Postprint: Advances in the Ocular Glymphatic System and Related Eye Diseases

Authors: Zhu Guangyu, Cheng Yuxin, Lu Xuejing, Lu Xuejing

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Abstract

The recently discovered ocular glymphatic system has updated our understanding of intraocular circulation. It is an aqueous humor-interstitial fluid exchange system driven by aquaporin-4 on glial cell end-feet and dependent on the perivascular spaces of retinal arteries and veins, ultimately serving to eliminate neurotoxic substances such as β-amyloid from the eye. This article reviews the composition and function of the ocular glymphatic system, describes the specific circulatory pathways of this system under physiological conditions and its impairment mechanisms in diseases such as glaucoma, optic disc edema, and Terson syndrome, aiming to provide insights for a deeper understanding of intraocular metabolic patterns and exploration of the pathological mechanisms of related ocular diseases.

Full Text

Preamble

Research Progress of Ocular Glymphatic System and Related Ocular Diseases

Authors: ZHU Guangyu[1,3], CHENG Yuxin[1,3], LU Xuejing[1,2,3*]
Affiliations:
1. Eye School of Chengdu University of Traditional Chinese Medicine, Chengdu 610075, China
2. Ineye Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu 610075, China
3. Key Laboratory of Sichuan Province Ophthalmopathy Prevention & Cure and Visual Function Protection With TCM, Chengdu 610075, China
*Corresponding author: LU Xuejing, Chief physician, Doctoral supervisor; E-mail: luxuejing@cdutcm.edu.cn

Abstract: The recently discovered ocular glymphatic system has transformed our understanding of intraocular fluid dynamics. This system facilitates aqueous humor-interstitial fluid exchange in the perivascular spaces of retinal arteries and veins, driven by aquaporin-4 (AQP4) on glial cell endfeet, ultimately clearing neurotoxic substances such as β-amyloid from the eye. This review synthesizes current knowledge on the composition and function of the ocular glymphatic system, detailing its circulatory pathways under physiological conditions and its impairment mechanisms in diseases including glaucoma, optic disc edema, and Terson syndrome, providing new perspectives for understanding intraocular metabolism and the pathogenesis of related ocular diseases.

Keywords: Ocular glymphatic system; Glaucoma; Optic disc edema; Terson syndrome

Literature Search Strategy: English databases (PubMed, Medline, Web of Science, SCI-hub) were searched using keywords "Glymphatic system, Lamina cribrosa, Glaucoma, Optic disc edema, Terson syndrome." Chinese databases (CNKI, Wanfang, VIP, SinoMed) were searched using corresponding Chinese terms. Search period: database inception to November 1, 2022. Inclusion criteria: published literature, prioritizing high-quality journal articles. Exclusion criteria: articles with insufficient data, duplicate publications, unavailable full text, or poor methodological quality.

1.1 Brain Glymphatic System

The glymphatic system was first discovered in the brain and has since become a focal point in neuroscience research. Findings on Virchow-Robin spaces (also known as perivascular spaces) [3], the glymphatic system [4], and meningeal lymphatic vessels [5] have progressively confirmed the existence of a brain-wide clearance network. Driven by respiration and arterial pulsation [6], cerebrospinal fluid (CSF) produced by the choroid plexus flows through the ventricular system into the subarachnoid space, then enters deep brain tissue along perivascular spaces surrounding penetrating arteries, arterioles, and capillaries. Mediated by AQP4 on astrocytic endfeet, CSF crosses the glial limitans into the brain parenchyma, where it mixes with interstitial fluid (ISF) to form a CSF-ISF exchange fluid. This fluid exits via venous perivascular spaces in a "bulk flow" manner, also AQP4-dependent, and is ultimately cleared by dural lymphatic vessels into the peripheral lymphatic system. This pathway not only removes metabolic waste and abnormal proteins but also delivers nutrients and neuroactive substances such as glucose, lipids, and apolipoproteins to brain tissue [7]. The process is regulated by circadian rhythms and anesthesia, with glymphatic clearance peaking during sleep in mice [8], partially explaining the causal relationship between sleep disorders and dementias like Alzheimer' s disease (AD) [9]. Additionally, glymphatic dysfunction has been observed in central nervous system diseases including ischemic stroke, traumatic brain injury, and idiopathic normal pressure hydrocephalus [10-12].

