

“Black Holes” and the Ocular Glymphatic System: Author Response to “The Glymphatic System: A New Player in Ocular Diseases?”

In early June 2015, *IOVS* published our novel hypothesis of the existence of an “ocular glymphatic system.”¹ At the time, it had some resemblance to cosmological predictions of the existence of “black holes”: it was based primarily on logic, in our case the embryological, anatomical, and physiological relationships between the eye and the brain, and indirect observations. Direct visualization was lacking. We argued that, assuming that Iliff and colleagues² were correct in the observations of a paravascular transport system within the central nervous system (CNS), then it seemed very likely that there would be a similar system within the eye. Various “thought experiments” showed how the existence of this additional fluid transport system could provide plausible explanations for a wide variety of poorly understood phenomena within the eye. Key examples from the major blinding diseases included the extent to which the ocular glymphatic system may contribute to the following: the reduced clearance of waste metabolites and toxins seen over time with implications for the development of age-related macular degeneration and possibly some hereditary dystrophies; the variable sensitivity of the optic disc to the level of IOP at which glaucomatous neuropathy occurs, contributing to a number of different types of glaucoma; and the tolerance of the retina to withstand ischemic insults including whether they develop macular edema and its distribution and severity in conditions such as diabetes and retinal vascular occlusion. We also had a particular interest in two other areas: whether an ocular glymphatic system might explain the variable tolerance of optic discs to different levels of raised intracranial pressure in terms of disc swelling and optic nerve function, as seen in idiopathic intracranial hypertension and other forms of papilledema, and the direction and pattern of spread of certain retinal infective or inflammatory processes. It was in the latter context that we looked for the first direct evidence of the ocular glymphatic system, speculating that some of the ultrastructural changes highlighted in cases of retinal vasculitis imaged by adaptive optics might represent paravascular flow (Errera M-H, et al. *IOVS* 2015;56:ARVO E-Abstract 5303).

We were therefore delighted to see the publication of the work by Wostyn et al,³⁻⁶ which they have appropriately highlighted here and which provides independent new evidence for the existence of the ocular glymphatic system. They have elegantly described how the ocular glymphatic system might contribute to the development of glaucoma, making the same argument that we had done previously and providing new direct and indirect evidence⁴; they also have highlighted how this may be affected by cerebrospinal fluid (CSF) pressure and how in turn it may affect the balance of production and clearance of neurotoxins, drawing an interesting link between the development of glaucoma and Alzheimer's disease.^{5,6} We suspect that this is just the start, and that there will be a rapid proliferation of work across a range of ocular diseases. This is likely to be initially focused around the aquaporin-4 channel,⁷ but then extended to encompass the broader picture of paravascular flow and the glymphatic system, and their relevance to a wide range of ophthalmic conditions.¹

It might be surprising that an entirely new transport system could exist in the eye without being noticed until now. After all, the systemic lymphatic system was described more than 350 years ago. But, to return to our previous analogy with black holes, these structures can be very difficult to visualize. The role of a conventional lymphatic system in the eye is itself an emerg-

ing field, and it was only in 2015 that the “missing link” of a true lymphatic system within the brain was established.⁸ In that important article, Louveau et al.⁸ noted its relevance to the glymphatic system, stating that, “The newly discovered meningeal lymphatics are a novel path for CSF drainage and represent a more conventional path for immune cells to egress the CNS. Our findings may represent the second step in the drainage of the interstitial fluid from the brain parenchyma into the periphery after it has been drained into the CSF through the recently discovered glymphatic system.”⁸ We believe that the next 10 years will see a major paradigm shift in our understanding of transport of fluid, solutes, and cells through the eye, with a new understanding of the relationship of the arteriovenous system and its integration to both an ocular glymphatic system and lymphatic system. We look forward to seeing how advances in imaging and functional analysis reveal the physiology and pathophysiology of these systems, but even more importantly to see if this process can be modified, providing an entirely new target for treatment for many blinding diseases.

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