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Review

Targeting Meningeal Lymphatic Vessels to Advance Stroke Therapy

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ABSTRACT: Meningeal lymphatic vessels (mLVs) have recently emerged as pivotal regulators of central nervous system homeostasis, orchestrating cerebrospinal fluid (CSF) drainage, metabolic waste clearance, and neuroimmune surveillance at the brain and meningeal interface. Stroke, ischemic or hemorrhagic, exerts profound functional insults on mLVs, disrupting clearance pathways. These disturbances not only exacerbate acute edema and neuroinflammation but also dictate long-term outcomes, including post-stroke cognitive decline. In this review, we synthesize current understanding of mLVs anatomy and physiology, emphasizing their dynamic remodeling after stroke. We further examine the context-dependent immune functions of mLVs, and their role in shaping post-stroke brain injury and repair. In addition, we discuss emerging therapeutic strategies targeting the glymphatic–lymphatic axis and outline key translational challenges. Although these findings support a framework in which impaired fluid clearance contributes to stroke pathophysiology, most mechanistic insights derive from preclinical models, and direct evidence in human stroke remains limited. Accordingly, therapeutic implications should be interpreted with caution and require rigorous clinical validation.

Keywords: meningeal lymphatic vessels, stroke, CSF clearance, neuroimmune regulation, therapeutic strategies

1. Introduction

Stroke comprises a heterogeneous group of acute cerebrovascular syndromes caused by either obstruction (ischemic stroke) or rupture (hemorrhagic stroke) of cerebral blood vessels and remains a leading cause of mortality and long-term disability worldwide [1]. Over the past two decades, advances in neuroimaging, endovascular thrombectomy, and neurocritical care have substantially reduced early mortality. However, long-term functional recovery remains limited. This discrepancy highlights fundamental gaps in our understanding of stroke pathophysiology and the limitations of current therapeutic paradigms.

In recent years, the brain's fluid clearance systems have emerged as critical yet underappreciated contributors to stroke pathophysiology [2-4]. Traditionally considered devoid of a conventional

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lymphatic vasculature, the central nervous system (CNS) is now recognized to harbor at least two complementary clearance pathways: the glymphatic system and mLVs [4-8]. The glymphatic pathway facilitates the exchange of cerebrospinal fluid (CSF) and interstitial fluid (ISF) through periarterial (Virchow–Robin) spaces lined by astrocytic endfeet enriched with aquaporin-4 (AQP4) water channels, thereby promoting the clearance of solutes and metabolic waste from the brain parenchyma [3, 9]. Concurrently, mLVs located in the dura mater transport CSF, ISF, and immune cells from the subarachnoid and meningeal compartments to the deep cervical lymph nodes (dCLNs), establishing a direct anatomical and functional conduit between the CNS and the peripheral immune system.

Accumulating evidence indicates that both the glymphatic system and mLVs become profoundly dysfunctional following stroke [10-16]. Experimental studies demonstrate that impaired glymphatic and meningeal lymphatic function after stroke leads to the accumulation of neurotoxic metabolites, amplification of neuroinflammation, and inefficient resolution of cerebral edema [15, 17, 18]. These observations support an integrative framework in which stroke is understood not only as a consequence of vascular occlusion or hemorrhage, but also as a “clearance failure syndrome” characterized by disrupted CSF circulation and lymphatic outflow. Within this framework, the lymphatic axis encompassing glymphatic influx, mLVs-mediated drainage, and dCLNs outflow, serves as a key interface linking central nervous system injury with peripheral immune responses. However, the molecular and cellular mechanisms by which lymphatic dysfunction regulates neuroinflammation, immune remodeling, and vascular repair after stroke remain incompletely defined.

In this review, we synthesize recent advances defining the roles of mLVs in CSF clearance and immune surveillance, with particular emphasis on their control of post-stroke neuroimmune responses and vascular remodeling. By consolidating evidence from glymphatic-lymphatic biology, neuroimmunology, and translational stroke research, we present a cohesive framework that reframes stroke pathophysiology as a “clearance failure syndrome” and highlights emerging therapeutic strategies. We further discuss the principal barriers to clinical translation and outline priorities for future investigation.

2. Search Strategy

This review provides a narrative synthesis of the literature informed by a structured but non-systematic search of published studies. Relevant articles were identified through electronic searches of the PubMed database, focusing on publications from January 2007 to December 2025. The search strategy combined Medical Subject Headings (MeSH) terms and free-text keywords, including mLVs, glymphatic system, CSF, waste clearance, stroke, ischemic stroke, subarachnoid hemorrhage (SAH), traumatic brain injury (TBI), aging, tumor, neuroinflammation, neurodegenerative diseases, imaging techniques, therapeutic targets, and cognitive function. Boolean operators (“AND” and “OR”) were applied to broaden or refine the search as appropriate.

Study selection was guided by relevance to the scope of this review. We prioritized original research articles and review papers addressing (i) the structure, function, and regulatory mechanisms of meningeal lymphatic vessels and/or the glymphatic system, and (ii) therapeutic strategies targeting lymphatic function in ischemic stroke or SAH. Studies from related neurological conditions, including traumatic brain injury and neurodegenerative diseases, were also considered when they provided mechanistic or translational insights relevant to cerebrovascular pathology. Studies were excluded if they did not address lymphatic or glymphatic biology or lacked relevance to regulatory or therapeutic mechanisms. In addition, reference lists of selected articles were examined to identify further relevant studies. Notably, the majority of included literature has been published since 2020, reflecting the rapid expansion of this field.

3. The Discovery and Structure Organization of mLVs

For decades, the brain was regarded as an “immune-privileged” organ devoid of conventional lymphatic drainage [19, 20]. This concept originated from classical anatomical studies and the prevailing belief that the CNS is strictly segregated from the peripheral immune system [21,22]. Nevertheless, historical observations occasionally suggested the presence of lymphatic-like structures within the cranium. In the 17th century, Thomas Bartholin described ambiguous “lymphatic” features in the head, and in 1787, Paolo Mascagni illustrated meningeal vessels resembling lymphatics [22-25]. These early findings were largely overlooked, and by the late 19th century, prominent anatomists such as Gustav Retzius and Alfred Key explicitly rejected the existence of lymphatic vasculature in the brain, reinforcing the long-standing dogma that the CNS lacks lymphatic vessels [26, 27].

This paradigm began to shift in the early 21st century with renewed interest in CSF dynamics and brain waste clearance, particularly following the discovery of the glymphatic system [5, 28-32]. The definitive breakthrough occurred in 2015, when two independent groups, one led by Kipnis at the University of Virginia, and the other by Alitalo in Finland conclusively demonstrated the presence of functional lymphatic vessels in the meninges. Using whole-mount immunostaining of the dura, transgenic mouse models, and advanced confocal and two-photon microscopy, they identified lymphatic vessels lining the dural sinuses of adult mice. These vessels expressed canonical lymphatic endothelial markers such as LYVE-1 and PROX1 [33-35], confirming their identity as bona fide lymphatic structures. Importantly, unlike most peripheral lymphatic vessels that form during embryogenesis, mLVs develop predominantly in the postnatal period [8, 36, 37]. The rediscovery of mLVs fundamentally reshaped our understanding of CNS physiology by providing a mechanistic explanation for how the brain communicates with the peripheral immune system and clears metabolic waste. This landmark finding has since catalyzed extensive investigation into mLVs development, neuroimmune interactions, and their roles in neurological disorders (Fig. 1).

