The Glymphatic System: A New Player in Ocular Diseases?

In June 2015, Denniston and Keane\(^1\) and our group\(^2\) 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.\(^3\) 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.\(^2\) This brain-wide anatomical pathway consists of three elements: a paravascular CSF influx route, a paravenous interstitial fluid (ISF) clearance route, and a transparenchymal pathway that is dependent upon astrogial water transport via the astrocytic aquaporin-4 (AQP4) water channel.\(^1\) One implication of these findings is that glymphatic pathway dysfunction may contribute to the deficient A\(\beta\) clearance in Alzheimer’s disease.\(^5\)

Denniston and Keane\(^1\) 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.\(^1\)

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.\(^6\) 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,\(^2\) 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.\(^2\)

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 multimeric immunochemistry.

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.\(^12\) In addition, ICP was reported to be lower in the normal-tension compared with the high-tension form of POAG.\(^12\) 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.\(^2\) An increase...
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 Aβ clearance and subsequent glaucomatous optic neuropathy.

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