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## The Glymphatic System

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## The Glymphatic System: A New Player in Ocular Diseases?

In June 2015, Denniston and Keane<sup>1</sup> and our group<sup>2</sup> independently hypothesized the existence of a paravascular transport system in the retina and the optic nerve, respectively, analogous to the described glymphatic system in the brain. Recent research is now providing more substantial evidence for a glymphatic system in the eye.

The glymphatic system was first described by Iliff et al.<sup>3</sup> in 2012. The authors defined for the first time a brain-wide network of paravascular channels in mice, which they called the “glymphatic” pathway, along which a large proportion of subarachnoid cerebrospinal fluid (CSF) recirculates through the brain parenchyma, facilitating the clearance of interstitial solutes, including amyloid- $\beta$  (A $\beta$ ), from the brain.<sup>3</sup> This brain-wide anatomical pathway consists of three elements: a para-arterial CSF influx route, a paravenous interstitial fluid (ISF) clearance route, and a transparenchymal pathway that is dependent upon astroglial water transport via the astrocytic aquaporin-4 (AQP4) water channel.<sup>4</sup> One implication of these findings is that glymphatic pathway dysfunction may contribute to the deficient A $\beta$  clearance in Alzheimer’s disease.<sup>5</sup>

Denniston and Keane<sup>1</sup> proposed that a similar glymphatic system, or at least a paravascular system, is present in the retina, and that this may be a key player in retinal diseases ranging from age-related macular degeneration to retinal vasculitis. Their hypothesis was originally based on extrapolation of the findings in the brain to the retina, but the authors also discussed evidence from adaptive optics imaging studies of patients with retinal vasculitis to support their theory.<sup>1</sup>

In our 2015 paper, we reviewed several lines of evidence suggesting that the glymphatic system may also have potential clinical relevance for the understanding of the pathophysiology of glaucoma.<sup>2</sup> Since the optic nerve is a white matter tract of the central nervous system that extends into the orbit where it is surrounded by CSF in the subarachnoid space,<sup>2</sup> an intriguing question is whether there is also evidence for the existence of a paravascular transport system within the optic nerve. In light of the key role that the glymphatic pathway may play in the clearance of interstitial solutes from the brain, the observation of such an anatomically distinct clearing system in the optic nerve could be of great importance for our understanding of how solutes are cleared from the ISF in the optic nerve, and could provide new insights into the pathogenesis of glaucoma. Indeed, if confirmed, one might expect that a dysfunctional glymphatic system could ultimately result in reduced neurotoxin clearance in the optic nerve leading to glaucomatous optic neuropathy.<sup>2</sup>

In a postmortem study to investigate the possibility of a paravascular fluid circulation, or at least paravascular spaces, in the human optic nerve, we examined cross-sections of human optic nerves by light microscopy after administering India ink by bolus injection into the subarachnoid space of the optic nerve (work in progress). The results demonstrated accumulation of India ink in paravascular spaces around the central retinal artery and vein, whereas the lumens of these vessels remained unlabeled. The deposits were located between collagen fiber bundles lining a slit-like space (Fig.).

In addition, in their report presented at this year’s ARVO Annual Meeting, Hu and colleagues (Hu P, et al. *IOVS* 2016;57:ARVO E-Abstract 996) provided evidence for a glymphatic system in human, primate, rat, and mouse retina. Retinas were examined using multimarker immunohistochem-

istry. A glial network of AQP4<sup>+</sup> ensheathed the entire retinal vascular system, including between blood vessels, and the authors concluded that this may be the anatomical correlate of a retinal glymphatic system.

Given the evidence for a glymphatic system in human retina, and given that our postmortem study demonstrated paravascular spaces around the central retinal artery and vein in the human optic nerve, it would be interesting to further investigate whether a “paravascular communication” exists between the surroundings of the retinal vascular system and the surroundings of the central retinal vessels in the optic nerve. On the basis of magnetic resonance imaging findings of Terson’s syndrome and their review of the literature, Sakamoto et al.<sup>6</sup> speculated that the branches of the central retinal vessels in the retina are probably also surrounded by paravascular spaces and that they may serve as drainage channels from the subarachnoid space around the optic nerve to beneath the internal limiting membrane forming the boundary of the retina with the vitreous body. Importantly, A $\beta$  has been reported to increase by chronic elevation of intraocular pressure (IOP) in animals with experimentally induced ocular hypertension and to cause retinal ganglion cell death.<sup>7–10</sup> At least theoretically, such a paravascular, “retino-orbital” continuity could facilitate elimination of neurotoxins, such as A $\beta$ , induced by high IOP. Demonstration of such a clearance system would support our hypothesis that glaucoma, just like Alzheimer’s disease, may occur when there is an imbalance between production and clearance of neurotoxins.<sup>2,11</sup> In normal-tension glaucoma, reduced clearance of A $\beta$  might predominate as a result of glymphatic pathway dysfunction.<sup>2</sup> In high-tension glaucoma, IOP-induced A $\beta$  generation might predominate and even mild impairment of glymphatic pathway function might result in glaucomatous optic nerve damage.<sup>2</sup>

Interestingly, a growing body of evidence indicates that intracranial pressure (ICP) is lower in patients with primary open-angle glaucoma (POAG) when compared with nonglaucomatous control subjects.<sup>12</sup> In addition, ICP was reported to be lower in the normal-tension compared with the high-tension form of POAG.<sup>12</sup> If the ICP is too low, fluid flow from the paravascular spaces in the optic nerve to the paravascular spaces in the retina may decline or stop, given that this paravascular flow must cross the trans-lamina cribrosa pressure barrier (IOP-ICP). Normally, IOP is higher than ICP.<sup>12</sup> An increase

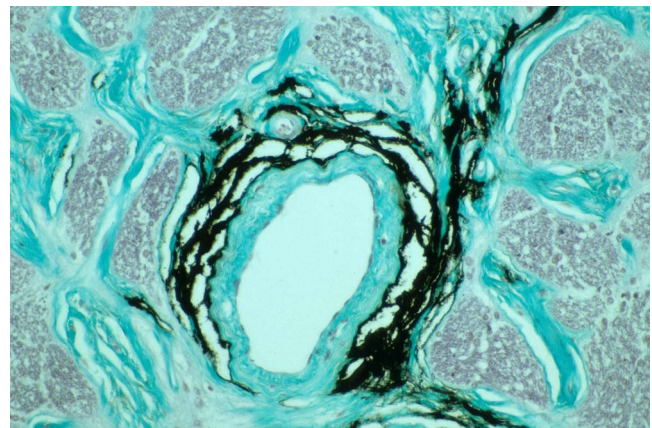


FIGURE. Cross-section through the optic nerve: distribution of ink in the surroundings of the central retinal artery showing the complex slit-like space (Holmes-Luxol,  $\times 400$ ).

in IOP, a decrease in ICP or a decrease in the thickness of the lamina cribrosa may increase the pressure barrier against which paravascular flow from the optic nerve to the retina needs to occur. Patients with low ICP and high trans-lamina cribrosa pressure barriers may therefore be more likely to develop suppression of glymphatic fluid transport leading to reduced A $\beta$  clearance and subsequent glaucomatous optic neuropathy.

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