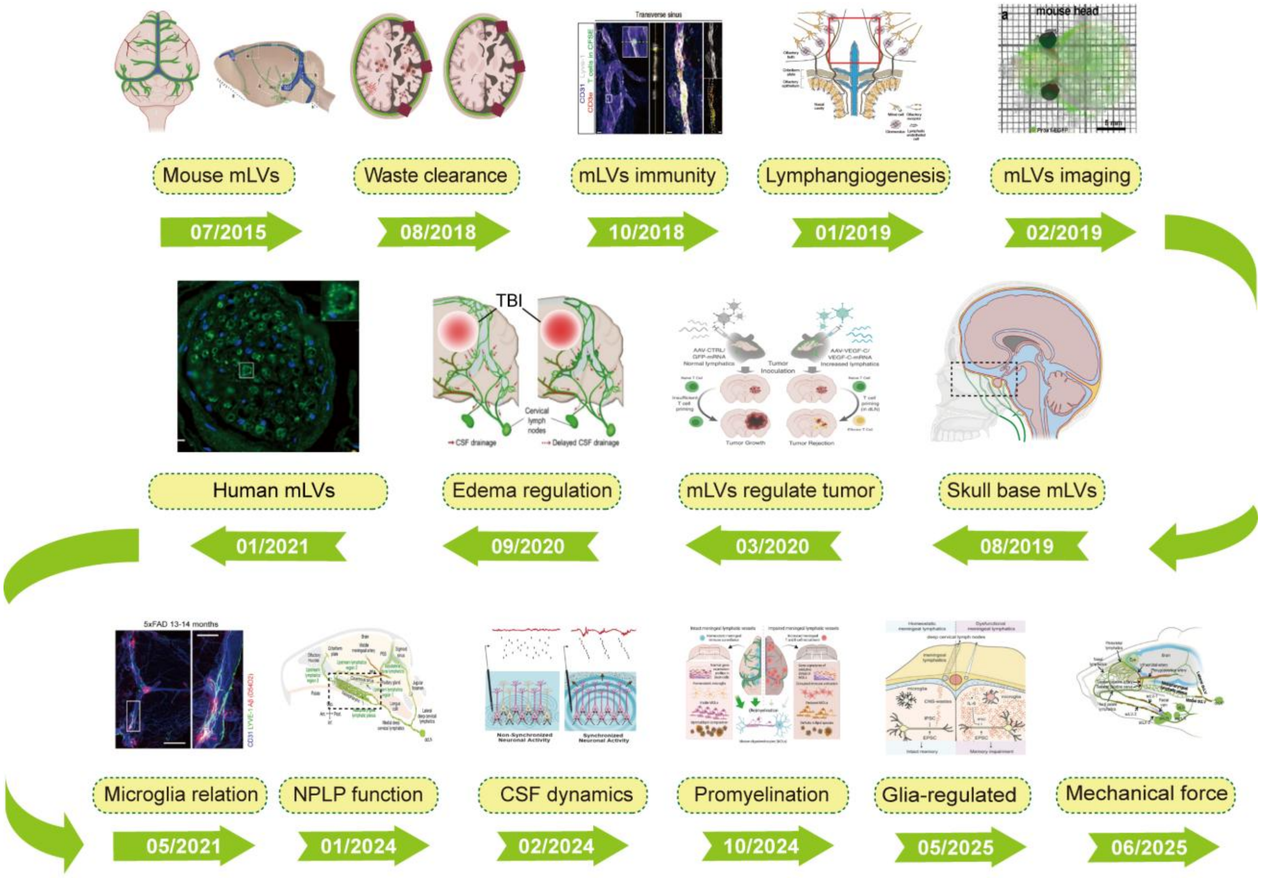

Figure 1. Timeline of major milestones in the discovery and functional characterization of meningeal lymphatic vessels (mLVs) and meningeal lymphatic drainage in the central nervous system (CNS). 07/2015, lymphatic vessels in the CNS discovered [6, 7]; 08/2018, mLVs-mediated waste clearance declines in Alzheimer's disease and aging [85]; mLVs regulate CNS immune drainage and inflammation [122]; 01/2019, neuroinflammation triggers meningeal lymphangiogenesis that enhances CNS drainage [261]; 02/2019, imaging reveals skull–meningeal connections in mice [262]; 08/2019, mLVs drain CSF at the skull base [39]; 03/2020, mLVs regulate drainage and antitumor immunity in brain tumors [44]; 09/2020, mLVs dysfunction worsens outcomes after traumatic brain injury [143]; 01/2021, human brain exhibits lymphatic pathways communicating with the periphery [263]; 05/2021: mLVs modulate microglia and responses to anti-Aβ immunotherapy [125]; 01/2024, nasopharyngeal lymphatic plexus (NPLP) regulates CSF drainage during aging [264]; 02/2024, neuronal activity drives meningeal-lymphatic-mediated brain clearance [265]; 10/2024, dysfunctional mLVs impair brain myelination and immunity [266]; 05/2025, dysfunctional mLVs disrupt synapses via microglial IL-6 signaling [126]; 06/2025, noninvasive cervical lymphatic manipulation enhances CSF drainage [267]).

3.1 The Anatomical Structure and Molecular Characteristics of mLVs

The mLVs are primarily located within the dura mater, the outermost meningeal layer, and exhibit a distinctive and highly organized anatomical architecture [8, 38]. Broadly, mLVs can be categorized into two major networks: a dorsal (parasagittal) network and a basal (skull base) network, each following distinct anatomical trajectories [39, 40].

The dorsal mLVs network runs along the superior sagittal and transverse sinuses, forming a linear plexus that drains CSF and ISF toward the dCLNs [41-43]. Experimental studies have demonstrated that surgical or genetic ablation of dorsal mLVs in mice markedly impairs CSF outflow and reduces dendritic cell trafficking to the dCLNs, thereby compromising CNS immune surveillance [40, 44]. These findings underscore the critical role of dorsal mLVs in mediating communication between the CNS and peripheral immune compartments. In contrast, basal mLVs course along meningeal arteries, including the middle meningeal artery, and connect to lymphatic outlets at the skull base [39, 45]. Owing to the anatomical complexity of the skull base, characterized by multiple foramina and densely packed neurovascular structures, the precise organization and functional significance of basal mLVs remain less well defined, particularly under pathological conditions involving extracranial compartments [46-48]. Recent work by Jacob et al. expanded this framework by identifying an anterior meningeal lymphatic vascular complex (aMLVC) surrounding the cavernous sinus [38]. The aMLVC appears to integrate dorsal and basal lymphatic networks, with branches aligned along skull base foramina and meningeal fissures, highlighting the highly interconnected and compartmentalized nature of meningeal lymphatic architecture. More recently, Zhao et al. reported the unexpected identification of a complete lymphatic network within the synovium of the temporomandibular joint (TMJ) [49]. Given the anatomical proximity of the TMJ to the skull base [50], this finding raises the intriguing possibility that TMJ-associated lymphatics may serve as an accessory route for cranial lymphatic drainage, potentially augmenting meningeal lymphatic outflow toward the cervical lymph nodes and expanding the recognized pathways for CSF and ISF clearance.

Structurally, mLVs exhibit several distinctive features compared to peripheral lymphatics [6]. Unlike collecting lymphatics in other tissues, they lack well-defined intraluminal valves, suggesting that fluid transport depends largely on extrinsic forces rather than intrinsic valve-mediated propulsion [43, 51-55]. Consistent with this property, mLVs also lack a surrounding smooth muscle cell layer and therefore do not exhibit autonomous contractility [55, 56]. Instead, lymphatic flow within mLVs is driven predominantly by external physiological forces, including sympathetic nervous system activity (e.g. norepinephrine tone), cardiac pulsatility, respiration-related intracranial pressure fluctuations, and sleep-associated brain oscillations [20, 57-61].

Table 1. Markers of the Meningeal Lymphatic System.

Gene Symbol	Illustration	Specialty	Reference
Prox1	Key transcription factors in lymphatic endothelial development	**High**	[229]
Vegfr3	Vascular endothelial growth factor receptor	**High**	[230]
Kdr	Vascular endothelial growth factor receptor	**Low**	[231]
Lyve1	Scavenger receptor that binds chylomicrons	**High**	[232]
Cspg4	Proteoglycans are expressed in immature and proliferative vascular endothelial cells	**Low**	[233]
Ccl21	Chemokines, which attract lymphocytes into the perilymphatic tissues	**Medium**	[234]
Vegfc	Ligand/receptor systems that promote lymphatic vessel development and function	**Low**	[235]
Aqp1	Aquaporins, involved in the transmembrane transport of water molecules	**Low**	[236]
Cd11b	Members of the integrin family, expressed in immune cells	**Low**	[237]

At the cellular level, meningeal lymphatic endothelial cells (LEC) express canonical lymphatic markers such as PROX1, VEGFR3, LYVE-1, podoplanin (PDPN), and CCL21, confirming their lymphatic identity and functional resemblance to peripheral lymphatic endothelium [62-64](Table 1). However, their junctional architecture is distinct: rather than the continuous "zipper-like" junctions characteristic of collecting lymphatics, meningeal lymphatic endothelial cells form discontinuous "button-like" junctions [65-67]. This specialized configuration, similar to that observed in initial lymphatic capillaries, facilitates the efficient entry of CSF macromolecules, immune cells, and particulate waste into the lymphatic lumen from surrounding meningeal and subarachnoid compartments. Additionally, the basement membrane of mLVs is thinner and more discontinuous than that of peripheral lymphatics [39, 67], further reflecting their specialization for fluid exchange and immune surveillance.

3.2 The Development of mLVs

The developmental origin of lymphatic vessels has been debated for more than a century. Early anatomical studies proposed two competing hypotheses: the venous origin theory, which posited that lymphatic vessels arise through sprouting from embryonic veins [68, 69], and the mesenchymal origin theory, which suggested that LECs differentiate from isolated mesenchymal progenitors that subsequently connect to the venous system [70, 71]. This longstanding controversy was largely resolved with the advent of genetic lineage-tracing approaches. In a landmark study, Srinivasan et al. employed a Prox1-CreERT2 lineage-tracing mouse model to demonstrate that the majority of peripheral LECs originate from venous endothelial cells during embryogenesis [69, 72]. Specifically, PROX1-expressing venous endothelial cells bud from the cardinal veins to form primitive lymph sacs, which subsequently expand and sprout to generate the peripheral lymphatic network [70]. Human embryological studies further corroborated this paradigm, establishing PROX1 as a master regulator of the endothelial-to-lymphatic cell fate transition [73-75]. Collectively, these findings support the prevailing view that most peripheral lymphatic vessels derive from a venous lineage.

