The lymphatic system is vital for maintaining fluid balance, supporting the immune response, and facilitating proper nutrient absorption and waste removal. It collects macromolecules, waste products, and excess fluid from most tissues, orchestrating an immune response to protect against pathogens and disease. Traditionally, the brain was believed to lack a lymphatic system and was considered a relatively immune-privileged region. Recent discoveries, however, have challenged that belief. The groundbreaking article by Antoine Louveau et al. in 2015 definitively revealed the existence of meningeal lymphatic vessels (MLVs) in the central nervous system (CNS). Subsequent studies, including those utilizing magnetic resonance imaging, have provided further visualization of major human dural lymphatic structures [2]. This area had remained neglected and disbelieved for nearly 200 years since Paolo Mascagni first described meningeal lymphatics in 1787 [3]. Emerging research has highlighted the role of MLVs in various neurological disorders, including brain tumors, traumatic brain injury, stroke, Alzheimer’s disease, Parkinson’s disease, multiple sclerosis, and in aging [4]. Understanding the meningeal lymphatic system is crucial for comprehending these diseases and exploring potential therapeutic breakthroughs.

1. MLVs

The meninges are integral to mammalian physiology; they envelop and protect the entire CNS. Comprising three layers - the dura mater, arachnoid mater, and pia mater - the meninges form a protective barrier. Within the dura mater, MLVs run alongside arteries and veins, including the superior sagittal sinus, transverse sinus, sigmoid sinus, retrolateral vein, rostral rinal vein, middle meningeal artery, and pterygopalatine artery [5]. Under normal conditions, fully developed MLVs are confined to the dura mater and do not directly interact with, or permeate, brain tissue [1]. Lymphatic vessels exit the skull through the jugular foramen, leading to the deep cervical lymph nodes (dCLNs) [5]. Waste products generated as metabolic byproducts are expelled from the brain in cerebrospinal fluid (CSF), with the brain producing approximately 500 mL of CSF daily [6]. CSF exits the CNS via arachnoid granulations and villi within the dural venous sinuses, peripheral lymphatic vessels near the cribriform plate, and MLVs. MLVs provide a newly discovered pathway for the uptake and drainage of CSF, immune cells, and CNS-derived antigens into the cervical lymph nodes, particularly the dCLNs [7]. Therefore, understanding the role of MLVs in immune surveillance of the lymphatic system is crucial for our understanding of brain-tumor growth, neuroinflammation, multiple sclerosis, and many other conditions. MLVs also play a significant role in aiding the exchange mechanism for CSF and interstitial fluid, known as the “glymphatic system”, to clear solutes from the brain parenchyma [8].

2. Role of Immune Surveillance of the Brain Lymphatic System

The immune surveillance of the brain lymphatic system, particularly through the meningeal lymphatics and their direct connection with the dCLNs, is essential for CNS immune surveillance [9]. Under normal conditions, healthy mammalian brain tissue harbors a substantial population of resident innate myeloid immune cells, with minimal quantities of adaptive immune cells present [10]. Adaptive immune cells within the brain parenchyma are typically found in periventricular regions, adjacent to blood vessels, or in the highly vascularized leptomeninges [10]. Although these immune cells cannot enter the brain parenchyma, MLVs transport numerous immune cells out of the CNS to contribute to immune surveillance [4].

In pathological conditions, dendritic cells recognize corresponding antigens and migrate to the dCLNs to promote antigen proliferation and activation [4]. Additionally, studies using experimental autoimmune encephalomyelitis have shown that ablation of MLVs resulted in a less severe disease, supporting the immune-cell trafficking role of the MLVs [4,9]. Therefore, immune surveillance of the brain lymphatic system plays a crucial role in the pathogenesis of brain tumors, including brain metastasis, and other immunological diseases like multiple sclerosis [11,12].

3. Role of the Clearance System in Neurodegenerative Diseases

The clearance system mediated by MLVs is implicated in various neurodegenerative diseases. In aged mice, reductions in the length and diameter of meningeal initial lymphatics resulted in reduced CSF drainage into the dCLNs, and were associated with cognitive decline [4,10].
Alzheimer’s disease is influenced by MLVs; ablation led to increased amyloid β deposition in the meninges and brain parenchyma, resulting in neuronal dysfunction and behavioral changes [4]. Mice with ablated meningeal lymphatics also showed decreased extracellular tau-protein clearance from brain parenchyma [9]. In transgenic mouse models of Parkinson’s disease, ligating the dCLNs aggravated α-synuclein pathology [4, 9]. Restoration of meningeal lymphatic drainage function alleviated traumatic brain-injury-induced gliosis [4]. MLVs also play a neuroprotective role in stroke by removing excess fluid from the brain and growing into the injured parenchyma to eliminate edema [4].

4. Conclusion
MLVs play crucial roles in immune surveillance, immune response, and brain metabolic waste clearance, in various neurological disorders. Recognizing the significance of MLVs is essential for understanding pathomechanism and identifying potential therapeutic targets. Further research in this area is anticipated to shed light on their intricate functions.

Author Contributions
MJ, DBB, HYK designed the study. HYK wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

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