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REVIEW ARTICLE

Central nervous system immunity in relation to aging and AD

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ABSTRACT

The present report discusses the immune and clearance system of the central nervous system (CNS) in terms of its anatomical, physiological, and biochemical properties. There is now a growing body of evidence that progressive dysfunction of the meningeal lymphatic system should be considered as a risk factor for aging-related brain disorders. In addition, the activity of meningeal lymphatics may alter the access of CSF-carried immune neuromodulators to brain parenchyma, which is also involved in the onset of aging and AD. In the CNS clearance system, impairment of the BBB and small arteries, as well as the major protein of the end feet of astrocytes, AQP4, are associated with aging or AD. The idea of maximizing brain "waste discharge" as a new preventive or therapeutic target for neurodegenerative diseases in the context of healthy aging has been accepted.

Introduction

The recognized core pathology of Alzhiemer's disease (AD) is amyloid (Aβ) plaques and neurofibrillary tangles (NFTs). Patients may exhibit pathological features of Aβ plaques for up to or more than a decade prior to any obvious AD diagnosis (Kinney et al., 2018; Cullen et al., 2021; Hascup et al., 2021; Oakley et al., 2006). In AD, tau proteins are phosphorylated at multiple sites, resulting in the detachment of tau proteins from microtubules and causing the collapse of microtubule structures and the destruction of some cells (Kinney et al., 2018; Cullen et al., 2021). In the last decade, many studies have shown that a third core feature of AD has emerged, namely, that in addition to A β plaques and NFT, the brains of AD patients exhibit a sustained inflammatory response (Mesquita et al., 2018; Kinney et al., 2018; Cullen et al., 2021), which may provide insight into the pathogenesis of AD and provide a link between the other two core pathologies. This inflammatory response has now been routinely observed in the brain autopsy tissue of postmortem AD patients (Mesquita et al., 2018; Kinney et al., 2018; Cullen et al., 2021; Benvenistea et al., 2019; Hascup et al., 2021; Oakley et al., 2006; Schneider et al., 2007; 2010; Crystal et al., 2014; Brandon et al., 2013; Lamar et al., 2022), and in preclinical animal model systems of AD.

This chronic neuroinflammation is associated with the activation of microglia and the release of many cytokines (Kinney et al., 2018, Cullen et al., 2021; Hascup et al., 2021; Oakley et al., 2006; Patrick et al., 2002). The persistence of an immune response in the brain is not unique to AD. It has also been associated with aging of the brain and other neurodegenerative diseases (Gabor et al., 2018). The inflammatory response in the brains of AD patients was once thought to be a response to the neuronal loss that occurs with the disease. However, a large body of research now suggests that this immune response is not only associated with neurodegeneration, but also promotes and exacerbates A β and NFT lesions. Furthermore, it has been suggested that the inflammatory response may provide a link between the initial A β pathology and the development of NFT (Mesquita et al., 2018; Kinney et al., 2018; Cullen et al., 2021; Benvenistea et al., 2019; Hascup et al., 2021). That is, a unique aspect of the physiology of the central nervous system (CNS) is neuro-immune interactions. So, what is the picture of immunity in the CNS associated with the inflammatory response in the brain? In recent years, a great deal of research has been done to address this question. Among them, Dr. Kipnis and Dr. Schneider (Schneider et al., 2007; 2010; Crystal et al., 2014; Brandon et al., 2014; Lamar et al., 2022; Kipnis et al., 2004, 2016; Voglaar et al., 2018; Filiano et al., 2016) made profound contributions to it.

The objective of this review is to summarize the physiological, biochemical, and anatomical aspects of the immune and clearance correlates of the central nervous system, including the parenchymal vascular system, glial cells, neurons, cytokines, and meningeal lymphatic immunity, and provided some thoughts on their potential sources and therapeutic ideas as possible biomarkers for aging and AD.

The research methodology is based on a review of the latest research findings in the field.