In contrast, the developmental program governing mLVs remains incompletely defined. Unlike peripheral lymphatic vessels, which are largely established by the end of embryogenesis, mLVs emerge predominantly during the postnatal period. Antila et al. reported that mLVs structures first become detectable around the second postnatal week in mice, initially appearing near the foramen magnum and along exiting cranial and spinal nerves [73]. From these entry points, lymphatic vessels progressively extend to populate the cranial meninges. This delayed, postnatal development distinguishes intracranial lymphatics from their peripheral counterparts and raises unresolved questions regarding their progenitor origins. Whether mLVs arise from venous endothelial cells, similar to peripheral lymphatics, or instead originate from a distinct pool of local progenitors remains unclear. Current evidence suggests that meningeal LECs may derive from specialized vascular niches or progenitor populations activated after birth [71]; however, definitive lineage-tracing studies are still required to resolve this issue [70].

The VEGF-C/VEGFR3 signaling axis is indispensable for the growth and maintenance of mLVs [76]. Genetic deletion of VEGF-C or VEGFR3, pharmacological inhibition using VEGFR3 tyrosine kinase inhibitors (e.g., sunitinib), or sequestration of VEGF-C/D via soluble trap receptors consistently results in regression of mLVs and impaired meningeal lymphatic drainage [76-78]. Conversely, exogenous delivery of VEGF-C into the CSF has been shown to induce robust meningeal lymphangiogenesis, promote vessel expansion, and enhance CSF clearance [79, 80].

Beyond endothelial-intrinsic programs, neuroglial–stromal interactions play a critical role in mLVs development. Li et al. recently identified a glia-to-LEC signaling axis operative during the neonatal period [81]. In this study, astrocyte-derived VEGF-C, acting in concert with CCBE1 secreted by meningeal fibroblasts, a cofactor essential for VEGF-C proteolytic maturation, was required for proper LEC growth and vessel patterning. Disruption of either astrocytic VEGF-C production or fibroblast-derived CCBE1 markedly impaired mLVs development, underscoring the importance of coordinated neuroglial, stromal crosstalk in synchronizing lymphatic growth with postnatal brain maturation.

4. Interface Between mLVs and CNS Drainage Pathways

Structurally and functionally, mLVs are interconnected with multiple clearance and communication pathways, including the glymphatic system, arachnoid granulations (AGs), and dCLNs. Together, these systems coordinate the removal of interstitial solutes, facilitate immune cell trafficking, and preserve CNS homeostasis.

4.1 Glymphatic System

The glymphatic system is a brain-wide perivascular pathway that mediates CSF–ISF exchange and works in close coordination with mLVs to support metabolic waste clearance from the CNS [82, 83]. In this pathway, CSF from the subarachnoid space enters the brain parenchyma along periarterial (Virchow–Robin) spaces [84]. Within the parenchyma, CSF mixes with ISF and drives the convective clearance of extracellular solutes, including neurotoxic proteins such as amyloid-β [85, 86]. The waste-laden fluid subsequently travels along perivenous pathways and re-enters the subarachnoid space. MLVs located in the dura mater function as the primary exit route for glymphatic outflow [38] . They absorb CSF–ISF solutes together with CNS-derived antigens, extracellular vesicles, and immune cells from the subarachnoid and perivascular compartments and transport them toward the dCLNs [83]. Although no direct anatomical conduit exists between the subarachnoid space and the lymphatic lumen, the functional coupling of glymphatic influx and mLVs-mediated efflux establishes a continuous clearance axis extending from the brain parenchyma to peripheral lymphoid organs.

4.2 Arachnoid Granulations

AGs have traditionally been described as protrusions of the arachnoid membrane into dural venous sinusesthat facilitate CSF absorption into the venous circulation [86, 87]. However, emerging evidence indicates that AGs are not merely passive outflow structures, but dynamic, lymphatic like interfaces integrated into the brain's clearance and immune networks [87]. A major conceptual advance in this field is the identification of arachnoid cuff exit (ACE) points, which are discontinuities formed where bridging veins traverse the arachnoid barrier [88]. ACE points function as specialized portals that permit bidirectional exchange of fluid, solutes, and immune cells between the subarachnoid space and the dura [88, 89]. Under physiological conditions, human MRI tracer studies have demonstrated CSF transit through these pathways, highlighting their role in maintaining intracranial fluid balance [90].

Dural mast cells play a crucial regulatory role at ACE points [89]. Upon activation, mast cells release histamine and other mediators that modulate perivascular spaces and bridging vein tone, thereby influencing CSF dynamics [89]. Under pathological conditions, ACE points emerge as key gateways for immune cell trafficking. During neuroinflammation, leukocytes residing in the dura infiltrate the subarachnoid space via ACE points, providing a direct link between meningeal and CNS immune responses [88]. In bacterial meningitis, mast cell activation reshapes CSF flow, promotes neutrophil recruitment, and restricts bacterial dissemination, whereas mast cell deficiency compromises these defenses and exacerbates pathogen burden [89, 91].

4.3 External Cervical Lymph Nodes

The dCLNs have long been recognized as the principal peripheral drainage hubs for CNS-derived fluids, solutes, and immune cells [44, 92-94]. In animal models, direct meningeal-to-cervical lymphatic connections have been visualized using high-resolution magnetic resonance imaging and lymphoscintigraphy [52, 95]. In humans, functional evidence further supports this pathway: radiotracers introduced into the CSF via lumbar puncture consistently accumulate in cervical lymph nodes, including in patients with CNS malignancies [96, 97]. These observations establish a direct anatomical and functional linkage between intracranial compartments and cervical lymphoid tissues.

At the ultrastructural level, lymphatic drainage pathways leading to the cervical nodes contain specialized valve-like structures [98].These consist of organized arrangements of LECs, including podoplanin-positive populations, together with associated perivascular elements. Functionally analogous to classical lymphatic valves, these structures enforce unidirectional flow from the cranial cavity toward the neck, thereby preventing reflux of CSF or immune cells back into the brain [99]. Such directional control is essential for effective waste clearance and for ensuring that CNS-derived antigens, cytokines, and immune cells are reliably delivered to peripheral lymph nodes for immune processing and presentation [100, 101].

5. Imaging and Visualization Techniques for mLVs

The discovery and subsequent characterization of mLVs have been driven largely by advances in imaging technologies, particularly in animal models. Contemporary imaging approaches now permit unprecedented visualization of mLVs structure, drainage routes, and functional dynamics [100, 102, 103]. Given that mLVs are thin, translucent structures embedded within the dura mater, multimodal imaging strategies are often required to comprehensively capture their anatomy and physiology [42].

5.1 Microscopy and Tracer-Based Approaches in Animal Models

High-resolution immunofluorescence microscopy of whole-mount meninges remains a foundational method for mapping mLVs. This approach is typically combined with immunolabeling for canonical lymphatic markers, including LYVE-1, PROX1, VEGFR3, and podoplanin [73]. To improve tissue transparency and enable volumetric imaging, optical clearing techniques such as iDISCO and 3DISCO are frequently applied, allowing light-sheet fluorescence microscopy to reconstruct the entire meningeal lymphatic network in three dimensions [104, 105]. These reconstructions provide detailed insights into vessel continuity, spatial relationships with adjacent blood vessels and cranial nerves, and structural remodeling associated with aging or disease. Genetic reporter mouse models, including PROX1-EGFP lines and inducible VEGFR3-CreER strains, further enhance specificity and enable dynamic interrogation of lymphatic endothelial cell populations in vivo [106].

Tracer-based assays are central to assessing the functional drainage capacity of mLVs [107, 108]. Fluorescent tracers and macromolecules, such as fluorescein isothiocyanate, dextran, Evans blue, or labeled ovalbumin, can be introduced into CSF via cisterna magna or ventricular injection and subsequently tracked as they traverse glymphatic pathways, enter mLVs, and accumulate in dCLNs [44, 52, 109, 110] . Quantification of tracer uptake in dCLNs provides a robust measure of CSF clearance efficiency and facilitates comparisons across developmental stages, experimental interventions, and disease models.

5.2 Intravital Optical Imaging

Intravital two-photon microscopy through chronic cranial windows enables real-time, high-resolution imaging of mLVs at subcellular resolution in vivo [111]. This technique permits longitudinal monitoring of lymphatic vessel remodeling and dynamic tracer transport. Photoacoustic microscopy, which combines optical excitation with ultrasonic detection, has also been adapted to visualize lymphatic flow. Using indocyanine green–labeled tracers, CSF drainage from the subarachnoid space through mLVs to dCLNs can be visualized within tens of minutes [112].

