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Review

Glymphatic Clearance Dynamics in Traumatic Brain Injury: Mechanisms, Imaging Biomarkers, and Application Prospects

Tao Yang[1], Yongxiang Yang[1], Mu Yuan[2], Xin Chen[1], Jingmin Cheng[1], Kexia Fan[1], Yuan Ma[1], Haifeng Shu[1], Sixun Yu[1,*]

[1]Department of Neurosurgery, Western Theater Command General Hospital, 610083 Chengdu, Sichuan, China
[2]Department of Hyperbaric Oxygen, Western Theater Command General Hospital, 610083 Chengdu, Sichuan, China
*Correspondence: bingyutian1982@126.com (Sixun Yu)
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Abstract

The pathological increase in brain catabolites after traumatic brain injury strongly correlates with a higher risk of neurodegenerative disease. This review examines the pathogenic role of glymphatic clearance dysfunction in that process. The glymphatic network enables cerebrospinal and interstitial fluid exchange and paracellular flow. These processes are mediated by astrocytic aquaporin-4. Glymphatic function is regulated by arterial pulsatility, sleep-wake cycles, and intramural periarterial drainage, with meningeal lymphatic vessels acting as the final drainage site. Mechanical trauma causes aquaporin-4 depolarization and mislocalization; it also triggers neuroinflammatory activation and blood-brain barrier disruption. These processes ultimately impair glymphatic function and neurotoxic proteins become more localized and overproduced. Previous studies have linked clearance defects to secondary neuron injury. Current evidence in humans has come mostly from pilot studies. Recent advances in neuroimaging provide new assessment tools. Dynamic contrast-enhanced magnetic resonance imaging (MRI) reveals delayed tracer clearance. Diffusion tensor imaging along perivascular spaces shows abnormalities in key parameters. These imaging findings preliminarily associate with fluctuations in cerebrospinal fluid catabolites. Therapeutic research suggests several reparative strategies. Physical exercise improves aquaporin-4 polarization integrity. Cannabidiol administration in experimental models increases meningeal lymphatic drainage and reduces tau pathology. Angiotensin II type 1 receptor antagonists may indirectly improve clearance by stabilizing the blood-brain barrier. Lymphatic pathways have been used as therapeutic targets for cannabidiol. Biological evidence also supports their role in traumatic brain injury progression. Further investigation is needed to validate whether these represent independent contributing processes. Multimodal imaging, novel biomarker assays, and chronobiological modulation strategies are improving visualization. Microfluidic modeling could clarify the glymphatic-biomarker relationship; it may also advance precision medicine approaches for traumatic brain injury.

Keywords: traumatic brain injury; glymphatic system; aquaporin-4; intramural periarterial drainage

1. Introduction

Traumatic Brain Injury (TBI) affects over 50 million individuals annually and represents a significant worldwide health burden [1–4]. Long-term neuropathological sequelae of TBI, such as chronic traumatic encephalopathy and Alzheimer's disease (AD), impose substantial socioeconomic costs [2,3,5]. As evidenced by clinical investigations, changes in cerebrospinal fluid (CSF) biomarker concentrations are directly associated with cognition deficits in months to years following moderate–severe TBI [4,6–11]. The exact mechanisms governing fluctuation in CSF biomarker levels remains incompletely understood. The majority of existing theories propose this fluctuation is caused by irregular production resulting from neuronal injuries, emerging evidence further reveal that deficits of neuronal clearance pathways may equally contribute to change in CSF biomarker levels [12–14].

As a main pathway for cerebral waste clearance, the glymphatic system maintains homeostasis through a tightly orchestrated, hierarchical mechanism. The glymphatic circulation initiates with arterial pulsations driving CSF influx along periarterial spaces into the brain parenchyma. Polarized aquaporin-4 (AQP4) channels distributed densely in the astrocyte endfeet mediate rapid CSF-interstitial fluid (ISF) exchange [8,13–18]. Following this exchange, metabolic waste products, such as β-amyloid (Aβ) and phosphorylated tau proteins (p-tau) are cleared from the brain via two different pathways. Primary drainage via perivenous spaces, with partial elimination through meningeal lymphatic vessels to deep cervical lymph nodes [15–17,19]. The complementary clearance pathway is the intramural periarterial drainage (IPAD) along vascular basement membranes. Efficiency of the glymphatic system is regulated by multiple physiological factors, including sleep-wake cycles, neurovascular coupling, and circadian regulation of AQP4 membrane trafficking [12,20]. Glymphatic dysfunction has been identified in AD and stroke models as a driver of Aβ plaque deposition and tau tangle formation, the extent to which glymphatic dysfunction influences the generation of peripheral

fluid biomarkers after TBI has not been adequately investigated [21–23].

This review introduces a novel glymphatic-biomarker axis model that unites the molecular, imaging, and clinical aspects to reveal the phenomenon of post-TBI clearance dysregulation, and reveals the molecular pathogenesis including different connected pathways and mechanisms. Mechanical shear forces in TBI disrupt astrocytic endfoot architecture, inducing AQP4 depolarization and mislocalization. Coexisting blood-brain barrier (BBB) damage will also promote extravasation of plasma proteins, forming unsoluble Aβ-protein aggregates to obstruct interstitial flow. Secondary neuroinflammation like NACHT, LRR and PYD domains-containing protein 3 (NLRP3)-caspase-1 mediated pyroptosis further degrades IPAD efficiency by impairing basement membrane integrity, creating a multi-hit clearance deficit. The clinical assessment of glymphatic function encompasses advanced neuroimaging techniques, including dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) and diffusion tensor imaging along the perivascular space (DTI-ALPS), which provide noninvasive evaluation methods. These complementary approaches allow for comprehensive characterization of glymphatic activity. DCE-MRI measures CSF-ISF exchange efficiency through gadolinium tracer kinetics, and DTI-ALPS evaluates interstitial flow dynamics by quantifying perivascular water diffusivity patterns. Both methods are associated with the extent of cerebrospinal fluid biomarkers for neurodegeneration, particularly Aβ and phosphorylated tau protein levels, suggesting their potential utility in clinical diagnostics and disease monitoring. Preclinical evidence supports several potential therapeutic interventions for modulating glymphatic dysfunction that have yielded promising findings. Aerobic exercise has been shown to enhance Aβ clearance through two distinct mechanisms: augmentation of arterial pulsatility and restoration of AQP4 polarization. Cannabidiol (CBD) can promote waste efflux via activation of meningeal lymphatic endothelial receptors. Angiotensin II Type 1 (AT1) receptor antagonists could protect the integrity of BBB by preserving tight junction proteins, thereby indirectly improve glymphatic flow. These interventions collectively address multiple aspects of glymphatic impairment, offering potential avenues for therapeutic development in neurodegenerative disorders.

