Twists and turns of ocular glymphatic clearance – new study reveals surprising findings in glaucoma

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Twists and turns of ocular glymphatic clearance – new study reveals surprising findings in glaucoma

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The central nervous system (CNS) is largely devoid of functional lymphatic vessels, apart from within the meningeal lining (Louveau et al. 2015). The brain can eliminate cellular waste and excess interstitial fluid from deep in the parenchyma using paravascular spaces facilitated by the water channel aquaporin-4 (AQP4) (Iliff et al. 2012). The hallmarks of the brain glymphatic system are unflow of fluid and solutes along arteries driven by hydrostatic pressure, convective interstitial fluid movement facilitated by AQP4 on astroglial endfeet and perivascular drainage, especially at the skull base. Despite the retina having higher metabolic and fluidic demands per gram than any other tissue in the body, all known pathways for fluid clearance exist in the anterior globe. Several groups have hypothesized the existence of an analogous glymphatic system in the eye (Denniston & Keane 2015; Wostyn et al. 2016). The presence of a glymphatic pathway in the optic nerve and the theory that a dysfunctional glymphatic system may be involved in the pathogenesis of glaucoma were first proposed by Wostyn et al. (2015). In 2017, Mathieu et al. demonstrated the movement of small cerebrospinal fluid (CSF) tracers from the brain into the optic nerve, consistent with glymphatic transport (Mathieu et al. 2017). Our group recently discovered an ‘antegrade’ ocular glymphatic clearance system from the retina and optic nerve to the CSF and meningeal lymphatics in rodents (Wang et al. 2020). Following tracer infusion into both CSF and the vitreous, whole mouse tissue clearing showed evidence of bidirectional glymphatic transport (Fig. 1). Tracer movement was facilitated by glial AQPs in both the retina and optic nerve. Small tracer molecules like amyloid-beta and radio-labelled potassium entered retinal ganglion cell (RGC) axons and the perivascular spaces of the retina and optic nerve head (ONH) before being cleared by the antegrade glymphatic pathway. Larger dextrans were blocked from posterior outflow both by the intact glial lamina in mice and the more developed lamina cribrosa in rats. Directional water and small solute movement inside axons are distinct from and sometimes have a different direction from the ATP-driven axonal transport along microtubules (Beaulieu 2002). We found that RGC axons appeared to use the hydrostatic pressure gradient to promote fluid and solute delivery across the ONH, where the axons take a sharp turn before exiting the eye. Raised intracranial pressure (ICP) abrogated the intraxonal tracer movement along the optic nerve, whilst lowering ICP or stimulating pupil movement increased it. The lamina cribrosa appears to have not only an anatomical function of supporting axon bundles, but also a vital physiological role as a hydrostatic barrier redirecting fluid and solute movement into axons and the perivenous spaces at the ONH and retrolaminar nerve (Wang et al. 2020). One of our most surprising findings was that two distinct animal models of glaucoma were both characterized by excessive and misdirected glymphatic

References


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In fact, excessive extracellular tracer important metabolites within axons. and may promote wash out of restraints, as is seen in papilloedema, movements across the ONH cannot be anteriorly located routes. Large fluid magnitude lower than clearance via outflow is likely to be orders of tous eyes is unknown. Glymphatic exit the eye via this posterior clear-
tial functional coupling with accom-
dation. The amount of fluid that 
tions for several potentially blinding 
system could be vital in the develop-
mental functional coupling with accom-
it, intraocular pressure, thus being a result of barrier failure rather than an 
creased pressure gradient in the long 
term.

We found enhanced glymphatic 
clearance by stimulation of the pupil-
ary light response. This enhancement 
was blocked by atropine, suggesting causality linked to the movement of 
the pupil. A proportion of supra-
choroidal tracer also exited via the 
glymphatic pathway. These results hint 
at an interplay between uveoscleral and glymphatic outflow, and a poten-
tial functional coupling with accom-
modation. The amount of fluid that 
exts the eye via this posterior clear-
ance route in normal and glaucoma-
tous damage to the lamina barrier 
impairs the clearance of small and 
potentially neurotoxic solutes such as 
amyloid beta via a novel glymphatic 
pathway. Several important questions 
remain. What other small solutes and 
ions are dependent on the ocular 
glymphatic clearance pathway for effi-
cient transport? Can we develop diag-
nostic tracers to study this pathway in 
a clinical setting and modulate trans-
port to delay or prevent optic nerve 
diseases like glaucoma? Further char-
etization of the ocular glymphatic 
system could be vital in the develop-
ment of new diagnostics and treat-
ments for several potentially binding 
conditions.

clearance, and not by impaired glym-
phatic outflow as previously suggested (Mathieu et al. 2018). In both models, 
the excessive outflow actually was also observed after normalization of 
intracocular pressure, thus being a result of barrier failure rather than an 
increased pressure gradient in the long 
term.

as ocular dementia. A key finding in our study is that glaucoma-
tous damage to the lamina barrier 
impairs the clearance of small and 
potentially neurotoxic solutes such as 
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