



Review Article

From Immune Sanctuary to Neurological Battlefield: The Role of Neuroimmune Cells



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Abstract

The brain, traditionally regarded as immune-privileged due to the blood-brain barrier, harbors a sophisticated immune system crucial for maintaining neural health and resilience against various challenges. Microglia, the resident immune cells of the central nervous system, actively monitor their environment, participating in immune surveillance, synaptic pruning, and neuroprotection. Astrocytes also play vital roles by regulating neurotransmitter levels, supporting metabolism, and maintaining the blood-brain barrier integrity. Recent research underscores the involvement of T cells and monocytes in modulating neuroinflammation and immune responses within the brain. Neurological disorders such as Alzheimer's and Parkinson's disease highlight the brain's vulnerability to immune dysregulation. This review aimed to elucidate the role of neuroimmune cells in brain health and the progression of neurological diseases. It aimed to identify critical mechanisms to enhance therapeutic strategies and improve outcomes. Understanding these interactions is essential for developing targeted therapies to mitigate neuroinflammation and preserve cognitive functions. This review critically examines neuroinflammation related to aging and disease, with a focus on neuroimmune cells and their underlying mechanisms. It highlights how chronic inflammation, driven by activated microglia and astrocytes, exacerbates neuronal damage, synaptic dysfunction, and cognitive decline. The disruption of immune privilege in these conditions involves complex pathways that trigger inflammatory responses, impairing essential neural functions. Despite its immune-privileged status, the brain's immune system, primarily involving microglia and astrocytes, is crucial for maintaining homeostasis and managing illness. Our review strongly suggests that neurological diseases, influenced by genetic, environmental, and aging factors, often involve heightened neuroinflammation. Targeted therapies are needed to address infections, chronic inflammation, and environmental impacts. Additionally, research into mental health disorders and advancements in imaging techniques are critical for understanding immune dysfunction and enhancing treatment strategies.

Introduction

The brain is a marvel of complexity, with its functions governed by intricate networks of cells and molecules. At its core lies a unique immune system that safeguards the central nervous system (CNS) from external threats. Central to this defense are microglia, specialized immune cells strategically positioned within the CNS, acting as vigilant sentinels that swiftly detect and eliminate abnormal

cells or pathogens.^{1–4} This ability is crucial for maintaining the brain's immune privilege—a phenomenon where tissue transplanted into the brain parenchyma can persist without eliciting the immune responses seen in peripheral tissues.^{5,6}

This immune privilege is further reinforced by the blood-brain barrier (BBB), a robust barrier formed by endothelial and glial cells that selectively permits the passage of essential nutrients and molecules while rigorously excluding toxins and pathogens.^{7–9} Unlike many other organs, the brain has a limited lymphatic system, reducing its exposure to circulating immune cells and antigens that could trigger immune responses.^{10–12}

However, despite these formidable defenses, the narrative of the brain's immune response is evolving. Alzheimer's diseases (AD) and Parkinson's diseases (PD), characterized by progressive neuronal dysfunction and cognitive decline, challenge the brain's immune privilege.^{12–14} Similarly, autoimmune disorders such as multiple sclerosis (MS), driven by immune attacks against self-antigens within the CNS, lead to significant neurological impair-

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ment.^{15–17} Additionally, infectious agents capable of breaching immune barriers can provoke inflammatory responses, resulting in a spectrum of neurological complications, from acute encephalitis to chronic neurodegeneration.^{18–20}

This evolving understanding challenges the traditional view of the brain as an immune-privileged organ, highlighting the dynamic role of the immune system in both brain health and disease. In essence, the immune system is both the brain's best ally and its adversary, embodying a double-edged sword. While it protects the brain from infections and aids in tissue repair, it can also trigger autoimmune diseases and cause inflammation that drives neurodegeneration.

Thus, the once tranquil concept of immune privilege gives way to a vivid portrayal of conflict—a battleground within the intricate landscape of the nervous system. This shift prompts deeper exploration into the enigmatic interplay between the brain and the immune system, aiming to unravel the complex mechanisms underlying the development of neurological disorders.

The changing landscape of brain diseases underscores a significant shift in our understanding of their immune implications. Once viewed as an immune-privileged domain, the brain and its complex neural networks now emerge as dynamic arenas where the immune system plays a crucial role. This transformative paradigm challenges conventional viewpoints while presenting new avenues for research and therapeutic strategies.

By embracing this new understanding, we can unlock deeper insights into neurological disorders and pave the way for more effective treatments, offering hope to millions affected by these complex conditions.

Building on this foundation, this article explores the brain's immune system, illustrating how its dysregulation can lead to neurological disorders, autoimmune diseases, and brain infections. By examining the underlying immune mechanisms, we aimed to provide a comprehensive understanding of these complex interactions and their implications for brain health.

Neuroimmune cells and their roles in brain health

The brain, traditionally viewed as “immune-privileged” due to the BBB and lack of conventional lymphatic drainage, actually hosts a diverse array of immune cells that are crucial for maintaining homeostasis, responding to injury, and defending against pathogens.^{1–6} These immune cells include microglia, astrocytes, perivascular macrophages, dendritic cells, and, under specific conditions, infiltrating peripheral immune cells such as T cells and B cells.^{21–25}

Microglia, which originate from yolk sac progenitors during embryonic development, are the primary resident immune cells in the CNS, comprising about 80% of the brain's immune cells. They continuously survey the brain parenchyma through highly motile processes, monitoring for signs of damage, infection, or abnormalities.^{21–25} Upon detecting such threats, microglia become activated, transitioning through various activation states (from M1-like to M2-like) and releasing pro-inflammatory cytokines to mount an immune response. Beyond immune defense, microglia play a critical role in synaptic pruning during brain development, refining neural circuits by eliminating excess synapses and optimizing connectivity.^{26–28}

In addition to their role in synaptic pruning, microglia are now recognized for their involvement in modulating neurogenesis and maintaining brain plasticity throughout life.^{29,30} Recent research has shown that microglia influence the generation of new neurons

in the hippocampus, a key region for learning and memory, by interacting with neural stem cells and regulating the microenvironment necessary for neurogenesis.^{31,32}

Moreover, microglia contribute to brain plasticity by responding to and shaping experiences and learning processes, ensuring that neural circuits adapt to new information and experiences. This dynamic role in supporting brain plasticity underscores the importance of microglia not only during development but also throughout adulthood.^{29–32}

Astrocytes, derived from neural progenitor cells, are another predominant CNS cell type. They provide metabolic support to neurons, maintain BBB integrity, regulate neurotransmitter levels, and modulate immune responses by producing cytokines and chemokines. This multifunctional role positions astrocytes as integral players in brain homeostasis and immune regulation.^{33–36}

Recent research has advanced our understanding of astrocyte differentiation into two distinct reactive forms: A1 and A2 astrocytes. A1 astrocytes, which arise in response to severe or chronic brain damage, release a range of cytotoxic substances, including inflammatory cytokines and reactive oxygen species (ROS).^{37,38} These harmful factors can lead to the death of neurons and oligodendrocytes, exacerbating neurodegenerative conditions and contributing to disease progression.^{39,40} The detrimental effects of A1 astrocytes underscore their role in promoting inflammation and neuronal damage in various neurodegenerative diseases (NDs).^{41,42}

In contrast, A2 astrocytes emerge in response to less severe damage or within regenerative contexts.³⁹ These cells are characterized by their production of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and insulin-like growth factor 1, which are crucial for supporting neuronal survival, promoting repair, and enhancing synaptic plasticity. The presence of these factors helps counteract neuronal damage and facilitates recovery and repair processes in the brain.^{43–45}

Recent insights have revealed that the transition between A1 and A2 states is regulated by specific molecular signals in the brain's microenvironment.⁴⁶ These signals, including various cytokines, growth factors, and signaling pathways, determine whether astrocytes adopt a neurotoxic or neuroprotective phenotype. Manipulating these signals could potentially shift astrocyte behavior from harmful A1 states to protective A2 states.^{47–50}

This evolving understanding points to the potential for targeted therapeutic interventions aimed at modulating astrocyte reactivity. Strategies that inhibit the detrimental effects of A1 astrocytes or enhance the beneficial functions of A2 astrocytes are currently being explored. Such approaches hold promise for improving outcomes in NDs, brain injuries, and neuroinflammatory disorders by fostering a more favorable environment for neural repair and recovery.^{51,52}

Perivascular macrophages, derived from bone marrow progenitors, surround blood vessels in the brain and act as sentinels, monitoring pathogens or debris entering the brain via the bloodstream. Dendritic cells, although less abundant in the brain compared to other tissues, are present in specialized regions like the meninges and choroid plexus, where they capture antigens and initiate adaptive immune responses by presenting them to T cells.^{53–55}

Importantly, distinguishing between resident microglia, perivascular macrophages, and infiltrating monocytes involves analyzing their specific markers, locations, and functions.^{56–58} Infiltrating monocytes are immune cells that enter the brain from the bloodstream in response to inflammation or injury, migrating into the brain to influence immune responses and contribute to tissue repair or inflammation.^{59,60} Resident microglia are identified by markers such as P2RY12 (purigenic 2Y type 12 receptor) and Iba1

(ionized calcium binding adaptor molecule 1). They are distributed throughout the brain parenchyma, playing a key role in maintaining brain homeostasis and responding to injury.^{61,62} Perivascular macrophages, marked by cluster of differentiation (CD) 163 and CD14, are located around blood vessels in the perivascular spaces and are involved in local immune responses.^{58,63,64}

In contrast, infiltrating monocytes, characterized by markers like Ly6C and CCR2(C-C chemokine receptor type 2), originate from the bloodstream and enter the brain during inflammation, where they may differentiate into macrophage-like cells.^{60,65,66} Techniques such as immunohistochemistry, flow cytometry, and single-cell RNA sequencing are used to accurately identify and differentiate these cell types based on their unique markers and roles.⁶⁷⁻⁶⁹

Additionally, T cells play diverse roles in brain function beyond traditional immune responses. They influence processes such as spatial learning, memory, emotional behavior, and stress responsiveness through cytokine signaling and immune modulation. For instance, CD4⁺ T cells release interleukin (IL)-4, promoting an anti-inflammatory M2 phenotype in microglia and stimulating astrocytes to produce BDNF, which is crucial for synaptic plasticity and cognitive function.⁷⁰⁻⁷³

Regulatory T cells (Tregs) are essential for maintaining the brain's immune-privileged environment by modulating immune responses and controlling inflammation, thus protecting neurons from collateral damage during immune activation.⁷⁴⁻⁷⁶ Recent research has emphasized the role of Tregs, including specialized brain-resident subsets adapted to the unique CNS environment, in sustaining immune tolerance.⁷⁷ These Tregs produce anti-inflammatory cytokines, such as IL-10 and transforming growth factor-beta, which help suppress excessive immune reactions. Additionally, Tregs play a role in preserving the integrity of the BBB, regulating immune cell entry into the CNS, and preventing unwanted neuroinflammation. By balancing immune activity and supporting neuronal health, Tregs are crucial for maintaining the brain's delicate immune equilibrium and ensuring long-term neuroprotection.^{78,79}

During pathological conditions, peripheral T cells, including cytotoxic CD8⁺ T cells and helper CD4⁺ T cells, can infiltrate the brain. They eliminate infected or damaged cells and modulate the local immune environment through cytokine release, influencing disease progression in NDs like AD and PD.⁸⁰⁻⁸²

Natural killer cells, another type of immune cell, contribute to neuroprotection by regulating immune responses, suppressing inflammation, and promoting neuronal recovery following CNS damage. Their ability to modulate T-cell responses highlights their potential therapeutic role in neurological conditions.⁸³⁻⁸⁵

Additionally, B cells are crucial for antibody production against pathogens and play a pivotal role in antigen presentation to T cells within the brain. This interaction shapes the local immune environment and is essential for defending against neurological threats. Regulatory B cells further modulate immune responses, preventing excessive inflammation and contributing to immune tolerance in the CNS.⁸⁶⁻⁸⁹

Moreover, B cells have been implicated in oligodendrogenesis, the process of generating oligodendrocytes responsible for myelin sheath formation in the CNS. This interaction underscores the broader impact of B cells on neural function and suggests potential therapeutic avenues for enhancing remyelination in neurodegenerative conditions.⁹⁰⁻⁹²

In summary, immune cells within the brain intricately regulate neural function, immune responses, and disease processes. Understanding their roles and interactions provides insights into neuro-

immune mechanisms and reveals potential targets for therapeutic interventions aimed at preserving brain health and combating NDs.

Breach of the brain's sanctuary: Unveiling the causes and mechanisms of neurological disorders

The human brain, often regarded as a sanctuary of cognitive and neural function, is remarkably resilient yet extraordinarily vulnerable. Neurological diseases, spanning a broad spectrum of disorders, disrupt this delicate sanctuary, leading to significant cognitive and motor deficits.^{93,94} The underlying mechanisms contributing to these conditions are complex and multifaceted, involving an interplay of genetic predispositions, environmental factors, and systemic physiological processes.⁹⁵ Recent research has underscored the pivotal role of immune system dysregulation, neuroinflammation, and the breach of the BBB in the development of neurological diseases and aging-related cognitive decline.^{96,97} Hence, this section aims to elucidate the intricate biological pathways, particularly those involving various types of brain immune cells, that lead to the breach of brain health and contribute to the onset of neurological diseases.