Conventional theory suggests that the brain is in an "immune privileged" state and that access of immune cells to the brain parenchyma is restricted. However, a new view has been accepted that the meninges that encase the brain contain lymphatic vessels that drain interstitial and cerebrospinal fluid and therefore function as lymphatic vessels for central nervous system drainage (Louveau et al. 2015). In addition, unlike brain parenchyma, the meningeal space contains a variety of immune cells whose activity is related to brain function, including learning and memory (Mesquita et al., 2018, 2021; Louveau et al., 2015; Absinta et al., 2017; James et al., 2015; Papadopoulos et al., 2020; Noel et al., 2010; Walsh et al., 2014; Kipnis et al., 2004, 2016; Voglaar et al., 2018; Filiano et al., 2016; Louveau et al., 2015).

The concept of the presence of lymphatic vessels in the meninges was introduced as early as the end of the 18th century by Paolo Mascagni, an Italian physician (Bucchieri et al., 2015). However, his claim that lymphatic vessels were present in the meninges was not accepted. Nearly two centuries later, another Italian scientist "discovered" lymphatic vessels when examining samples of human dura mater (Bucchieri et al., 2015), and in the 1960s, Csanda and colleagues described the existence of a lymphatic connection between the CNS and the periphery, suggesting that it was involved in the excretion of CNS molecules. But this concept was also met with skepticism by contemporaries. At the end of the last century, Dr. Li and his team, using scanning electron microscopy, claimed to have discovered meningeal lymphatic vessels, which they named meningeal stomata which localized between the mesothelial cells of the cerebral meninges (Mesquita et al., 2018, 2021; Louveau et al., 2015; Absinta et al., 2017; James et al., 2015; Papadopoulos et al., 2020; Noel et al., 2010; Walsh et al., 2014; Kinney et al., 2018; Cullen et al., 2021; Benvenistea et al., 2019; Bucchieri et al., 2015). However, given the limitations of the experimental methods available at the time, they could not identify these stomata, which are located between the mesothelial cells of the meninges (Bucchieri et al., 2015), as actually being lymphatic vessels. Afterwards, Dr. Kipnis and his team demonstrated that the observed rounds to oval stomata were meningeal lymphatic vessels (Mesquita et al., 2018, 2021; Louveau et al., 2015; Absinta et al., 2017; James et al., 2015; Papadopoulos et al., 2020; Noel et al., 2010; Walsh et al., 2014). The topography of the meningeal lymphatic vessels network associated with the dura mater has been mapped by immunohistochemistry and specific lymphatic endothelial labeling in mouse, nonhuman primate, and human brain, including along venous sinuses (e.g., superior sagittal sinus, transverse sinus, sigmoid sinus) and the middle meningeal artery , then out of the CNS, draining to the jugular veins (jugular veins) (Zhao et al., 2015; Louveau et al., 2017; Mesquita et al., 2018, 2021; Louveau et al., 2015; Absinta et al., 2017; James et al., 2015; Papadopoulos et al., 2020; Noel et al., 2010; Walsh et al., 2014)). In this way, the meningeal lymphatic vessels, and the accompanying true CNS lymphatic network associated with the cranial nerves and the large vessels leaving the skull, are depicted.

By now, more than 200 years had passed before Mascagni's initial observation was confirmed by sufficiently detailed structural

and functional features as meningeal lymphatic vessels (Mesquita et al., 2018, 2021; Louveau et al., 2015; Absinta et al., 2017; James et al., 2015; Papadopoulos et al., 2020; Noel et al., 2010; Walsh et al., 2014; Louveau, 2015, 2017). This arduous journey has found a good explanation for many diseases of the central nervous system, especially neurodegenerative diseases, such as Alzheimer's disease. It breaks a long-held dogma that the central nervous system is an "immune privileged" organ with no direct communication or interaction with the systemic immune system (Louveau et al., 2015).

