



Unveiling the Fourth Meningeal Layer: Implications for Brain Structure, Function, and Neurological Disease

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Abstract

The central nervous system (CNS), comprising the brain and spinal cord, is protected by specialized connective tissue layers known as the meninges. These were traditionally regarded as passive barriers that offer mechanical protection and maintain the circulation of cerebrospinal fluid (CSF). Nonetheless, recent studies have identified a fourth meningeal layer, the subarachnoid lymphatic-like membrane (SLYM), located within the subarachnoid space. The SLYM serves as a physical and immunological barrier that isolates CSF and mediates local immune surveillance. Aging-related changes in this membrane have been associated with neurodegenerative diseases, such as Alzheimer's disease, while its mechanical and inflammatory properties suggest a potential role in traumatic brain injury. This finding challenges classical neuroanatomical concepts and highlights the active role of the meninges in brain homeostasis and pathology. If future in vivo imaging methods enable reliable visualization of the SLYM, this membrane may emerge as a potential diagnostic biomarker and therapeutic target for CNS disorders. This review summarizes the architecture and role of the SLYM, its involvement in neurological diseases, and its potential to revolutionize the understanding of brain barriers and interactions with the immune system.

Keywords:

meningeal layers; subarachnoid lymphatic-like membrane; cerebrospinal fluid; traumatic brain injury; blood-brain barrier

1. Introduction

The brain and spinal cord constitute the central nervous system (CNS), which regulates and coordinates essential body functions in vertebrates [1]. The CNS has evolved into an exceptionally complex system that integrates diverse sensory inputs and generates the outputs required to transmit and receive intercellular signals over long distances. During neuronal development, neurons acquire specialized functions such as action potential generation, neurotransmitter-mediated signaling, and intracellular transport, all of which support complex CNS activity [2]. In vertebrates, the peripheral nervous system includes the somatic nervous system, which relays sensory and motor information between the CNS and structures

such as the skin and skeletal muscles, and the autonomic nervous system, which regulates involuntary physiological functions, including heart rate, respiration, and visceral activity. Neurons likely provided the initial control of opposing effectors in early animals, conferring several evolutionary advantages, including the ability to regulate body temperature and overcome constraints imposed by a hydrostatic skeleton.

The meninges are connective tissue membranes that surround and protect the brain and spinal cord. They consist of three layers: the dura mater, arachnoid mater, and pia mater [3]. The outermost layer, the dura mater, forms a sac that encloses the underlying meningeal layers and is collectively referred to as the pachymeninges ("pachy"

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meaning thick) (Figure 1). It forms three dural folds, including the diaphragma sellae, which encloses the sella turcica and pituitary gland; the tentorium cerebelli and falx cerebelli, which separate the occipital lobes from the cerebellum; and the falx cerebri, which separates the two cerebral hemispheres [4]. It encloses and supports the dural venous sinuses. The two inner meningeal layers are collectively referred to as the leptomeninges, a term de-

rived from the Greek word meaning "thin." The arachnoid mater, named for its spider-like appearance, is the outer layer, whereas the pia mater is the innermost layer. The subarachnoid space contains cerebrospinal fluid (CSF), produced mainly by the choroid plexus, and is traversed by arachnoid trabeculae that connect the arachnoid mater to the pia mater [5].