Immune cell dynamics in the aging brain: Microglia, astrocytes, and beyond

The aging brain undergoes profound structural and functional changes, particularly affecting its primary immune cells, microglia, and astrocytes.⁹⁸⁻¹⁰² Microglia, essential for CNS immune surveillance, become increasingly reactive with age, characterized by heightened pro-inflammatory cytokine expression, reduced phagocytic activity, and impaired resolution of inflammation. These changes contribute to chronic neuroinflammation, a hallmark of age-related NDs.¹⁰³⁻¹⁰⁷

Astrocytes, another critical glial cell type, also undergo significant alterations during aging. Aging astrocytes exhibit dystrophic changes, including a reduction in the size and complexity of their processes, leading to decreased synaptic coverage.^{108,109} This astrocytic atrophy, along with reduced expression of glutamate transporters, impairs the clearance of glutamate and potassium buffering. Excessive glutamate accumulation can induce excitotoxicity, contributing to neuronal damage and dysfunction seen in various neurological disorders, including epilepsy and NDs.¹¹⁰⁻¹¹³

Additionally, the decline in astrocytic function affects the brain's extracellular environment, which is vital for extrasynaptic signaling and ion balance.^{114,115} Astrocytes play a crucial role in clearing neurotransmitters and supporting neuronal metabolism, functions that are compromised with age-related astrocytic hypertrophy, altered gene expression, and increased production of inflammatory mediators. These changes disrupt brain homeostasis and exacerbate neuronal stress, further contributing to neurodegeneration in aging brains.¹¹⁶⁻¹¹⁸

The interplay between aging microglia and astrocytes is pivotal for maintaining brain health. Age-related alterations in microglial function, marked by excessive pro-inflammatory signaling, stimulate astrocytes to release inflammatory mediators, perpetuating a cycle of neuroinflammation. This chronic inflammation significantly contributes to neuronal damage and the progression of NDs. Understanding these intricate interactions offers potential therapeutic avenues to mitigate neuroinflammation and preserve cognitive function in aging individuals.¹¹⁹⁻¹²¹

Aging particularly affects microglial and astrocytic functions in PD.¹²²⁻¹²⁴ As people age, microglia, the brain's resident immune cells, become more activated, leading to chronic low-grade

inflammation that exacerbates neurodegeneration. This heightened inflammatory state, driven by increased production of pro-inflammatory cytokines such as IL-1 β and tumor necrosis factor- α (TNF- α), can further damage dopaminergic neurons, which are already compromised in PD.^{125–127}

Furthermore, aging impairs microglial phagocytic activity, reducing the clearance of toxic aggregates such as alpha-synuclein and shifting microglial phenotypes toward a more pro-inflammatory state, amplifying local inflammation.^{128,129} Astrocytes, which support neurotransmitter balance and neuronal function, also undergo significant changes with aging. Increased reactive astrogliosis and impaired regulation of neurotransmitters, like dopamine, contribute to heightened neuronal stress and degeneration.^{130–132}

Aging disrupts astrocyte-neuron interactions and impairs BBB integrity, further aggravating neuroinflammation and disease progression. The interplay between age-related changes and Parkinson's pathology results in a compounded effect, accelerating the disease and worsening cognitive and motor symptoms.^{133,134} Understanding these interactions is crucial for developing effective therapeutic strategies to mitigate the impact of aging on neuroimmune function and PD progression.

Aging also affects the brain's adaptive immune system, particularly T cells and B cells. Thymic involution and reduced production of naïve T cells lead to an accumulation of autoreactive T cells, impaired Treg function, and diminished immune surveillance.^{135,136} First, aging impairs negative selection, leading to an accumulation of autoreactive T cells that may target the body's own tissues, increasing the risk of age-related autoimmune disorders. Second, it disrupts the balance of Treg production, impairing immune tolerance and resulting in heightened inflammation and immune dysfunction.¹³⁷ Third, the reduction in thymopoiesis decreases the production of new T cells, weakening the immune system's ability to respond to new infections and malignancies, contributing to overall immunosenescence.¹³⁸ In the brain, aging T cells contribute to increased neuroinflammation, impair synaptic plasticity, and exacerbate cognitive decline in NDs.^{139,140}

Similarly, aging B cells undergo immunosenescence, characterized by reduced diversity in B cell receptors, heightened autoreactivity, and altered cytokine production.^{141,142} These changes promote chronic inflammation, or "inflammaging." Age-related alterations in T cells and B cells exacerbate neuroinflammatory conditions and may worsen CNS disorders such as AD and MS.^{143–147}

In summary, despite the brain's immune privilege, aging induces significant structural and functional changes in immune cells, particularly microglia and astrocytes. Reactive microglia drive chronic neuroinflammation, while astrocytic dysfunction disrupts neurotransmitter balance and exacerbates neuronal stress. Aging T cells and B cells further contribute to neuroinflammation and neurodegenerative processes. Understanding these immune cell dynamics is critical for developing targeted therapies aimed at reducing neuroinflammation and preserving cognitive health in aging populations.

The impact of infections and pathogens on neurological diseases

Infections and pathogens can lead to neurological diseases through several mechanisms, despite the brain's immune privilege, which typically offers enhanced protection.^{148–150} Neurotropic viruses, such as herpes simplex virus, varicella-zoster virus, and enteroviruses, can breach the BBB and infect neural tissues, causing encephalitis or meningitis.^{151–154}

Similarly, bacteria such as *Neisseria meningitidis*, *Streptococ-*

cus pneumoniae, and *Mycobacterium tuberculosis* can invade the CNS, resulting in bacterial or tuberculous meningitis. The immune response to these infections often involves releasing cytokines and other inflammatory mediators that, while fighting the infection, can also cause neuroinflammation and neuronal damage.^{155–158}

In some cases, pathogens carry antigens that resemble host proteins, causing the immune system to mistakenly attack neural tissues, as seen in Guillain-Barré syndrome, which is primarily triggered by *Campylobacter jejuni*.^{159–164}

Chronic infections, such as those caused by the human immunodeficiency virus (HIV), can result in continuous neuroinflammation and neurodegeneration. Certain pathogens produce neurotoxins that directly damage neural tissues, like *Clostridium botulinum* and *Clostridium tetani*, which cause botulism and tetanus, respectively.^{165–171}

Infections can also disrupt normal brain metabolism, leading to conditions such as hepatic encephalopathy and sepsis-associated encephalopathy. Infections may increase BBB permeability, allowing pathogens and immune cells to infiltrate the brain, and causing cerebral edema and neuronal damage.^{172–176}

Post-infectious autoimmune reactions can trigger neurological conditions such as acute disseminated encephalomyelitis and MS.^{177,178} Thus, despite the brain's immune privilege, which typically limits immune responses to protect sensitive neural tissues, some pathogens have evolved mechanisms to bypass these defenses.^{179–181}

Understanding these mechanisms is essential for developing targeted therapies to prevent and treat infection-induced neurological diseases.

The interplay of genetic and environmental factors in neurological diseases

Neurological diseases arise from a complex interplay between genetic and environmental factors. Inherited and *de novo* mutations, such as those associated with Huntington's disease and autism spectrum disorders, along with genetic predispositions such as apolipoprotein E variations linked to AD, increase the risk of developing neurological disorders.^{182–186}

Environmental factors also play a significant role. For example, infections such as the Epstein-Barr virus in MS, exposure to pollutants (e.g., heavy metals and pesticides in PD), nutrient deficiencies (e.g., vitamin B12), and traumatic brain injury (TBI) all contribute to neurological disorders. Lifestyle choices and chronic stress further exacerbate these conditions.^{187–191}

The interaction between genetics and the environment is crucial, as genetic vulnerabilities combined with environmental influences increase disease risk.¹⁹² Environmental factors can also induce epigenetic changes, altering gene expression and brain function. Additionally, gut microbiota dysbiosis, influenced by both genetics and environmental factors, has been linked to conditions like PD and MS.^{193–196}

Chronic inflammation and its neurological impact

Chronic inflammation, or persistent immune system activation, plays a pivotal role in the development of neurological diseases such as AD, PD, MS, and brain cancer.¹⁹⁷ This sustained inflammatory state often originates from various sources, including chronic infections, exposure to environmental toxins, and autoimmune reactions.¹⁹⁸ Within the brain, this inflammatory environment triggers immune cells to release cytokines and chemokines, which disrupt neural balance and directly harm neurons.¹⁹⁹ Chronic inflammation also contributes to the accumulation of misfolded

proteins, increases oxidative stress, and impairs the brain's mechanisms for clearing toxic protein aggregates.^{200,201}

In the brain, inflammatory responses involve the activation of microglia and the release of various cytokines and chemokines. For example, cytokines such as TNF- α , IL-1 β , and IL-6 are produced, which can disrupt neuronal function by promoting abnormal protein aggregation and altering cellular signaling pathways. Chemokine such as CCL2 (C-C motif chemokine ligand 2) MCP-1 (monocyte chemoattractant protein-1) attract additional immune cells to the site of inflammation, potentially exacerbating the inflammatory response.^{202–204}

Similarly, in neuroinflammatory conditions, cytokines such as interferon-gamma and IL-17 contribute to immune cell activation and migration, while chemokines like CCL5 (RANTES) (regulated on activation, normal T cell expressed and secreted) and CXCL10 (C-X-C-motif chemokine ligand 10) (IP-10) (interferon- γ -inducible protein 10) facilitate immune cell movement within the CNS, collectively disrupting neural balance and affecting neuronal health.^{205–208}

Chronic neuroinflammation initiates a cascade of detrimental effects in the brain, primarily through the activation of microglia and astrocytes, which release pro-inflammatory cytokines such as TNF- α , IL-1 β , and IL-6. These cytokines interfere with the brain's protein homeostasis by disrupting protein folding processes and enhancing the aggregation of misfolded proteins. Recent research has shown that IL-1 β can promote the aggregation of tubulin associated unit (tau) protein, a hallmark of AD.²⁰⁹ Table S1 provides a list of cytokines and chemokines involved in chronic neuroinflammation.

This inflammatory environment also significantly increases oxidative stress, as activated microglia and astrocytes generate ROS and reactive nitrogen species.^{210,211} These oxidative molecules damage proteins, lipids, and DNA, further promoting protein misfolding and aggregation. Studies have demonstrated that increased oxidative markers and weakened antioxidant defenses are prominent in NDs, emphasizing the role of oxidative stress in disease progression, which is linked to chronic neuroinflammation.^{212,213}

Chronic inflammation also impairs the brain's ability to clear toxic protein aggregates. The ubiquitin-proteasome system and autophagy, both critical for protein degradation and cellular maintenance, are disrupted by inflammatory cytokines.^{214,215} For instance, IL-1 β can inhibit the function of the ubiquitin-proteasome system, reducing the degradation of misfolded proteins and worsening their accumulation.²¹⁶

Similarly, inflammation affects autophagic processes by impairing lysosomal function and autophagosome formation, leading to the buildup of amyloid- β plaques and tau tangles in AD.^{217,218} Neuroinflammation also compromises BBB integrity, allowing more inflammatory cells and molecules to enter the brain, further intensifying oxidative stress and protein aggregation.^{219,220}

Emerging evidence suggests that targeting specific inflammatory cytokines, such as IL-6, could restore cellular protein homeostasis and mitigate the impact of these disruptions.^{202,203} Overall, chronic neuroinflammation creates a vicious cycle of protein misfolding, oxidative damage, and impaired clearance, contributing to progressive neuronal damage and functional decline.^{204–206}

Chronic inflammation and long-term neurological effects post-COVID-19

Following a COVID-19 infection, the body may experience an intense immune reaction known as a cytokine storm. This response involves the excessive release of inflammatory cytokines and chemokines throughout the body, including the CNS. The resulting

widespread inflammation, which affects both systemic and brain functions, contributes to a range of neurological complications, including viral encephalitis, acute disseminated encephalomyelitis, and Guillain-Barré syndrome.^{221–223} Notably, the neurological impacts of COVID-19 may arise from direct invasion of the CNS by the virus as well as indirect effects caused by the immune system's response.^{224–229}

Recent studies highlight the potential long-term neurological consequences of chronic inflammation following COVID-19. Beyond the acute phase of infection, sustained immune activation and neuroinflammation may lead to persistent cognitive impairment and exacerbate pre-existing neurodegenerative conditions.^{230–232} Evidence suggests that the inflammatory response triggered by COVID-19 may further promote neurodegeneration through mechanisms involving neurotoxic cytokines, disruption of BBB integrity, and dysregulation of neuronal function and connectivity.^{233–235}

Understanding these complex immunological and pathological processes is crucial for developing targeted therapies to mitigate long-term neurological sequelae in COVID-19 survivors. By identifying the mechanisms that link chronic inflammation to neurological disease progression, researchers can discover potential biomarkers and therapeutic targets to improve clinical outcomes and quality of life for affected individuals.