In recent years, the meningeal lymphatic system has been recognized as a new player in neurophysiology, assuming an important role in the complex circulation and exchange of soluble contents between the cerebrospinal fluid (CSF) and the interstitial fluid (ISF) (Mesquita et al., 2018, 2021; Louveau et al., 2015; Absinta et al., 2017; James et al., 2015; Papadopoulos et al., 2020; Noel et al., 2010; Walsh et al., 2014). The more accepted hypothesis is that CSF from the subarachnoid space flows deeper into the brain along the Virchow-Robin space (paravalvular inflow), and that solutes in CSF reach the brain parenchyma via this paravalvular pathway, interchange substances with ISF in the brain parenchyma, and then carry toxic products out along the perivascular space (paravalvular outflow) back to the subarachnoid space, where they converge again into a network of venous sinuses (e.g., supratentorial sagittal sinus) out of the CNS (Benvenistea et al., 2019; Aspelund et al. 2015; Eide et al., 2018; Hladky et al., 2014, 2018; Cserr et al., 1992; Knopf et al., 1995). Studies by Dr Kipnis and his team have shown that these two systems, although without any obvious anatomical connection, are directly linked through the CSF (Mesquita et al., 2018, 2021; Louveau et al., 2015; Absinta et al., 2017; James et al., 2015; Papadopoulos et al., 2020; Noel et al., 2010; Walsh et al., 2014). In the central nerve parenchyma of the brain, excretion of cellular debris and waste products from cellular metabolism is partly completed by the paravascular pathway, via the interchange pathway between CSF and ISF (Benvenistea et al., 2019; Hascup et al., 2021; Oakley et al., 2006; Aspelund et al., 2015; Eide et al., 2018; Hladky et al., 2014, 2018; Cserr et al., 1992; Knopf et al., 1995; Iliff et al., 2012; Kress et al., 2014). The complex network of brain parenchymal vessels that supply oxygen and nutrients to nerve cells, where the structure of the blood-brain barrier (BBB) and the proteins associated with it play a key role in the execution of function as well as in the development of disease (Hladky et al., 2018; Zhao et al., 2015).

The existence of the BBB was first observed by Paul Ehrlich in 1885. When arteries enter the brain from the subarachnoid space, they consist of endothelial cells (EC), basement membrane, smooth muscle cells, perivascular (Virchow-Robin) spaces, pia mater, and astrocytic end foot. However, as the vessels continue to penetrate deeper into the brain, they lose coverage of smooth muscle cells and cortical material, thus gaining pericytes between the EC and astrocyte ends. Along the length of the cerebral vasculature, there is connection between the cells of the vascular system and the neurons and glial cells adjacent to the vascular system (Daneman et al., 2015). Between 80% and 99% of the basement membrane surface of the CNS

microvascular system is covered with the end foot of astrocytes. The other part of the protrusion also extends from the astrocyte body to the cell body and axon of the neuron and covers it with end feet that surround the synaptic cleft, preventing neurotransmitters from leaking elsewhere and allowing the excess to go out. Astrocytes act as bridges, where bidirectional signaling occurs between neurons and the vascular system, transmitting signals from neurons to the vascular system of the CNS to coordinate blood flow with neuron activity, thus forming the neurovascular unit (NVU), whose function is to be able to strictly regulate cerebral blood flow (CBF) in the presence of different neuronal activities. Therefore, the regional electrical activity of the brain and the blood regulation of the corresponding regions are mainly accomplished through astrocytes, not neurons. On the other hand, the main mediator of cerebrovascular permeability, astrocytes perceive changes in blood composition more acutely and communicate them to neurons. These new findings, which go beyond conventional theories, also reveal a possible close relationship between astrocytes and neurodegenerative diseases and psychiatric disorders (Stanimirovic et al., 2012; McConnell et al., 2017).

Given such anatomical properties, the functions of astrocytes are much broader and more important than conventional theories suggested, for example, it can act as a vasomodulator to regulate blood flow, excretion of wastes (they have a role in the removal of harmful metabolites and waste products from the CNS); It is also an important component of cellular networks (astrocytes can freely communicate with one another through gap junctions). In this way. They form a very large highly coordinated cellular network throughout the CNS. It helps in the regulation of various activities in the brain and spinal cord. Proteins associated with astrocytes, including gap junction proteins (connexins 40 and 43), water channel aquaporin-4 (AQP4), calcium binding protein S100B and glutamatergic excitatory amino acid transport proteins 1 and 2 (EAAT1, EAAT2) and glutamine synthetase. Among them, water channel AQP4 was expressed at a high level at the end feet of astrocyte. AQP4 is a water channel that regulates water and ion homeostasis in the brain and is an important protein component of the neurovascular unit (VNU). In addition to its role in water redistribution, AQP4 regulates cerebral blood flow, glucose transport and metabolism, BBB integrity, glutamate conversion, and synaptic plasticity. Most importantly, AQP4 is also involved in functional waste removal pathways in the CNS of vertebrates (Smith et al., Mader et al., 2019; Xu et al., 2015; Zeppenfeld et al., 2017; Hoshi et al., 2012). AQP4 is widely expressed throughout the brain, especially in the BBB, where it is highly polarized into astrocytic end feet in contact with blood vessels. The role of AQP4 in synaptic plasticity, learning and memory has only recently been clarified. If AQP4 polarization is lost (as occurs in many brain injuries) it may lead to BBB collapse and to impaired clearance, which may be closely related to brain aging and AD (Smith et al., 2019; Mader et al., 2019; Xu et al., 2015; Zeppenfeld et al. 2017; Hoshi et al., 2012; Tamura et al., 2020).