2. Physiological Architecture and Dynamic Characteristics of the Glymphatic System

2.1 Definition and Structural Composition

The glymphatic system, a recently characterized intracranial clearance pathway, derives its nomenclature from the functional integration of glial cells and lymphatic-like drainage mechanisms [8,12,13,20,24–26]. This system drives uni-directional flow of CSF into the brain parenchyma via periarterial spaces, where astrocytic endfoot AQP4 channels mediate exchange with ISF [8,13,20,24–27]. Substantial AQP4-mediated paracellular flow within the interstitial fluid (ISF) contributes to the active clearance of metabolic waste products toward the venous drainage system [28,29]. These wastes are transported along perivenous pathways into meningeal lymphatics and deeper cervical nodes through meningeal lymphatics [12,16–19,30,31]. The polarized distribution of AQP4 on astrocytic vascular endfeet serves as the structural foundation of glymphatic dynamics [9,10,32–37]. This spatial arrangement, which is anchored on the vascular interface, engages in tripartite interactions with neurons and cerebral vasculature. It creates an exclusive brain-fluid microenvironment [12,38]. Beyond the classical glymphatic route, the IPAD pathway contributes significantly to interstitial solute clearance [16,32,36,39,40]. This alternative mechanism relies on the structural integrity of the vascular basement membrane, extracellular matrix composition, and the homeostasis of scaffolding proteins such as α-dystrobrevin [9,41,42]. Recent investigations have identified surfactant protein-G (SP-G) as a novel participant in CSF rheology and waste clearance [9]. SP-G exhibits co-localization with AQP4, glial fibrillary acidic protein, and platelet endothelial cell adhesion molecule-1 (PECAM-1) at perivascular and choroid plexus epithelial sites, suggesting its potential role in modulating glymphatic efficiency [9]. These findings allow us to add more specific molecular targets for the modulation of glymphatic functions.

2.2 Glymphatic Transport Dynamics

The kinetics of CSF-ISF exchange within the brain are driven mainly by physiologic forces. Mechanical factors including arterial pulsations from cardiac cycles, respiratory movements, and vasomotion collectively push CSF influx along periarterial spaces into the parenchyma, while perivenous spaces serve as efflux pathways for metabolic waste products [12,18,30,31,35,43]. Water transport occurs selectively through the interstitial space via highly specific AQP4 water channels, which are densely expressed in astrocytic end-feet enveloping the central nervous system vasculature [28]. The efficiency of this system exhibits marked state-dependent modulation. During sleep, the cerebral interstitial space undergoes transient expansion exceeding 30%, resulting in enhanced CSF influx and accelerated clearance of neurotoxic metabolites. Wakefulness is correlated with lower activity of the systemic circuit and reduced removal of the waste product [12]. Circadian rhythms show significant regulatory influence on both AQP4 polarization patterns and glymphatic flux [33,44,45]. Core clock genes and circadian signaling pathways modulate the subcellular localization and expression of AQP4 in astrocytic endfeet through complex molecular mechanisms, resulting in temporally stratified clearance efficiency that correlates with diurnal variations in cognitive performance observed in aged murine models [38,46–49]. The cerebral

surfactant protein SP-G demonstrates abundant expression in CSF outflow-associated structures. Its marked elevation in CSF from normal pressure hydrocephalus and central nervous system (CNS) infection cases suggests potential involvement in both cerebrospinal fluid rheology and immunoprotection, with positive correlation to total CSF protein levels reflecting dynamic alterations in CSF drainage under pathological conditions [9]. This leads to multifactorial processes that include not only bidirectional transport across the CSF-ISF exchange but also BBB function. Multiple related systems together function to preserve overall brain homeostasis through such multipoint flux dynamics [39].

2.3 Role of AQP4 and IPAD in Clearance Dynamics

Aquaporins (AQPs) constitute a family of integral membrane proteins initially characterized as passive channels dedicated to facilitating water movement across biological membranes, thereby playing an essential role in maintaining osmotic balance [50,51]. Over the last ten years, growing evidence has broadened the understanding of their functional diversity beyond mere water permeability [52–54]. In addition to water, certain AQPs, known as aquaglyceroporins, enable transmembrane passage of small neutral solutes including glycerol and various metabolites, linking them to metabolic and inflammatory pathways as well as diverse physiological processes such as renal water reabsorption, cerebral fluid dynamics, adipocyte-liver triglyceride flux, and ocular lens stability [53,55]. AQPs are also implicated in cellular volume regulation. Recent findings suggest their involvement extends beyond passive pore function to include potential roles in signal transduction, though the underlying mechanisms remain poorly elucidated. The concurrent expression of multiple AQP isoforms in many cell types raises the possibility of physical or functional interactions among different family members [50,51].

Despite being promising drug targets for conditions like cerebral edema, metabolic dysregulation, and impaired glymphatic clearance, no pharmacological agent targeting AQPs has achieved clinical approval to date [56–59]. The development of such therapies is hindered by the challenge of simultaneously addressing comorbid processes like edema and dysfunctional waste clearance with a single agent. As a result, the cooperative mechanisms between AQPs and other therapeutic targets remain an underinvestigated area deserving further exploration [54].

AQP4 is the primary aquaporin water channel expressed in the CNS, where it is highly enriched in astrocytic end-feet and serves as a key regulator of water homeostasis and glymphatic clearance. Its polarized localization on astrocytic endfoot membranes facilitates rapid water exchange between CSF and ISF, with its spatial distribution critically determining the directionality and efficiency of fluid transport [11,38,47,48]. MR imaging utilizing $H_2{}^{17}O$ as a tracer revealed a substantial bulk flow of ISF, facilitating significantly accelerated clearance of waste molecules from the parenchyma compared to purely diffusion-driven transport [28]. Experimental evidence demonstrates that AQP4-knockout mice exhibit markedly reduced CSF-ISF exchange efficiency, accompanied by impaired clearance of Aβ and p-tau, ultimately exacerbating neuropathological alterations [60]. Administration of an AQP4 inhibitor resulted in significantly delayed tracer imaging within the brain [28]. AQP4 dysfunction is manifested not only by alterations in protein expression levels but also by aberrant subcellular localization [61]. Dysregulation of glymphatic clearance has been linked to disrupted perivascular polarization of AQP4. In rodent models, the dynamic redistribution of AQP4 to both the blood-spinal cord and blood-brain barriers attenuates CNS edema and promotes functional recovery [29,62].

The IPAD pathway represents an alternative clearance mechanism that depends on the structural integrity of the vascular basement membrane and extracellular matrix [16,63,64]. Genetic ablation of α-dystrobrevin, a key scaffolding protein, not only disrupts AQP4 polarization but also induces vascular basement membrane remodeling. These changes lead to compromised IPAD efficiency, ISF accumulation, and protein deposition, thereby promoting cerebrovascular amyloid pathology [41]. Schematic patterns of glymphatic system is shown in Fig. 1.