Chronic neuroinflammation and glioblastoma progression

Chronic neuroinflammation plays a significant role in brain cancer, particularly glioblastoma, through complex mechanisms involving the persistent activation of microglia and astrocytes. In glioblastoma, these activated glial cells secrete pro-inflammatory cytokines such as IL-6, TNF- α , and IL-1 β .^{236,237} These cytokines activate key signaling pathways, including nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) and signal transducer and activator of transcription 3 (STAT-3), which enhance tumor cell proliferation and survival by inhibiting apoptosis. For instance, NF- κ B activation increases the expression of anti-apoptotic proteins, enabling glioblastoma cells to resist cell death.^{238,239}

Furthermore, activated microglia and astrocytes contribute to a tumor-supportive environment by releasing growth factors and extracellular matrix components that promote tumor development and invasion.^{240,241} Recent research indicates that glioblastoma cells exploit these inflammatory signals to enhance their own growth and evade treatment. Specifically, glioblastoma cells release factors that attract and activate microglia, which then secrete cytokines that promote tumor proliferation and the formation of new blood vessels.^{242,243} Additionally, chronic neuroinflammation triggers the production of ROS, which inflicts DNA damage and accelerates tumor progression.^{244,245}

In contrast, astrocytes in glioblastoma often exhibit altered expression of molecules such as fibroblast growth factor and vascular endothelial growth factor, which are crucial for angiogenesis, providing tumors with the necessary nutrients and oxygen for growth.^{246,247} Vascular endothelial growth factor, secreted by reactive astrocytes, is particularly important for glioblastoma's ability to develop an extensive and abnormal blood supply.²⁴⁸ Glioblastoma-associated inflammation also disrupts the BBB through matrix metalloproteinases, facilitating tumor invasion and exacerbating the disease.^{249,250} This inflammatory environment not only supports tumor progression but also leads to neurodegeneration and cognitive impairments, complicating treatment and impacting the patient's quality of life.

Recent research into glioblastoma emphasizes the potential of targeting the tumor microenvironment as a therapeutic strat-

egy.^{251,252} Efforts are underway to modulate microglial and astrocytic activity to disrupt their roles in tumor growth and improve the efficacy of existing treatments.

Overall, understanding the interplay between chronic neuroinflammation and glioblastoma underscores the need for innovative approaches to managing this aggressive cancer.

Neurological battlefield: Manifestations of brain diseases

The human brain, essential for numerous functions, is increasingly vulnerable to neurological diseases. These conditions present significant clinical challenges, often involving immune mechanisms mediated by brain cells like microglia and astrocytes. The following sections explore the role of these immune cells in the development and progression of selected NDs, highlighting their immune mechanisms.

Immune responses in neurodegenerative diseases

Brain diseases such as NDs involve complex immune responses within the CNS, driven by cortical atrophy and abnormal protein accumulation that stress neurons and lead to their degeneration. This neuronal damage triggers an innate immune response, with microglia and astrocytes undergoing reactive changes to manage diseased neurons and contain abnormal proteins.^{253,254} Additionally, adaptive immune cells, such as CD8⁺ T cells, CD4⁺ T cells, and B cells, are recruited, shaping the neuroinflammatory environment to either support neuronal health or exacerbate disease progression.^{255–257}

In AD, characterized by amyloid- β plaques and neurofibrillary tangles, microglia initially attempt to clear A β plaques but become chronically activated, leading to sustained inflammation, neurotoxicity, and synapse loss.²⁵⁸ This persistent activation not only fails to clear A β efficiently but also exacerbates neuronal damage. CD8⁺ T cells may worsen neurodegeneration by directly interacting with compromised neurons, while CD4⁺ T cells modulate microglial activity, influencing the balance between neuroprotection and neuroinflammation.^{259,260} B cells play a dual role by producing antibodies against abnormal proteins, potentially aiding clearance but also exacerbating inflammation through cytokine release.^{260–262}

Microglial cells, the brain's primary immune responders, exhibit distinct activation states known as M1 and M2 phenotypes, which play critical roles in neuroinflammatory diseases such as AD and MS.^{3–7} The M1 phenotype, associated with pro-inflammatory responses, is activated by stimuli such as lipopolysaccharides or pro-inflammatory cytokines. M1 microglia release cytokines like TNF- α , IL-1 β , and IL-6, along with ROS, which contribute to neurodegeneration. In AD, M1 microglia exacerbate A β plaque formation and tau phosphorylation, leading to increased neuronal damage and cognitive decline. Similarly, in MS, M1 microglia promote autoimmune responses and myelin damage, contributing to demyelination and neurodegeneration.^{263,264}

In contrast, the M2 phenotype is generally associated with anti-inflammatory and repair functions. Activated by signals such as IL-4 and IL-13, M2 microglia secrete anti-inflammatory cytokines such as IL-10 and transforming growth factor- β (TGF- β) and are involved in tissue repair and debris clearance.²⁶⁵ In AD, M2 microglia help clear A β plaques and promote tissue repair, although their functionality may be impaired during chronic inflammation.^{107,108} In MS, M2 microglia contribute to remyelination and repair processes, though their effects are often overshadowed by the dominant M1 response, especially during acute

disease phases.^{266,267}

Recent insights suggest that modulating the balance between M1 and M2 microglial states could offer therapeutic benefits. Research indicates that shifting the microglial response towards the M2 phenotype may reduce A β plaque accumulation in AD and improve cognitive outcomes.^{268,269}

Similarly, in MS, targeting pathways that promote M2 polarization or inhibit M1 activation shows promise for slowing disease progression and enhancing repair.²⁷⁰ Understanding the dynamics of these microglial phenotypes provides potential strategies for managing neuroinflammatory diseases by balancing their roles in inflammation and repair.

On the other hand, astrocytic dysfunction plays a critical role in the progression of brain diseases, particularly in AD. Astrocytes are essential for maintaining brain homeostasis, including the clearance of A β through processes such as phagocytosis and the release of A β -degrading enzymes. In AD, astrocytes often exhibit impaired functionality, leading to a failure to clear A β . This accumulation of A β contributes to the formation of neurotoxic plaques and disrupts neuronal function.^{113,116}

Recent research has uncovered several mechanisms underlying astrocytic dysfunction in AD. Studies have shown that astrocytes in AD brains exhibit reduced expression of key receptors and transporters involved in A β clearance, such as low-density lipoprotein receptor-related protein 1 and aquaporin-4 channels, which are part of the glymphatic system.^{271,272} This impairment compromises their ability to effectively remove A β from the extracellular space. Additionally, oxidative stress and chronic inflammation further exacerbate astrocytic dysfunction by damaging cellular components and impairing their ability to maintain neurovascular integrity.^{273,274}

Research has also explored the impact of impaired astrocytic clearance on disease progression. For example, studies have demonstrated that genetic or pharmacological restoration of astrocytic function can reduce A β levels and alleviate cognitive deficits in animal models of AD.^{275,276} Activation of astrocytic signaling pathways, such as NF- κ B and peroxisome proliferator-activated receptor- γ (PPAR- γ), has been shown to enhance A β clearance and reduce plaque burden.^{38–44}

Furthermore, research into the role of the glymphatic system has revealed that disruptions in cerebrospinal fluid (CSF) flow and waste clearance, due to dysfunctional astrocytes, significantly contribute to disease progression.²⁷⁷

Overall, the dysfunction of astrocytes in AD, particularly their failure to clear A β , is a key driver of disease progression. Recent research underscores the importance of restoring astrocytic function as a potential therapeutic strategy, aiming to enhance A β clearance and mitigate the neurodegenerative processes associated with AD.

Interestingly, research has revealed significant sex-based differences in the structure and function of microglia. These variations can affect how microglia respond to injuries, diseases, and changes in brain function. Male and female microglia may differ in terms of density, shape, and activity levels, which impacts their susceptibility to neurological disorders and influences the overall immune response in the brain.^{278–280} Gaining insights into these sex-specific differences is essential for developing more tailored and effective treatments for neurological conditions.

The higher incidence of AD in women compared to men is strongly associated with sex-specific differences in microglia, the brain's primary immune cells. Studies show that microglia in females and males react differently to the pathological changes seen

in AD.^{281–283}

One key factor is the inflammatory response. Research suggests that female microglia may exhibit more pronounced inflammatory reactions than their male counterparts. This heightened response could accelerate neurodegeneration and contribute to the higher incidence of Alzheimer's in women.²⁸⁴

Hormonal influences also play a significant role. Estrogen, more prevalent in females, can affect microglial function and inflammation. Fluctuations in estrogen levels, especially during menopause, may impact how microglia interact with A β plaques and tau tangles, both of which are central to Alzheimer's pathology.^{285,286}

Genetic and epigenetic factors also contribute to these differences. Changes in genes associated with immune responses and neuroinflammation can alter microglial function, resulting in varied susceptibilities to AD between genders. Additionally, differences in microglial density and activity between males and females impact the efficiency of A β plaque clearance and the handling of neurotoxic conditions. These differences may help explain the increased vulnerability to AD observed in women.^{287,288}

Understanding these sex-dependent differences in microglial structure and function is crucial for developing more targeted and effective approaches to prevent and treat AD in both men and women.³²

Recent studies have shown that microglia play dual roles in AD.^{64,67} While traditionally viewed as contributors to neuroinflammation and plaque accumulation, recent evidence suggests that microglia are also crucial for clearing A β plaques and supporting neuronal health. New research using advanced imaging and genetic tools has revealed that microglial depletion can lead to increased A β plaque buildup and worsening cognitive deficits, but it may also alleviate inflammation in some contexts.^{202–204} This reflects the complex balance between the beneficial and detrimental aspects of microglial activity, which must be carefully considered.^{208,211}

On the other hand, emerging data suggest that peripheral immune cells, such as T cells and monocytes, play a significant role in Alzheimer's pathology. Studies have found that depleting peripheral immune cells can reduce systemic inflammation and alleviate some aspects of disease progression.^{289,290} However, the overall impact can be mixed, as removing these cells might disrupt essential immune functions and impair the brain's ability to respond effectively to injury.

In PD, cognitive assessments often show that men perform worse than women.²⁹¹ Specifically, males tend to struggle more with verbal fluency, inhibition, and processing speed. This cognitive decline in men is often more pronounced, affecting their ability to generate words, control impulsive responses, and process information quickly. These differences underscore the need for gender-specific approaches to understanding and addressing cognitive impairments in PD.²⁹²

As previously mentioned, variations in microglial density, morphology, and activity between males and females may influence the progression of NDs. Male microglia, in particular, may show less effective neuroinflammatory responses and compromised synaptic maintenance, which could contribute to the exacerbation of cognitive decline in men. This highlights the importance of considering sex-based differences in neuroinflammatory processes when developing targeted treatments for PD.

Additionally, in PD, there is growing evidence that T cells play a role in driving neuroinflammation and disease progression.²⁹³ T cells influence microglial polarization toward the pro-inflammatory M1 phenotype while suppressing the protective M2 pheno-

type.^{294,295} This dysregulation creates a neurotoxic environment that contributes to the degeneration of dopaminergic neurons, which is central to PD pathology. Understanding the interplay between T cells and microglia reveals potential therapeutic avenues for restoring immune balance and preserving neuronal integrity in PD.^{293–296}

Furthermore, evidence suggests that individuals in the prodromal stage of PD, who are at a heightened risk of progressing to the disease, show elevated levels of alpha-synuclein antibodies.²⁹⁷ This suggests a potential involvement of B lymphocytes in PD progression. Although these antibodies are not found in early PD patients, their presence indicates a potential pathological role for alpha-synuclein antibodies.²⁹⁸

There is also speculation that these antibodies could be protective, aiding in the clearance of pathological proteins. Supporting this notion, a study by Li *et al.*²⁹⁹ demonstrated that certain alpha-synuclein antibodies derived from patients were capable of inhibiting the seeding of alpha-synuclein *in vitro*.

Moreover, B cells perform multiple functions beyond antibody production, including presenting antigens, regulating T cells and innate immune cells, producing cytokines, and maintaining subcapsular sinus macrophages. Considering the significant inflammation observed in both the CNS and the periphery in PD, it is likely that B lymphocytes contribute to the disease. Many of their effects are likely mediated through these various roles. Further research is needed to clarify the specific contributions of B lymphocytes to PD progression.

Additionally, recent research has provided new insights into the role of microglia in PD. While earlier studies suggested that microglial depletion could reduce neuroinflammation and improve motor symptoms, newer research indicates that microglial activity is also essential for responding to neuronal damage and supporting neuronal survival.^{300,301} This suggests that complete depletion of microglia might impair the brain's repair mechanisms and exacerbate neurodegeneration. Therefore, targeted modulation of microglial activity, rather than total depletion, may be more beneficial.³⁰²

On the other hand, recent studies on peripheral immune cell depletion in PD models show that reducing the activity of these cells can decrease systemic inflammation and potentially slow disease progression.^{303,304}

However, evidence also suggests that such depletion might disrupt normal immune surveillance and repair processes, potentially leading to adverse outcomes.³⁰⁵ This highlights the importance of balancing immune responses to support neuronal health while minimizing harmful effects.

These findings emphasize the complex, often context-dependent roles of immune cells in NDs, suggesting that therapeutic strategies must carefully target immune cell functions to balance their protective and harmful effects.