Recent studies have shown that there is a CSF/ISF-filled space next to the vasculature (Zhao et al., 2015) and that cerebral arterial pulsation facilitates CSF flow into the cerebral vasculature, while AQP4 is another important mechanism of arterial pulsation, which is essential for paravascular fluid and macromolecular exchange. In addition, AQP4 protein plays a key role in protecting the integrity of the glial cell limit of the BBB (Smith et al., 2019; Mader et al., 2019; Xu et al., 2015; Zeppenfeld et al. 2017; Hoshi et al., 2012; Zhao et al., 2015; Asqari et al., 2016).

The steps involved in the removal of solute waste from the brain can be summarized as (1) the flow of CSF from the subarachnoid space into the periarterial space, (2) the deep transport of AQP4-dependent CSF from the periarterial space into the periarterial space of the brain parenchyma where material is exchanged with ISF, (Louveau et al., 2015) the para-venous drainage of interstitial brain waste, and the connection of the meningeal lymphatics to the extracerebral lymphatic circulation (Absinta et al., 2017).

So far, we have reviewed the anatomical, physiological, and biochemical features associated with central nervous immunity. During aging, the above-mentioned anatomical structures and associated proteins are subject to changes and damage, which are closely related to pathogenicity. In addition, the impairment of meningeal lymphatic vessel function and the pro-inflammatory tilt of meningeal immunity are closely related to the development and progression of AD.

The meningeal lymphatics on aging and AD

In the central nervous system, aging has been shown to be associated with impaired function of the meningeal lymphatics (Mesquita et al., 2021; Kinney et al., 2018; Cullen et al., 2021; Benvenistea et al., 2019; Oakley et al., 2006). In a recently published article, it was demonstrated that CSF solute efflux to supraclavicular lymph node (sCLNs) is reduced in aged mice (Eide et al., 2018; Cserr et al., 1992). The lack of dual lymphatics in transgenic mouse models has been shown to obstruct the clearance of macromolecules from the brain to the cervical lymph nodes (Louveau et al., 2015; Dando et al., 2019). In aging mammals, impaired function of the meningeal lymphatics can lead to an accelerated accumulation of toxic amyloid β-proteins in the brain parenchyma, thereby exacerbating the pathological changes associated with AD (Rua, et al., 2018; Patrick et al., 2002). In testing CLNs in AD transgenic mice, Pappolla et al. observed that impaired meningeal lymphatic drainage of CSF affects Aβ clearance, thereby exacerbating brain amyloid deposition in AD (Louveau et al., 2015; Louveau et al., 2017). Animal experiments found that ablation of meningeal lymphatic drainage in young adult AD transgenic mice (J20 and 5xFAD models) resulted in more severe cerebral amyloid lesions. Both the amyloid deposits in the meninges after lymphatic ablation and the recruitment of macrophages around A β deposits were like those observed in the meninges of human AD patients. Surprisingly, this feature was not observed in comparable

mice with intact meningeal lymphatic vessels (Mesquita et al., 2021). These observations suggest that the decline in meningeal lymphatic function during aging may exacerbate amyloid lesions in the brain and meninges and ultimately contribute to the emergence of AD cognitive dysfunction.