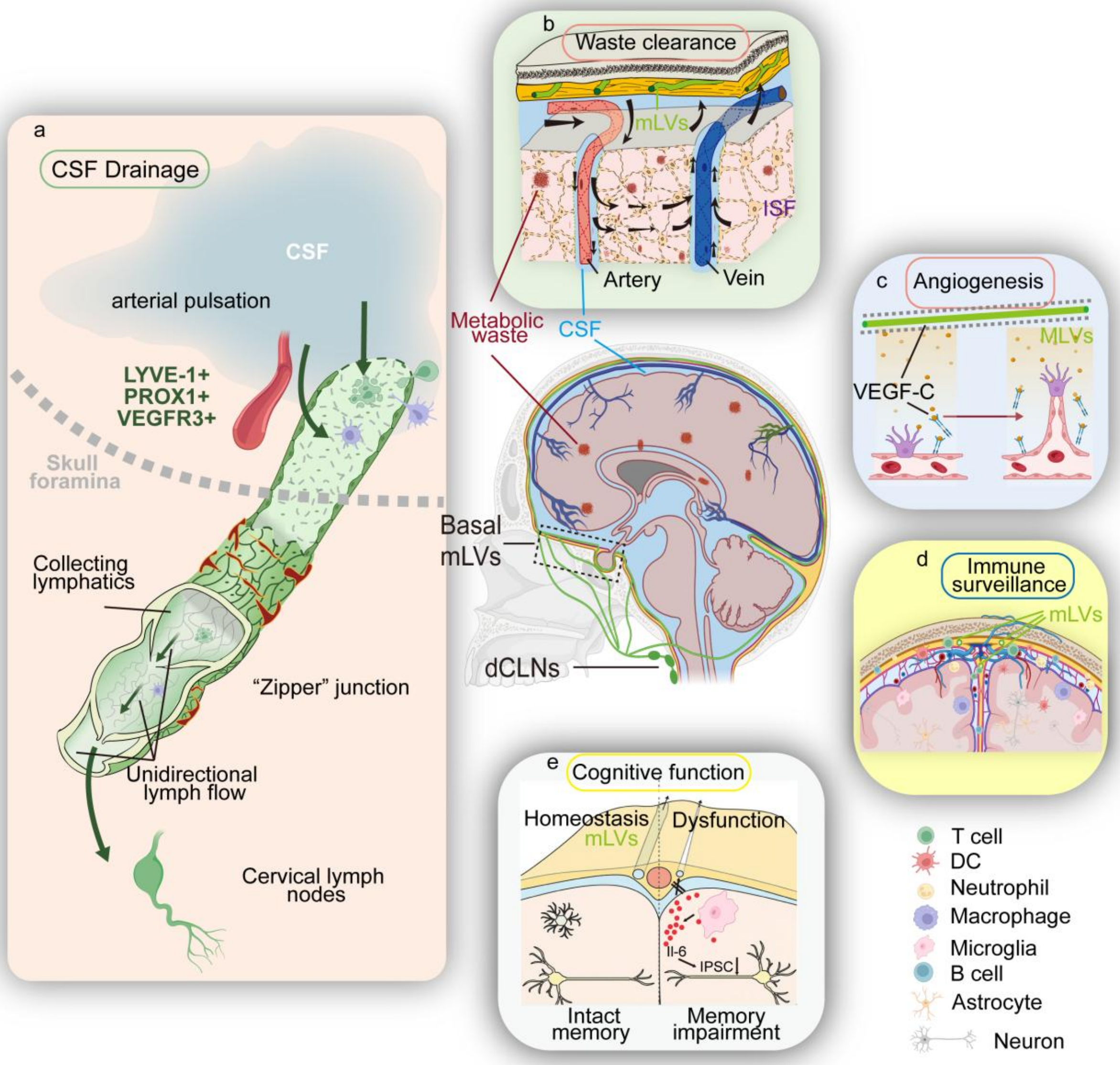

Figure 2. Characteristics and functions of human meningeal mLVs. (a) Structural organization of mLVs. Arterial pulsations drive lymphatic drainage of CSF-borne solutes, promoting predominantly unidirectional flow toward the cervical lymph nodes. Canonical lymphatic endothelial markers: LYVE-1, PROX1, and VEGFR3. (b) Clearance function of mLVs. mLVs facilitate removal of Aβ and other metabolites from interstitial fluid (ISF) and CSF into the meningeal lymphatic network. (c) Angiogenic role of mLVs. mLVs support and modulate angiogenesis, reflecting lymphatic–vascular coupling within the meningeal milieu. (d) Immune landscape of mLVs. The meninges contain diverse immune populations at steady state—including T and B lymphocytes, neutrophils, dendritic cells, and macrophages—with particularly high diversity in the dura mater; microglia are included for contextual relevance. Aβ, amyloid-β; LYVE-1, lymphatic vessel endothelial hyaluronan receptor-1; PROX1, prospero homeobox 1; VEGFR3, vascular endothelial growth factor receptor 3.

Near-infrared II (NIR-II) fluorescence imaging (1000–1700 nm) represents a more recent advance that exploits improved tissue penetration and reduced light scattering in this spectral window [113, 114]. NIR-II probes enable noninvasive visualization of glymphatic and lymphatic flow even through the intact skull, allowing assessment of mLVs function under diverse physiological and pathological conditions, including sleep, anesthesia, and stroke [115, 116].

5.3 Magnetic Resonance Lymphangiography and Clinical Translation

Magnetic resonance (MR) lymphangiography has emerged as a promising noninvasive tool for visualizing mLVs in both experimental models and humans [95, 117]. Absinta et al. first reported the identification of human mLVs using gadolinium-enhanced MRI, revealing lymphatic structures adjacent to dural venous sinuses that closely resemble those described in rodents [100]. Subsequently, Albayram et al. developed a non-contrast three-dimensional T2-FLAIR MRI approach capable of detecting protein-rich lymphatic fluid signals, enabling visualization of dorsal channels along the superior sagittal and transverse sinuses as well as ventral channels associated with cranial nerves [118]. These studies also uncovered age-related alterations, including cervical lymph node atrophy and thickening of dural lymphatic channels, consistent with reduced clearance efficiency in the aging brain [119].

In animal models, contrast-enhanced MR approaches involving intracisternal administration of gadolinium-based tracers have been used to track CSF outflow to dCLNs in rats and dogs [120, 121]. These techniques provide an important translational bridge, supporting potential clinical applications in neurological disorders characterized by impaired CSF and lymphatic clearance, such as idiopathic intracranial hypertension and neuroinflammatory diseases.

6. Functional Networks of mLVs

Initially recognized primarily for their role in CSF drainage, mLVs are now understood to be multifunctional structures essential for CNS homeostasis [122]. Beyond fluid transport, mLVs contribute to the regulation of intracranial pressure, the clearance of metabolic waste and cellular debris, immune surveillance, and the modulation of angiogenesis and neuroplasticity [44, 117, 123-126] (Fig. 2).

6.1 CSF Drainage and Intracranial Pressure Regulation

mLVs are particularly important for the clearance of large or aggregation-prone macromolecules that do not readily traverse the blood brain barrier (BBB). Evidence from animal studies underscores the functional relevance of this pathway. In AD models, genetic ablation or physical obstruction of mLVs accelerates amyloid-β deposition [127, 128]. Similar observations have been reported for α-synuclein pathology, implicating mLVs in the clearance of neurotoxic aggregates in Parkinson's disease and related synucleinopathies [129]. In addition to soluble macromolecules, mLVs contribute to the removal of cellular debris and senescent elements. For example, aging astrocytes secrete chemokines such as CCL21 to recruit immune cells, and the subsequent clearance of these cells and their debris occurs, at least in part, via meningeal and perivascular lymphatic routes [130]. Following acute brain injury, including SAH, mLVs have been shown to take up erythrocytes and hemoglobin degradation products from the CSF, thereby facilitating the resolution of blood derived toxic components that contribute to vasospasm and secondary injury[131, 132]. Experimental studies estimate that dorsal and basal mLVs networks together may account for up to ~50% of total CSF outflow [133]. Rather than acting as passive conduits, lymphatic drainage through mLVs is dynamically regulated by extrinsic physiological forces, including respiration, arterial pulsatility, body posture, and circadian rhythms, all of which modulate transport efficiency [61, 134-136]. In addition, local immune populations, such as border-associated macrophages and dural mast cells, interact structurally and via paracrine signaling with lymphatic endothelium to fine-tune lymphatic function [89, 134, 137].