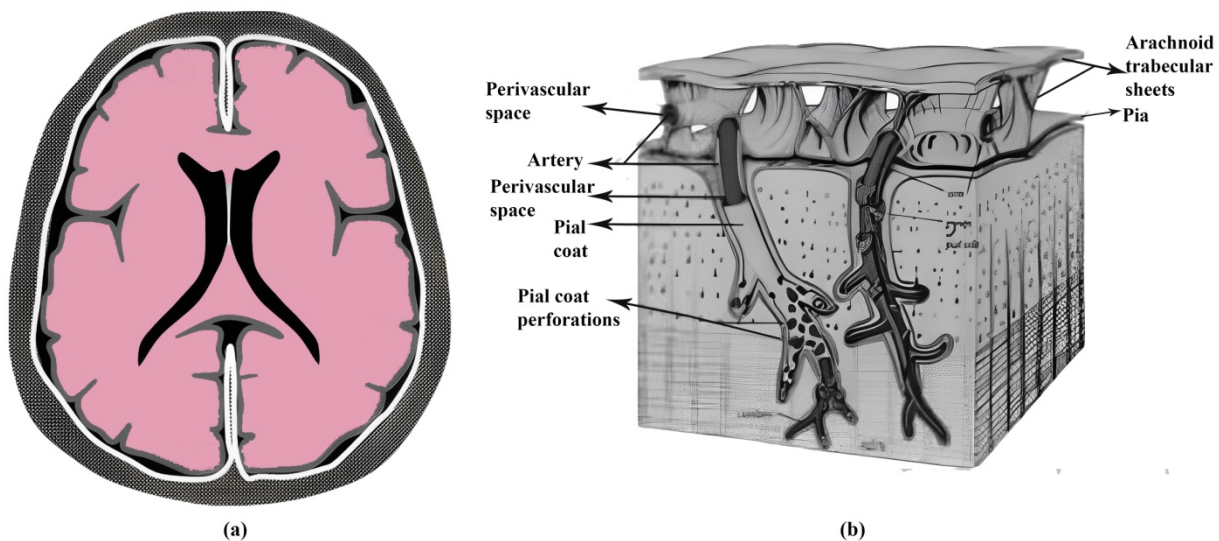


Figure 1: (a) The falx in the interhemispheric fissure, the tentorium between the cerebellum, the vermis, and the occipital lobes, and the inner table of the skull are regions in the diagram where dura-arachnoid augmentation could be present. Pure dural augmentation cannot fill sulci or basilar cisterns without pial or subarachnoid involvement. (b) A schematic illustration of the brain leptomeninges, showing the subarachnoid space enclosed by the arachnoid mater and pia mater. The pia mater closely adheres to the brain surface and extends along vessels within the subarachnoid space. It enters the brain only along the perivascular regions of penetrating vessels.

The meninges and cerebrospinal fluid (CSF) are well recognized for their essential roles in protecting the central nervous system. This protective function is largely attributed to the ability of the meninges to firmly anchor the CNS to the surrounding bones, thereby restricting movement and enhancing stability [6]. The periosteal layer, the outer layer of the dura, is securely attached to the skull. In the spinal cord, denticulate ligaments further contribute to mechanical stabilization by anchoring the spinal cord to surrounding meningeal structures. Additionally, the meninges enclose the cerebrospinal fluid (CSF), which allows the central nervous system to remain buoyant and provides protection against mechanical trauma.

1.1. Literature Search Strategy

This narrative review was conducted using literature retrieved from major scientific databases including PubMed, Scopus, and Google Scholar. Keywords used in the search included "meninges", "subarachnoid lymphatic-

like membrane", "SLYM", "meningeal immunity", and "cerebrospinal fluid dynamics". Articles published between 2015 and 2025 were primarily considered, with emphasis on studies addressing the discovery, structure, and functional significance of the SLYM. Relevant review articles and experimental studies were evaluated to provide a narrative overview of current knowledge regarding meningeal biology and its implications for neurological disease.

2. Origin and Structure of the Fetal Meninges

Early evidence of an established meningeal layer can be observed in chick embryos at HH15 (embryonic day 2; E2), in mouse embryos between embryonic days 9 and 10 (E9–E10), and in human embryos at Carnegie stage 15, corresponding to the fourth week of gestation [7]. The initial meningeal cell layer in the forebrain originates from a subset of cranial neural crest cells that migrate rostrally

from the diencephalic neural crest. These early meningeal cells contribute to the formation of the leptomeninges, which later differentiate into the pia mater and arachnoid mater [8]. In embryos, a loose network of cells known as the leptomeninges develops along the blood vessels of the perineural vascular plexus at the glia limitans, the outer boundary of the brain. In mice, the leptomeninges first appear at embryonic day 13 (E13), whereas in humans, they develop between Carnegie stages 17 and 18. The dura mater, the outermost meningeal layer, is located between the leptomeninges and the calvarial mesenchyme, which later develops into the calvarial bones. Studies have shown that the transcription factor *Foxc1* is required for meningeal assembly in the forebrain, providing important insight into meningeal development. Although the precise role of *Foxc1* in meningeal development remains unclear, the milder meningeal phenotype observed in amorphic *Foxc1* mutants suggests that *Foxc1* regulates meningeal cell migration [9]. In *Foxc1* hypomorphs, in particular the more dorsal regions, the meninges are absent; the dural and arachnoid layers partially encircle the forebrain in the *Foxc1*hith/*lacZ* hybrid (*Foxc1*hith/*lacZ*). This finding suggests that *Foxc1* plays a critical role in meningeal development, particularly in the forebrain, where meningeal cell migration occurs in a ventral-to-dorsal wave.

