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Review article

Lymphatic drainage system of the brain: A novel target for intervention of neurological diseases

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ABSTRACT

The belief that the vertebrate brain functions normally without classical lymphatic drainage vessels has been held for many decades. On the contrary, new findings show that functional lymphatic drainage does exist in the brain. The brain lymphatic drainage system is composed of basement membrane-based perivascular pathway, a brain-wide glymphatic pathway, and cerebrospinal fluid (CSF) drainage routes including sinus-associated meningeal lymphatic vessels and olfactory/cervical lymphatic routes. The brain lymphatic systems function physiological as a route of drainage for interstitial fluid (ISF) from brain parenchyma to nearby lymph nodes. Brain lymphatic drainage helps maintain water and ion balance of the ISF, waste clearance, and reabsorption of macromolecular solutes. A second physiological function includes communication with the immune system modulating immune surveillance and responses of the brain. These physiological functions are influenced by aging, genetic phenotypes, sleep-wake cycle, and body posture. The impairment and dysfunction of the brain lymphatic system has crucial roles in age-related changes of brain function and the pathogenesis of neurovascular, neurodegenerative, and neuroinflammatory diseases, as well as brain injury and tumors. In this review, we summarize the key component elements (regions, cells, and water transporters) of the brain lymphatic system and their regulators as potential therapeutic targets in the treatment of neurologic diseases and their resulting complications. Finally, we highlight the clinical importance of ependymal route-based targeted gene therapy and intranasal drug administration in the brain by taking advantage of the unique role played by brain lymphatic pathways in the regulation of CSF flow and ISF/CSF exchange.

Contents

Abbreviations: Aβ, amyloid β; AD, Alzheimer's disease; ADC, apparent diffusion coefficient; AFM, atomic force microscope; APC, antigen presenting cells; ApoE, apolipoprotein E; AQP4, aquaporin-4; BBB, blood brain barrier; BCSFB, blood–cerebrospinal fluid barrier; BM, basement membrane; CAA, cerebral amyloid angiopathy; CBF, cerebral blood flow; C/EBP, CCAAT-enhancer-binding protein; CLB, cervical lymphatic blockade; CLN, cervical lymph nodes; CNS, central nervous system; CSF, cerebrospinal fluid; dCLN, deep cervical lymph node; DCs, dendritic cells; EAE, experimental autoimmune encephalomyelitis; ECS, extracellular space; G-CSF, granulocyte colony-stimulating factor; ICP, intracranial pressure; ISF, interstitial fluid; MCAO, middle cerebral artery occlusion; MRI, magnetic resonance imaging; PDE, phosphodiesterase; PVS, perivascular space; RAGE, receptor for advanced glycation end products; SAH, subarachnoid hemorrhage; SAS, subarachnoid space; SCARA-1, scavenger receptor A-1; TBI, traumatic brain injury; TH1, T helper 1; TH17, T helper 17; t-PA, tissue-type plasminogen activator; VRS, Virchow-Robin spaces; VSMCs, vascular smooth muscle cells.

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1. Introduction

Lymphatic drainage is essential for maintenance of overall tissue water and solute balance, homeostasis, metabolism, and immunity. The lymphatic system is made up of a network of blind-ended capillaries that drain into larger vessels responsible for removing lymph that contains waste materials, fluid, proteins, and cells from the interstitial fluid (ISF) surrounding tissues and most organs (Clapham et al., 2010; Dissing-Olesen et al., 2015). Eventually, the lymphatic system drains to the venous system for recirculation (Foldi, 1999). Despite the high metabolic rate of brain tissue, the brain parenchyma lacks conventional lymphatic vessels like other peripheral tissues and organs. However, the central nervous system (CNS) has its own unique lymphatic drainage structures (Laman and Weller, 2012, 2013). The existence of an irregular lymphatic drainage system in vertebrate brain has been proposed based on physiological and immunological evidence of communication between brain parenchyma, extracellular space (ECS), perivascular spaces (PVS), perineural space, subarachnoid space (SAS), meningeal lymphatics and cervical lymph nodes.

These lymphatic drainage pathways or routes in the brain have been examined by using the different types of tracer dyes Indian ink (Zhang et al., 1992) and Evans blue, radioactive protein tracers (Bradbury et al., 1981; Szentistvanyi et al., 1984), and various fluorescent tracers with different molecular structure (Carare et al., 2008). In 2008, the Weller-Carare group suggested that the basement membranes (BM) of cerebral arteries contained a perivascular pathway for the lymphatic drainage of the brain parenchyma based on data obtained from studies using florescent tracers and confocal microscopy. In 2012, Iliff et al. (Iliff et al., 2012) discovered a brain-wide network of paravascular pathways surrounding arterioles, capillaries, and venules lined with astrocytic vascular endfeet utilizing two-photon imaging. The “glia lymphatic”, or “glymphatic” drainage system has been proposed by Nedergaard (2013), Iliff and Nedergaard (2013) and Jessen et al. (2015) that integrates cerebrospinal fluid (CSF) circulation and ISF exchange with brain parenchyma via aquaporin-4 (AQP4) water channels expressed in astrocytes. Remarkably, in 2015, Louveau et al. (2015) and Aspelund et al. (2015) independently characterized the presence of meningeal lymphatic vessels lined with typical lymphatic endothelial cells in the mouse brain, which confirmed earlier observations by Foldi et al. (1966) and Andres et al. (1987). Furthermore, Bower et al. (2017) and van Lessen et al. (2017), very recently, discovered meningeal mural lymphatic endothelial cells in the zebrafish. This new type of brain lymphatic cells functions as a ‘scavenger' and participate in meningeal angiogenesis. These novel data demonstrated how the brain uses its own inbuilt lymphatic drainage system to process ISF/CSF exchange, clean wastes, and carry fluid, macromolecules, and immune cells from brain toward the deep cervical lymph nodes (Kida et al., 1995).

There are several excellent reviews regarding the structure and functional characteristics of the unique lymphatic drainage system in the vertebrate brain. Weller et al. (2009, 1996) systematically analyzed pathways of lymphatic drainage defined by anatomical features and tracer studies in rodent and other species and their correlation with human brain. Comprehensive reviews (Brinker et al., 2014; Matsumae et al., 2016) based on new findings utilizing cellular, molecular, and neuroimaging techniques have demonstrated the intimate exchange between CSF and ISF utilizing the brain lymphatic drainage pathways. Jessen et al. (2015) reviewed the structural elements, organization, regulation and functions of the brain glymphatic system. Bakker et al. (2016) discussed the partially conflicting data on CSF and ISF circulation regulated by the peri- and paravascular drainage pathways, especially in the

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