Targeting microglia and astrocytes in AD and PD requires advanced strategies to modulate their complex roles in neurodegeneration and inflammation. Several methods can be used to target microglia. Anti-inflammatory agents and immunomodulatory therapies aim to mitigate the detrimental effects of chronic inflammation by inhibiting the production of pro-inflammatory cytokines and ROS.^{306,307}

Additionally, strategies to enhance plaque clearance involve developing pharmaceuticals or employing genetic techniques to boost microglial activity, which is essential for removing A β plaques and slowing AD progression. Targeting specific receptors, such as TREM2 (triggering receptor expressed on myeloid cells

2), has also been shown to improve microglial uptake of plaques and enhance neuroprotection. These approaches seek to balance the beneficial and harmful effects of microglial activity to better manage NDs.^{308,309}

Similarly, strategies for modulating astrocytes focus on their reactive states. A1 astrocytes, which are neurotoxic, can be shifted toward a more protective A2 state using signaling pathway inhibitors or enhancers. Increasing the production or delivery of neurotrophic factors, such as BDNF and insulin-like growth factor 1, which are produced by A2 astrocytes, supports neuronal survival and repair.^{310,311}

Additionally, targeting calcium signaling and astrocytic transport systems helps normalize astrocyte functions critical for maintaining synaptic health and ion balance. Efforts to reduce excessive astrogliosis aim to prevent astrocyte overactivation and scarring, which can further damage neurons.^{312,313}

Combining these approaches while ensuring therapeutic specificity and evaluating long-term outcomes is crucial for developing effective treatments. By targeting both microglia and astrocytes, these strategies aim to address the multifaceted nature of neurodegenerative diseases, potentially improving cognitive function and slowing disease progression in AD and PD.

In AD and PD, the roles of immune cells evolve throughout disease progression, necessitating tailored therapeutic approaches at each stage. In the early stages of AD, microglia are initially activated to respond to A β plaques and tau pathology. Targeting these cells with anti-inflammatory agents can help manage inflammation and prevent excessive plaque buildup, potentially delaying disease onset.³¹⁴

As AD progresses to the intermediate stage, chronic inflammation becomes more pronounced, and the balance between protective and harmful microglial responses can shift. At this point, therapies should aim to reduce persistent inflammation and promote neuroprotection by modulating both microglial activity and astrocyte states, particularly by shifting neurotoxic A1 astrocytes to a more protective A2 state.

In the late stages of AD, where extensive neuronal loss and severe inflammation are present, treatments may focus on controlling chronic inflammation and preserving the remaining neurons, potentially using advanced immunomodulatory therapies and novel approaches like gene and cell-based therapies.^{315,316}

In PD, therapeutic strategies also adapt to the disease stage. During the early stage, localized inflammation in the substantia nigra, where dopaminergic neurons are initially compromised, can be managed by targeting microglial activation with anti-inflammatory drugs to slow neuronal loss.

As the disease progresses to the intermediate stage, inflammation becomes more widespread, involving both central and peripheral immune cells. At this point, combined therapies are necessary to address the contributions of both microglia and astrocytes to neurodegeneration, aiming to reduce sustained inflammation and protect neuronal function.

In the late stage, characterized by significant dopaminergic neuron loss and severe motor symptoms, the focus shifts to managing chronic inflammation and supporting the remaining neurons. Advanced therapies and innovative treatments may be employed to enhance patient quality of life and slow disease progression. Adapting treatments to these stage-specific immune cell dynamics is essential for effective management and improved therapeutic outcomes in PD.^{317,318}

Last but not least, emerging evidence suggests a role for B cells in PD, particularly through their potential involvement in alpha-

synuclein pathology. Elevated levels of alpha-synuclein antibodies in prodromal PD stages indicate B cell activation, though their exact role—whether protective or pathogenic—remains unclear. B cells contribute to PD pathogenesis through diverse functions beyond antibody production, including antigen presentation, cytokine modulation, and interaction with other immune cells in both CNS and peripheral inflammation contexts.^{319–323}

Neuroinflammation and Alzheimer's biomarkers

Recent advances in AD research have enhanced our understanding of how various biomarkers, including MRI (magnetic resonance imaging), fluorodeoxyglucose-positron emission tomography (FDG-PET), tau PET, and CSF levels of amyloid and tau, are linked with immune responses.^{324,325} MRI detects brain atrophy, particularly in the hippocampus and cortical regions, which is associated with increased neuroinflammation.³²⁶ Studies have indicated that the activation of microglia and proliferation of astrocytes play a significant role in these structural changes, highlighting that inflammation-driven neuronal loss and synaptic damage are critical contributors to the observed atrophy.³²⁷

FDG-PET, which measures glucose metabolism, often reveals reduced metabolic activity in areas affected by AD. Recent research indicates that this hypometabolism is not only a result of neuronal loss but also a consequence of neuroinflammation.³²⁸ Activated microglia and astrocytes can disrupt neuronal function and energy metabolism, further contributing to the metabolic declines observed on FDG-PET scans.³²⁹

Tau PET imaging, which visualizes hyperphosphorylated tau deposits, has shown that tau pathology is closely linked with neuroinflammation.³³⁰ Recent findings suggest that tau deposition can trigger inflammatory responses, with microglial activation potentially exacerbating tau-related damage. This interaction underscores the bidirectional relationship between tau pathology and inflammation, influencing the severity of neurodegeneration.³³¹

CSF analysis of amyloid and tau levels reveals that neuroinflammation can affect these biomarkers. Elevated tau levels in CSF often correspond with higher neuroinflammatory activity, as tau release from damaged neurons can stimulate inflammatory responses.³³²

Similarly, reduced amyloid- β levels in CSF may be influenced by impaired clearance due to inflammation. Emerging research is exploring how inflammatory markers in CSF correlate with AD biomarker levels and disease progression, providing insights into the complex interplay between inflammation and AD pathology.³³³

Overall, recent studies highlight that neuroinflammation significantly impacts AD biomarkers, emphasizing the need to consider inflammatory processes when interpreting these biomarkers and developing targeted therapies. This integrated perspective may lead to more effective strategies for diagnosing and treating AD by addressing both pathological and inflammatory aspects of the disease.^{117,124,125}

In summary, NDs exhibit complex immune responses triggered by cortical atrophy and protein aggregation in the CNS. AD and PD exemplify distinct patterns of neuroinflammation driven by A β and alpha-synuclein, respectively, impacting microglial activation and neuronal health. T cells exacerbate neuroinflammation in PD by skewing microglial responses, while B cells potentially influence disease progression through multiple immune functions. Clarifying these immune dynamics is crucial for developing targeted therapies to mitigate neuroinflammation and preserve neuronal function in NDs.

Therapeutic strategies for combating neuroinflammation

Targeted therapeutic strategies for neuroinflammation are crucial in mitigating the adverse effects of chronic inflammation on brain health and NDs. Current approaches include modulating microglial activity, targeting astrocytes, and employing immunomodulatory and neuroprotective strategies.

Anti-inflammatory agents such as minocycline and pioglitazone are being studied for their potential to reduce microglial activation and inflammation, with minocycline showing promise in preclinical models for PD.^{334,335} Small molecules like clopidogrel, a P2Y₁₂ receptor antagonist, are also under investigation for their ability to modulate microglial responses.³³⁶

In terms of astrocyte targeting, GSK3 β inhibitors and adenosine A_{2A} receptor antagonists are being explored for their roles in reducing reactive astrogliosis and inflammatory responses.^{337,338} Immunomodulatory approaches include monoclonal antibodies targeting specific cytokines, such as anti-TNF- α and anti-IL-1 β antibodies, which are being tested in clinical trials to assess their efficacy in reducing neuroinflammation and improving symptoms in neurodegenerative conditions.^{339,340}

Additionally, vaccination approaches designed to elicit an immune response against pathological proteins, like alpha-synuclein in PD, aim to reduce toxic protein accumulation and modulate the neuroimmune response.³⁴¹ Nutraceuticals and dietary interventions, including compounds like curcumin and omega-3 fatty acids, are also being investigated for their anti-inflammatory and neuroprotective properties.³⁴²

Ongoing clinical trials, such as those evaluating minocycline's effects on PD and aducanumab for AD, are crucial for determining the effectiveness of these targeted treatments.^{343,344} Another clinical study is investigating how clopidogrel affects neuroinflammation in AD, while an additional study is exploring the effects of the anti-IL-1 β antibody canakinumab on various neurodegenerative conditions.^{345,346} These strategies and trials provide a comprehensive understanding of how targeted treatments aim to address neuroinflammation and their potential implications for managing NDs. Additional details about the clinical trials are provided in [Table 1](#).

Future directions

Although the brain is considered immune-privileged, its immune system—primarily composed of microglia and astrocytes—is essential for maintaining balance and addressing challenges. During illness, external immune cells can alter the brain's immune dynamics, highlighting a complex relationship with neurological health. The development of neurological diseases is influenced by genetic, environmental, and lifestyle factors, with age-related changes in brain immune cells often leading to increased neuroinflammation.

Infections, pathogens, and chronic inflammation are critical factors that require targeted therapeutic approaches. Recent advancements in neuroimmunology focus on understanding and addressing neuroinflammation, which is a common element in numerous neurological disorders. Nanomedicine shows promise by using engineered nanoparticles to deliver treatments directly to the brain, capable of breaching the BBB.

Precision medicine aims to customize treatments by considering genetic and environmental influences, utilizing biomarkers, and performing genetic screening. Current research explores the communication pathways of immune cells both within the brain and systemically, as well as their dysfunction in neurological disorders, to discover new therapeutic targets.³⁴⁷ Age-related changes

in microglia and astrocytes play a major role in neuroinflammation and neuronal injury, driving efforts to develop strategies that support healthy brain aging.

Studies investigating the influence of environmental factors on the brain's immune system aim to reduce harmful effects. The examination of immune system dysfunction in mental health disorders, including depression, anxiety, and schizophrenia, is a rapidly growing field that presents opportunities for new treatments. Advanced imaging techniques and machine learning play crucial roles in understanding brain immune responses, identifying biomarkers, and predicting disease trajectories.

This review study encounters several limitations. One major challenge is fully clarifying the intricate interactions between brain immune cells, such as microglia and astrocytes, and the overall systemic immune response. The complex and sometimes overlapping functions of these cells make it difficult to pinpoint the exact mechanisms contributing to neuroinflammation and neurological disorders. Additionally, while the review focuses on age-related changes, it may not fully address the variability in individual aging processes, which makes it hard to generalize the findings across different groups.

Furthermore, the varied influence of environmental factors on brain immune systems is not entirely understood, which may limit the review's ability to explore how these exposures affect neuroinflammation and brain health.

Although we aimed to provide a comprehensive overview of how neuroimmune cells support health and how their dysfunction contributes to brain disorders, covering every underlying mechanism in detail is challenging. Instead, we have highlighted key mechanisms to emphasize their importance and to provide a clear understanding of their roles.

Future research should focus on elucidating the dynamic interactions between neuroimmune cells and neural circuits in both physiological and pathological contexts. Employing advanced imaging techniques, such as two-photon microscopy and *in vivo* imaging, along with single-cell genomics, could offer unprecedented insights into the behavior and differentiation of resident microglia, perivascular macrophages, and infiltrating monocytes throughout various stages of neurological disorders. Understanding how the roles and functions of these cells evolve over time, particularly during disease progression or resolution, may reveal critical mechanisms driving neuroinflammation and neurodegeneration.

Additionally, investigating the influence of systemic immune signals—such as cytokines and chemokines—on neuroimmune cell function and recruitment could uncover novel therapeutic targets. Insights into how peripheral immune responses affect brain inflammation and pathology could lead to innovative treatment strategies that bridge systemic and central immune interventions.

Moreover, exploring interactions between neuroimmune cells and neuronal populations will deepen our understanding of how immune responses impact cognitive functions and mood, potentially guiding new approaches to address mental health disorders and NDs.

A crucial focus for future research is investigating the impact of neuroinflammation on brain stem cells and neuronal regeneration.³⁴⁸ Understanding how chronic inflammation disrupts the stem cell microenvironment is essential, as it affects processes such as cell proliferation, differentiation, and survival. Identifying key cytokines, signaling pathways, and sources of oxidative stress involved could provide new targets for counteracting the harmful effects of inflammation.