Recent advances in microphysiological systems have enabled the development of "glymphatics-on-a-chip" platforms [47,65]. These *in vitro* models have validated the mechanistic link between neuroinflammation (e.g., lipopolysaccharide or Aβ oligomer exposure), extracellular matrix degradation, and impaired fluid transport under conditions of AQP4 inhibition. These technological advancements provide the necessary means to manipulate the AQP4 polarization and the reconstruction of the extracellular matrix in subsequent, forward-facing therapies [47]. These studies highlight the indispensable functional roles of both AQP4 and IPAD in regulating the cerebral clearance rate and they offer a theoretical groundwork on glymphatic dysfunction after TBI [47,65].

3. Manifestations of Glymphatic Dysfunction in Neurological Disorders

3.1 Glymphatic Dysfunction and Protein Aggregation in AD

A hallmark neuropathological feature of AD is cerebellar Aβ plaque deposit and neurofibrillary tangles constituted of p-tau which is the main mediator for neuronal degeneration. Currently growing evidence indicates that glymphatic impairment plays an important part in AD pathogenesis [15,16,26]. The tauopathies exhibit reduced CSF-ISF exchange efficiency and abnormal AQP4 polarity, and such functional disorders might induce faster aggregation of tau protein, as well as more rapidly transmit among

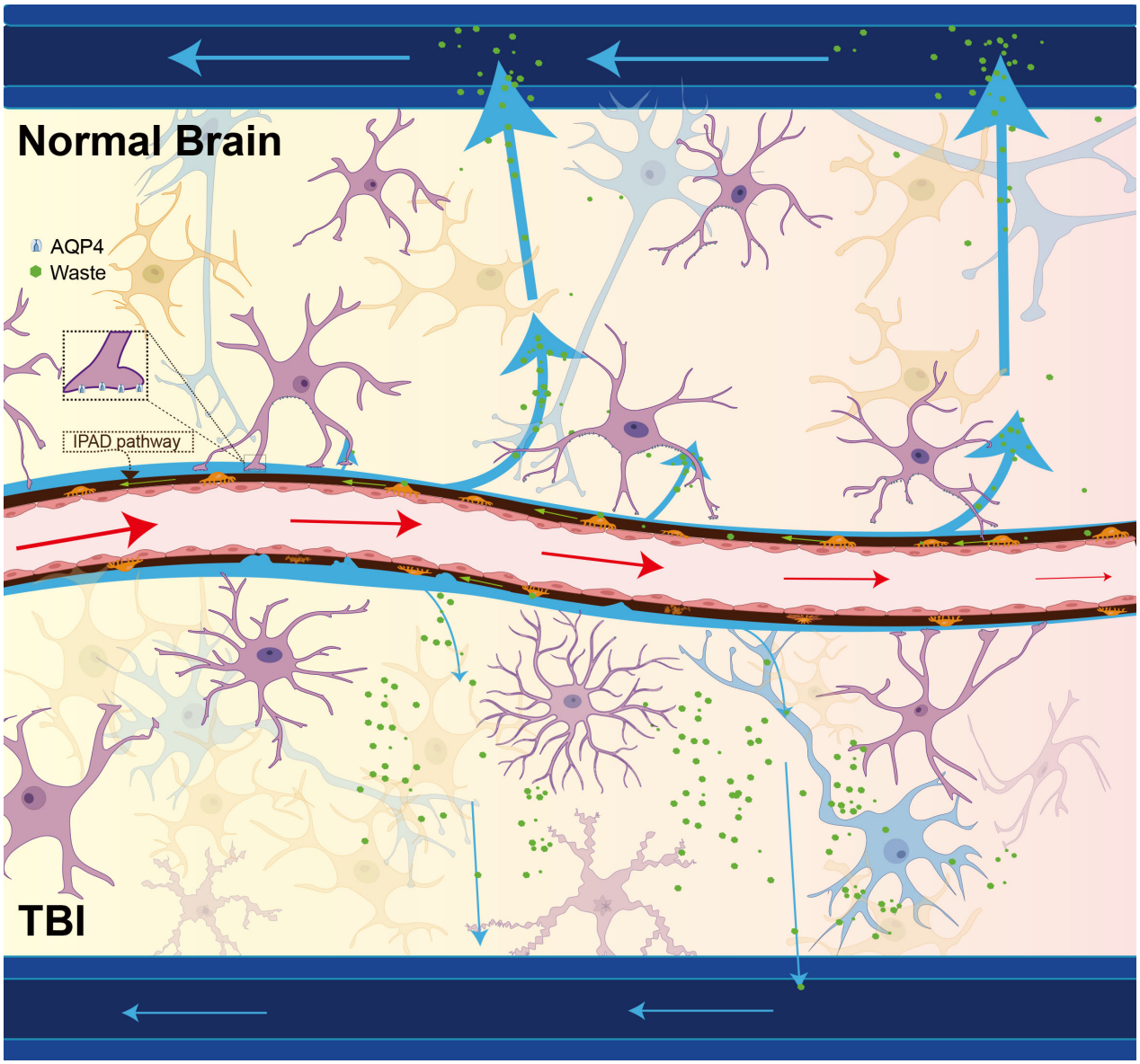

Fig. 1. Comparative schematic of the glymphatic system. The glymphatic system facilitates CSF circulation and interstitial waste clearance through a coordinated paravascular network. CSF originating from the subarachnoid space flows along periarterial channels into the brain parenchyma, driving bulk ISF movement toward perivenous drainage routes. Solutes and fluids subsequently exit through either SAS reabsorption or meningeal lymphatic vessel connected to cervical lymph nodes. A critical component of this pathway involves AQP4 water channels, densely clustered in astrocytic endfeet, which mediate efficient CSF-ISF exchange across paravascular spaces. This system primarily supports the clearance of metabolic byproducts, including lactate and soluble Aβ, thereby maintaining cerebral metabolic homeostasis. The IPAD system enables ISF efflux via capillary and arteriolar BM. TBI disrupts these clearance mechanisms through multiple pathological changes. Loss of AQP4 polarization severely impairs CSF-ISF exchange, leading to toxic metabolite accumulation. Meanwhile, structural damage to vascular BM, pericyte apoptosis, and reactive astrogliosis collectively obstruct interstitial drainage. The red arrows indicate the direction of arterial blood flow. The blue arrows indicate the direction of interstitial waste clearance. The green arrows indicate the direction of intramural periarterial drainage. CSF, cerebrospinal fluid; SAS, Subarachnoid space; AQP4, aquaporin-4; ISF, interstitial fluid; Aβ, β-amyloid; IPAD, intramural periarterial drainage; BM, basement membrane; TBI, traumatic brain injury. The figure was created with Adobe Illustrator (version 29.0).

neurons, thus aggravate neurodegenerative disease process and cognitive dysfunction [60,66].