Studies by Jonathan Kipnis et al. have hypothesized that age-related functional impairment of the meningeal lymphatics leads to the accumulation and aggregation of Aβ first in the meningeal space, triggering a pro-inflammatory innate immune response that underlies cognitive impairment (Mesquita et al., 2018, 2021; Louveau et al., 2015). This phenomenon is often seen during neuropathological examinations of the aging brain. If this hypothesis is correct, then restoring/enhancing drainage through the meningeal lymphatics may remove aggregates from the meninges and block the meningeal proinflammatory immune response, thereby alleviating AD pathology and cognitive decline. Other experiments have also shown that ablation of meningeal lymphatic vessels in 5xFAD mice (a mouse model of amyloid deposition expressing five mutations found in familial AD) exacerbates Aβ deposition, microgliosis, neurovascular dysfunction, and behavioral deficits, thereby worsening outcomes in mice receiving passive immunotherapy against Aβ (Richard et al., 2015). Notably, the genetic signature of microglia with impaired meningeal lymphoid function in 5xFAD mice overlaps significantly with the transcriptional signature of activated microglia in the brains of AD patients. These data suggest that impaired meningeal lymphatic drainage exacerbates the microglial inflammatory response in AD and that enhanced meningeal lymphatic function combined with immunotherapy leads to better clinical outcomes for these experiments in which A β is drained from the ISF of the brain through the meningeal lymphatics (Louveau et al., 2015; Iliff et al., 2012; Richard et al., 2015; Louveau et al., 2017). The investigators propose that progressive dysfunction of the meningeal lymphatic system should be considered as a risk factor for aging-related brain disorders. Animal studies offer the idea of maximizing brain "waste discharge" as a new preventive or therapeutic target for neurodegenerative diseases in the context of healthy aging, AD models, etc.

The condition of the cerebral parenchymal vascular system upstream of the meningeal lymphatics affects the exchange of material between the paravascular CSF and the ISF and its cleansing. The main risk factor for late onset AD is age. Aging is accompanied by a progressive deterioration of cerebrovascular function (Schneider et al., 2007, 2010; Crystal et al., 2014; Brandon et al., 2013; Lamar et al., 2022; Lee et al., 2022; 40, 60). The BBB clearance mechanism is responsible for 75% of A β excretion from the brain (Hladky et al., 2018; Kress et al. 2014; Conway et al., 2016). Several genetic risk factors for late-onset AD, such as variants of the lipoprotein E4 (ApoE4) gene, have also been associated with BBB dysfunction and impaired vascular clearance of Aβ (Zhao et al., 2015; Zlokovic et al., 1996).

Arterial stiffness and reduced compliance occur gradually during aging and are characterized by degradation of the highly elastic lamellar structure of the arterial wall (Schneider et al., 2007, 2010; Crystal et al., 2014; Brandon et al., 2013; Lamar et al., 2022;

Lee et al., 2022). Under normal conditions, the brain retains pressure pulsations throughout the capillary network; recent analysis of clinical data suggests that increased intracranial pulse fluctuations may play an important role in the pathophysiology of cerebral small vessel disease, which contributes to up to 45% of dementia and 20% of strokes worldwide (Schneider et al., 2007, 2010; Crystal et al., 2014; Brandon et al., 2013; Lamar et al., 2022). The results of the study by Dr. Schneider and her team showed that more than 85% of clinically diagnosed AD neuropathological examinations revealed a combination of varying degrees and types of cerebrovascular pathology. Mixed cerebrovascular disease (CVD), more common than single CVD, is associated with cognitive decline, and distinct mixed CVD profiles show domain-specific associations with cognitive decline. CVD is not monolithic but consists of heterogenous person-specific combinations with distinct contributions to cognitive decline (Schneider et al., 2007, 2010; Crystal et al., 2014; Brandon et al., 2013; Lamar et al., 2022).

For more than 20 years, scientists have known that people with high blood pressure, diabetes, high cholesterol, or obesity are more likely to develop Alzheimer's disease. Recently, Mayeux and his team found a gene called FMNL2 links cerebrovascular disease and Alzheimer's and suggests changes in FMNL2 activity caused by cerebrovascular disease prevent the efficient clearance of toxic proteins from the brain, eventually leading to Alzheimer's disease. So, it is considered that FMNL2 might operate in the BBB, where brain cells meet the vasculature. Researchers studied postmortem human brains and found increased expression of FMNL2 in patients with AD, along with disruption of the BBB and retraction of astrocytes. The researchers propose that FMNL2 opens the BBB by controlling astrocytes and promotes the clearance of extracellular aggregates from the brain. In contrast, cerebrovascular disease reduces amyloid clearance in the brain by interacting with FMNL2 (Lee et al., 2022).