2.1. Developmental and Age-Related Changes of Meninges and SLYM

The development of the meninges begins early during embryogenesis, primarily originating from neural crest cells and mesodermal contributions. In humans, primitive meningeal layers can be identified around the fourth gestational week, with progressive differentiation into dura mater, arachnoid mater, and pia mater occurring during subsequent stages of fetal development [10]. The leptomeninges (arachnoid and pia) develop earlier, while the dura mater forms later as a more fibrous protective layer. Emerging evidence suggests that the SLYM develops as part of the leptomeningeal system during the maturation of the subarachnoid space. Although precise developmental timelines remain incompletely defined, studies indicate that SLYM formation coincides with cerebrospinal fluid compartmentalization and meningeal maturation.

Aging-related changes in meningeal structures, including potential alterations in SLYM integrity, have been proposed. Structural thinning, reduced barrier function, and altered immune cell distribution may occur with advancing age, potentially impacting cerebrospinal fluid dynamics and immune surveillance [11]. These changes may contribute to age-associated neurological disorders; how-

ever, direct evidence in humans remains limited and warrants further investigation.

3. Meninges and Other Barriers

The meninges, consisting of the dura mater, arachnoid mater, and pia mater, play essential roles in CNS protection, homeostasis, immune surveillance, and CSF regulation [12]. These layers provide physical protection and contribute to the segregation of essential physiological processes, including immunological surveillance and cerebrospinal fluid (CSF) transport. The dura mater is attached to the inner surface of the skull and forms the outermost meningeal layer, characterized by its thickness and durability. The dura mater consists of two sublayers that form its structure, the meningeal layer, which is closer to the brain tissue, and the periosteal layer, which lies adjacent to the cranial bone [13]. Dural venous sinuses are located between dural layers and drain venous blood from the brain (Figure 2).

The arachnoid mater derives its name from its web-like appearance and is located beneath the dura mater. It spans the cerebral sulci, separating the dura mater from the pia mater. The space between the arachnoid mater and the pia mater, known as the subarachnoid space, is filled with cerebrospinal fluid (CSF) [14]. Arachnoid trabeculae extend across the subarachnoid space, maintaining the structural integrity of the arachnoid and pia mater. The innermost meningeal layer, the pia mater, closely adheres to the surface of the brain, extending into its sulci and fissures. The pia mater is a thin, semipermeable membrane with a rich vascular supply, allowing the passage of cerebrospinal fluid (CSF) across this tissue layer [15]. The Virchow–Robin spaces within the pia mater allow blood vessels to penetrate the brain parenchyma while facilitating the movement of cerebrospinal fluid and immune cells throughout the tissue. The meninx initially evolved as a single layer in fish before developing into the three-layered structure observed in birds and mammals. Consequently, the human meninx represents a more evolutionarily complex organization. This evolutionary pattern may reflect increasing requirements for mechanical protection, immune regulation, and control of the CNS microenvironment [16].

Notably, these meningeal barriers regulate the exchange of substances between the bloodstream and brain tissue through their interactions with brain barriers, including the blood–brain barrier (BBB) and the blood–cerebrospinal fluid (blood–CSF) barrier [17]. The subarachnoid space contains CSF, supports metabolic waste clearance, and provides buoyancy that reduces the effective weight of the brain. These multifunctional meninges

actively regulate immunity, support disease processes, and maintain central nervous system stability. A comparative overview of the structural and functional characteristics of the meningeal layers, including the recently pro-

posed SLYM, is presented in Table 1. Collectively, these layers serve functions that extend beyond providing basic structural protection.