Pharmacological studies using the selective AQP4 inhibitor TGN-020 have established the central importance of AQP4-mediated glymphatic flow in tau clearance [31,60,67]. TGN-020 has been proposed as a potential AQP4 inhibitor candidate. Huber *et al.* [68] demonstrated, through osmotic swelling assays in *Xenopus laevis* oocytes, that

this compound inhibits AQP4-mediated water transport in a dose-dependent manner. Experiments conducted in primary human and rat astrocytes have indicated a lack of AQP4 inhibitory activity, suggesting that its functional efficacy requires further investigation [69,70]. Experimental inhibition not only obstructs CSF-ISF exchange but also significantly reduces tau clearance rates, identifying this pathway as a potential therapeutic target [60]. The analysis of experiments that tracked the fluorescent label of tau injected into mouse brain *in vivo* provided a clear sign of glymphatic outflow path, and through the quantification of the data it was indicated that the outflow was reliant upon the function of AQP4, showing the exact steps needed to allow for the movement of tau and its removal [71].

Neuroinflammatory mediators such as Chitinase-3-like protein 1 (CHI3L1, commonly referred to as YKL-40), elevated in AD and other neuroinflammatory disorders, are secreted by activated astrocytes and may indirectly impair glymphatic waste clearance through Chemoattractant Receptor-Homologous Molecule expressed on T Helper 2 Cells (CRTH2) receptor-mediated suppression of neural stem cell β-catenin signaling, ultimately disrupting neurogenesis [11,15,34,72]. These findings establish a positive correlation between glymphatic dysfunction and Aβ/p-tau accumulation in AD, suggesting that therapies aimed at increasing AQP4 polarization and restoring CSF-ISF circulation may help to attenuate neurodegeneration [73].

3.2 Dysregulation of the Glymphatic System in Proteinopathies (SAH, PD, and Related Disorders)

Evidences implicate glymphatic dysfunction plays an important role in multiple protein aggregation disorders like subarachnoid hemorrhage (SAH) and Parkinson's disease (PD). In contrast to the initial view focusing only on alterations in Aβ and tau proteostasis via CSF analysis, numerous CSF protein biomarkers associated with pathways affecting glymphatic function have also been found in patient groups with decreased cerebrospinal fluid drainage, such as congenital hydrocephalus. Some cases have elevated levels of soluble amyloid precursor protein alpha (sAPPα), soluble amyloid precursor protein beta (sAPPβ), Aβ42 in CSF and lack apparent changes in the level of AQP4, suggesting a disequilibrium between CSF production and clearance is the fundamental pathophysiologic mechanism [6,16,40]. In PD and related movement disorders, the accumulation of neurotoxic proteins such as α-synuclein may be exacerbated by compromised glymphatic clearance. Current reviews highlight that the synergistic effects of AQP4 depolarization, neuroinflammation, and sleep fragmentation collectively promote cerebral protein accumulation, representing a potential final common pathway in neurodegenerative processes [16,74]. The functional roles of novel surfactant proteins (e.g., SP-G) in neuroinflammation and CSF rheology remain to be fully elucidated. Similar to conventional surfactant proteins (SP-A/B/C/D), these molecules may modulate CSF viscosity and flow dynamics at the molecular level, thereby influencing protein clearance kinetics [9]. The precise mechanisms of glymphatic function alteration in proteinopathic disorder cases still need more studies in detail [75].

3.3 Cerebrovascular Disorders and Glymphatic Dysfunction (Stroke, Cerebral Hemorrhage, and Hydrocephalus)

Cerebrovascular pathologies, including ischemia-reperfusion injury, post-stroke neuroinflammation, subdural hematoma, and intracerebral hemorrhage with consequent CSF pathway obstruction, consistently demonstrate glymphatic impairment accompanied by pathological accumulation of metabolic byproducts such as Aβ and p-tau [76]. Experimental investigations using middle cerebral artery occlusion/reperfusion (MCAO/R) models in rats reveal that pyroptosis-mediated neuroinflammatory responses not only compromise BBB integrity but also induce AQP4 mislocalization, resulting in cerebral edema and intraparenchymal aggregation of Aβ1–42 oligomers that exacerbate neuronal dysfunction [77]. Complementary multimodal studies combining dynamic contrast-enhanced MRI with immunofluorescence in rat thalamic secondary injury zones demonstrate synchronous peaking of contrast agent retention and amyloid precursor protein (APP) deposition at two weeks' post-stroke, coinciding with significant reduction in AQP4 polarization ratios. These findings establish that temporal deterioration of glymphatic function can be effectively monitored through advanced neuroimaging modalities [19]. Clinical analyses further identify sAPPα in congenital hydrocephalus patients' CSF as exhibiting exceptional diagnostic sensitivity (Area Under the Curve (AUC) = 0.99), confirming strong correlations between CSF protein composition alterations, ventricular dilation severity, and CSF drainage dysregulation. This biomarker profile provides valuable clinical chemistry parameters for evaluating glymphatic-CSF outflow capacity [6,78]. Edema formation following injury-induced hypoxia is AQP4-dependent and correlated with both an upregulation of total AQP4 expression and its subcellular translocation to the blood-spinal cord barrier (BSCB) [79]. Pharmacological inhibition of AQP4 translocation to the BSCB was shown to attenuate CNS edema and enhance functional recovery in injured rats. This role of AQP4 has been further corroborated by another study, which utilized a photothrombotic stroke model to show that targeting AQP4 effectively mitigates cerebral edema in the early acute phase of stroke [80]. Their study also revealed an associated alteration in brain energy metabolism, evidenced by elevated glycogen levels.

These observations indicate that the coexistent abnormality of glymphatic and BBB transport systems is the essential mechanism responsible for the buildup of pathological proteins in cerebrovascular disorders, while both neuro-

logical imaging and biochemistry play an essential role in diagnosis and prognosis.

4. Alterations in Glymphatic Function Following TBI

4.1 Alterations in Glymphatic Flux and AQP4 Polarization Following TBI

Mechanical shear forces and pressure waves induced by TBI trigger immediate astrocyte activation and loss of AQP4 polarization. Astrocytes play a complex and dual role in the progression of TBI, with their functions differing significantly between acute and chronic phases. During the acute phase, reactive astrogliosis primarily exerts protective effects. Activated astrocytes form a glial scar, referred to in the literature as the perilesional glial barrier, which sequesters the core injury area and confines the spread of damage and infiltration of inflammatory cells, thereby preserving surrounding healthy tissue. Astrocytes also contribute to the formation and regulation of cerebral edema through specific ion channels like AQP4 [79]. Although this activity may initially exacerbate cytotoxic edema, astrocyte activation and barrier formation are crucial for controlling subsequent secondary injury. During the chronic phase, the function of astrocytes is more contradictory: they maintain the activation and stabilization of the glial scar through long-term activity, thereby forming an obstacle to axonal regeneration and the recovery of neural circuits; yet, at the same time, it also has an impact on recovery in some active ways, including secretion of various neurotrophic factors. To promote neurogenesis and synaptogenesis, sustain angiogenesis, and aid in axonal remodelling, GDNF and VEGF stimulate additional factors, such as astrocytes. Through their effects on inflammation, cellular homeostasis, and the establishment of an appropriate environment for brain plasticity and repair, astrocytes ensure sufficient levels of GDNF and VEGF that facilitate these processes [79,81,82]. Experimental studies utilizing murine TBI models demonstrate significant reductions in parenchymal CSF-ISF exchange efficiency post-injury, accompanied by decreased polarized distribution of AQP4 at astrocytic endfeet membranes [44,83]. These pathological changes facilitate rapid cerebral accumulation of metabolic byproducts (including Aβ and tau species), subsequently exacerbating neuroinflammatory responses and cellular apoptosis [18]. Notably, TBI models employing AT1 receptor knockout mice exhibit preserved expression of BBB tight junction proteins (Occludin and ZO-1), restoration of AQP4 polarization, and concomitant reductions in both Aβ40 and Aβ42 levels [13,18,84,85]. These observations suggest that the adrenergic-angiotensin system modulates glymphatic functionality and exerts neuroprotective effects on post-TBI waste clearance [85]. The progressive actions of pyroptotic inflammation within secondary TBI pathogenesis merit special attention. Induced via NLRP3-caspase pathway engagement, this inflammatory response results in the simultaneous polarized depolarization of AQP4 and increased BBB permeability, leading to further obstructions for metabolic waste efflux [77].