In AD, the toxic A β peptide is present in the extracellular ISF (Kress et al., 2014; Peng et al., 2016), and it has two clearance pathways, one through receptor-mediated transcytosis, internalized and degraded by phagocytes in the brain (Shaul et al., 2017), and the second pathway is transported back to the CSF via the cerebral lymphatic pathway (Iliff et al., 2012). A β excretion from ISF to CSF depends on the effectiveness of the paravascular pathway, and ISF function is significantly reduced when AQP4 function is diminished. AQP4 is another important mechanism of arterial pulsation to push CSF flows into the cerebral paravascular spaces, where it is exchanged with ISF and carries away waste products. In addition, AQP4 protein plays a key role in protecting the integrity of the BBB (Smith et al., 2019; Mader et al., 2019; Xu et al., 2015; Zeppenfeld et al., 2017; Hoshi et al., 2012; Iliff et al., 2012; Asqari et al., 2016). Emerging data suggest that the major protein of the end feet of astrocytes, AQP4, may also be involved in the clearance of β-amyloid in AD. The results of related experiments support the hypothesis that increased β-amyloid deposition is found in APP / PS1 mice deficient in AQP4. It was found that Aqp4 deletion significantly increased amyloid deposition in the cerebral cortex of 5xFAD mice and increased the relative number of protofibrils to dense core plaques. 5xFAD

mice lacking AQP4 also show a significant reduction in the density of GFAP-labeled plaque-like astrocytic processes. The coverage of microglial plaques was also significantly reduced, suggesting that astrocytes are involved in organizing the glial response around the plaques. In addition, human AQP4 polymorphisms have been reported as genetic risk factors for AD. The effect of aging on the distribution pattern of AQP4 water channels has also been studied in mice and human brain (Smith et al., 2019; Mader et al., 2019; Xu et al., 2015; Zeppenfeld et al., 2017; Hoshi et al., 2012; Gabor et al., 2018; Kress et al., 2014). Kress et al. reported that AQP4 polarization in end-feet processes of astrocytes around cortical penetrating arteries (but not capillaries) was significantly reduced in older (18-month-old) mice compared to younger (2- to 3-month-old) mice.

Aging and the cytokines of the brain

In addition, studies by Dr. Kipnis' team have shown that, unlike brain parenchyma, the meningeal space contains a variety of immune cells whose activity is related to brain function, including learning and memory (Noel et al., 2010; Kipnis et al., 2004, 2016; Voglaar et al., 2018; Filiano et al., 2016). Given that meningeal lymphatics are functionally associated with paravascular inflow/outflow of CSF/ISF and given the recent discovery of neuromodulatory effects of certain cytokines (often considered immune molecules), it is reasonable to assume that the activity of meningeal lymphatics may alter the accessibility of immune neuromodulators carried by CSF to the brain parenchyma (Kipnis et al., 2004, 2016; Voglaar et al., 2018; Filiano et al., 2016), which is also related to the mechanisms of aging and AD (Mesquita et al., 2018, 2021; Louveau et al., 2015; Absinta et al., 2017; James et al., 2015; Papadopoulos et al., 2020; Walsh et al., 2014; Kipnis et al., 2016).

As explained earlier, the regional electrical activity of the brain and the blood regulation of the corresponding regions are mainly performed through astrocytes, not neurons (Stanimirovic et al., 2012; McConnell et al., 2017). Under physiological conditions, TNF released from astrocytes regulates normal synaptic plasticity (Stellwagen et al., 2006). Increased cytokine production in response to exogenous pathological stimuli has also been shown to affect synaptic plasticity in neurons. In addition to transmitting electrical and chemical signals and modulating inflammatory responses, neurons express cytokine receptors that mediate immune cell-to-cell communication and are important players in the innate and adaptive immune response (Kipnis et al., 2004, 2016; Gasteiger et al., 2014). Cytokines, together with neurotransmitters, play an important role in synaptic plasticity, a process that is closely linked to learning and memory (Noel et al., 2010; Walsh et al., 2014). For example, TNF produced by peripheral monocyte-derived immune cells can cause loss of dendritic spines in neurons, such as those leading to loss of dendritic spines in the primary motor cortex of mice, producing impairment in learning-dependent dendritic spine formation and deficits in multiple learning tasks (Ajami et al., 2018; McMenamin et al., 2003; Dando et al., 2019; Garre et al., 2017). Another pro-inflammatory cytokine, interleukin 1β (IL-1 β),