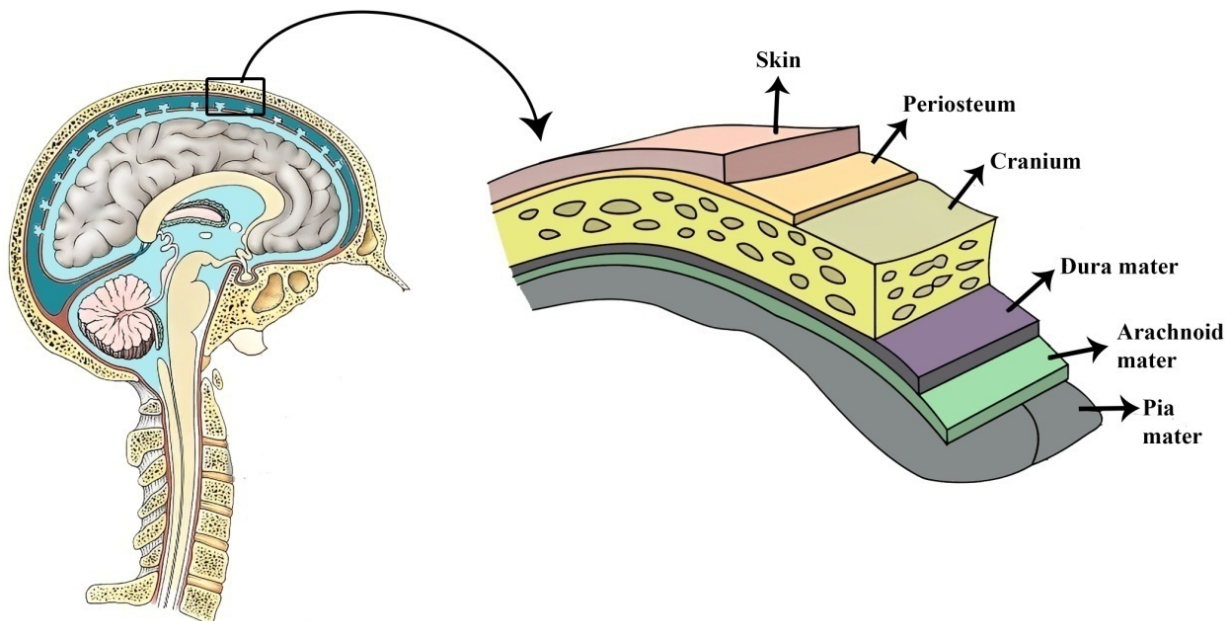


Figure 2: Overview of the meninges and their connection to the skull and brain.

Table 1: Comparison of meningeal layers.

Layer	Location	Structure	Function
Dura mater	Outer layer	Thick fibrous tissue	Mechanical protection
Arachnoid mater	Middle layer	Web-like membrane	Maintains CSF space
Pia mater	Inner layer	Thin vascular membrane	Covers brain surface
SLYM	Subarachnoid space	Thin mesothelial membrane	CSF compartmentalization and immune surveillance

4. Role of Meninges

4.1. Role of Meninges in Corticogenesis

The meninges are essential for the proper development and function of the CNS. However, the molecular mechanisms through which the meninges and meningeal cells contribute to these processes remain poorly understood [18]. The anterior neural folds give rise to the neural crest, which differentiates into connective tissue cells and pericytes. Meanwhile, mesodermal components of the forebrain meninges contribute to the formation of vascular structures that interact with the developing neuroepithelium. Deletion of the posterior diencephalic and mesencephalic neural folds induces apoptosis throughout the

forebrain neuroepithelium [19]. Neural crest-derived cells in the neural folds may be replaced by paraxial mesoderm-derived cells, contributing to the primitive leptomeninges required for encephalon formation. During later stages of development, degeneration of the meninges surrounding the cerebellum results in subarachnoid space neuronal ectopia, gliosis, cerebellar hypoplasia, and the loss of granule cells [20].

Meningeal loss in the hippocampus can lead to secondary abnormalities in the dentate gyrus. Due to their privileged location within the parenchyma and their close association with blood vessels, the meninges are able to provide short-range signals to neural cells during the maturation of brain structures [21]. Since it may bind several trophic and morphogenetic components, the ex-

tracellular matrix that makes up the basal membrane is only employed during corticogenesis. The extracellular matrix of the meninges is composed primarily of collagens, with types I, III, and IV being the most abundant. Meningeal cells also produce non-collagenous extracellular matrix proteins, including fibronectin, laminin, and tenascin [22]. Radial processes provide a migratory scaffold for neurons during cortical and cerebellar development, ensuring proper cellular layering. Genetic ablation of proteins involved in extracellular matrix attachment, including laminin $\alpha 1$, $\alpha 2$, and $\alpha 5$ subunits, disrupts cortical and cerebellar histogenesis. It may also compromise pial integrity and cause separation of radial glial endfeet. One proposed mechanism is that laminins are involved in the functional localization of connexins [23]. Targeted deletion of focal adhesion kinase in the brain meninges disrupts cortical histogenesis and causes neuronal invasion of the marginal zone, retraction of radial glial endfeet, impaired midline fusion of the cerebral hemispheres, and gliosis. This produces a phenotype resembling type II cobblestone lissencephaly, as observed in congenital muscular dystrophy [24].