It is clear that the outcomes can reveal possible impacts of post-TBI on various causes responsible for the glymphatic function disorders in general as well as present a basis for a targeted intervention to improve neurological outcomes after TBI. Besides, it has been demonstrated that the TBI affected clearance may involve neurovascular regulation and inflammatory pathways. Both seem essential elements of a treatment.

4.2 Mechanistic Interplay Between the BBB and Glymphatic System in TBI Pathogenesis

The BBB and the GL arranged for their separate but coordinated functions to accomplish the maintenance of neural homeostasis; however, a TBI would concurrently impair the BBB and GL despite their inherently divergent physiology. The TBI damages not only the tight junctional protein of the vascular endothelium (claudin-5 and occludin) in the BBB to increase its permeability, but also alters cerebral hemodynamics to decrease the glymphatic inflow driven by cardiac pulsation [39]. Extravasated blood components including albumin and hemoglobin infiltrate the interstitial compartment, triggering activation of neuroinflammatory cascades in astrocytes and microglia, and formation of persistent Aβ-protein complexes that obstruct interstitial channels and impair CSF-ISF exchange networks [86]. Genetic ablation studies using AT1 receptor knockout mice reveal a neuroprotective paradigm wherein BBB stabilization facilitates AQP4 repolarization at perivascular endfeet, partially restoring glymphatic flow and enhancing Aβ clearance—highlighting the therapeutic potential of combined BBB-glymphatic system protection [85].

The relationship between the BBB, iron deposition, and cognitive function is increasingly recognized as a critical axis in both neurodevelopmental and neurodegenerative processes. The BBB serves as a dynamic interface that regulates the exchange of substances between the blood and the brain, including iron, an essential element for neuronal metabolism, myelination, and neurotransmitter synthesis. Dysfunction of the BBB, through increased permeability or impaired water exchange, can lead to aberrant iron accumulation in susceptible brain regions such as the globus pallidus, substantia nigra, and thalamus [87,88].

Quantitative susceptibility mapping (QSM) studies reveal that iron deposition follows a region-specific trajectory, with rapid accumulation during early development and a plateau in later life. These iron dynamics are closely coupled to BBB function, as measured by techniques such as diffusion-prepared pseudo-continuous arterial spin labeling (DP-pCASL), which quantifies the water exchange rate across the BBB. This rate serves as a sensitive indicator of BBB efficiency, with lower values associated with

higher iron accumulation and potentially impaired clearance mechanisms [89].

In pathological contexts such as AD and cerebral small vessel disease, BBB breakdown facilitates the extravasation of neurotoxic substances promoting oxidative stress, neuroinflammation, and neuronal damage. The APOE ε4 allele, a major genetic risk factor for AD, exacerbates BBB dysfunction and iron deposition, further accelerating cognitive decline. Conversely, in early development, regulated iron transport via the BBB is essential for normal cognitive maturation, and disruptions in this process may contribute to neurodevelopmental impairments [90].

These pathophysiological insights demonstrate that optimal post-TBI metabolic clearance requires coordinated therapeutic strategies targeting both BBB integrity restoration and glymphatic pathway reconstruction, emphasizing the need for dual-system intervention approaches in clinical management.

4.3 Post-TBI Protein Accumulation and Neurodegenerative Risk

The pathological accumulation of metabolic byproducts following TBI represents a critical determinant of long-term neurodegenerative consequences [91]. Impaired fluid dynamics coupled with elevated Aβ and p-tau levels in both cerebrospinal fluid and interstitial compartments not only acutely compromise neuronal synaptic function but also induce sustained neuroinflammatory responses and glial activation, thereby potentiating the risk of developing AD-like pathology or chronic traumatic encephalopathy [18,92]. Beyond classical amyloid and tau pathology, astrocyte-derived secretory factors such as CHI3L1 demonstrate significant post-TBI elevation. These molecules may impair neural repair mechanisms by suppressing neural stem cell proliferation and differentiation, further compromising neuroregenerative capacity [15]. Concurrent activation of oxidative stress and pyroptotic pathways promotes the release of inflammatory mediators (caspases and IL-1β), which synergistically exacerbate the neurotoxic effects of Aβ and tau aggregates, establishing a self-perpetuating pathological cycle [77,93]. Discoveries made using models with simulated microgravity show that endogenous formaldehyde accumulated via plasma protein cross-linking leads to Aβ interstitial space obstruction; hence, environmental co-factors could contribute to continued post-TBI interstitial congestion, synergistically contributing to the pathological process [86,92]. The alterations in glymphatic function following TBI and the therapeutic interventions is shown in Fig. 2.

4.4 Advancements in Murine and Clinical Research

Preclinical investigations with murine TBI models indicated that CBD administration could enhance motor and cognitive recovery, accelerate cerebral tracer clearance, restore AQP4 polarization, and reduce p-tau/Aβ burden, suggesting therapeutic potential through glymphatic-lymphatic system modulation. All these beneficial effects disappeared when deep cervical lymphatics were ligated, providing definitive evidence for the essential role of the meningeal lymphatic network in CBD-mediated clearance enhancement [94].

Translational clinical studies employing DTI-ALPS have pioneered noninvasive glymphatic assessment in TBI patients. Initial correlational analyses reveal an inverse relationship between diminished ALPS indices and elevated CSF Aβ/tau concentrations, supporting the utility of this imaging biomarker for evaluating glymphatic clearance capacity [18]. Complementary DCE-MRI techniques quantitatively characterize glymphatic kinetics through contrast agent retention/clearance profiles, with methodology validation established in stroke models [19].

Even though existing clinical reports of accumulating evidence are currently few in number, such proof-of-concept studies lay an important groundwork for future multicenter clinical trials. Combining our preclinical mechanistic insights with the growing body of clinical biomarkers will continue to form the basis upon which we may provide disease-targeted interventions.