Table 1. Clinical trials investigating the impact of immunomodulation on neurological disorders

Trial ID	Title	Conditions	Interventions
NCT06177028	MCLENA-2: A Phase II Clinical Trial for the Assessment of Lenalidomide in Patients With Mild Cognitive Impairment Due to Alzheimer's Disease	Alzheimer's disease	Lenalidomide 10 mg
NCT05173701	Effects of Probiotics on Peripheral Immunity in Parkinson's Disease	Parkinson's disease	Probiotics
NCT01545518	IVIg Treatment for Refractory Immune-Related Adult Epilepsy	Epilepsy	Intravenous immunoglobulin (IVIg).
NCT05864534	Phase 2a Immune Modulation With Ultrasound for Newly Diagnosed Glioblastoma	Glioblastoma, gliosarcoma	Balstilimab, botensilimab, liposomal doxorubicin
NCT03879512	Autologous Dendritic Cells, Metronomic Cyclophosphamide and Checkpoint Blockade in Children With Relapsed HGG	Childhood glioblastoma	Drug: Depletion of regulatory T cells; Procedure: Reoperation; Biological: Cancer vaccine
NCT03152318	A Study of the Treatment of Recurrent Malignant Glioma With rQNestin34.5v.2 (rQNestin)	Glioma	Oncolytic virus called rQNestin34.5v.2. Immunomodulation with cyclophosphamide
NCT06146062	Effects of Intravascular Administration of Mesenchymal Stromal Cells Derived From Wharton's Jelly of the Umbilical Cord on Systemic Immunomodulation and Neuroinflammation After Traumatic Brain Injury. (TRAUMACELL)	Traumatic brain injuries (TBI)	Drug: Mesenchymal stromal cells (MSC); Drug: Placebo
NCT04106830	Clinical and Imaging Patterns of Neuroinflammation Diseases in China (CLUE)	Neuroinflammatory and demyelination disease	Drug: Intravenous steroid
NCT05858515	REVERSE-Long COVID-19 With Baricitinib Study (REVERSE-LC)	Neurocognitive impairment, which can manifest as a type of Alzheimer's Disease and Related Dementias (ADRD), or cardiopulmonary symptoms resulting from Long COVID.	Drug: Baricitinib 4 mg; Drug: Placebo
NCT00645749	Helminth-induced Immunomodulation Therapy (HINT) in Relapsing-remitting Multiple Sclerosis (HINT)	Relapsing-remitting multiple sclerosis	Biological: Helminth ova
NCT04106830	Clinical and Imaging Patterns of Neuroinflammation Diseases in China (CLUE)	Neuromyelitis optica spectrum disorder and multiple sclerosis	Drug: Intravenous steroid
NCT05654818	Peripheral Immunological Effects of High-dose Vitamin D Treatment in Healthy Subjects (VDSS)	Multiple sclerosis	Drug: Vitamin D
NCT05080270	Feasibility Study of Tolerogenic Fibroblasts in Patients With Refractory Multiple Sclerosis (MSFibroblast)	Relapsing-remitting multiple sclerosis resistant to interferon.	Biological: Tolerogenic fibroblasts
NCT02983708	Neuroregenerative Potential of Intravenous G-CSF (Granulocyte-Colony Stimulating Factor) and Autologous Peripheral Blood Stem Cells	Neurodegeneration	Biological: Peripheral blood mononuclear cells (mPBMC); Drug: G-CSF; Drug: Placebo

Additionally, studying how neuroinflammation affects the migration and integration of new neurons into existing neural circuits will be critical for developing strategies to promote effective neuronal regeneration. By improving conditions for stem cells through targeted modulation of neuroinflammation, it may be possible to enhance brain repair and recovery, particularly in NDs and brain injuries.

Future research should also focus on elucidating the role of the

gut-brain axis in the development and progression of NDs.^{349,350}

Understanding how dysregulation of the gut microbiota affects neuroinflammation could reveal potential intervention strategies. By investigating the mechanisms through which gut microbial imbalances influence brain inflammation, we may identify novel therapeutic approaches to mitigate neuroinflammatory processes and improve outcomes for individuals with neurodegenerative conditions.

Conclusions

Integrating multi-omics approaches and developing advanced animal models that replicate human disease conditions will be crucial for translating these findings into clinical applications. This approach will enhance our ability to target neuroimmune pathways more effectively, offering hope for novel therapeutic interventions in neurological and psychiatric conditions. Furthermore, research should investigate the potential for targeting neuroimmune cells to counteract cognitive decline, exploring interventions that modulate microglial and astrocytic activity to restore or enhance their beneficial functions in the aging brain. This could involve pharmacological agents, lifestyle changes, or genetic modifications aimed at modifying immune cell behavior. Expanding research into the interactions between neuroimmune cells and other age-related factors, such as vascular health and metabolic changes, will provide new insights into their collective impact on cognitive function. Innovations in imaging technologies and machine learning will be crucial for diagnosing and treating neurological disorders more effectively, enhancing our ability to visualize and analyze complex brain processes and pathology. Interdisciplinary collaboration across neuroscience, immunology, genetics, clinical medicine, nanotechnology, and data science will be essential for advancing treatments and deepening our understanding of the brain's immune system.

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Conflict of interest

The authors declare that they have no conflicts of interest concerning the publication of this research.

Author contributions

Conceptualization (SKC), data curation (SKC), formal analysis (SKC), investigation (SKC), methodology (SKC), project administration (SKC), supervision (SKC), original draft writing (SKC), review and editing (SKC, DC).

References

- Ransohoff RM, Perry VH. Microglial physiology: unique stimuli, specialized responses. *Annu Rev Immunol* 2009;27:119–45. doi:10.1146/annurev.immunol.021908.132528, PMID:19302036.
- Salter MW, Stevens B. Microglia emerge as central players in brain disease. *Nat Med* 2017;23(9):1018–1027. doi:10.1038/nm.4397, PMID:28886007.
- Wolf SA, Boddeke HW, Kettenmann H. Microglia in Physiology and Disease. *Annu Rev Physiol* 2017;79:619–643. doi:10.1146/annurev-physiol-022516-034406, PMID:27959620.
- Colonna M, Butovsky O. Microglia Function in the Central Nervous System During Health and Neurodegeneration. *Annu Rev Immunol* 2017;35:441–468. doi:10.1146/annurev-immunol-051116-052358, PMID:28226226.
- Carson MJ, Doose JM, Melchior B, Schmid CD, Ploix CC. CNS immune privilege: hiding in plain sight. *Immunol Rev* 2006;213:48–65. doi:10.1111/j.1600-065X.2006.00441.x, PMID:16972896.
- Galea I, Bechmann I, Perry VH. What is immune privilege (not)? *Trends Immunol* 2007;28(1):12–8. doi:10.1016/j.it.2006.11.004, PMID:17129764.
- Daneman R, Prat A. The blood-brain barrier. *Cold Spring Harb Perspect Biol* 2015;7(1):a020412. doi:10.1101/cshperspect.a020412, PMID:30250261.
- Sweeney MD, Kisler K, Montagne A, Toga AW, Zlokovic BV. The role of brain vasculature in neurodegenerative disorders. *Nat Neurosci* 2018;21(10):1318–1331. doi:10.1038/s41593-018-0234-x, PMID:30250261.
- Abbott NJ, Patabendige AA, Dolman DE, Yusof SR, Begley DJ. Structure and function of the blood-brain barrier. *Neurobiol Dis* 2010;37(1):13–25. doi:10.1016/j.nbd.2009.07.030, PMID:19664713.
- Louveau A, Smirnov I, Keyes TJ, Eccles JD, Rouhani SJ, Peske JD, *et al*. Structural and functional features of central nervous system lymphatic vessels. *Nature* 2015;523(7560):337–341. doi:10.1038/nature14432, PMID:26030524.
- Aspelund A, Antila S, Proulx ST, Karlsen TV, Karaman S, Detmar M, *et al*. A dural lymphatic vascular system that drains brain interstitial fluid and macromolecules. *J Exp Med* 2015;212(7):991–999. doi:10.1084/jem.20142290, PMID:26077718.
- Da Mesquita S, Fu Z, Kipnis J. The Meningeal Lymphatic System: A New Player in Neurophysiology. *Neuron* 2018;100(2):375–388. doi:10.1016/j.neuron.2018.09.022, PMID:30359603.
- Heneka MT, Carson MJ, El Khoury J, Landreth GE, Brosseron F, Feinstein DL, *et al*. Neuroinflammation in Alzheimer's disease. *Lancet Neurol* 2015;14(4):388–405. doi:10.1016/S1474-4422(15)70016-5, PMID:25792098.
- Block ML, Hong JS. Microglia and inflammation-mediated neurodegeneration: multiple triggers with a common mechanism. *Prog Neurobiol* 2005;76(2):77–98. doi:10.1016/j.pneurobio.2005.06.004, PMID:16081203.
- Compston A, Coles A. Multiple sclerosis. *Lancet* 2008;372(9648):1502–1517. doi:10.1016/S0140-6736(08)61620-7, PMID:18970977.
- Frohman EM, Racke MK, Raine CS. Multiple sclerosis—the plaque and its pathogenesis. *N Engl J Med* 2006;354(9):942–955. doi:10.1056/NEJMra052130, PMID:16510748.
- Freedman MS, Thompson EJ, Deisenhammer F, Giovannoni G, Grimsley G, Keir G, *et al*. Recommended standard of cerebrospinal fluid analysis in the diagnosis of multiple sclerosis: a consensus statement. *Arch Neurol* 2005;62(6):865–870. doi:10.1001/archneur.62.6.865, PMID:15956157.
- Maccioni RB, González A, Andrade V, Cortés N, Tapia JP, Guzmán-Martínez L. Alzheimer's Disease in the Perspective of Neuroimmunology. *Open Neurol J* 2018;12:50–56. doi:10.2174/1874205X01812010050, PMID:30069256.
- Tyler KL. Acute Viral Encephalitis. *N Engl J Med* 2018;379(6):557–566. doi:10.1056/NEJMra1708714, PMID:30089069.
- Saylor D, Dickens AM, Sacktor N, Haughey N, Slusher B, Pletnikov M, *et al*. HIV-associated neurocognitive disorder—pathogenesis and prospects for treatment. *Nat Rev Neurol* 2016;12(4):234–248. doi:10.1038/nrneurol.2016.27, PMID:26965674.
- Ransohoff RM, Brown MA. Innate immunity in the central nervous system. *J Clin Invest* 2012;122(4):1164–1171. doi:10.1172/JCI58644, PMID:22466658.
- Prinz M, Priller J. Microglia and brain macrophages in the molecular age: from origin to neuropsychiatric disease. *Nat Rev Neurosci* 2014;15(5):300–312. doi:10.1038/nrn3722, PMID:24713688.
- Kierdorf K, Prinz M. Microglia in steady state. *J Clin Invest* 2017;127(9):3201–3209. doi:10.1172/JCI90602, PMID:28714861.
- Liddel SA, Barres BA. Reactive Astrocytes: Production, Function, and Therapeutic Potential. *Immunity* 2017;46(6):957–967. doi:10.1016/j.immuni.2017.06.006, PMID:28636962.
- Engelhardt B, Ransohoff RM. Capture, crawl, cross: the T cell code to breach the blood-brain barriers. *Trends Immunol* 2012;33(12):579–589. doi:10.1016/j.it.2012.07.004, PMID:22926201.
- Ransohoff RM. A polarizing question: do M1 and M2 microglia exist? *Nat Neurosci* 2016;19(8):987–991. doi:10.1038/nn.4338, PMID:27459405.