The relevance of this regulatory network becomes evident in disease states. In hydrocephalus and idiopathic intracranial hypertension (IIH), impaired meningeal lymphatic absorption contributes to CSF accumulation and elevated intracranial pressure [138, 139]. Conversely, in spontaneous intracranial hypotension (SIH), typically caused by dural CSF leaks [140], excessive patency or permeability of mLVs may exacerbate fluid loss and worsen pressure imbalance [141, 142]. Traumatic brain injury (TBI) likewise disrupts mLVs through mechanical and inflammatory insults, impairing clearance and prolonging edema, with direct consequences for neurological recovery [143]. Aging is likewise associated with progressive decline in mLVs efficiency, characterized by fibrosis, luminal narrowing, and structural degeneration, changes that correlate with perivascular space enlargement, impaired solute clearance, and heightened susceptibility to neurodegenerative processes [144].

6.2 Angiogenesis

Beyond clearance functions, mLVs are increasingly recognized as modulators of CNS angiogenesis. Angiogenesis is critical for development, repairing following injury, and adaptive plasticity [145, 146]. Although lymphatic and blood vasculatures are anatomically distinct, mLVs influence angiogenesis through structural coupling, molecular crosstalk, and immune regulation.

(1) Structural and Molecular Interactions

MLVs are located in highly vascularized regions of the dura and pia, where their patency is closely linked to dural venous sinus function [39]. Impaired lymphatic drainage or local inflammation can alter venous pressure and fluid balance, thereby influencing cerebral microcirculation [147]. At the molecular level, lymphatic and blood vessels share key signaling cascades. Canonical lymphangiogenic factors such as VEGF-C and VEGF-D, acting through VEGFR3, also affect subsets of angiogenic endothelial cells [148]. Similarly, pro-inflammatory mediators including TNF-α, IL-1β, and VEGF-A can act on both lymphatic and blood vasculature [149, 150]. Efficient lymphatic clearance helps prevent the accumulation of these signals, whereas impaired drainage promotes pathological neovascularization, a hallmark of chronic CNS inflammation [151, 152]. Circadian regulation further modulates this interaction: sleep enhances glymphatic–lymphatic clearance and suppresses angiogenic signaling, while sleep deprivation has the opposite effect [153].

(2) Coupled Angiogenesis and Lymphangiogenesis after Injury

After stroke or trauma, angiogenesis and lymphangiogenesis often occur in parallel [154, 155]. Augmenting mLVs function reduces cerebral edema and supports vascular regeneration in peri-infarct regions, potentially by clearing debris and shaping reparative immune responses [141]. Paracrine communication is also likely, as LEC may release soluble factors or extracellular vesicles that act on pericytes and endothelial cells within the neurovascular unit [89, 156-158]. Mast cells, strategically positioned near both blood and lymphatic vessels, may further integrate these responses by releasing vasoactive and angiogenic mediators in response to altered lymphatic flow [89]. Compelling evidence for direct lymphatic participation in angiogenesis derives from zebrafish models, in which mLVs rapidly invade injured parenchyma, serving both as drainage conduits and as scaffolds guiding nascent blood vessels [159]. A subset of these lymphatic structures can transdifferentiate into blood vessels through Notch-dependent mechanisms, revealing an unexpected plasticity that enables emergency vascular regeneration after injury.

6.3 Immune Surveillance and Neuroinflammation

The identification of mLVs has revised the classical concept of CNS “immune privilege”. mLVs facilitate the egress of dendritic cells, macrophages, T cells, and soluble immunomodulators to cervical lymph nodes, where CNS-derived antigens are presented to naïve lymphocytes, thereby initiating adaptive immune responses [105, 177]. Mast cells further regulate this interface by acting as meningeal gatekeepers that coordinate immune cell trafficking from skull bone marrow reservoirs into the CNS [169].

Importantly, mLV function in neuroinflammation is highly context-dependent and bidirectional. In experimental autoimmune encephalomyelitis (EAE), mLV dilation and expansion have been observed [46, 178], which may enhance clearance of inflammatory mediators but also facilitate the trafficking of autoreactive lymphocytes [179]. Similarly, during CNS infections, mLV-mediated antigen drainage activates systemic immune responses; however, lymphatic remodeling and increased permeability may concurrently exacerbate inflammation and potentially promote pathogen dissemination [131].

6.4 Synaptic Physiology and Cognitive Function

Emerging evidence indicates that meningeal lymphatic function influences synaptic physiology and cognition. Efficient clearance of extracellular waste and signaling molecules is essential for maintaining synaptic homeostasis. During wakefulness, neuronal activity generates neurotransmitters, extracellular potassium, and metabolic byproducts that must be removed to preserve circuit stability [160, 161]. Glymphatic clearance, most active during sleep, funnels these materials through mLVs [162]. Impairment of this pathway leads to waste accumulation that disrupts synaptic signaling and plasticity [162].

Direct experimental support is growing. Chronic impairment of meningeal lymphatic drainage in mice induces long-term imbalances in cortical excitatory–inhibitory transmission, attenuates synaptic plasticity, and produces learning and memory deficits reminiscent of accelerated aging [126]. Conversely, Wang et al. reported that non-invasive enhancement of meningeal lymphatic flow using low-frequency pulsatile stimulation improved amyloid-β clearance in aged mice, restored dendritic spine density in the hippocampus, and enhanced memory performance [163]. mLVs may also participate in clearing synaptic debris generated during activity-dependent remodeling [126]. Synaptic pruning and microglial phagocytosis produce membrane fragments and protein remnants that require efficient removal, particularly in superficial cortical regions near the subarachnoid space [164]. Obstruction of lymphatic outflow may permit accumulation of synaptic proteins, fostering aggregation and dysfunction [165]. Although direct evidence for clearance of specific synaptic proteins by mLVs remains limited, converging data strongly link impaired glymphatic–lymphatic function to cognitive decline [78]. Sleep provides a critical physiological context for this interaction. During slow-wave sleep, interstitial space expands due to transient neuronal shrinkage, enhancing CSF flux and metabolite clearance [162, 166, 167]. Disruption of sleep or lymphatic function interrupts this cycle, and experimental ablation of mLVs impairs hippocampal long-term potentiation, a core substrate of memory formation [168].

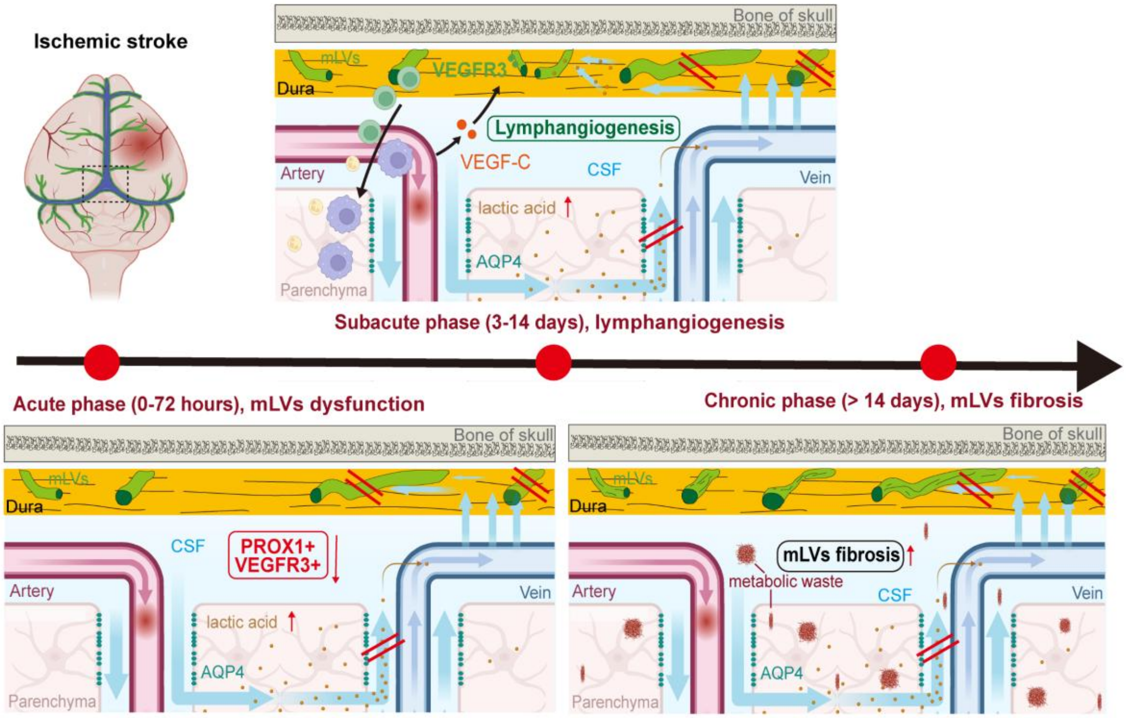

Figure 3. Changes in mLVs following ischemic stroke. Acute phase (0–72 h), mLV function is impaired by disrupted fluid dynamics, accompanied by downregulation of PROX1 and VEGFR3 in lymphatic endothelial cells, which compromises vessel integrity and transport capacity. Subacute phase (3–14 days), mLVs remodel dynamically under VEGF-C/VEGFR3 signaling. Enhanced immune-cell trafficking via these vessels may exacerbate neuroinflammation while facilitating antigen drainage to the cervical lymph nodes. Chronic phase (>14 days), fibrotic alterations and reduced lymphatic pulsatility emerge, weakening coupling between the glymphatic and meningeal lymphatic systems and delaying clearance of metabolic waste.