4.2. Role of Meninges in CNS Homeostasis

Numerous extracellular matrix components, including heparan sulfate proteoglycans, collagens IV, XV, and XVIII, laminin, and fibronectin, are present on the surface of the brain and surrounding the blood vessels [25]. This structure was traditionally considered to form a distinct interface that provides both a physical and functional separation between the brain parenchyma (neurons and glial cells) and the extraparenchymal tissues, including the meninges and blood vessels. Other significant trophic factors derived from the meninges include retinoic acid, CXCL12, FGF-2, and insulin-like growth factor-II. FGF2 and EGF, heparin-binding molecules that could interact with the heparan Sulfate chains of the heparan Sulfate proteoglycan that is abundantly present in meninges, are found in numerous growth factors and cytokines [26]. Interestingly, meningeal cells have been shown to be highly responsive to major mitogenic factors, including epidermal growth factor (EGF), fibroblast growth factor-2 (FGF-2), and brain-derived neurotrophic factor (BDNF). The expression of gap junction proteins further supports the close association between the meninges and brain tissue. Specifically, connexins Cx43, Cx30, and Cx26 have been identified in the meningeal sheaths of blood vessels, the stroma of the choroid plexus, and a network of meningeal cells with projections extending into the brain [27]. These proteins may support anatomical and functional connections

among ependymocytes, astrocytes, meningeal cells, and meningeal perivascular cells.

4.3. Maintenance of the Pial Basement Membrane by the Meninges

A basement membrane (BM) that is rich in extracellular matrix components covers the pial meningeal layer. The pial basement membrane (BM) anchors the endfeet of radial glial processes that originate from neural progenitor cells in the ventricular zone (VZ). It also serves as a physical barrier to migrating neurons [28]. Radial glial processes provide a migratory scaffold for neurons during cortical and cerebellar development, facilitating proper cellular layering. Ablation of genes involved in cell–extracellular matrix (ECM) adhesion disrupts cortical and cerebellar histogenesis, compromises the integrity of the pial basement membrane (BM), and causes separation of radial glial endfeet [29]. Premature separation of radial glial endfeet leads to increased neural progenitor cell death and reduced cortical neuron formation.

Similar to findings in *Foxc1* mutants and *Zic1/3* double mutants, basement membrane (BM) defects in the neocortex have also been associated with abnormalities in meningeal cells. The radial glial scaffold and cortical organization are severely disrupted in *Foxc1*-null mutants because of a gradual breakdown in the pial BM beginning in mid-corticogenesis. Certain cell types in the developing forebrain and meninges express the zinc-finger transcription factors *Zic1* and *Zic3* [30]. In *Zic1/3* mutants, the expression of meningeal genes, including *Cxcl12* and *Foxc1*, as well as meningeal-derived laminin, is reduced. These mutants exhibit separation of the radial glial endfeet and a disruption of the pial BM. This shows that initial meningeal abnormalities may disturb the pial BM and ultimately result in problems in cerebral cortex formation [31].

4.4. Recent Discovery of Fourth Meningeal Layer

The identification of a fourth meningeal layer has revolutionized the understanding of meningeal architecture and its significance in brain health. The subarachnoid lymphatic-like membrane (SLYM) is a newly identified meningeal layer located between the arachnoid mater and the pia mater [8]. Researchers identified SLYM through two-photon imaging of genetically modified mice expressing fluorescent markers. The continuous thin membrane expresses both podoplanin (PDPN), a lymphatic marker, and cellular retinoic acid-binding protein 2 (CRABP2), a meningeal marker, thereby demonstrating its mesothelial characteristics [32]. Immunostaining studies have con-

firmed the presence of SLYM in human tissues, highlighting its potential significance in human health and supporting the evolutionary conservation of this tissue throughout biological history.

