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Nasopharyngeal Lymphatic Plexus is a Hub for CSF Drainage

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The drainage of cerebrospinal fluid (CSF) from the subarachnoid space surrounding the brain into cervical lymph nodes has been a recognized for a considerable time. However, identifying the connections and regulatory mechanisms were still elusive. Using CSF tracers in Prox1-GFP lymphatic reporter mice, tissue clearing, whole-mount immunofluorescent imaging, and intravital imaging, we identified the extracranial lymphatic vessels that serve as a hub for CSF drainage. The nasopharyngeal lymphatic plexus (NPLP) serves as a major hub for CSF outflow to deep cervical lymph nodes. This plexus exhibited unusual valves and short lymphangions but lacked smooth muscle coverage. In contrast, downstream deep cervical lymphatics had typical semilunar valves, long lymphangions, and smooth muscle coverage, facilitating the transportation of CSF to the deep cervical lymph nodes. α-adrenergic and nitric oxide signaling in the smooth muscle cells (SMCs) regulated CSF drainage to deep cervical lymphatics. By extracranial controlling the SMCs, the CSF drainage can be modulated. With ageing, the NPLP undergoes atrophy, although deep cervical lymphatics remain unaffected, and surrounding SMCs can still be controlled by adrenergic or nitric oxide signaling. The significance of evidence supporting the NPLP as a hub for CSF outflow is underscored by its regression with age. However, the pharmacological activation of deep cervical lymphatic transport, which remains resistant to aging, can still enhance CSF outflow. This presents a potential strategy for boosting CSF clearance in age-related neurological conditions where increased efflux would be advantageous.

Keywords: *Cerebrospinal fluid, Lymphatic drainage, Lymphatic vessel*