasculature remain unexplored.

The blood vasculature is formed via two fundamentally different mechanisms, *de novo* formation of vessels from endothelial progenitors (vasculogenesis) and sprouting of vessels from pre-existing ones (angiogenesis). Lymphatic vasculature was thought until recently to form exclusively by sprouting from embryonic veins (lymphangiogenesis). However, we recently uncovered an unexpected organ-specific mechanism of vessel morphogenesis that we termed lymphvasculogenesis, and a novel developmental origin of lymphatic vessels. We hypothesize that the distinct morphogenic processes and multiple developmental origins of lymphatic vessels determine their tissue-specific properties and functions.

Project plan

The student will participate in work addressing one or both of the following aims:

1) Identify the developmental origins of lymphatic vasculature using Cre/loxP lineage tracing and define their contribution to the mature vasculature. We will cross transgenic mouse lines expressing Cre recombinase under the control of cell type specific promoters with reporter strains to allow genetic marking of Cre expressing cells and their lineage. In particular, we will utilise our novel unpublished mouse lines that allow tracing of the blood forming hemogenic endothelium that we previously proposed to generate mesenteric lymphatic endothelial cell (LEC) progenitors. The student will assess the contribution of reporter-expressing cells to lymphatic vasculature of different organs by whole-mount immunofluorescence, confocal microscopy, and fluorescence activated cell sorting (FACS).
2) Determine genetic signatures of LEC progenitors to identify markers for their isolation and to provide targets for functional characterization. We will perform single-cell RNA sequencing of LECs and progenitors from different organs. The student will verify RNAseq results by whole-mount immunofluorescence or RNA in situ hybridization of various tissues, and by qRT-PCR analysis of FACS-sorted cells.

This work is expected to generate novel understanding of organ-specific mechanisms of vascular development, functional specialization and disease manifestation.

Contact details

If you are highly motivated, dedicated to research and would like to answer these challenging questions, please contact us.

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