7. Dynamic Remodeling of mLVs following Stroke

Stroke induces profound and dynamic remodeling of mLVs, with consequences that extend from acute exacerbation of brain injury to long-term neurodegenerative risk [169]. Both ischemic and hemorrhagic stroke subtypes elicit temporally distinct functional alterations in mLVs, reflecting the divergent pathophysiological mechanisms of vascular occlusion versus vascular rupture (Fig. 3).

Elucidating the temporal and subtype-specific dynamics of mLVs remodeling is therefore critical for identifying therapeutic windows to restore lymphatic function and improve stroke outcomes.

7.1 Dynamic Alterations of mLVs after Ischemic Stroke

Ischemic stroke initiates a cascade of metabolic and structural disturbances affecting both parenchymal and vascular compartments. Arterial occlusion leads to energy failure, excitotoxicity, oxidative stress, and BBB disruption, thereby triggering secondary injury pathways including inflammation, apoptosis, and necroptosis [170, 171]. Delayed or incomplete reperfusion further aggravates mitochondrial dysfunction and glutamate toxicity, resulting in irreversible neuronal loss within the ischemic core and penumbra [172, 173].

During the acute phase of ischemic stroke (0–72 h), cytotoxic edema rapidly compresses periarterial spaces, severely impairing glymphatic inflow and disrupting CSF dynamics [13, 14]. Concurrently, hypoxia-induced activation of hypoxia-inducible factor-1α (HIF-1α) suppresses key lymphatic endothelial transcriptional programs, including PROX1 and VEGFR3, leading to compromised mLVs integrity and transport capacity [174]. As the infarct progresses into the subacute phase (3–14 days), mLVs undergo compensatory remodeling driven predominantly by VEGF-C/VEGFR3 signaling, with pronounced lymphangiogenesis occurring in dorsal mLVs adjacent to the superior sagittal sinus [80]. Newly formed lymphatic vessels partially restore CSF–ISF circulation and facilitate the clearance of necrotic debris and inflammatory cytokines. However, their increased density and permeability also permit enhanced trafficking of $CD4^+$ T cells and monocytes into the meninges and parenchyma, sustaining neuroinflammatory responses [175]. Despite this dualistic role, experimental ablation of mLVs during the subacute period consistently aggravates infarct size and impairs functional recovery, indicating that compensatory lymphangiogenesis confers a net protective effect in ischemic stroke [174].

7.2 Hemorrhagic Stroke Induced Meningeal Lymphatic Alterations

Hemorrhagic stroke including intracerebral hemorrhage (ICH) and SAH exerts profound mechanical and biochemical stress on mLVs, driving subtype-specific yet convergent dysfunction. ICH, most commonly caused by hypertensive vessel rupture, trauma, or vascular malformations, is characterized by hematoma expansion, perihematomal edema, and iron-mediated ferroptosis, processes that accelerate neuronal death and perihematomal ischemia [176]. In contrast, SAH results from aneurysmal rupture and sudden flooding of the subarachnoid space with blood, triggering intense meningeal inflammation and delayed cerebral vasospasm, typically developing between 3 and 14 days after rupture, which compromises cerebral perfusion and induces secondary ischemic injury [177]. Despite their distinct initiating events, both ICH and SAH converge on severe disruption of mLVs structure and function, with pathological consequences that span from acute injury to chronic neurological decline [178, 179].

In the acute phase (0–72 h) of SAH, rapidly rising intracranial pressure and accumulation of intraparenchymal or subarachnoid blood physically compress mLVs, causing luminal collapse and abrupt restriction of CSF outflow, a phenomenon consistently observed in rodent and large-animal models [121]. Hemoglobin degradation products generate intense oxidative stress via iron-catalyzed Fenton reactions, suppressing lymphatic endothelial markers such as LYVE-1 and VEGFR3 and further impairing vessel integrity [131]. Specifically, activation of thrombospondin-1 (THBS1)–CD47 signaling engages STAT3/Bcl-2 pathways, promoting lymphatic endothelial apoptosis and compounding structural damage [16].

As hemorrhagic injury evolves into the subacute phase (3–14 days), mLVs exhibit a biphasic remodeling response. VEGF-C/VEGFR3 signaling induces lymphangiogenesis, generating new lymphatic sprouts around dural dorsal sinuses and partially restoring drainage of erythrocyte debris and inflammatory mediators [180-182]. However, ongoing oxidative stress and persistent hemoglobin byproducts maintain a hostile microenvironment, rendering newly formed lymphatic vessels morphologically abnormal and excessively permeable [131, 183]. These immature vessels can inadvertently facilitate infiltration of neutrophils and pro-inflammatory macrophages, thereby exacerbating secondary injury [184, 185]. Functional studies highlight this duality: transient suppression of mLVs may reduce acute edema yet ultimately worsens long-term neurological outcomes, underscoring the simultaneous reparative and pro-inflammatory potential of lymphatic remodeling [186]. In SAH, additional spiral-like distortions of mLVs around the Circle of Willis further disrupt CSF outflow and contribute to delayed cerebral ischemia [179].

In the chronic phase (>14 days), compensatory lymphangiogenic responses give way to persistent and often irreversible dysfunction. Surviving mLVs undergo fibrosis-like remodeling characterized by basement membrane thickening, reduced compliance, and diminished pulsatility, leading to sustained impairment of lymphatic drainage [52, 169]. Hemosiderin deposition within perivascular and meningeal spaces inflicts lasting damage on the glymphatic–lymphatic interface, predisposing to post-hemorrhagic hydrocephalus and progressive cognitive decline [121, 187]. Clinical evidence from dynamic contrast-enhanced MRI demonstrates long-lasting deficits in meningeal lymphatic clearance that correlate with adverse neurological outcomes in patients [188]. Concurrently, chronic oxidative stress disrupts astrocytic AQP4 polarity, further decoupling glymphatic inflow from lymphatic outflow [132, 179, 189].

8. Innovative Stroke Therapeutics Targeting mLVs

Therapeutic modulation of mLVs represents a multifaceted strategy for addressing the dynamic pathophysiology of stroke. During the acute (hours to days), interventions primarily aim to enhance CSF drainage, alleviate cerebral edema, and temper neuroinflammation. At later stages, targeting mLVs function may support vascular remodeling, immune resolution, and long-term neurological recovery. Before outlining specific approaches, it is important to acknowledge the heterogeneity of the supporting evidence. To convey the relative translational maturity of different strategies, we categorized the available evidence as follows: (✓) direct evidence from rodent stroke models (ischemic or hemorrhagic); (◐) indirect evidence derived from other CNS disorders (e.g., Alzheimer's disease, traumatic brain injury, experimental autoimmune encephalomyelitis) or physiological studies; and (○) conceptual or extrapolated strategies that have not yet been evaluated in CNS disorders. This classification is summarized in Tables 2 and 3.

Table 2. Therapeutic Strategies Targeting Meningeal Lymphatic Vessels (mLVs).

Therapy Approach	Mechanism	Primary Effects	Clinical Challenges	References	Evidence
VEGF-C/VEGFR3 Pathway Activation	Activates VEGF-C/VEGFR3 signaling to promote mLVs growth and drainage. Delivered via recombinant protein or gene therapy.	Improves CSF drainage, reduces neuroinflammation in stroke and neurodegeneration.	Optimizing timing and minimizing off-target effects of VEGF-C therapies.	[15, 55, 79, 202, 238]	✓
Immune Cell Trafficking Modulation	Regulates T-cell entry to CNS by blocking CCL21/CCR7 axis in mLVs.	Reduces pathogenic immune cell trafficking and CNS inflammation.	Balancing immune modulation without compromising protection.	[122, 239, 240]	◐
Non-Invasive CSF Clearance Enhancement	Interstitial fluid dynamics via NIR photobiomodulation, focused ultrasound, etc.	Improves brain waste clearance non-invasively.	Standardizing protocols and demonstrating long-term safety.	[116, 226, 241, 242]	○
Behavioral Maneuvers	Exercise, Cervical lymphatic massage, sleep-posture optimization.	Facilitates glymphatic–meningeal lymphatic clearance.	Standardizing protocols and demonstrating long-term safety.	[243-245]	◐
Nanoparticle & Scaffold-Based Delivery	Targets LYVE-1/ podoplanin using antibody-conjugated nanoparticles or scaffolds for sustained release.	Improves specificity and duration of therapeutic delivery to mLVs.	Validating targeting precision and safety in vivo.	[246-249]	○
Surgery	LVA，lymphatic ligation and lymph node excision.	Enhance the rapid elimination of harmful substances.	Concerns about surgical safety.	[94, 194, 207, 250-252]	◐

This table organizes interventions into five domains: (1) pro-lymphangiogenic signaling, principally VEGF-C/VEGFR3 activation to expand mLVs and enhance CSF efflux; (2) immune-axis modulation via mLVs, including constraining maladaptive T-cell trafficking and attenuating oxidative injury to reduce neuroinflammation; (3) Non-invasive augmentation (photobiomodulation, posture, or breathing) to increase lymphatic contractility/drainage and improve interstitial fluid transport; (4) behavioral maneuvers (e.g., cervical lymphatic massage, sleep-posture optimization) that facilitate glymphatic–meningeal lymphatic clearance; and (5) targeted delivery platforms, such as mLVs-addressed nanoprobes, enabling spatially precise immunomodulation with applications in cancer metastasis, neuroinflammation, and cerebrovascular disease (e.g., stroke).✓ Direct = Direct experimental evidence in rodent stroke models (ischemic or hemorrhagic); ◐ Indirect = Evidence from other CNS disorders (e.g., EAE, TBI, AD) or physiological studies, but limited direct stroke data; ○ Conceptual = Hypothesis-generating or extrapolated from non-stroke fields, with no direct stroke model validation.

