*Nature Reviews Neurology* **11**, 367 (2015); published online 23 June 2015; doi:10.1038/nrneurol.2015.105

NEUROIMMUNOLOGY

# Uncovering the secrets of the 'brain drain' —the CNS lymphatic system is finally revealed

The traditional concept of the brain as an immune privileged site is gradually being eroded, and has been dealt a further blow by the recent demonstration of lymphatic vessels in the CNS. In a study published in *Nature*, Antoine Louveau, Jonathan Kipnis and their colleagues at the University of Virginia identified functional lymphatic vasculature in the meninges. In addition to providing new insights into the anatomy of the brain, the findings could have important implications for understanding the mechanisms underlying neurodegenerative and neuroinflammatory disease.

"We have been interested in the role of the immune system in brain function for some time," comments Kipnis. "We showed that mice deficient in T cells are cognitively impaired, and that meningeal T cells play an important part in brain function, but we did not know what were the gateways for immune cells to get into and out of the meninges."

Louveau established a whole-mount immunohistochemical technique to examine the expression of various cell-specific markers in mouse meningeal tissue. Using this technique, the researchers identified T lymphocytes aligned along endothelial structures that ran parallel to the dural sinuses (vessels that drain blood from the brain into the internal jugular veins).

"We realized that these structures were not blood vessels, so we explored the unlikely possibility that they are lymphatic vessels," explains Kipnis. "We were amazed with our findings."

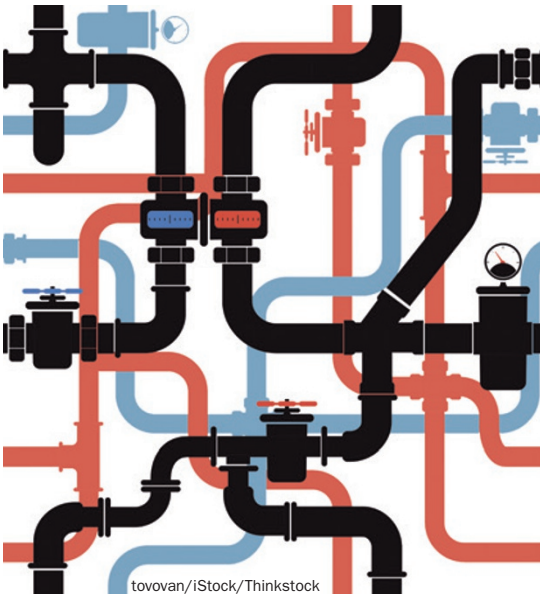
The researchers showed that the newly discovered perisinusal vessels expressed various lymphatic endothelial cell markers, including Lyve-1, thereby confirming their identity as lymphatic vessels. Intriguingly, preliminary investigations indicated the presence of similar Lyve-1-expressing structures in human dural tissue, although this finding awaits further confirmation.

Next, the authors used fluorescent tracers to explore the drainage capabilities of the perisinusal vessels. In anaesthetized mice, fluorescein was injected intravenously, while QDot655 was injected into the cerebral ventricles. QDot655—but not fluorescein—could subsequently be detected in Lyve-1-expressing vessels in the meninges. From these results, the team concluded that the meningeal lymphatic vessels provide a drainage route from the cerebrospinal fluid (CSF).

Intracerebroventricular injection of Evans blue dye revealed drainage of fluid from the CSF to deep cervical lymph nodes via the meningeal lymphatic vessels. "We knew that the brain drains to deep cervical lymph nodes, but we did not know how, and we had no control over the process," explains Kipnis. "Now we know that lymphatic vessels exist in the brain, and that they drain immune cells and macromolecules from the CSF to the draining lymph nodes."

A team led by Maiken Nedergaard at the University of Rochester Medical Center previously identified a perivascular pathway known as the glymphatic system, which uses the CSF to clear waste products from the interstitial compartments of the CNS. The word 'glymphatic' derives from the system's reliance on glial cells, and its functional resemblance to the lymphatic system. On the basis of their new findings, Kipnis and colleagues propose a model in which the meningeal lymphatic vessels are connected to the glymphatic system via the CSF.

Commenting on the new paper, Nedergaard says "the most significant observation in my mind is that the authors showed that the meningeal lymphatic vessels act as a reservoir for leukocytes; it is not entirely novel that the meninges have lymphatic vessels, but prior papers on the subject had not studied these vessels from an immunological point of view." Moreover, she advocates further research into the relationship between the glymphatic system and the meningeal lymphatic vessels.



tovovan/iStock/Thinkstock

Kipnis believes that the discovery of lymphatic vessels in the CNS could provide the impetus for new experimental approaches to probe the mechanisms of neurological disease. "We can control these vessels—for example, expand them or ablate them—and we can then ask how manipulation of these vessels affects various neurological conditions," he explains. "We are particularly interested in the roles these vessels are playing in initiation and progression of multiple sclerosis, meningitis and Alzheimer disease."

*Heather Wood*

**Original article** Louveau, A. *et al.* Structural and functional features of central nervous system lymphatic vessels. *Nature* doi:10.10.1038/nature14432

**Further reading** Iliff, J. J. *et al.* Brain-wide pathway for waste clearance captured by contrast-enhanced MRI. *J. Clin. Invest.* **123**, 1299–1309 (2013) | Jessen, N. A. *et al.* The glymphatic system: a beginner's guide. *Neurochem. Res.* doi:10.1007/s11064-015-1581-6