The concept of the SLYM gained significant attention following the landmark study by Møllgård et al. (2023), which demonstrated that a mesothelial membrane divides the subarachnoid space into functionally distinct compartments [33]. This discovery challenges the traditional view that the subarachnoid space is a single continuous cavity. The SLYM appears to function as a selective barrier that regulates the movement of CSF, immune cells, and macromolecules. By compartmentalizing the subarachnoid space, the membrane may contribute to immune surveillance and controlled CSF circulation, thereby playing a role in maintaining central nervous system homeostasis [34].

Located within the subarachnoid space, the SLYM may act as a barrier that regulates CSF flow and supports local immune functions [35]. The potential immune func-

tion of SLYM is supported by reports of leukocyte densities comparable to those found in the dura mater. The study results challenge traditional concepts of brain immunity by demonstrating that the brain retains immune privilege, contrary to previous understanding of its immunological status [36]. Research examining meningeal immune functions continues to grow (Figure 3). Traditionally considered to protect the brain from the systemic immune response, the BBB provides a partial state of immunological privilege. Many diseases, including multiple sclerosis, delirium, severe systemic inflammation, and brain injury, have been linked to increased blood-brain barrier permeability. The meninges surrounding the brain have been demonstrated to play a crucial role in CNS immunity. Meningeal immunity and psychopathology are related because the loss of certain immune cells in the meninges and skull directly affects anxiety-like behavior [37]. Moreover, brain injury has been shown to enhance the bone marrow's capacity to generate immune cells, establishing an immune cell reservoir in close proximity to the brain.

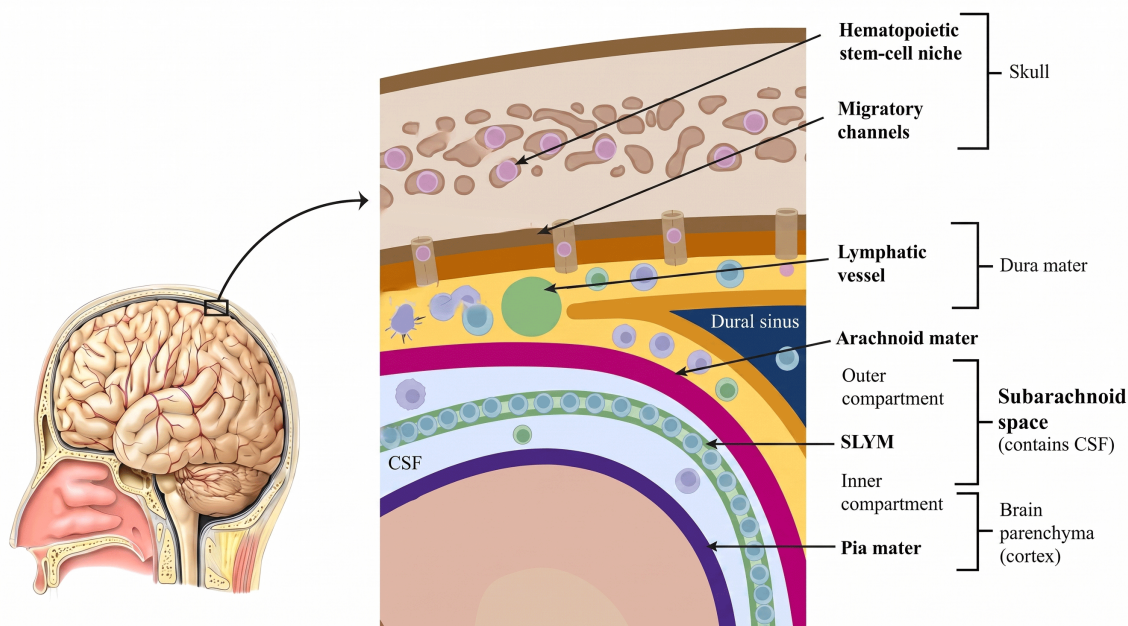


Figure 3: In relation to SLYM. The subarachnoid area is divided into functional spaces by a recently found membrane.

Current evidence suggests that SLYM develops as part of the leptomeningeal system during early meningeal formation. While detailed embryological characterization remains limited, available studies indicate that the membrane develops during maturation of the subarachnoid space, as mesothelial cells organize into a thin bar-

rier structure. Age-related structural alterations have also been proposed. Experimental studies suggest that thinning or disruption of SLYM may occur during aging, potentially influencing cerebrospinal fluid circulation and immune regulation. However, these age-related changes

remain an area of ongoing investigation and require validation through human studies [38].