1.2.1 Retrograde Pathway

As the optic nerve represents a direct extension of the central nervous system, both structures are surrounded by abundant subarachnoid CSF and encased in three meningeal layers (dura mater, arachnoid, and pia mater). The discovery of the brain glymphatic system prompted speculation that the retina and optic nerve might possess similar clearance pathways [13-14]. Yücel' s team [15-16] used in vivo hyperspectral imaging to demonstrate quantum dot tracers in submandibular lymph nodes after injection into both the anterior chamber and cisterna magna of mice. Wostyn et al. [17] injected India ink into the subarachnoid space of cadavers, observing ink accumulation in optic nerve perivascular spaces and collagen fiber bundles. In 2017, Mathieu et al. [18] provided the first evidence for a glymphatic pathway in the optic nerve: after injecting four sizes of fluorescein isothiocyanate (FITC) into mouse CSF, FITC molecules smaller than 70 kDa entered the optic nerve via perivascular spaces and reached the glial layer corresponding to the human lamina cribrosa. Jacobsen et al. [19] validated this pathway in vivo, showing CSF tracers injected into the subarachnoid space reaching perivascular spaces of the optic nerve, chiasm, tract, and primary visual cortex. Since this retrograde pathway does not extend to the optic disc, the authors suggested it may represent an extension of the brain glymphatic system rather than a distinct ocular pathway [18].

1.2.2 Anterograde Pathway

Aqueous humor circulation, the previously known intraocular fluid pathway, primarily includes the trabecular meshwork and uveoscleral routes. However, these pathways are confined to the anterior segment, making efficient clearance of metabolites from the metabolically active retina problematic. While anatomical evidence supported the existence of the aforementioned retrograde pathway [20], it failed to explain how waste products exit the eye. In 2020, Nedergaard et al. [2] discovered an anterograde glymphatic clearance pathway for Aβ in rodent eyes: driven by the trans-lamina pressure difference (TLPD) and pupil constriction, aqueous humor produced by the ciliary body mixes posteriorly with retinal ISF. This mixture travels along retinal ganglion cell (RGC) axons, traverses the lamina cribrosa, collects in perivascular spaces surrounding retinal veins, and is cleared from the optic nerve by dural lymphatic vessels. This entire process depends on AQP4 expressed on Müller cells and astrocytic endfeet, enabling anterograde clearance of neurotoxic substances like Aβ to maintain fluid balance and homeostasis in the retina and optic nerve [21]. The ocular glymphatic system mirrors the brain' s transport mechanism, with aqueous humor/CSF entering via arterial perivascular spaces, mixing with ISF, and exiting through venous perivascular spaces, ultimately converging in dural lymphatic vessels [22]. The lamina cribrosa serves as a critical hub and represents the most distinct difference from the brain system, as its deformation or defects may impair glymphatic clearance efficiency [23].

2.1 Glaucoma

The precise pathological mechanisms of glaucoma remain uncertain, though Aβ-induced optic nerve damage is considered a significant contributing factor. Excess retinal Aβ activates microglia-mediated neuroinflammation and induces RGC apoptosis [24], while $ 2-adrenergicreceptoragoniststhatinhibitA $ and its precursor protein APP significantly reduce RGC apoptosis, providing neuroprotection both in vivo and in vitro [25]. In the central nervous system, Aβ is cleared via the ubiquitin-proteasome pathway, autophagy-lysosome pathway, and blood circulation [26], with impaired clearance representing the fundamental cause of pathological Aβ accumulation. Ocular glymphatic dysfunction has also been implicated in excessive Aβ deposition in the retina and optic nerve [27-28].

Wostyn et al. [17] proposed that increased TLPD may cause transport blockade at the lamina cribrosa in primary open-angle glaucoma (POAG), with Aβ deposition near the lamina cribrosa contributing to optic nerve damage. Mathieu [27] observed tracer distribution in optic nerve cross-sections using confocal microscopy, finding significantly reduced concentration and distribution of 10 kDa dextran tracers in 10-month-old DBA/2J mice compared to age-matched controls. Half of these mice exhibited decreased phosphorylated neurofilament immunoreactivity associated with RGC axonopathy, suggesting that retrograde pathway obstruction reduces Aβ clearance and damages axons. Altered CSF hydrodynamics due to retrograde pathway obstruction may represent another pathogenic factor in glaucoma, as the difference between CSF production and outflow rates determines intracranial pressure (ICP). Lower ICP correlates positively with glaucoma incidence [29]; for instance, normal tension glaucoma (NTG) patients show smaller optic nerve subarachnoid space areas 3-7 mm posterior to the globe (indicating lower CSF pressure) [30].

