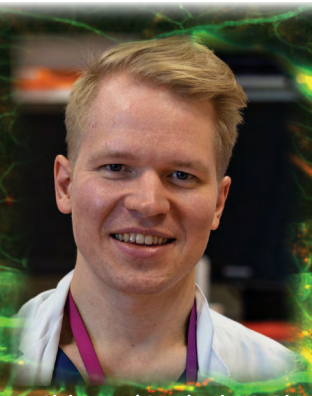
Hidden passageways and secret tunnels—

dural lymphatic vessels and the lymphatic-like phenotype of Schlemm's canal



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On August 16, 2024, Aleksanteri Aspelund defended his thesis "Discovery of dural lymphatic vessels and the lymphatic-like phenotype of Schlemm's canal" at the Faculty of Medicine of the University of Helsinki. His supervisor was Academician and Academy Professor Kari Alitalo, MD, PhD, Translational Cancer Medicine Program, Faculty of Medicine, University of Helsinki and Wihuri Research Institute, Helsinki, Finland.

The mammalian eye and central nervous system (CNS) have previously been considered organs devoid of conventional lymphatic drainage. In the eye, the anterior segment is filled with aqueous humor (AH), which is produced by the ciliary body epithelium. AH flows out of the anterior chamber mainly through the trabecular meshwork (TM) and Schlemm's canal (SC) into venous circulation. In the CNS, the brain ventricular choroid plexus produces cerebrospinal fluid (CSF), which flows via the ventricular system into the subarachnoid space and out of the CNS.

SC shares structural and functional parallels with lymphatic vessels (LVs), but it has been considered a venous sinus. During this thesis, we discovered that SC is a VEGF-C/VEGFR-3-responsive lymphatic-like vessel. We reported that the endothelial cells (ECs) of SC express many, but not all, lymphatic EC markers. The early stages of SC development involve induction of the lymphatic master regulator PROX1 and the lymphangiogenic receptor tyrosine kinase VEGFR-3 in blood vascular ECs in postnatal mice. Functional experiments using gene deletion and function-blocking antibodies indicated that VEGF-C and its receptor, VEGFR-3, have essential functions in SC development. Intriguingly, the delivery of VEGF-C into the adult eye prompted sprouting, proliferation, and growth of SC ECs. These findings not only highlight the lymphatic-like phenotype of SC but also suggest that VEGF-C and VEGFR-3 act as regulators of SC lymphangiogenesis, offering a potential avenue for therapeutic intervention in glaucoma treatment.

The second study of the thesis revealed a previously unrecognized lymphatic vascular network in the dural layer of the meninges surrounding the mouse brain. These vessels express all hallmarks of conventional lymphatic ECs and serve as a downstream conduit for CSF flow downstream of the subarachnoid space. The dural LVs subsequently transport the CSF fluid into deep cervical lymph nodes (dcLNs). Transgenic mice that express a soluble inhibitor of the major lymphangiogenic growth factors (VEGF-C/D trap) exhibit a complete developmental aplasia of dural LVs. These mice exhibited an attenuation of macromolecule clearance from the brain and lack of transport from the subarachnoid space into the dcLNs, while the brain interstitial fluid pressure and water content remained unaffected. These revelations have prompted a re-evaluation of the role of the lymphatic system in CNS physiology and pathophysiology.

In summary, the discoveries illuminate previously uncharted facets of lymphatic physiology in the CNS and the ocular system. The findings open new avenues for understanding ocular fluid drainage and neurophysiology, and they should provide potential targets for the treatment of glaucoma and neurological disorders.

Key points:

- Schlemm's canal is a hybrid blood–lymphatic vessel regulated by VEGF-C/VEGFR-3 signaling.
- Dural lymphatics provide a novel cerebrospinal fluid outflow pathway to cervical lymph nodes.

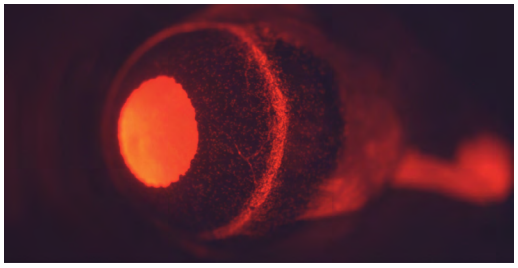

Figure 1. Expression of the Prox1 in the Schlemm's canal of a Prox1-Cre^{ERT2}; LSL-tdTomato *reporter mouse*

Future directions:

- Defective Schlemm's canal morphogenesis is a novel mechanism of congenital glaucoma; regulatory genes are under investigation, which may provide new therapeutic avenues
- Dural lymphatic vessels may be implicated in multiple sclerosis, Alzheimer's disease, Parkinson's disease, stroke, brain tumors, migraine, CNS infections, and traumatic brain injury.

References

1. Aspelund A, et al. The Schlemm's canal is a VEGF-C/VEGFR-3-responsive lymphatic-like vessel. *J Clin Invest*. 2014;124(9):3975-86.
2. Aspelund A, et al. A dural lymphatic vascular system that drains brain interstitial fluid and macromolecules. *J Exp Med*. 2015;212(7):991-9.