The SLYM may contribute to mechanical protection by reducing local shear forces within the subarachnoid space; however, this function requires further validation [39]. Some studies have suggested that age-related alterations in SLYM may influence cerebrospinal fluid dynamics and immune responses, which are processes also implicated in neurodegenerative diseases such as Alzheimer's disease. However, current evidence remains preliminary and further research is needed to establish a direct causal relationship. The recent identification of SLYM raises several unanswered questions. Further investigations are required to determine how SLYM connects to the spinal meninges, its role within the glymphatic system, and its specific functions in the human immune system [40]. Future research must validate the present findings by further examining how SLYM affects illnesses present in the central nervous system. The discovery of SLYM provides promising opportunities for developing novel therapeutic approaches that specifically target this layer for the treatment of neuroinflammatory and neurodegenerative diseases [41].

SLYM may also interact with other central nervous system barrier systems, including the BBB and the glymphatic system. The BBB regulates the entry of substances from the bloodstream into the brain, while the glymphatic pathway facilitates the clearance of metabolic waste through cerebrospinal fluid circulation. By compartmentalizing the subarachnoid space, SLYM may contribute to the regulation of CSF flow and immune cell trafficking, thereby indirectly modulating glymphatic clearance mechanisms.

Although the structural characteristics of SLYM have been convincingly demonstrated in animal models, particularly in mice, direct functional evidence in humans remains limited. The delicate nature and thin structure of the membrane make it challenging to visualize using conventional imaging methods or routine histological techniques. Consequently, some researchers suggest that the presence and functional significance of SLYM in humans require further validation through advanced imaging approaches and larger histological studies.

5. Conclusions and Future Directions

The meninges, once considered merely protective layers of the brain, are now recognized as dynamic and multifunctional structures that are essential for CNS development, homeostasis, and immune regulation. The paper discusses the classical roles of the dura mater, arach-

noid mater, and pia mater, while also introducing the recently discovered subarachnoid lymphatic-like membrane as a fourth meningeal layer. The SLYM signifies a transformative advancement in neuroanatomy and neuroimmunology, providing novel perspectives on cerebrospinal fluid compartmentalization and central nervous system immune control. The distinctive structural and functional characteristics of SLYM, including immune cell retention, fluid barrier formation, and potential involvement in aging and disease, suggest that it may play a pivotal role in the pathophysiology of neurodegenerative disorders, such as Alzheimer's disease, and traumatic brain injuries. Understanding this novel meningeal component presents intriguing opportunities for future research. Specifically, in vivo imaging methods and molecular analysis of SLYM in humans may uncover novel biomarkers or treatment targets for central nervous system illnesses. Additionally, pharmacological regulation of meningeal-derived signals and stem cell function may offer promising approaches for neuroregeneration. The incorporation of SLYM into the existing meningeal model enhances our understanding of brain structure and function, prompting the scientific community to reassess conventional neurobiological concepts and investigate novel avenues in brain disorder research and treatment.

From a therapeutic perspective, targeting SLYM presents both opportunities and challenges. Potential strategies may include modulation of its barrier function, immune activity, or cerebrospinal fluid dynamics using pharmacological or nanotechnology-based approaches. However, significant technical barriers remain, including the difficulty of accessing this delicate structure in vivo, lack of specific molecular targets, and limitations in current imaging techniques. Future research should focus on confirming the presence and functional significance of SLYM in humans through advanced imaging techniques and histological studies. Understanding how this membrane interacts with cerebrospinal fluid circulation, the glymphatic system, and immune mechanisms may provide novel insights into diagnostic and therapeutic strategies for neurological disorders [42].

List of Abbreviations

BBB	Blood-Brain Barrier
BDNF	Brain-Derived Neurotrophic Factor
BM	Basement Membrane
CNS	Central Nervous System
CRABP2	Cellular Retinoic Acid-Binding Protein 2
CSF	Cerebrospinal Fluid
ECM	Extracellular Matrix
EGF	Epidermal Growth Factor

FGF-2 Fibroblast Growth Factor-2
PDPN Podoplanin
SLYM Subarachnoid Lymphatic-Like Membrane
VZ Ventricular Zone

Author Contributions

Conceptualization, writing—original draft preparation: K.; Writing—review and editing: K., Y.M., and S.K.; Visualization: K. and Y.M.; Supervision: S.K. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

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AI Declaration

The authors confirm that no AI tools were used to generate any content of this manuscript. The authors take full responsibility for all content presented in this work.

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