Conversely, Nedergaard [28] argued that glaucomatous optic nerve damage results not from reduced Aβ clearance but from excessive and aberrant Aβ efflux, with defects in the lamina cribrosa representing the root cause. In normal mice, the lamina cribrosa transfers extracellular fluid anterior to it into RGC axons for directional anterograde transport. In DBA/2J mice, extracellular fluid leaks directly through lamina cribrosa defects, reducing normal glymphatic transport. Additionally, changes in the trans-lamina cribrosa pressure gradient (TLPG), defined as TLPD divided by lamina cribrosa thickness, may participate in glaucoma pathogenesis. Elevated TLPD, observed in multiple glaucoma types, causes mechanical damage to the optic disc and prelaminar neural tissue [31] while inducing posterior displacement of the anterior lamina cribrosa surface [32]. Compared to healthy individuals and ocular hypertension patients, NTG patients exhibit thinner lamina cribrosa with greater curvature [33].

2.2 Optic Disc Edema

Spaceflight-associated neuro-ocular syndrome (SANS) refers to optic disc edema, choroidal folds, and globe flattening caused by long-duration spaceflight, with over 15% of astronauts developing optic disc edema during or after missions [34]. The pathogenesis of SANS remains unclear, though some attribute it to bilateral optic nerve sheath distension and intracranial fluid shifts in microgravity [35]. The discovery of the ocular glymphatic system has revolutionized understanding of fluid and solute transport in the optic nerve, leading researchers to propose that astronaut optic disc edema may result from glymphatic dysfunction [36-37].

Wostyn et al. suggested that SANS-related optic disc edema may arise from retrograde CSF influx into the eye via the ocular glymphatic system [34]. The proposed mechanism involves microgravity-induced redistribution of intracranial fluids (including CSF) and altered optic nerve sheath anatomy and compliance, enabling CSF to enter the optic nerve via perivascular spaces surrounding the central retinal artery and infiltrate the prelaminar optic disc. A study investigating microgravity' s effect on ICP supported this concept, finding that spaceflight prevents the normal ICP reduction that occurs upon standing and maintains ICP values consistently higher than terrestrial measurements throughout 24-hour monitoring [38]. Considering TLPD' s driving role in glymphatic fluid transport, elevated ICP would accelerate CSF retrograde flow in the optic nerve, inducing optic disc edema—a conclusion consistent with these findings. Alternative theories propose that edema results from obstructed anterograde outflow of intraocular fluid along the optic nerve [34]. In microgravity, elevated ICP or CSF retention in the optic nerve subarachnoid space increases optic nerve sheath pressure, potentially reversing the normal TLPD and blocking intraocular fluid efflux, thereby causing optic disc edema. Studies on long-duration spaceflight and ocular structure found that microgravity-induced optic disc edema requires 30-90 days for peripapillary choroidal thickness to return to baseline [39]. Given that posterior ocular glymphatic clearance is far less efficient than anterior aqueous humor circulation [2], this may explain the slow resolution of optic disc edema post-flight. Anatomical evidence further validates this relationship, with MRI detecting increased perivascular space volumes in cerebral white matter and basal ganglia after spaceflight [40-41]. In summary, imbalance between fluid influx and efflux at the optic disc via ocular glymphatic pathways may provide novel insights into this condition. Future monitoring of optic disc structure using OCT and analysis of optic nerve/sheath morphology via MRI in astronauts may further elucidate the specific mechanisms and enable targeted therapeutic strategies to minimize unnecessary ocular damage during long-term space missions.