is also involved in the formation and maintenance of memory. Other cytokines such as IL-4 and gamma interferon (IFN- γ), when present in the ISF and CSF, can bind to cytokine receptors on neurons and induce changes in neuronal transmission that affect higher brain functions such as social and learning behaviors. In turn, the execution of cognitive tasks increases the number of IL-4-producing T cells in the meninges (Noel et al., 2010; Walsh et al., 2014). As seen in mouse experiments, learning and memory are impaired in the presence of T-cell depletion and lack of IL4 (IL4-null mice) (Noel et al., 2010; Walsh et al., 2014; Kipnis et al., 2004). Other experimental results have further confirmed that IL-4 produced by T cells can be directly recognized by neurons (which express IL-4 receptors), thereby inhibiting axonal degeneration, and improving disease outcome in CNS injury or autoimmune models (Voglaar et al., 2018). Another T cell-derived cytokine, IFN- g, is also required for synaptic transmission of GABAergic neurons in the prefrontal cortex, which supports normal social interactions in mice (Filiano et al., 2016). In mice, fetuses exposed to high maternal levels of IL-17 show behavioral deficits (behavioral disorders associated with autism spectrum disorders) and abnormal cortical development (Choi et al., 2016), suggesting a critical role for IL-17 in brain development and homeostasis. All these facts give us reason to believe that the body's immune system has a critical impact on cognition.

Although cytokines can act as neuromodulators under both physiological and pathological conditions, their exact origin is still debated. Dr. Kipnis and his team believe that there are three possible sources of neuromodulator cytokines and believe that the most characteristic source is brain parenchymal cells, particularly glial cells. For example, TNF release from astrocytes is essential for homeostatic plasticity of neurons (Stellwagen et al., 2006). However, in most cases, the increase of cytokines in the brain occurs in response to lesion stimuli, such as the release of IL-33 from oligodendrocytes in response to injury (Gadani et al., 2015). Another source of cytokines in the CNS is the meningeal immune cells, including bone marrow and lymphocytes (Mesquita et al., 2018, 2021; Louveau et al., 2015; Absinta et al., 2017; James et al., 2015; Papadopoulos et al., 2020; Noel et al., 2010; Walsh et al., 2014; McMenamin et al., 2003; Dando et al., 2019; Filiano et al. 2016). Cytokines are produced by meningeal immune cells released into the CSF and diffused to the brain via the paravascular system, where they interact with neurons and glial cells through binding receptors. Some researchers have suggested that the response of meningeal immune cells to different stimuli from the brain may lead them to express different cytokines. A third potential source of cytokines in the CNS is blood. Cytokines in the blood may act directly on brain endothelial cells, especially when inflammation in the brain leads to a dramatic increase in BBB permeability (Hladky et al., 2018; McMenamin et al., 2003; Gadani et al., 2015). Recent studies have proposed the hypothesis that age-dependent impairment of lymphatic drainage will lead to changes in the frequency of specific meningeal immune cell populations, altering the accessibility of immunogenic cytokines to brain parenchyma

and ultimately affecting glial and neuronal activity (Mesquita et al., 2018, 2021; Louveau et al., 2015; Absinta et al., 2017; James et al., 2015; Papadopoulos et al., 2020; Noel et al., 2010; Walsh et al., 2014; Louveau et al., 2017; Filiano et al., 2016).

Conclusion

Many neurological disorders are associated with aging, the most prominent of which is AD. These neurological disorders associated with aging may all be related to immune system dysfunction. Recent findings suggest that, yet unexplored meninges are a potential source of AD biomarkers and a target for therapeutic intervention and will shed new light on the pathogenesis of AD and search effectiveness of new approaches to alleviate AD-related cognitive impairment.

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