- [27] Hanisch UK, Kettenmann H. Microglia: active sensor and versatile effector cells in the normal and pathologic brain. *Nat Neurosci* 2007;10(11):1387–1394. doi:10.1038/nn1997, PMID:27459405.
- [28] Paolicelli RC, Bolasco G, Pagani F, Maggi L, Scianni M, Panzanelli P, *et al*. Synaptic pruning by microglia is necessary for normal brain development. *Science* 2011;333(6048):1456–1458. doi:10.1126/science.1202529, PMID:21778362.
- [29] Cornell J, Salinas S, Huang HY, Zhou M. Microglia regulation of synaptic plasticity and learning and memory. *Neural Regen Res* 2022;17(4):705–716. doi:10.4103/1673-5374.322423, PMID:34472455.
- [30] Mehl LC, Manjally AV, Bouadi O, Gibson EM, Tay TL. Microglia in brain development and regeneration. *Development* 2022;149(8):dev200425. doi:10.1242/dev.200425, PMID:35502782.
- [31] Fang S, Wu Z, Guo Y, Zhu W, Wan C, Yuan N, *et al*. Roles of microglia in adult hippocampal neurogenesis in depression and their therapeutics. *Front Immunol* 2023;14:1193053. doi:10.3389/fimmu.2023.1193053, PMID:37881439.
- [32] Al-Onaizi M, Al-Khalifah A, Qasem D, ElAli A. Role of Microglia in Modulating Adult Neurogenesis in Health and Neurodegeneration. *Int J Mol Sci* 2020;21(18):6875. doi:10.3390/ijms21186875, PMID:32961703.
- [33] Sofroniew MV, Vinters HV. Astrocytes: biology and pathology. *Acta Neuropathol* 2010;119(1):7–35. doi:10.1007/s00401-009-0619-8, PMID:20012068.
- [34] Abbott NJ, Rönnbäck L, Hansson E. Astrocyte-endothelial interactions at the blood-brain barrier. *Nat Rev Neurosci* 2006;7(1):41–53. doi:10.1038/nrn1824, PMID:16371949.
- [35] Clarke LE, Barres BA. Emerging roles of astrocytes in neural circuit development. *Nat Rev Neurosci* 2013;14(5):311–321. doi:10.1038/nrn3484, PMID:23595014.
- [36] Colombo E, Farina C. Astrocytes: Key Regulators of Neuroinflammation. *Trends Immunol* 2016;37(9):608–620. doi:10.1016/j.it.2016.06.006, PMID:16371949.
- [37] Lawrence JM, Schardin K, Wigdahl B, Nonnemacher MR. Roles of neuropathology-associated reactive astrocytes: a systematic review. *Acta Neuropathol Commun* 2023;11(1):42. doi:10.1186/s40478-023-01526-9, PMID:36915214.
- [38] Yu G, Zhang Y, Ning B. Reactive Astrocytes in Central Nervous System Injury: Subgroup and Potential Therapy. *Front Cell Neurosci* 2021;15:792764. doi:10.3389/fncel.2021, PMID:35002629.
- [39] Ding ZB, Song LJ, Wang Q, Kumar G, Yan YQ, Ma CG. Astrocytes: a double-edged sword in neurodegenerative diseases. *Neural Regen Res* 2021;16(9):1702–1710. doi:10.4103/1673-5374.306064, PMID:33510058.
- [40] Stoklund Dittlau K, Freude K. Astrocytes: The Stars in Neurodegeneration? *Biomolecules* 2024;14(3):289. doi:10.3390/biom14030289, PMID:38540709.
- [41] Yang K, Liu Y, Zhang M. The Diverse Roles of Reactive Astrocytes in the Pathogenesis of Amyotrophic Lateral Sclerosis. *Brain Sci* 2024;14(2):158. doi:10.3390/brainsci14020158, PMID:38391732.
- [42] Brandebura AN, Paumier A, Onur TS, Allen NJ. Astrocyte contribution to dysfunction, risk and progression in neurodegenerative disorders. *Nat Rev Neurosci* 2023;24(1):23–39. doi:10.1038/s41583-022-00641-1, PMID:36316501.
- [43] Pitt J, Wilcox KC, Tortelli V, Diniz LP, Oliveira MS, Dobbins C, *et al*. Neuroprotective astrocyte-derived insulin/insulin-like growth factor 1 stimulates endocytic processing and extracellular release of neuron-bound A β oligomers. *Mol Biol Cell* 2017;28(20):2623–2636. doi:10.1091/mbc.E17-06-0416, PMID:28963439.
- [44] Linnerbauer M, Rothhammer V. Protective Functions of Reactive Astrocytes Following Central Nervous System Insult. *Front Immunol* 2020;11:573256. doi:10.3389/fimmu.2020.573256, PMID:33117368.
- [45] Palasz E, Wilkaniec A, Stanaszek L, Andrzejewska A, Adamczyk A. Glia-Neurotrophic Factor Relationships: Possible Role in Pathobiology of Neuroinflammation-Related Brain Disorders. *Int J Mol Sci* 2023;24(7):6321. doi:10.3390/ijms24076321, PMID:37047292.
- [46] Santiago-Balmaseda A, Aguirre-Orozco A, Valenzuela-Arzeta IE, Villegas-Rojas MM, Pérez-Segura I, Jiménez-Barrios N, *et al*. Neurodegenerative Diseases: Unraveling the Heterogeneity of Astrocytes. *Cells* 2024;13(11):921. doi:10.3390/cells13110921, PMID:38891053.
- [47] Li T, Liu T, Chen X, Li L, Feng M, Zhang Y, *et al*. Microglia induce the transformation of A1/A2 reactive astrocytes via the CXCR7/PI3K/Akt pathway in chronic post-surgical pain. *J Neuroinflammation* 2020;17(1):211. doi:10.1186/s12974-020-01891-5, PMID:32665021.
- [48] Fei X, Dou YN, Wang L, Wu X, Huan Y, Wu S, *et al*. Homer1 promotes the conversion of A1 astrocytes to A2 astrocytes and improves the recovery of transgenic mice after intracerebral hemorrhage. *J Neuroinflammation* 2022;19(1):67. doi:10.1186/s12974-022-02428-8, PMID:35287697.
- [49] Khodadadei F, Arshad R, Morales DM, Gluski J, Marupudi NI, McAllister JP 2nd, *et al*. The effect of A1 and A2 reactive astrocyte expression on hydrocephalus shunt failure. *Fluids Barriers CNS* 2022;19(1):78. doi:10.1186/s12987-022-00367-3, PMID:36171630.
- [50] Li K, Li J, Zheng J, Qin S. Reactive Astrocytes in Neurodegenerative Diseases. *Aging Dis* 2019;10(3):664–675. doi:10.14336/AD.2018.0720, PMID:31165009.
- [51] Liu YX, Sun H, Guo WY. Astrocyte polarization in glaucoma: a new opportunity. *Neural Regen Res* 2022;17(12):2582–2588. doi:10.4103/1673-5374.339470, PMID:35662185.
- [52] Lee HG, Wheeler MA, Quintana FJ. Function and therapeutic value of astrocytes in neurological diseases. *Nat Rev Drug Discov* 2022;21(5):339–358. doi:10.1038/s41573-022-00390-x, PMID:35173313.
- [53] Goldmann T, Wieghofer P, Jordão MJ, Prutek F, Hagemeyer N, Frenzel K, *et al*. Origin, fate and dynamics of macrophages at central nervous system interfaces. *Nat Immunol* 2016;17(7):797–805. doi:10.1038/ni.3423, PMID:27135602.
- [54] D'Agostino PM, Gottfried-Blackmore A, Anandasabapathy N, Bulloch K. Brain dendritic cells: biology and pathology. *Acta Neuropathol* 2012;124(5):599–614. doi:10.1007/s00401-012-1018-0, PMID:22825593.
- [55] Anandasabapathy N, Victora GD, Meredith M, Feder R, Dong B, Kluger C, *et al*. Flt3L controls the development of radiosensitive dendritic cells in the meninges and choroid plexus of the steady-state mouse brain. *J Exp Med* 2011;208(8):1695–1705. doi:10.1084/jem.20102657, PMID:21788405.
- [56] Andoh M, Koyama R. Comparative Review of Microglia and Monocytes in CNS Phagocytosis. *Cells* 2021;10(10):2555. doi:10.3390/cells10102555, PMID:34685535.
- [57] Lee E, Eo JC, Lee C, Yu JW. Distinct Features of Brain-Resident Macrophages: Microglia and Non-Parenchymal Brain Macrophages. *Mol Cells* 2021;44(5):281–291. doi:10.14348/molcells.2021.0060, PMID:33972475.
- [58] Wen W, Cheng J, Tang Y. Brain perivascular macrophages: current understanding and future prospects. *Brain* 2024;147(1):39–55. doi:10.1093/brain/awad304, PMID:37691438.
- [59] Park J, Chang JY, Kim JY, Lee JE. Monocyte Transmodulation: The Next Novel Therapeutic Approach in Overcoming Ischemic Stroke? *Front Neurol* 2020;11:578003. doi:10.3389/fneur.2020.578003, PMID:33193029.
- [60] Wicks EE, Ran KR, Kim JE, Xu R, Lee RP, Jackson CM. The Translational Potential of Microglia and Monocyte-Derived Macrophages in Ischemic Stroke. *Front Immunol* 2022;13:897022. doi:10.3389/fimmu.2022.897022, PMID:35795678.
- [61] Gómez Morillas A, Besson VC, Lerouet D. Microglia and Neuroinflammation: What Place for P2RY12? *Int J Mol Sci* 2021;22(4):1636. doi:10.3390/ijms22041636, PMID:33561958.
- [62] Liu YJ, Ding Y, Yin YQ, Xiao H, Hu G, Zhou JW. Cspg4(high) microglia contribute to microgliosis during neurodegeneration. *Proc Natl Acad Sci U S A* 2023;120(8):e2210643120. doi:10.1073/pnas.2210643120, PMID:36795751.
- [63] Kim WK, Alvarez X, Fisher J, Bronfin B, Westmoreland S, McLaurin J, *et al*. CD163 identifies perivascular macrophages in normal and viral encephalitic brains and potential precursors to perivascular macrophages in blood. *Am J Pathol* 2006;168(3):822–834. doi:10.2353/ajpath.2006.050215, PMID:16507898.
- [64] Xie L, Zheng L, Chen W, Zhai X, Guo Y, Zhang Y, *et al*. Trends in perivascular macrophages research from 1997 to 2021: A bibliometric analysis. *CNS Neurosci Ther* 2023;29(3):816–830. doi:10.1111/cns.14034, PMID:36514189.
- [65] Yang J, Zhang L, Yu C, Yang XF, Wang H. Monocyte and macrophage differentiation: circulation inflammatory monocyte as biomarker for inflammatory diseases. *Biomark Res* 2014;2(1):1. doi:10.1186/2050-

- 7771-2-1, PMID:24398220.
- [66] Bai M, Sun R, Cao B, Feng J, Wang J. Monocyte-related cytokines/chemokines in cerebral ischemic stroke. *CNS Neurosci Ther* 2023;29(12):3693–3712. doi:10.1111/cns.14368, PMID:37452512.
- [67] Spiteri AG, Wishart CL, Pamphlett R, Locatelli G, King NJC. Microglia and monocytes in inflammatory CNS disease: integrating phenotype and function. *Acta Neuropathol* 2022;143(2):179–224. doi:10.1007/s00401-021-02384-2, PMID:34853891.
- [68] Hammond TR, Dufort C, Dissing-Olesen L, Giera S, Young A, Wysoker A, *et al.* Single-Cell RNA Sequencing of Microglia throughout the Mouse Lifespan and in the Injured Brain Reveals Complex Cell-State Changes. *Immunity* 2019;50(1):253–271.e6. doi:10.1016/j.immuni.2018.11.004, PMID:30471926.
- [69] Bobotis BC, Halvorson T, Carrier M, Tremblay MÈ. Established and emerging techniques for the study of microglia: visualization, depletion, and fate mapping. *Front Cell Neurosci* 2024;18:1317125. doi:10.3389/fncel.2024.1317125, PMID:38425429.
- [70] Kipnis J, Gadani S, Derecki NC. Pro-cognitive properties of T cells. *Nat Rev Immunol* 2012;12(9):663–669. doi:10.1038/nri3280, PMID:22903149.
- [71] Morimoto K, Nakajima K. Role of the Immune System in the Development of the Central Nervous System. *Front Neurosci* 2019;13:916. doi:10.3389/fnins.2019.00916, PMID:31551681.
- [72] Matejuk A, Vandenbark AA, Offner H. Cross-Talk of the CNS With Immune Cells and Functions in Health and Disease. *Front Neurol* 2021;12:672455. doi:10.3389/fneur.2021.672455, PMID:34135852.
- [73] Zhao X, Wang H, Sun G, Zhang J, Edwards NJ, Aronowski J. Neuronal Interleukin-4 as a Modulator of Microglial Pathways and Ischemic Brain Damage. *J Neurosci* 2015;35(32):11281–11291. doi:10.1523/JNEUROSCI.1685-15.2015, PMID:26269636.
- [74] Sakaguchi S, Yamaguchi T, Nomura T, Ono M. Regulatory T cells and immune tolerance. *Cell* 2008;133(5):775–787. doi:10.1016/j.cell.2008.05.009, PMID:18510923.
- [75] Autoimmunity: from the origin to the loss of self-tolerance. *Nature Immunology* 2020;21:761–773.
- [76] Dominguez-Villar M, Hafler DA. Regulatory T cells in autoimmune disease. *Nat Immunol* 2018;19(7):665–673. doi:10.1038/s41590-018-0120-4, PMID:29925983.
- [77] Oparaugo NC, Ouyang K, Nguyen NPN, Nelson AM, Agag GW. Human Regulatory T Cells: Understanding the Role of Tregs in Select Autoimmune Skin Diseases and Post-Transplant Nonmelanoma Skin Cancers. *Int J Mol Sci* 2023;24(2):1527. doi:10.3390/ijms24021527, PMID:36675037.
- [78] Olson KE, Mosley RL, Gendelman HE. The potential for treg-enhancing therapies in nervous system pathologies. *Clin Exp Immunol* 2023;211(2):108–121. doi:10.1093/cei/uxac084, PMID:36041453.
- [79] Choi J, Kim BR, Akuzum B, Chang L, Lee JY, Kwon HK. T(REG)king From Gut to Brain: The Control of Regulatory T Cells Along the Gut-Brain Axis. *Front Immunol* 2022;13:916066. doi:10.3389/fimmu.2022.916066, PMID:35844606.
- [80] Tondo G, Aprile D, De Marchi F, Sarasso B, Serra P, Borasio G, *et al.* Investigating the Prognostic Role of Peripheral Inflammatory Markers in Mild Cognitive Impairment. *J Clin Med* 2023;12(13):4298. doi:10.3390/jcm12134298, PMID:37445333.
- [81] Brochard V, Combadière B, Prigent A, Laouar Y, Perrin A, Bera-Berthet V, *et al.* Infiltration of CD4+ lymphocytes into the brain contributes to neurodegeneration in a mouse model of Parkinson disease. *J Clin Invest* 2009;119(1):182–192. doi:10.1172/JCI36470, PMID:19104149.
- [82] Sochocka M, Diniz BS, Leszek J. Inflammatory Response in the CNS: Friend or Foe? *Mol Neurobiol* 2017;54(10):8071–8089. doi:10.1007/s12035-016-0297-1, PMID:27889895.
- [83] Earls RH, Lee JK. The role of natural killer cells in Parkinson's disease. *Exp Mol Med* 2020;52(9):1517–1525. doi:10.1038/s12276-020-00505-7, PMID:32973221.
- [84] Lünemann JD, Münz C. Do natural killer cells accelerate or prevent autoimmunity in multiple sclerosis? *Brain* 2008;131(Pt 7):1681–1683. doi:10.1093/brain/awn132, PMID:18586760.
- [85] Chen C, Ai QD, Chu SF, Zhang Z, Chen NH. NK cells in cerebral ischemia. *Biomed Pharmacother* 2019;109:547–554. doi:10.1016/j.biopha.2018.10.103, PMID:30399590.
- [86] Mauri C, Bosma A. Immune regulatory function of B cells. *Annu Rev Immunol* 2012;30:221–241. doi:10.1146/annurev-immunol-020711-074934, PMID:22224776.
- [87] Prüss H. Autoantibodies in neurological disease. *Nat Rev Immunol* 2021;21(12):798–813. doi:10.1038/s41577-021-00543-w, PMID:33976421.
- [88] Ran Z, Yue-Bei L, Qiu-Ming Z, Huan Y. Regulatory B Cells and Its Role in Central Nervous System Inflammatory Demyelinating Diseases. *Front Immunol* 2020;11:1884. doi:10.3389/fimmu.2020.01884, PMID:32973780.
- [89] Catalán D, Mansilla MA, Ferrier A, Soto L, Oleinika K, Aguilón JC, *et al.* Immunosuppressive Mechanisms of Regulatory B Cells. *Front Immunol* 2021;12:611795. doi:10.3389/fimmu.2021.611795, PMID:33995344.
- [90] Weber MS, Hemmer B. Cooperation of B cells and T cells in the pathogenesis of multiple sclerosis. *Results Probl Cell Differ* 2010;51:115–126. doi:10.1007/400_2009_21, PMID:19582406.
- [91] Li R, Patterson KR, Bar-Or A. Reassessing B cell contributions in multiple sclerosis. *Nat Immunol* 2018;19(7):696–707. doi:10.1038/s41590-018-0135-x, PMID:29925992.
- [92] Stern JN, Yaari G, Vander Heiden JA, Church G, Donahue WF, Hintzen RQ, *et al.* B cells populating the multiple sclerosis brain mature in the draining cervical lymph nodes. *Sci Transl Med* 2014;6(248):248ra107. doi:10.1126/scitranslmed.3008879, PMID:25100741.
- [93] Heneka MT, Carson MJ, El Khoury J, Landreth GE, Brosseron F, Feinstein DL, *et al.* Neuroinflammation in Alzheimer's disease. *Lancet Neurol* 2015;14(4):388–405. doi:10.1016/S1474-4422(15)70016-5.
- [94] Sweeney MD, Zhao Z, Montagne A, Nelson AR, Zlokovic BV. Blood-Brain Barrier: From Physiology to Disease and Back. *Physiol Rev* 2019;99(1):21–78. doi:10.1152/physrev.00050.2017, PMID:30280653.
- [95] Salter MW, Stevens B. Microglia emerge as central players in brain disease. *Nat Med* 2017;23(9):1018–1027. doi:10.1038/nm.4397, PMID:28886007.
- [96] Cunningham C. Microglia and neurodegeneration: the role of systemic inflammation. *Glia* 2013;61(1):71–90. doi:10.1002/glia.22350, PMID:22674585.
- [97] Nation DA, Sweeney MD, Montagne A, Sagare AP, D'Orazio LM, Pachicano M, *et al.* Blood-brain barrier breakdown is an early biomarker of human cognitive dysfunction. *Nat Med* 2019;25(2):270–276. doi:10.1038/s41591-018-0297-y, PMID:30643288.
- [98] Nimmerjahn A, Kirchhoff F, Helmchen F. Resting microglial cells are highly dynamic surveillants of brain parenchyma in vivo. *Science* 2005;308(5726):1314–1318. doi:10.1126/science.1110647, PMID:15831717.
- [99] Harry GJ. Microglia during development and aging. *Pharmacol Ther* 2013;139(3):313–326. doi:10.1016/j.pharmthera.2013.04.013, PMID:23644076.
- [100] Antignano I, Liu Y, Offermann N, Capasso M. Aging microglia. *Cell Mol Life Sci* 2023;80(5):126. doi:10.1007/s00018-023-04775-y, PMID:37081238.
- [101] Clarke LE, Barres BA. Emerging roles of astrocytes in neural circuit development. *Nat Rev Neurosci* 2013;14(5):311–321. doi:10.1038/nrn3484.
- [102] Dilger RN, Johnson RW. Aging, microglial cell priming, and the discordant central inflammatory response to signals from the peripheral immune system. *J Leukoc Biol* 2008;84(4):932–939. doi:10.1189/jlb.0208108, PMID:18495785.
- [103] Mosher KI, Wyss-Coray T. Microglial dysfunction in brain aging and Alzheimer's disease. *Biochem Pharmacol* 2014;88(4):594–604. doi:10.1016/j.bcp.2014.01.008, PMID:24445162.
- [104] Sierra A, Gottfried-Blackmore A, Milner TA, McEwen BS, Bulloch K. Steroid hormone receptor expression and function in microglia. *Glia* 2008;56(6):659–674. doi:10.1002/glia.20644, PMID:18286612.
- [105] Njie EG, Boelen E, Stassen FR, Steinbusch HW, Borchelt DR, Streit WJ. Ex vivo cultures of microglia from young and aged rodent brain reveal age-related changes in microglial function. *Neurobiol Aging* 2012;33(1):195.e1–195.12. doi:10.1016/j.neurobiolaging.2010.05.008, PMID:20580465.
- [106] Hickman SE, El Khoury J. Mechanisms of mononuclear phagocyte recruitment in Alzheimer's disease. *CNS Neurol Disord Drug Targets* 2010;9(2):168–173. doi:10.2174/187152710791011982, PMID:202