2.3 Terson Syndrome

Terson syndrome (TS) typically presents as vitreous hemorrhage associated with acute subarachnoid hemorrhage and ICP elevation, though hemorrhage may also occur beneath the internal limiting membrane, within the retina, or in the

subretinal space. The exact mechanism remains uncertain; the prevailing hypothesis suggests that acutely elevated ICP drives CSF into and expands the optic nerve sheath, mechanically compressing the central retinal vein and causing retinal vessel rupture. However, TS frequently presents unilaterally despite ICP acting bilaterally, highlighting limitations in this theory. The discovery of the ocular glymphatic system established the only known extracerebral anatomical channel between the subarachnoid space and retina, prompting proposals that blood may enter the eye via this pathway [42-43].

A 2007 case report first documented a TS patient whose preoperative CT showed subarachnoid hemorrhage, bilateral optic nerve sheath hemorrhage, and bilateral intraocular hemorrhage [44], suggesting intracranial blood transmission into the eye. To investigate TS histopathology, Ko et al. examined ocular histological sections from 109 TS patients, finding that intracranial hemorrhage extended continuously through the optic nerve, subdural, and subarachnoid spaces within the optic nerve sheath. Pre-retinal hemorrhages appeared diffuse, while sub-internal limiting membrane hemorrhages showed clear boundaries [45]. Subsequent T2-weighted MRI in a TS patient revealed subarachnoid hemorrhage entering both optic nerves, with high signal intensity indicating congestion and dilation of perivascular spaces around the central retinal vessels, leading authors to hypothesize that intracranial hemorrhage enters the sub-internal limiting membrane space via central perivascular spaces within the optic nerve sheath [46]. A 2014 case report further validated this hypothesis, suggesting that vitreal blood originates from the retinal vasculature or perivascular spaces, as diffusion within the retina is restricted [47]. The ocular glymphatic system concept corroborates these pathological findings, proposing that acute ICP elevation drives subarachnoid hemorrhage into the optic nerve via arterial and capillary perivascular spaces, with subsequent transmission into the retina and vitreous. Kumaria et al. reported a case of primary intraocular hemorrhage causing intraventricular hemorrhage, termed "reverse TS" [48]. The patient' s CT angiography demonstrated ocular blood entering the systemic circulation via perivascular spaces, consistent with glymphatic circulation. Additionally, reports of fluorescein angiography leakage sites near the retinal astrocyte basement membrane after vitrectomy [49-50] raise questions about the role of glial cells in the ocular glymphatic system, warranting further investigation.

2.4 Other Diseases

Age-related macular degeneration (AMD) may also involve ocular glymphatic system impairment. AMD shares features with glaucoma as a retinal degenerative disease, and both conditions exhibit Aβ and phosphorylated Tau (p-Tau) deposition, chronic inflammation, and iron homeostasis imbalance—pathologies also observed in AD [51]. Furthermore, aging impairs glymphatic clearance efficiency, representing a major risk factor for AMD [52].

AD and glaucoma also show considerable overlap [53], with both exhibiting Aβ and p-Tau deposition, synaptic dysfunction [54], RGC loss, and retinal nerve

fiber layer thinning [55]. The glymphatic system discovery establishes a novel connection between these diseases: AD pathological products (Aβ and p-Tau) are cleared via the brain glymphatic system [56-57], while perivascular space dilation impedes this clearance [58-59]. Consequently, researchers have suggested that AD and glaucoma may respectively reflect brain and ocular glymphatic system impairment [60], potentially reframing AD as a special form of ocular disease amenable to treatment via ocular glymphatic modulation.

3 Summary and Outlook

In summary, the discovery of the ocular glymphatic system introduces new possibilities for understanding the pathogenesis of glaucoma, optic disc edema, Terson syndrome, and other ocular diseases. Research on this system remains in its infancy, with limited evidence from case studies and animal experiments, leaving numerous questions unanswered. Whether ocular glymphatic dysfunction and Aβ deposition in glaucoma represent causally related events or parallel processes requires clarification, as do the specific roles of astrocytes, AQP4, and perivascular spaces. Given similar anatomical structures and physiological functions, current research primarily utilizes rodent models; however, non-invasive imaging studies in primates and humans are needed for deeper evaluation. Future identification of specific regulatory components in the ocular glymphatic system and targeted interventions to enhance its function and promote metabolic waste clearance may offer therapeutic hope for glaucoma and other ocular diseases, as well as certain central nervous system disorders.

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Conflict of Interest: The authors declare no conflicts of interest.

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Note: Figure translations are in progress. See original paper for figures.