Unraveling the link between brain and lymphatic system

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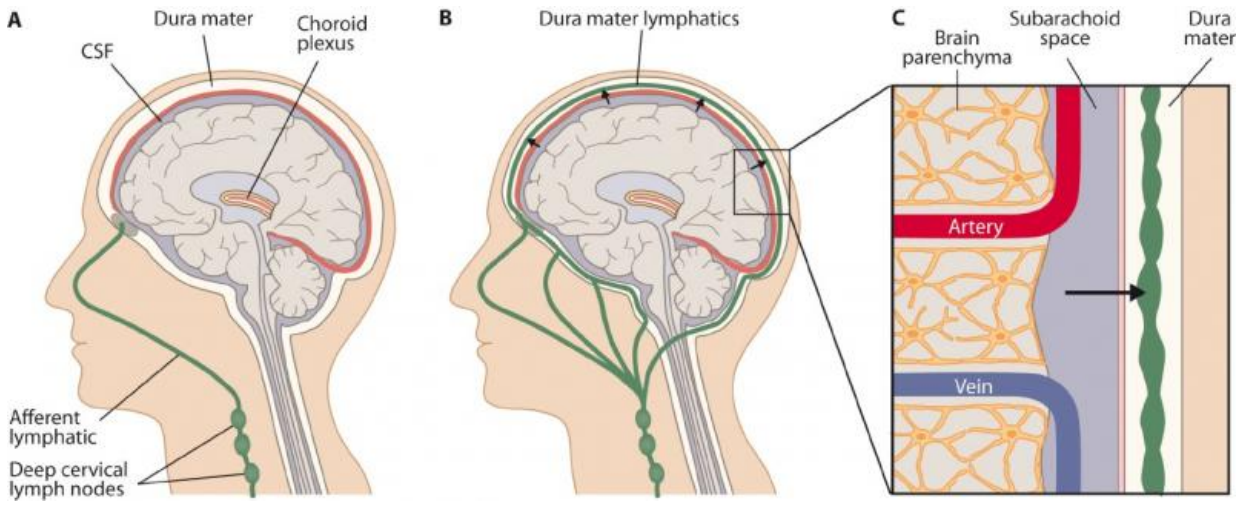


A schematic image of the novel lymphatic vessel network in the meningeal linings of the brain, discovered by Aleksanteri Aspelund and collaborators. (A) Previously, lymphatic vessels in the nasal mucosa were known to drain cerebrospinal fluid, but it was thoughts that the lymphatic vessels did not extend into the brain. (B-C) The new findings revealed that the dura mater lymphatic system is important for the drainage of brain interstitial fluid, macromolecules and cerebrospinal fluid. Credit: Kari Alitalo

In a study published in *The Journal of Experimental Medicine*, researchers working at the Wihuri Research Institute and the University of Helsinki report a surprising finding that challenges current anatomy and histology textbook knowledge: Lymphatic vessels are found in the