5. Aberrant Fluid Biomarkers in TBI and Their Association With Glymphatic Impairment

5.1 Clearance Kinetics of β-Amyloid and Phosphorylated Tau Proteins

The Aβ peptides and p-tau represent considerable fluid biomarkers of TBI-induced injury and subsequent axonal insult and deterioration that heavily depend on glymphatic pathways for cerebral clearance. Exercise interventions increase Aβ clearance rates with upregulated AQP4 and enhanced polarization efficiency while decreasing neuroinflammatory responses and restoring cognition deficits, irrespective of age-related change. However, no changes were noted for BBB permeability, suggesting specificity in the glymphatic mediations of Aβ clearance [37].

Limbrick *et al.* [6] reported in their clinical investigation elevated concentrations of CSF sAPPα, sAPPβ, Aβ42, p-tau in congenital hydrocephalus and postulated the increase in biomarkers as a consequence of CSF stasis and dysfunction of flow-out-of-cisterns. CSF stasis and inhibited flow lead to massive overproduction of CSF biomarkers, consistent with a previous report on TBI biomarkers [6]. Cutting-edge molecular biological approaches employing *in vivo* microinjection coupled with mass spectrometric detection have further validated tau transport through AQP4-dependent glymphatic routes into the CSF, enabling quantitative assessment of tau clearance kinetics via tracer methodology [71].

All these findings present a deeper understanding on how the glymphatic system is controlling the levels of certain proteins after TBI by regulating post-TBI changes in

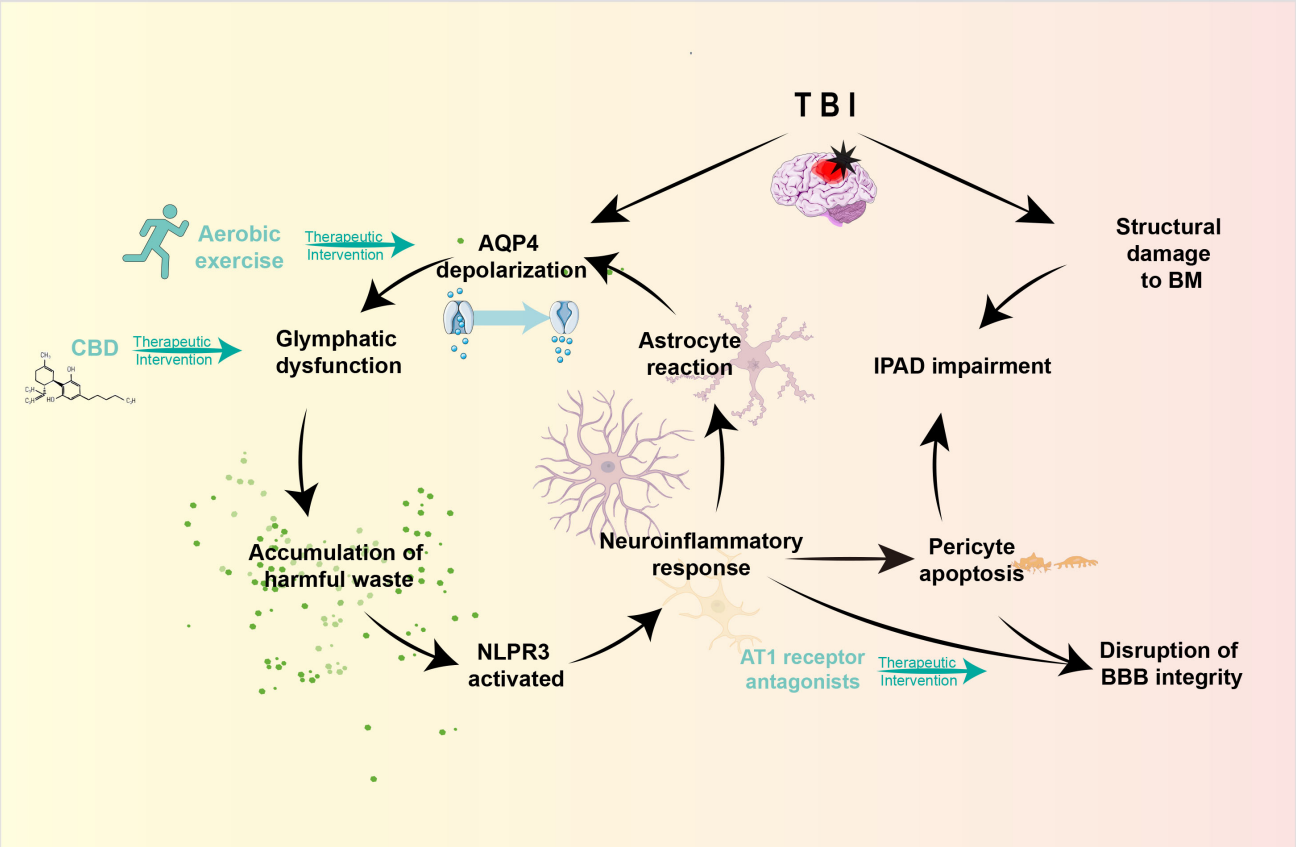

Fig. 2. The alterations in glymphatic function following TBI and the therapeutic interventions. TBI induces multifaceted pathological alterations that compromise both the glymphatic system and the IPAD pathway. The disruption of AQP4 polarization critically diminishes CSF-ISF exchange, resulting in the accumulation of neurotoxic metabolites and subsequent NLRP3 inflammasome activation. This neuroinflammatory cascade triggers reactive astrogliosis, which further exacerbates AQP4 depolarization. Concurrently, structural degradation of BM, pericyte loss, and reactive astrogliosis synergistically impede interstitial clearance. These pathological modifications establish a self-perpetuating cycle of dysfunctional waste clearance and sustained neuroinflammation, ultimately amplifying secondary injury progression post-TBI. NLRP3, NACHT, LRR and PYD domains-containing protein 3; BBB, blood-brain barrier. The figure was created with Adobe Illustrator (version 29.0).

Aβ or p-tau concentration, while simultaneously linking all evidence. The integrated collection of interventional, clinical, and molecular evidence supports a general unifying framework that describes how proteinopathies resulting from neural injury change over time.

5.2 AQP4 Expression, Polarization and Localization Dynamics

The water channel protein AQP4 serves as the principal molecular effector of glymphatic function, with its quantitative expression and polarized distribution directly governing CSF-ISF exchange efficiency. Aerobic exercise training has been shown to upregulate AQP4 expression while reorganizing its polarized orientation, thereby enhancing Aβ clearance capacity and attenuating astrocytic/microglial activation [37]. TBI and stroke models have both demonstrated decreases in polarized AQP4 localization at the endfoot membrane along with a corresponding shift towards diffuse cellular localization. This depolazised state correlates highly with neuro-inflammation and the pyroptotic pathway activation, which also contributes to basement membrane remodelling. All of this results in impaired glymphatic flux and an increased accumulation of metabolic waste products [19,77]. Clinical investigations have explored the diagnostic potential of AQP4-containing exosomes in CSF and plasma, with emerging evidence suggesting correlations between exosomal AQP4 levels and TBI severity/outcome measures. These findings support the development of AQP4 depolarization as a novel biochemical marker for TBI assessment. Recent mechanistic studies have identified the p38MAPK/NF-κB signaling pathway as a regulator of AQP4 expression and its co-localization with tight junction proteins (Occludin, ZO-1) in intestinal epithelial cells. This discovery provides new insights into the tissue-specific regulatory mechanisms of AQP4 dynamics [95]. It might be the future development of therapies altering glymphatic drainage that extend to multiple organs. Dysregulation of glymphatic clearance has been

linked to disrupted perivascular polarization of AQP4. In rodent models, the dynamic redistribution of AQP4 to both the blood-spinal cord and BBB attenuates CNS edema and promotes functional recovery [29,62]. Therapeutics targeting AQP4 subcellular localization can halt CNS edema in rats [79].