- 05643.
- [107] Perry VH, Nicoll JA, Holmes C. Microglia in neurodegenerative disease. *Nat Rev Neurol* 2010;6(4):193–201. doi:10.1038/nrneur.2010.17. PMID:20234358.
- [108] Rodríguez JJ, Olabarria M, Chvatal A, Verkhratsky A. Astroglia in dementia and Alzheimer's disease. *Cell Death Differ* 2009;16(3):378–385. doi:10.1038/cdd.2008.172. PMID:19057621.
- [109] Verkhratsky A, Nedergaard M. Physiology of Astroglia. *Physiol Rev* 2018;98(1):239–389. doi:10.1152/physrev.00042.2016. PMID:29351512.
- [110] Simard M, Arcuino G, Takano T, Liu QS, Nedergaard M. Signaling at the gliovascular interface. *J Neurosci* 2003;23(27):9254–9262. doi:10.1523/JNEUROSCI.23-27-09254.2003. PMID:14534260.
- [111] Walz W. Role of astrocytes in the clearance of excess extracellular potassium. *Neurochem Int* 2000;36(4-5):291–300. doi:10.1016/s0197-0186(99)00137-0. PMID:10732996.
- [112] Sofroniew MV, Vinters HV. Astrocytes: biology and pathology. *Acta Neuropathol* 2010;119(1):7–35. doi:10.1007/s00401-009-0619-8. PMID:20012068.
- [113] Seifert G, Schilling K, Steinhäuser C. Astrocyte dysfunction in neurological disorders: a molecular perspective. *Nat Rev Neurosci* 2006;7(3):194–206. doi:10.1038/nrn1870. PMID:16495941.
- [114] Boisvert MM, Erikson GA, Shokhiev MN, Allen NJ. The Aging Astrocyte Transcriptome from Multiple Regions of the Mouse Brain. *Cell Rep* 2018;22(1):269–285. doi:10.1016/j.celrep.2017.12.039. PMID:29298427.
- [115] Deitmer JW, Verkhratsky AJ, Lohr C. Calcium signalling in glial cells. *Cell Calcium* 1998;24(5-6):405–416. doi:10.1016/s0143-4160(98)90063-x. PMID:10091009.
- [116] Maragakis NJ, Rothstein JD. Mechanisms of Disease: Astrocytes in neurodegenerative disease. *Nat Clin Pract Neurol* 2006;2(12):679–689. doi:10.1038/ncpneuro0355.
- [117] Wyss-Coray T, Mucke L. Inflammation in neurodegenerative disease—a double-edged sword. *Neuron* 2002;35(3):419–432. doi:10.1016/s0896-6273(02)00794-8. PMID:12165466.
- [118] Sidoryk-Wegrzynowicz M, Aschner M. Role of astrocytes in manganese mediated neurotoxicity. *BMC Pharmacol Toxicol* 2013;14:23. doi:10.1186/2050-6511-14-23. PMID:23594835.
- [119] Pekny M, Pekna M, Messing A, Steinhäuser C, Lee JM, Parpura V, *et al*. Astrocytes: a central element in neurological diseases. *Acta Neuropathol* 2016;131(3):323–345. doi:10.1007/s00401-015-1513-1. PMID:26671410.
- [120] Heneka MT, Golenbock DT, Latz E. Innate immunity in Alzheimer's disease. *Nat Immunol* 2015;16(3):229–236. doi:10.1038/ni.3102.
- [121] Jha MK, Jeon S, Suk K. Glia as a Link between Neuroinflammation and Neuropathic Pain. *Immune Netw* 2012;12(2):41–47. doi:10.4110/in.2012.12.2.41. PMID:22740789.
- [122] Kam TI, Hinkle JT, Dawson TM, Dawson VL. Microglia and astrocyte dysfunction in parkinson's disease. *Neurobiol Dis* 2020;144:105028. doi:10.1016/j.nbd.2020.105028. PMID:32736085.
- [123] Chen K, Wang H, Ilyas I, Mahmood A, Hou L. Microglia and Astrocytes Dysfunction and Key Neuroinflammation-Based Biomarkers in Parkinson's Disease. *Brain Sci* 2023;13(4):634. doi:10.3390/brainsci13040634. PMID:37190599.
- [124] Isik S, Yeman Kiyak B, Akbayir R, Seyhali R, Arpacı T. Microglia Mediated Neuroinflammation in Parkinson's Disease. *Cells* 2023;12(7):1012. doi:10.3390/cells12071012. PMID:37048085.
- [125] Latham AS, Moreno JA, Geer CE. Biological agents and the aging brain: glial inflammation and neurotoxic signaling. *Front Aging* 2023;4:1244149. doi:10.3389/fragi.2023.1244149. PMID:37649972.
- [126] Tansey MG, Wallings RL, Houser MC, Herrick MK, Keating CE, Jowers V. Inflammation and immune dysfunction in Parkinson disease. *Nat Rev Immunol* 2022;22(11):657–673. doi:10.1038/s41577-022-00684-6. PMID:35246670.
- [127] Cossu D, Hatano T, Hattori N. The Role of Immune Dysfunction in Parkinson's Disease Development. *Int J Mol Sci* 2023;24(23):16766. doi:10.3390/ijms242316766. PMID:38069088.
- [128] Deyell JS, Sriparna M, Ying M, Mao X. The Interplay between α -Synuclein and Microglia in α -Synucleinopathies. *Int J Mol Sci* 2023;24(3):2477. doi:10.3390/ijms24032477. PMID:36768798.
- [129] Jurcau A, Andronie-Cioara FL, Nistor-Cseppento DC, Pascalau N, Rus M, Vasca E, *et al*. The Involvement of Neuroinflammation in the Onset and Progression of Parkinson's Disease. *Int J Mol Sci* 2023;24(19):14582. doi:10.3390/ijms241914582. PMID:37834030.
- [130] Bouvier DS, Fixemer S, Heurtaux T, Jeannelle F, Frauenknecht KBM, Mittelbronn M. The Multifaceted Neurotoxicity of Astrocytes in Ageing and Age-Related Neurodegenerative Diseases: A Translational Perspective. *Front Physiol* 2022;13:814889. doi:10.3389/fphys.2022.814889. PMID:35370777.
- [131] Verkhratsky A, Butt A, Li B, Illes P, Zorec R, Semyanov A, *et al*. Astrocytes in human central nervous system diseases: a frontier for new therapies. *Signal Transduct Target Ther* 2023;8(1):396. doi:10.1038/s41392-023-01628-9. PMID:37828019.
- [132] Wang T, Sun Y, Dettmer U. Astrocytes in Parkinson's Disease: From Role to Possible Intervention. *Cells* 2023;12(19):2336. doi:10.3390/cells12192336. PMID:37830550.
- [133] Manu DR, Slevin M, Barcutean L, Forro T, Boghitou T, Balasa R. Astrocyte Involvement in Blood-Brain Barrier Function: A Critical Update Highlighting Novel, Complex, Neurovascular Interactions. *Int J Mol Sci* 2023;24(24):17146. doi:10.3390/ijms242417146. PMID:38138976.
- [134] Adesse D, Gladulich L, Alvarez-Rosa L, Siqueira M, Marcos AC, Heider M, *et al*. Role of aging in Blood-Brain Barrier dysfunction and susceptibility to SARS-CoV-2 infection: impacts on neurological symptoms of COVID-19. *Fluids Barriers CNS* 2022;19(1):63. doi:10.1186/s12987-022-00357-5. PMID:35982454.
- [135] Thomas R, Wang W, Su DM. Contributions of Age-Related Thymic Involution to Immunosenescence and Inflammaging. *Immun Ageing* 2020;17:2. doi:10.1186/s12979-020-0173-8. PMID:31988649.
- [136] Palatella M, Guillaume SM, Linterman MA, Huehn J. The dark side of Tregs during aging. *Front Immunol* 2022;13:940705. doi:10.3389/fimmu.2022.940705. PMID:36016952.
- [137] Liang Z, Dong X, Zhang Z, Zhang Q, Zhao Y. Age-related thymic involution: Mechanisms and functional impact. *Aging Cell* 2022;21(8):e13671. doi:10.1111/ace1.13671. PMID:35822239.
- [138] Lagou MK, Anastasiadou DP, Karagiannis GS. A Proposed Link Between Acute Thymic Involution and Late Adverse Effects of Chemotherapy. *Front Immunol* 2022;13:933547. doi:10.3389/fimmu.2022.933547. PMID:35844592.
- [139] Gonzales MM, Garbarino VR, Pollet E, Palavicini JP, Kellogg DL Jr, Kraig E, *et al*. Biological aging processes underlying cognitive decline and neurodegenerative disease. *J Clin Invest* 2022;132(10):e158453. doi:10.1172/JCI158453. PMID:35575089.
- [140] Fonken LK, Gaudet AD. Neuroimmunology of healthy brain aging. *Curr Opin Microbiol* 2022;77:102649. doi:10.1016/j.conb.2022.102649. PMID:36368270.
- [141] Aw D, Silva AB, Palmer DB. Immunosenescence: emerging challenges for an ageing population. *Immunology* 2007;120(4):435–446. doi:10.1111/j.1365-2567.2007.02555.x. PMID:17313487.
- [142] Rosenkranz D, Weyer S, Tolosa E, Gaenslen A, Berg D, Leyhe T, *et al*. Higher frequency of regulatory T cells in the elderly and increased suppressive activity in neurodegeneration. *J Neuroimmunol* 2007;188(1-2):117–127. doi:10.1016/j.jneuroim.2007.05.011. PMID:17582512.
- [143] Baruch K, Schwartz M. CNS-specific T cells shape brain function via the choroid plexus. *Brain Behav Immun* 2013;34:11–16. doi:10.1016/j.bbi.2013.04.002. PMID:23597431.
- [144] Frasca D, Blomberg BB. Aging affects human B cell responses. *J Clin Immunol* 2011;31(3):430–435. doi:10.1007/s10875-010-9501-7. PMID:21318330.
- [145] Fulop T, Larbi A, Witkowski JM, McElhaneey J, Loeb M, Mitnitski A, Pawelec G. Aging, frailty and age-related diseases. *Biogerontology* 2010;11(5):547–563. doi:10.1007/s10522-010-9287-2. PMID:20559726.
- [146] Schwartz M, Baruch K. The resolution of neuroinflammation in neurodegeneration: leukocyte recruitment via the choroid plexus. *EMBO J* 2014;33(1):7–22. doi:10.1002/embj.201386609. PMID:24357543.
- [147] Hampel H, Caraci F, Cuello AC, Caruso G, Nisticò R, Corbo M, *et al*. A Path Toward Precision Medicine for Neuroinflammatory Mechanisms in Alzheimer's Disease. *Front Immunol* 2020;11:456. doi:10.3389/fimmu.2020.00456. PMID:32296418.
- [148] Whitley RJ. Herpes simplex encephalitis: adolescents and adults. *An-*