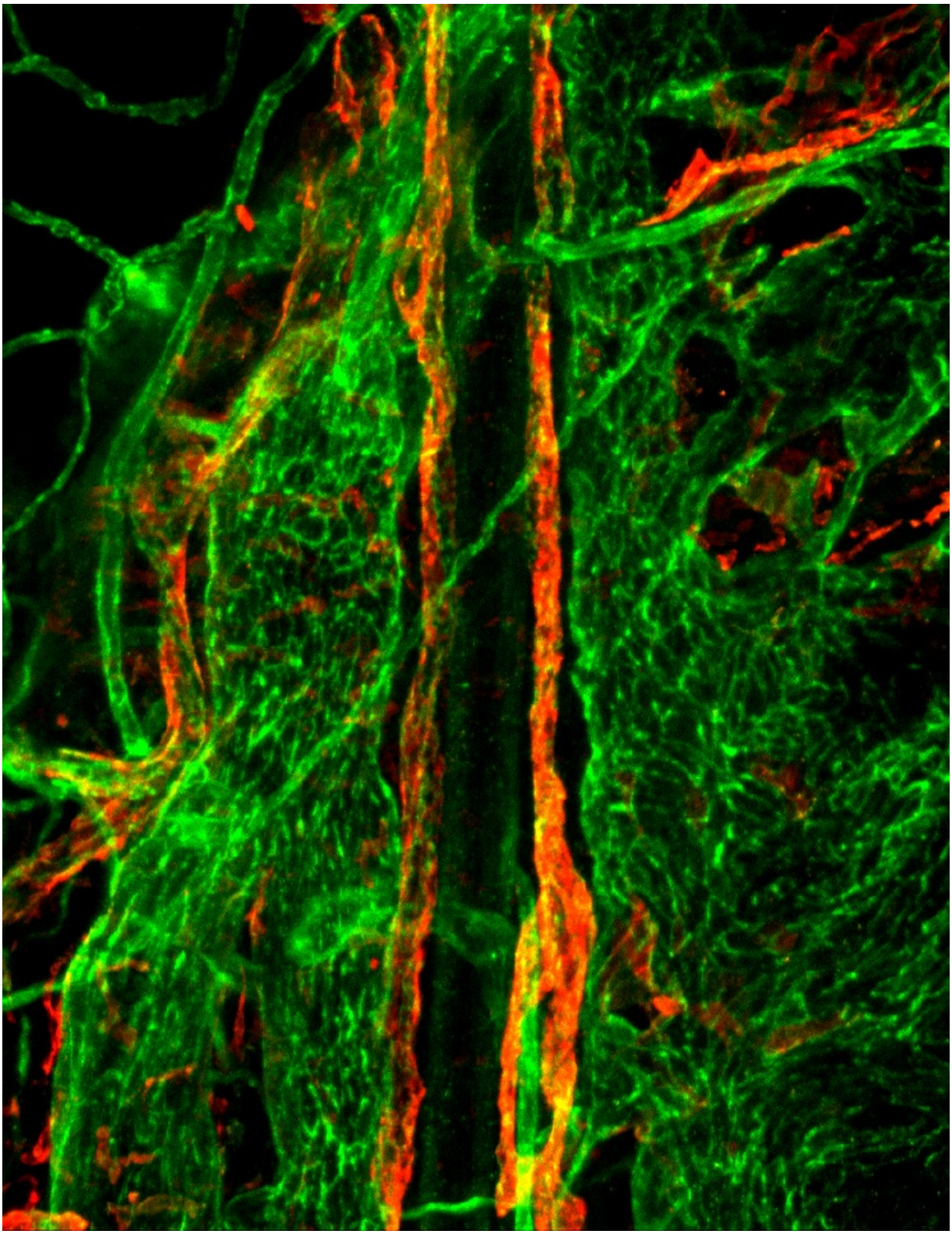
central nervous system where they were not known to exist. Aleksanteri Aspelund and colleagues discovered the meningeal linings of brain have a lymphatic vessel network that has direct connections to the systemic lymphatic network elsewhere in the body.

Lymphatic circulation forms a network that covers almost the whole body and is especially important to the tissue clearance of fluids and macromolecules as well as for immune defense mechanisms. Until now, the central nervous system has been considered an immune-privileged organ devoid of lymphatic vasculature.

"We have recently discovered that in the eye, which is another immune-privileged organ previously considered to lack lymphatic circulation, there exists a lymphatic-like vessel that is important for the regulation of eye pressure. This led me to reinvestigate the brain in this regard," says Aleksanteri Aspelund, who is working in Academy Professor Kari Alitalo's research group.

"We were stunned to find such an extensive network in connection to the brain. This incredible finding completely changes our understanding of how to brain is cleared of excess fluid and gives a chance to look at brain diseases from a completely new angle," he continues.

The researchers performed a thorough job in characterizing the structure and function of these previously unknown vessels. They showed that these meningeal lymphatic vessels drain out of the skull alongside arteries, veins and cranial nerves. These vessels show all molecular hallmarks of the lymphatic vessels and function as a direct clearance routes for the brain and cerebrospinal fluid macromolecules out of the skull and into the deep cervical lymph nodes.



The authors' original image shows two dura mater lymphatic vessels (red)

running along meningeal blood vessels (green). Credit: Kari Alitalo

How did the lymphatic vessels manage to escape notice until now?

"This is no wonder," says medical student Salli Antila, who has also been working with the project.

Lymphatic vessels are collapsed structures between the meninges, and if one does not know how to look, they cannot be found. Although we had already found the vessels, it took some time to develop good imaging methods to visualize these vessels.

The discovery has raised several new questions concerning some fundamental brain functions and the mechanisms of brain diseases. Researchers find it highly possible that lymphatic clearance of the brain proves to be important in neuro-immunological diseases as well as in diseases characterized by the pathological accumulation of misfolded proteins or fluid into the brain parenchyma, for example in Alzheimer's disease, which affects tens of millions of people worldwide.

More information: The findings were published online by The *Journal of Experimental Medicine* and will appear in a forthcoming print edition.

Provided by University of Helsinki