5.3 Alterations in Lysosomal-Associated Markers LAMP-1/2

The research into both lysosome-associated membrane proteins LAMP-1 and LAMP-2 in the field of neurodegenerative diseases and lysosomal storage disorders is very extensive. Little attention has been given to the assessment of glymphatic biomarkers following TBI [42,74]. Given the critical dependence of astrocytes and neurons on endosomal-lysosomal pathways for clearing both exogenous and endogenous protein aggregates, quantitative changes in LAMP-1/2 expression may serve as indicators of compromised intracellular degradative capacity. Such impairment could significantly influence the glymphatic system's ability to intercept and transport metabolic waste products to clearance pathways [42].

Future investigations should employ integrated methodologies combining ELISA-based quantification of CSF LAMP-1/2 levels with advanced neuroimaging techniques to elucidate their biological significance in post-TBI clearance dysfunction. This multimodal approach may reveal novel mechanistic insights into the dysregulation of protein homeostasis following neural trauma [17]. SP-G is postulated to reflect alterations in the extracellular matrix, while LAMP-1/2 is indicative of lysosomal function/autophagy activity. These emerging molecular biomarkers have the potential to complement and enrich the AQP4-centric framework from orthogonal perspectives. They may provide critical insights into distinct pathological processes, such as neuroinflammation and impaired protein degradation. Looking forward, it may be feasible to construct a multimodal biomarker panel that integrates AQP4 (water transport), neuroimaging (system-level function), and these molecular indicators (microscopic pathology), thereby enabling more precise disease subtyping and therapeutic target selection. The key molecules of glymphatic system and their functional consequences following TBI are summarized in Table 1.

6. Predictive Utility of DCE-MRI and DTI-ALPS for TBI Fluid Biomarker Concentrations

6.1 Quantitative Assessment of Glymphatic Function Using DCE-MRI Kinetics

Dynamic contrast-enhanced MRI enables real-time visualization and quantification of glymphatic fluid dynamics through sequential monitoring of contrast agent (Gd-DTPA) influx, retention, and clearance patterns in cerebral tissue [96]. As reviewed by Verheggen *et al.* [39], this technique provides critical metrics including CSF-ISF exchange rates and contrast retention duration, reflecting both arterial pulsation-driven flow and AQP4 functional status [97].

The experimental application on rodent models of ischemic stroke verifies that the DCE-MRI parameters undergo synchronous changes in association with the APP deposition in secondary thalamic infarcts, confirming the feasibility of utilizing this method to analyze the abnormal glymphatic function due to post-traumatic or vascular injuries [19,97]. Some preliminary studies applied DCE-MRI on the TBI population and found that compared to un-injured groups, both the lesioned and peri-lesional areas showed prolonged CSF clearance time which correlated with higher CSF Aβ and p-tau concentrations. Thus, DCE-MRI is highly suitable for identifying an altered glymphatic function after neural trauma [98].

6.2 Correlation Between DTI-ALPS Indices and Fluid Biomarkers

The DTI-ALPS approach is an objective method to quantify the glymphatic system by depicting the wa-

Table 1. Alterations in the expression of glymphatic system key molecules and their functional consequences following TBI.

Key molecules	Consequences following TBI	Influence on clearance efficiency	Interventions
AQP4	Depolarization and reduced expression	Impaired CSF-ISF exchange leads to pathological accumulation of metabolic waste products.	Aerobic exercise, CBD
LAMP-1/2	Lysosomal storage disorders	Compromised endosomal-lysosomal system leads to defective exogenous and endogenous protein aggregates clearance.	A potential candidate
SP-G	Elevated in CSF	Alterations in fluid rheological properties result in drainage resistance.	Uncertain
CHI3L1	Excessively released by activated astrocytes	Indirectly impair glymphatic waste clearance through CRTH2 receptor-mediated suppression of neural stem cell β-catenin signaling.	CRTH2/β-catenin signaling pathway antagonists

CBD, cannabidiol; LAMP, lysosome-associated membrane protein; SP-G, surfactant protein-G; CHI3L1, Chitinase-3-like protein 1; CRTH2, Chemoattractant Receptor-Homologous Molecule expressed on T Helper 2 Cells.

ter molecule diffusion pattern inside the peri-vessels and demonstrate the reduction of ALPS index after TBI presents strong inverse correlations with cognitive impairment and increased Aβ/tau species levels in CSF; meanwhile, the proposed method demonstrates excellent reproducibility, non-invasiveness and full-brain coverage [18]. Some preliminary validations have been performed on small TBI cohort that the association between the ALPS parameters and fluid biomarkers are consistent and robust, providing theoretical foundation for this non-invasive neuroimaging surrogate for assessing glymphatic function in different condition and pathological states [99].

6.3 Integrated Multimodal Neuroimaging Analysis

In order to cope with the inherent shortcomings of single-modality imaging techniques, researchers in today's era increasingly rely on multimodal neuroimaging. For example, there is a typical scheme that jointly employs kinetic parameters acquired from DCE-MRI and DTI-ALPS indices to evaluate the rates of contrast agent clearance and the flow of aqueous diffusion simultaneously [17,97]. This integrated approach, when correlated with multi-omics data including CSF/plasma concentrations of Aβ, p-tau, and AQP4-containing exosomes, yields a comprehensive assessment of glymphatic system functionality [17]. The primary challenges in translating DCE-MRI and DTI-ALPS into clinical practice include the need to standardize data acquisition and analysis protocols across different centers and scanner platforms, to improve technical reproducibility and standardization, and to establish normative values and diagnostic thresholds in large-scale, diverse TBI cohorts. It is essential to evaluate the specificity and sensitivity of these imaging techniques in distinguishing TBI from other neurological disorders, and to longitudinally correlate imaging findings with clinical outcomes, such as cognitive recovery. Considerations of accessibility and cost-effectiveness are critical to ensure that these advanced MRI sequences can be widely adopted and sustainably implemented in routine clinical settings. Future investigations should focus on validating the diagnostic and prognostic utility of such combined imaging protocols through large-scale multicenter studies. This effort will establish a robust dual-parameter biomarker system integrating neuroimaging and biochemical profiles to advance personalized therapeutic strategies for TBI management [32,35,99].