8.1 Enhancing CSF Drainage and Edema Resolution

Augmenting the drainage capacity of mLVs has emerged as a promising approach for mitigating cerebral edema, one of the most devastating early complications of stroke. In experimental ICH, VEGF-C delivery promotes hematoma clearance, attenuates perihematomal swelling, and improves neurological outcomes. Similarly, prophylactic or early VEGF-C treatment in ischemic stroke models enhances lymphangiogenesis and reduces infarct volume [15, 178, 190, 191]. Upstream strategies that restore glymphatic inflow may further potentiate lymphatic clearance. Approaches that repolarize AQP4 channels on astrocytic endfeet or enhance arterial pulsatility can re-establish glymphatic–lymphatic coupling, thereby facilitating bulk removal of edema fluid [192, 193]. Given that the therapeutic window for edema control is largely restricted to the acute and early subacute phases, early initiation of mLVs-targeted interventions is likely to yield the greatest benefit. When combined with conventional treatments such as osmotic therapy or decompressive craniectomy, these approaches may confer synergistic protection against malignant cerebral edema.

Beyond molecular and pharmacological strategies, microsurgical modulation of extracranial lymphatic outflow represents an emerging complementary approach. Lymphaticovenular anastomosis (LVA), a supermicrosurgical technique originally developed for peripheral lymphedema, has recently attracted attention in neurosurgical contexts. By anastomosing cervical lymphatic vessels to adjacent venules, LVA establishes a low-resistance outflow pathway that can decompress the cervical lymphatic network and potentially augment downstream drainage capacity. Recent clinical studies in Alzheimer's disease suggest that cervical LVA enhances the efflux of CSF and ISF, thereby facilitating the clearance of metabolic waste products such as amyloid-β[194, 195]. In the context of stroke, accumulating evidence indicates that the pathological cascade extends beyond arterial occlusion or rupture to include dysfunction of the glymphatic–meningeal lymphatic–cervical lymph node axis[196, 197]. Within this framework, LVA represents a conceptually attractive strategy to restore lymphatic outflow. By reducing cervical lymphatic outflow resistance, LVA may facilitate the clearance of CSF-borne toxic substrates and mitigate post-stroke inflammation and edema. This approach may be particularly relevant during the acute and subacute phases, when fluid accumulation and inflammatory burden are most pronounced. However, in the context of stroke, this concept remains largely hypothesis-generating, as direct experimental validation in stroke models is currently limited.

Table 3. Non-invasive methods for enhancing mLV capacity in stroke.

Intervention	Mechanism	MLVs Function	Potential Stroke Benefits	Evidence
Exercise[243]	Improves cerebral perfusion, regulates inflammation, may boost neurotrophic factor secretion	Optimizes mLVs microenvironment, indirectly affects function	Promotes neurofunctional recovery, reduces ischemia-reperfusion injury	◐
Sleep quality[244]	Deep sleep strongly linked to daytime clearance (including glymphatic system)	Increases CSF/ISF flow, directly enhances mLVs clearance efficiency	Reduces cognitive impairment, improves emotional issues	✓
TUS[242]	Acoustic cavitation alters membrane permeability/blood flow; indirectly affects skull/CSF flow	Temporarily regulates mLVs permeability or microenvironment	Improves cerebral edema, clears metabolites (e.g., Aβ), aids drug delivery	◐
Music[253]	May affect cerebral blood flow, neural activity/inflammation (mechanism unclear)	Indirectly regulates cerebral physiology, influences mLVs microenvironment	Theoretically improves mood, indirectly supports rehabilitation	○
BP/Glu/Lipid Control[254-256]	Reduces vascular damage, improves overall cerebral perfusion and metabolic environment	Alleviates cerebral inflammation/oxidative stress, optimizes mLVs microcirculation	Lowers stroke recurrence risk, maintains MLVs basic function	✓
fNIRS/PAI[257-259]	Monitors cerebral oxygenation/blood flow; explores if light parameters regulate blood flow/inflammation	Primarily for monitoring; phototherapy's regulatory effect on mLVs is preliminary	Monitors post-stroke cerebral recovery, explores phototherapy potential	✓
Cognitive training[260]	Enhances brain region activity/blood flow via task-based training for impaired cognition	Indirectly affects local waste production/clearance by regulating brain metabolism	Improves cognitive deficits, boosts daily self-care ability	○

Transcranial ultrasound; BP: Blood pressure; fNIRS/PAI: Functional near-infrared spectroscopy/photoacoustic imaging

8.2 Immunomodulation via mLVs Pathways

A second therapeutic objective is to regulate post-stroke inflammation through mLVs-mediated communication between the brain and the peripheral immune system. VEGF-C-induced lymphangiogenesis and chemokine modulation (e.g., CCL21 upregulation) have been associated with improved immune cell egress and reduced inflammatory burden in some models[132, 186]. On the other hand, mLVs mediated drainage of CNS-derived antigens may enhance antigen presentation in dCLNs, potentially triggering maladaptive systemic immune activation. Consistently, inhibition of VEGF-C/VEGFR3 signaling or disruption of lymphatic drainage has been shown to reduce immune cell activation and attenuate infarct progression after MCAO [198, 199]. These seemingly conflicting findings underscore a key unresolved issue: the immunological role of mLVs is stage-dependent and quantitatively regulated. While early enhancement of lymphatic clearance may be beneficial for limiting local inflammation, excessive or sustained antigen trafficking may promote peripheral immune priming and contribute to chronic neuroinflammation.

To reconcile these divergent findings, we propose a "lymphatic–immune gatekeeper" framework. This gatekeeping function represents a double-edged mechanism: while necessary for immune surveillance, it may also facilitate autoreactive T- and B-cell responses against brain antigens under pathological conditions [200] [201]. Accordingly, the therapeutic goal should not be simply to augment or inhibit lymphatic function, but to fine-tune this gatekeeper role, enhancing clearance of toxic metabolites while selectively modulating antigen presentation and immune cell trafficking. Strategies such as temporally controlled VEGF-C delivery, selective targeting of dCLNs immune activation, or compartment-specific modulation of lymphatic signaling may offer more precise immunoregulation. Achieving this balance remains a central challenge for the clinical translation of mLVs targeted therapies.

8.3 Promoting Angiogenesis and NVU Repair

MLVs also appear to facilitate post-stroke angiogenesis and neurovascular unit (NVU) restoration. Stimulating lymphangiogenesis in peri-infarct regions, for example through intrathecal administration of VEGF-C or related growth factors, may create a permissive microenvironment for neovascularization while preserving fluid homeostasis. Notably, lymphatic and blood vessels often co-sprout after injury, coordinated by shared molecular mediators such as VEGF-C/VEGFR3 and angiopoietins [80, 202]. Evidence from myocardial infarction models indicates that induction of lymphangiogenesis enhances vascular remodeling and improves functional recovery [203]. In experimental stroke, ingrowing mLVs have been observed to guide nascent capillaries at the infarct border, providing both structural scaffolding and protective clearance functions [204, 205]. Therapeutic amplification of these processes may accelerate reperfusion, protect fragile neovessels from toxic metabolites, stabilize BBB integrity, and ultimately expedite NVU repair and neurological recovery.

8.4 Enhancing Cognitive and Functional Recovery

In the long term, restoration of mLVs function may help prevent post-stroke cognitive decline, a major determinant of quality of life [163, 169]. Studies in aging and Alzheimer's disease models demonstrate that declining mLVs function correlates with cognitive deterioration, whereas enhancement of lymphatic drainage improves memory and executive function [206, 207]. In aged mice, VEGF-C treatment rejuvenates mLVs function, attenuates neuroinflammation, and improves cognitive performance [208]. Comparable strategies may be particularly beneficial for stroke survivors of advanced age, in whom accelerated mLVs aging is common [85, 163] .

