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The role of meningeal lymphatic system in Alzheimer disease

Fatima Ezzahra Errachidi*
Independent Researcher, Turkey

SUMMARY

Alzheimer's disease is one of the most common neurodegenerative disorders that affects millions globally. It is characterized by loss of neurons, neurofibrillary tangles, and beta-amyloid accumulation, however, the mechanism behind these pathological features is still unclear. Recently, increasing evidence demonstrates the role of the meningeal lymphatic system (MLS) in cerebrospinal fluid (CSF) transportation, beta-amyloid clearance, and neuroinflammation. Thus, MLS may be considered a potential therapeutic target for neurodegenerative diseases. Here, we discuss the multiple functions of the meningeal lymphatic system and its potential role in the progression of Alzheimer's disease.

Keywords: Lymphatic vessels; Cervical lymph nodes; Alzheimer's disease; Inflammation

Address for correspondence:

Fatima Ezzahra Errachidi
Independent Researcher, Turkey
E-mail: kimfatimal68@gmail.com

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INTRODUCTION

The central nervous system (CNS) was assumed to be an immune-privileged organ until the end of the 18th century when an Italian physician named Paolo Mascagni mentioned a lymphatic system within the brain meninges of human wax models [1]. Nearly two decades later, further studies have been focused on meninges within the CNS. Louveau and colleagues discovered functional lymphatic vessels lining the dural sinuses in mice models that express all of the molecular hallmarks of lymphatic endothelial cells, are able to carry both fluid and immune cells from the CSF, and are connected to the deep cervical lymph nodes [2]. Absinta and his colleagues achieved to visualize an accurate imaging of meningeal lymphatic vessels (MLVs) in the human brain by using T1 and T2 MRI imaging techniques [3]. As a result, the number of studies regarding this system has increased significantly.

The system that comprises a network of lymphatic vessels located in the dorsal skull, transverse sinus, superior sagittal sinus, and lateral or basal parts of the skull is named the meningeal lymphatic system. Due to the absence of smooth muscle cells, the dorsal meningeal lymphatic vessels in the dorsal skull are classified as capillary lymphatic vessels, they are specialized in carrying macro-molecules and fluid. Basal meningeal lymphatic vessels found in the basal part of the skull, are categorized as both collecting and capillary lymphatic vessels, due to the existence of valves that allow them to uptake and transport cerebrospinal fluid (CSF) [4].

The meningeal lymphatic system can be thought of as a transport route for CSF from the subarachnoid space to the peripheral blood; it can also move fluid via foramina at the skull base into deep cervical lymph nodes [2]. In an effort to demonstrate that meningeal lymphatic vessels (MLVs) have access to CSF, a group of Prox1GFP mice had their cerebral spinal fluid injected with a red fluorescent tracer Qdot655. The tracer was recognized within the MLVs near the transverse sinus one hour after injection using multiphoton intravital imaging, indicating that MLVs can transport CSF [5]. Furthermore, by transporting leukocytes such as T cells within their vessels, meningeal lymphatic vessels can play a significant role in the inflammatory response and immune surveillance of the central nervous system [2]. According to another study conducted by Louveau and his peers, MLVs and C-C chemokine receptor type 7 (CCR7) cooperate to allow immune cells to access draining lymph nodes, where they participate in the immune response, implying that MLVs damage can alleviate inflammation within the CNS [6]. These two primary functions can aid meningeal lymphatic vessels in their involvement in

neuroinflammatory and neurodegenerative diseases such as Alzheimer's disease.

Alzheimer's disease (AD) is a neurodegenerative disease associated with aging, it is caused by two pathological dysfunctions: ß-amyloid plaque accumulation and neurofibrillary tangles of hyperphosphorylated tau. It can be considered the most common cause of dementia, which is characterized by a severe, progressive loss of brain functions such as, cognition and memory. Currently, the only available treatments are used to improve patients' quality of life. Individuals with any stage of Alzheimer's disease, for instance, are advised to use cholinesterase inhibitors such as donepezil, rivastigmine, and galantamine. Memantine is suggested to patients with moderate to severe Alzheimer's disease dementia [7]. Hence, finding a cure for AD has been the core concern for many years, many researchers are considering different route including the meningeal lymphatic system, to treat AD by clearing accumulation of amyloid-beta and tau.

The meningeal lymphatic system can transport macromolecules such as amyloid-beta through CSF drainage and may also play a role in neuroinflammation in Alzheimer's disease. A dysfunction in meningeal lymphatic vessels may result in a decrease of CSF drainage which may cause instability of amyloid-beta production and clearance, leading to amyloid-beta accumulation that worsens Alzheimer's disease symptoms. In order to emphasize the importance of meningeal lymphatic vessels in both CSF drainage flow and memory and cognitive skills. Da Mesquita and colleagues used Visudyne to ablate meningeal lymphatic vessel, and injected 5 μl of fluorescent ovalbumin–lexa Fluor 647 (OVA-A647) into the subarachnoid space to measure the impact of impaired MLVs on CSF drainage, resulting in a reduction of OVA-A647 tracer in deep cervical lymph nodes. As for the influence of MLVs on brain functions, the behavior of visudyne with photoconversion group of mice was evaluated after performing the ablation of meningeal lymphatic vessels twice, significant changes were detected in both contextual fear conditioning (CFC) and Morris water maze(MWM) tests, indicating the effect of meningeal lymphatic system on fear memory and spatial learning skills [5].

Since impaired meningeal lymphatic vessels can reduce amyloid-beta clearance by limiting CSF drainage, beta amyloid plaques deposition may initiate an immune response that stimulates inflammation in the brain. A recent study has demonstrated that type 2 innate lymphoid cells (ILC2s) discovered in meningeal lymphatic vessels play a role in cognitive processing and repairing nervous tissues, as well as endorsing the production of several cytokines in order to regulate inflammation in the brain [8]. In addition, Da Mesquita and collegues found a connection between the meningeal lymphatic system and microglia, as ablation of the meningeal lymphatic vessels can result in a loss of homeostatic microglia functions, leading to a rise in amyloid-beta deposition [9]. Both of these studies indicates the role of meningeal lymphatic vessels in inflammation, nerve repair and microglia functions, however, it is unknown if the same role applies to human brain.

If the impaired meningeal lymphatic system leads to an increase of amyloid-beta plaque deposition that aggravates Alzheimer's disease, then it may also take part in the potential treatment of AD by using MLVs as a route to reduce the deposition. To test this hypothesis, a recent study revealed that using Melatonin in mice models can enhance lymphatic clearance of Aβ deposition, implying that Aβ in lymph nodes increased significantly high after melatonin treatment. Furthermore, the level of oligomeric Aβ significantly dropped within the brain of mice. Whereas, the Aβ levels in plasma remained unchanged, implying that using the meningeal lymphatic system as a clearance route may be more effective than via the blood-brain barrier BBB clearance pathway [10].

To summarize, the meningeal lymphatic system clearly plays an important role in the progression and treatment of Alzheimer's disease. Since MLVs damage can be a cause of AD aggravation, the meningeal lymphatic system could be used as a new drug delivery route to decrease amyloid-beta deposition in the brain. However, more human-based researches and clinical trials should be conducted to understand the role of the meningeal lymphatic system in the human brain and whether this system can be considered as a therapeutic approach for AD patients.

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