7. Therapeutic Interventions and Future Directions

7.1 Therapeutic Interventions Targeting Glymphatic Function: Exercise, Pharmacological and Molecular Approaches

Evidences show that glymphatic-targeted interventions improve the efficiency of waste clearance in TBI as well as other neuropathologies. Aerobic exercise changes both the cardiac-induced arterial pulsatility and AQP4 expression/repolarization to boost the CSF-ISF exchange and diminish the deposition and inflammation of Aβ, which confer cognitive protections on aging mouse models [37]. Given its exceptional safety profile, low cost, and broad health benefits, we consider it the most feasible strategy worthy of prioritization for large-scale clinical trials, particularly in the context of rehabilitation management. Therapeutic strategies targeting AQP4 relocalization demonstrate considerable potential. For instance, administration of trifluoperazine (TFP) to inhibit AQP4 relocalization has been shown to significantly ameliorate CNS edema in rat models [79,100,101]. The neuroprotective phytocannabinoid CBD exhibits multimodal therapeutic actions in TBI, including augmentation of meningeal lymphatic and glymphatic flow velocities, restoration of AQP4 polarization, and reduction of p-tau/Aβ burden. These mechanisms collectively improve motor and memory deficits, with complete abolition of therapeutic effects following cervical lymphatic blockade—confirming the essential role of the brain-lymphatic axis [94]. Molecular targeting strategies show particular promise, as demonstrated by AQP4 inhibitors regulating tau clearance in AD models, suggesting potential applications for modulating dysfunctional AQP4 in chronic TBI [60]. Despite encouraging preclinical results, clinical evidence remains preliminary. Complicated regulatory landscapes across regions, alongside unresolved issues related to dosing and standardization, suggest that CBD should be investigated at a later stage, following further resolution of these constraints. AT1 receptor antagonists preserve BBB integrity and restore glymphatic flow post-TBI, identifying novel pharmacological targets for post-traumatic waste clearance [85]. As approved antihypertensive agents with well-established safety profiles and substantial preclinical and emerging epidemiological evidence, these compounds present a clear translational pathway. Their strong supporting evidence justifies priority consideration for drug repurposing clinical trials. Interventions targeting the CHI3L1/CRTH2/β-catenin signaling pathway may dually modulate astrocytic function and neurogenesis, offering therapeutic potential for chronic neuroinflammatory conditions with impaired clearance [15]. These findings collectively establish a framework for developing precision therapies targeting glymphatic dysfunction across neurological disorders. The therapeutic strategies targeting the glymphatic system are summarized in Table 2.

7.2 Biomimetic Microfluidic Models for In Vitro Investigation of Glymphatic Dynamics

The development of microfluidic chip technology (glymphatics-on-a-chip) represents a significant advancement in elucidating the molecular regulatory mechanisms governing glymphatic system dynamics. These innovative platforms employ co-culture systems incorporating human astrocytes and cerebral microvascular endothelial cells to

Table 2. Therapeutic strategies targeting the glymphatic system and their priorities.

Interventions	Mechanisms	Preclinical findings	Clinical translation potential
Priority 1: Aerobic exercise	Augmenting arterial pulsatility Upregulated AQP4 expression Improved AQP4 polarization efficiency	Cognitive deficits improved and enhanced Aβ clearance rates in aged murine models	An effective prevention strategy in high-risk populations
Priority 2: T1 receptor antagonists	Preserve BBB integrity Restore glymphatic flow	AT1 receptor knockout mice exhibit preserved expression of BBB tight junction proteins, restoration of AQP4 polarization, and concomitant reductions in both Aβ40 and Aβ42 levels	A new indication for an established drug with a favorable safety profile
Priority 3: CBD	Augmentation of meningeal lymphatic and glymphatic flow velocities Restoration of AQP4 polarization Reduction of p-tau/Aβ burden	Enhances motor and cognitive recovery in TBI rat	Phase I clinical trial is currently in progress

accurately simulate CSF-ISF flow dynamics [102]. Experimental validation using this model has demonstrated the dual effects of LPS, Aβ oligomers, and AQP4 inhibitors on both fluid transport pathways and Aβ clearance efficiency. Flow resistance increased in cells following LPS treatment even after cell lysis, indicating that both matrix degradation and cell-dependent clearance mechanisms might coexist simultaneously [47]. When integrated with experimental TBI paradigms, such microfluidic systems enable precise modulation of injury severity, inflammatory status, and AQP4 polarization patterns *in vitro*. This technological approach establishes a high-throughput, cost-effective platform for subsequent pharmacological screening and pathological mechanism investigation, offering substantial advantages over conventional *in vivo* models.

7.3 Chronobiological Rhythms and Sleep Modulation of Glymphatic Function

Research on the circadian regulation of glymphatic activity suggests that good sleep quality and circadian rhythms stabilization may be alternative ways to improve post-TBI metabolic clearance without pharmaceutical intervention. Chronic sleep-deprivation animal models reveal much higher nocturnal AQP4 polarization and glymphatic clearance capacity than those during daytime [103]. Sustained sleep limitation annihilates this circadian difference with correspondingly high brain Aβ1–42 and p-tau accumulation leading to accelerated cognitive deterioration, which underpins the need to preserve normal sleep wake cycles to ensure physiologically normal clearance kinetics [46].

7.4 Future Directions

Advancing investigations should focus on multidimensional data integration (incorporating neuroimaging, CSF/plasma biomarkers, and genomic profiles) to establish international consensus standards for the glymphatic-biomarker axis, facilitating early TBI diagnosis and precision therapeutics. Beyond AQP4, emerging molecular targets including surfactant protein SP-G, CHI3L1, and LAMP-1/2 may expand both diagnostic and therapeutic landscapes [9,42,102,104]. Multifactorial studies incorporating microgravity simulation and environmental stressors will elucidate complex endogenous/exogenous influences on glymphatic function. Ultimately, interdisciplinary collaboration will prove pivotal in transforming fundamental discoveries into innovative clinical management strategies for neural trauma and related disorders.

8. Conclusion

We present glymphatic dysfunction as an important pathologic feature observed after TBI in post-TBI biomarkers for development of TBI precision therapies, and propose the foundations of chronotherapeutic targeting to restore glymphatic function clearance. Continued investigation regarding multimodal biomarker validation is needed along with investigation of chronotherapeutic interventions aimed at maximally enhancing glymphatic function.

Author Contributions

TY and SY conceptualized the study, established the research framework, and coordinated the project. YY conceived the review topic, provided overall supervision and guidance, and critically revised the manuscript for important intellectual content. YM and MY contributed to the conceptualization and scope of the review, and designed the literature search and synthesis strategy. JC and XC conducted the literature review and drafted the initial manuscript. TY played a leading role in manuscript writing and was responsible for figure preparation and visualization. HS contributed to data interpretation from in-

cluded studies and assisted in manuscript revision and final editing. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

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