9. Key Barriers to the Clinical Translation of mLVs-Targeted Therapies in Stroke

Despite compelling preclinical evidence demonstrating the therapeutic potential of mLVs modulation, no clinical trials targeting this system are currently registered in the North American Clinical Trials Registry (https://clinicaltrials.gov/). This conspicuous gap underscores the urgent need to bridge basic discovery and human application.

9.1 Biological and Translational Gaps

Although rodent and zebrafish models have provided important insights into the fundamental biology of mLVs, they do not fully recapitulate human physiology[38, 209].Human mLVs exhibit greater spatial complexity, extending beyond dorsal peri-sinusoidal regions to include skull base structures and cranial nerve exit sites, with region-specific variability in vessel density and caliber [38] [210]. In addition, lymphatic flow dynamics differ between species: rodent mLVs drainage is tightly coupled to intracranial pressure oscillations and vessel contractility, whereas human mLVs function is primarily inferred from imaging-based kinetics and must operate against hydrostatic constraints associated with upright posture[7, 210].

Importantly, the translational gap is further amplified by the clinical context of stroke, which predominantly affects elderly individuals with comorbidities. Aging is associated with fibrotic remodeling and lymphatic rarefaction, resulting in impaired drainage and "stasis-like" states [211]. Common comorbidities, including hypertension, diabetes, and cerebral small vessel disease, further compromise mLVs structure and function by promoting basement membrane thickening and reduced vessel pulsatility [212].

Future studies should prioritize age- and comorbidity-matched preclinical models, integrate large-animal systems, and incorporate human validation approaches, including advanced imaging of lymphatic drainage and analysis of patient derived CSF and meningeal tissues. Standardization of cross-species readouts will also be critical to improve translational alignment.

9.2 Barriers to Drug Delivery

Efficient and safe delivery of therapeutics to mLVs remains a formidable challenge. These vessels reside within the dura mater, a compartment shielded by both the blood-brain and blood-dura barriers, which severely limits the penetration of systemically administered agents. Although intrathecal or intraventricular delivery can achieve high local concentrations, such approaches are invasive and carry risks of infection and hemorrhage, concerns that are particularly salient in the hyperacute phase of stroke [213]. Timing further constrains feasibility: during the acute window, clinical priorities such as thrombolysis or thrombectomy may preclude invasive procedures. As a result, mLVs-targeted therapies may be more practicable during the subacute phase or in carefully selected patient subgroups [15]. Innovative delivery strategies, including intranasal administration, intracalvarial injection, skull base-localized drug depots, or engineered molecules capable of crossing the BBB and selectively targeting lymphatic endothelium, represent promising alternatives. However, these approaches remain technically complex, are largely experimental, and require substantial refinement before clinical application [214-216].

9.3 Safety and Immune Balance

The safety profile of mLVs directed interventions warrants careful evaluation. As mLVs function as a conduit linking central nervous system-derived signals with peripheral immune responses, augmenting their CSF clearance capacity may carry the risk of altering peripheral immune homeostasis. This consideration is particularly relevant in stroke, where patients commonly develop systemic immunosuppression during the post-acute phase.

9.4 Conceptual Barriers

In addition to biological and technical challenges, conceptual inertia within the stroke research community represents a nontrivial obstacle. For decades, therapeutic development has focused predominantly on reperfusion, neuroprotection, and repair of the neurovascular unit, with relatively limited emphasis on clearance systems. As a result, targeting a "secondary" lymphatic network may initially be met with skepticism unless supported by robust clinical evidence.

10. Perspectives and Conclusion

Recognition of mLVs as active regulators of stroke pathophysiology has expanded current frameworks of brain injury and repair, offering a perspective that complements traditional vascular-centric models. Progress in this field will likely depend on cross-disciplinary integration. Insights from cancer biology have elucidated molecular programs governing lymphangiogenesis, while cardiovascular research has established precedents for lymphatic-targeted interventions that enhance tissue repair following myocardial infarction [217, 218]. Stroke research now stands at a similar inflection point, with a growing opportunity to translate lymphatic biology into therapeutic strategies that improve neurological recovery.

10.1 Deepening Mechanistic Understanding

A central priority for future investigation is to define, at cellular and molecular resolution, how mLVs respond to stroke. Several key questions remain unresolved. Which upstream signals emanating from injured brain tissue initiate lymphatic dysfunction or expansion? Although elevations in VEGF-C have been detected in CSF after stroke, the broader network of cytokines, growth factors, metabolic cues, and biomechanical forces orchestrating lymphatic remodeling remains incompletely characterized. Equally critical is delineating downstream immunological consequences: how antigens drained to dCLNs shape the activation, differentiation, and polarization of T cells, B cells, and macrophages, and how these immune responses feedback to peripheral organs such as the spleen, lungs, and heart. Addressing these questions will require integrative approaches, including single-cell and spatial multi-omics to resolve lymphatic endothelial and immune heterogeneity, coupled with high-resolution and dynamic imaging to map CSF–ISF flux and visualize real-time mLVs function. Such mechanistic insights will be essential for selectively targeting pathogenic pathways while preserving beneficial clearance and immune-surveillance functions.

10.2 Biomarkers and Imaging Innovations

Successful clinical translation will also depend on the ability to noninvasively assess mLVs structure and function in humans. Advanced magnetic resonance imaging, including intrathecal contrast–enhanced protocols, can quantify CSF drainage to cervical lymph nodes, while near-infrared fluorescence lymphography using indocyanine green offers a minimally invasive approach to visualize skull-base lymphatic flow [219, 220]. These techniques may help stratify patients, particularly elderly stroke survivors with impaired clearance, and enable precision targeting of interventions. Complementary circulating and CSF biomarkers could further enhance monitoring [221]. Reductions in CSF inflammatory cytokines, coupled with changes in lymph node derived immune signatures, could serve as dynamic indicators of therapeutic engagement and as surrogate endpoints in early-phase clinical trials. Integrating imaging biomarkers with molecular readouts will be critical for mechanistic validation and clinical decision-making.

10.3 Therapeutic Development and Clinical Translation

The coming decade is likely to witness the first clinical trials of mLVs-targeted therapies, marking a pivotal step toward translation. Several pharmacological strategies appear particularly promising. Intrathecal delivery of VEGF-C may promote lymphangiogenesis and enhance CSF clearance, whereas agents that restore astrocytic AQP4 polarity could augment glymphatic inflow and improve fluid–waste coupling. In parallel, targeted immunomodulatory approaches directed toward dCLNs may attenuate maladaptive systemic immune activation without compromising central clearance, offering a form of precision immunotherapy [44, 222]. More recently, Gao et al. demonstrated that drug-loaded albumin nanoparticles can hijack calvarial immune cells to bypass the blood–brain barrier via skull–meningeal microchannels, enabling efficient CNS drug delivery and therapeutic benefit in stroke patients [223]. Such innovative delivery strategies may likewise be adapted to modulate post-stroke mLVs structure and function, opening new avenues for lymphatic-targeted interventions.

Beyond pharmacological interventions, surgical and device-based strategies are rapidly emerging. Cervical LVA, already explored as a clearance-enhancing therapy in Alzheimer’s disease [194], may be repurposed for selected stroke patients with severe lymphatic dysfunction. Noninvasive modalities, including infrared photobiomodulation, low-frequency focused ultrasound, and cervical lymphatic stimulation, also show promise in enhancing CSF lymphatic outflow [224-226] and may serve as adjunctive therapies alone or in combination with drugs. Finally, lifestyle-based interventions such as structured aerobic exercise and optimization of sleep quality offer low-cost, widely accessible means of strengthening glymphatic–lymphatic function and may synergize with pharmacological or surgical approaches as part of a multimodal stroke rehabilitation strategy [227, 228].

Among emerging strategies aimed at enhancing glymphatic–lymphatic CSF clearance, noninvasive approaches, including infrared photobiomodulation, low-frequency focused ultrasound, and interventions such as aerobic exercise or sleep optimization, are likely to be prioritized in early-phase clinical studies, given their favorable safety profiles and practical feasibility. Pharmacological interventions may represent the next tier of translational advancement. In contrast, surgical approaches such as LVA, while mechanistically compelling, currently lack sufficient evidence regarding safety and efficacy in stroke and will require rigorous preclinical validation before clinical investigation can be justified.

In summary, mLVs represent a promising yet underexplored therapeutic axis in stroke. Targeting this system may not only mitigate acute complications, including cerebral edema and excessive neuroinflammation, but also contribute to improved long-term outcomes, such as cognitive recovery, reduced recurrence, and resilience to secondary neurodegeneration. Importantly, the immunological consequences of mLV targeted interventions are context-dependent and may vary according to disease stage and systemic immune status, necessitating careful consideration in therapeutic design. Future advances in stroke therapy may therefore depend not only on restoring cerebral perfusion, but also on re-establishing lymphatic flow as a co-determinant of neurovascular recovery.

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Author contributions

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Competing interests

The authors declare no competing interest

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