- tiviral Res 2006;71(2-3):141–8. doi:10.1016/j.antiviral.2006.04.002, PMID:16675036.
- [149] Gildea D, Nagel M, Cohrs R, Mahalingam R, Baird N. Varicella Zoster Virus in the Nervous System. *F1000Res* 2015;4(F1000 Faculty Rev):1356. doi:10.12688/f1000research.7153.1, PMID:26918131.
- [150] Rhoades RE, Tabor-Godwin JM, Tsueng G, Feuer R. Enterovirus infections of the central nervous system. *Virology* 2011;411(2):288–305. doi:10.1016/j.virol.2010.12.014, PMID:21251690.
- [151] Ayala-Nunez NV, Gaudin R. A viral journey to the brain: Current considerations and future developments. *PLoS Pathog* 2020;16(5):e1008434. doi:10.1371/journal.ppat.1008434, PMID:32437459.
- [152] Miner JJ, Diamond MS. Mechanisms of restriction of viral neuroinvasion at the blood-brain barrier. *Curr Opin Immunol* 2016;38:18–23. doi:10.1016/j.coi.2015.10.008, PMID:26590675.
- [153] Stephens DS, Greenwood B, Brandtzaeg P. Epidemic meningitis, meningococcaemia, and *Neisseria meningitidis*. *Lancet* 2007;369(9580):2196–2210. doi:10.1016/S0140-6736(07)61016-2, PMID:17604802.
- [154] Mook-Kanamori BB, Geldhoff M, van der Poll T, van de Beek D. Pathogenesis and pathophysiology of pneumococcal meningitis. *Clin Microbiol Rev* 2011;24(3):557–591. doi:10.1128/CMR.00008-11, PMID:21734248.
- [155] Rock RB, Olin M, Baker CA, Molitor TW, Peterson PK. Central nervous system tuberculosis: pathogenesis and clinical aspects. *Clin Microbiol Rev* 2008;21(2):243–261. doi:10.1128/CMR.00042-07, PMID:18400795.
- [156] Moraes CA, Zaverucha-do-Valle C, Fleurance R, Sharshar T, Bozza FA, d'Avila JC. Neuroinflammation in Sepsis: Molecular Pathways of Microglia Activation. *Pharmaceuticals (Basel)* 2021;14(5):416. doi:10.3390/ph14050416, PMID:34062710.
- [157] van de Beek D, Drake JM, Tunkel AR. Nosocomial bacterial meningitis. *N Engl J Med* 2010;362(2):146–154. doi:10.1056/NEJMra0804573, PMID:20071704.
- [158] Koedel U, Klein M, Pfister HW. Modulation of brain injury as a target of adjunctive therapy in bacterial meningitis. *Curr Infect Dis Rep* 2010;12(4):266–273. doi:10.1007/s11908-010-0116-1, PMID:21308541.
- [159] Yuki N, Hartung HP. Guillain-Barré syndrome. *N Engl J Med* 2012;366(24):2294–2304. doi:10.1056/NEJMra1114525, PMID:22694000.
- [160] Ang CW, Jacobs BC, Laman JD. The Guillain-Barré syndrome: a true case of molecular mimicry. *Trends Immunol* 2004;25(2):61–66. doi:10.1016/j.it.2003.12.004, PMID:15102364.
- [161] McGrogan A, Madle GC, Seaman HE, de Vries CS. The epidemiology of Guillain-Barré syndrome worldwide. A systematic literature review. *Neuroepidemiology* 2009;32(2):150–163. doi:10.1159/000184748.
- [162] van den Berg B, Walgaard C, Drenthen J, Fokke C, Jacobs BC, van Doorn PA. Guillain-Barré syndrome: pathogenesis, diagnosis, treatment and prognosis. *Nat Rev Neurol* 2014;10(8):469–482. doi:10.1038/nrneurol.2014.121.
- [163] Nachamkin I, Allos BM, Ho T. *Campylobacter* species and Guillain-Barré syndrome. *Clin Microbiol Rev* 1998;11(3):555–567. doi:10.1128/CMR.11.3.555, PMID:9665983.
- [164] Willison HJ, Jacobs BC, van Doorn PA. Guillain-Barré syndrome. *Lancet* 2016;388(10045):717–727. doi:10.1016/S0140-6736(16)00339-1.
- [165] Gannon P, Khan MZ, Kolson DL. Current understanding of HIV-associated neurocognitive disorders pathogenesis. *Curr Opin Neurol* 2011;24(3):275–283. doi:10.1097/WCO.0b013e32834695fb, PMID:21467932.
- [166] Anthony IC, Bell JE. The Neuropathology of HIV/AIDS. *Int Rev Psychiatry* 2008;20(1):15–24. doi:10.1080/09540260701862037.
- [167] Hong S, Banks WA. Role of the immune system in HIV-associated neuroinflammation and neurocognitive implications. *Brain Behav Immun* 2015;45:1–12. doi:10.1016/j.bbi.2014.10.008, PMID:25449672.
- [168] Sobel J. Botulism. *Clin Infect Dis* 2005;41(8):1167–1173. doi:10.1086/444507.
- [169] Simpson LL. Identification of the major steps in botulinum toxin action. *Annu Rev Pharmacol Toxicol* 2004;44:167–193. doi:10.1146/annurev.pharmtox.44.101802.121554, PMID:14744243.
- [170] Farrar JJ, Yen LM, Cook T, Fairweather N, Binh N, Parry J, *et al*. Tetanus. *J Neurol Neurosurg Psychiatry* 2000;69(3):292–301. doi:10.1136/jnnp.69.3.292, PMID:10945801.
- [171] Pellizzari R, Rossetto O, Schiavo G, Montecucco C. Tetanus and botulinum neurotoxins: mechanism of action and therapeutic uses. *Philos Trans R Soc Lond B Biol Sci* 1999;354(1381):259–268. doi:10.1098/rstb.1999.0377, PMID:10212474.
- [172] Butterworth RF. Hepatic encephalopathy: a central neuroinflammatory disorder? *Hepatology* 2011;53(4):1372–1376. doi:10.1002/hep.24228, PMID:21480337.
- [173] Chaudhry N, Duggal AK. Sepsis Associated Encephalopathy. *Adv Med* 2014;2014:762320. doi:10.1155/2014/762320, PMID:26556425.
- [174] Ballabh P, Braun A, Nedergaard M. The blood-brain barrier: an overview: structure, regulation, and clinical implications. *Neurobiol Dis* 2004;16(1):1–13. doi:10.1016/j.nbd.2003.12.016.
- [175] Iadecola C. Neurovascular regulation in the normal brain and in Alzheimer's disease. *Nat Rev Neurosci* 2004;5(5):347–60. doi:10.1038/nrn1387, PMID:15100718.
- [176] Noorbakhsh F, Johnson RT, Emery D, Power C. Acute disseminated encephalomyelitis: clinical and pathogenesis features. *Neurol Clin* 2008;26(3):759–780. doi:10.1016/j.ncl.2008.03.009, PMID:18657725.
- [177] Pohl D, Alper G, Van Haren K, Kornberg AJ, Lucchinetti CF, Tenenbaum S, *et al*. Acute disseminated encephalomyelitis: Updates on an inflammatory CNS syndrome. *Neurology* 2016;87(9 Suppl 2):S38–45. doi:10.1212/WNL.0000000000002825.
- [178] Wucherpfennig KW. Mechanisms for the induction of autoimmunity by infectious agents. *J Clin Invest* 2001;108(8):1097–1104. doi:10.1172/JCI14235, PMID:11602615.
- [179] Venkatesan A, Johnson RT. Infections and multiple sclerosis. *Handb Clin Neurol* 2014;122:151–171. doi:10.1016/B978-0-444-52001-2.00007-8, PMID:24507517.
- [180] Owens GP, Bennett JL. Trigger, pathogen, or bystander: the complex nexus linking Epstein-Barr virus and multiple sclerosis. *Mult Scler* 2012;18(9):1204–1208. doi:10.1177/1352458512448109, PMID:22685062.
- [181] Javed A, Khan O. Acute disseminated encephalomyelitis. *Handb Clin Neurol* 2014;123:705–717. doi:10.1016/B978-0-444-53488-0.00035-3, PMID:25015513.
- [182] MacDonald ME, Ambrose CM, Duyao MP, Myers RH, Lin C, Srinidhi L, *et al*. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. *Cell* 1993;72(6):971–983. doi:10.1016/0092-8674(93)90585-e.
- [183] State MW, Levitt P. The conundrums of understanding genetic risks for autism spectrum disorders. *Nat Neurosci* 2011;14(12):1499–1506. doi:10.1038/nn.2924, PMID:22037497.
- [184] Harold D, Abraham R, Hollingworth P, Sims R, Gerrish A, Hamshere ML, *et al*. Genome-wide association study identifies variants at *CLU* and *PICALM* associated with Alzheimer's disease. *Nat Genet* 2009;41(10):1088–1093. doi:10.1038/ng.440, PMID:19734902.
- [185] Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, *et al*. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* 1993;261(5123):921–923. doi:10.1126/science.8346443, PMID:8346443.
- [186] Goate A, Chartier-Harlin MC, Mullan M, Brown J, Crawford F, Fidani L, *et al*. Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. *Nature* 1991;349(6311):704–706. doi:10.1038/349704a0.
- [187] Ascherio A, Munger KL. Environmental risk factors for multiple sclerosis. Part I: the role of infection. *Ann Neurol* 2007;61(4):288–299. doi:10.1002/ana.21117.
- [188] Goldman SM. Environmental toxins and Parkinson's disease. *Annu Rev Pharmacol Toxicol* 2014;54:141–164. doi:10.1146/annurev-pharmtox-011613-135937.
- [189] O'Leary F, Allman-Farinelli M, Samman S. Vitamin B₁₂ status, cognitive decline and dementia: a systematic review of prospective cohort studies. *Br J Nutr* 2012;108(11):1948–61. doi:10.1017/S0007114512004175.
- [190] Gardner RC, Yaffe K. Epidemiology of mild traumatic brain injury and neurodegenerative disease. *Mol Cell Neurosci* 2015;66(Pt B):75–

80. doi:10.1016/j.mcn.2015.03.001, PMID:25748121.
- [191] Shields GS, Moons WG, Slavich GM. Better executive function under stress mitigates the effects of recent life stress exposure on health in young adults. *Stress* 2017;20(1):75–85. doi:10.1080/10253890.2017.1286322, PMID:28114849.
- [192] Bell JT, Spector TD. A twin approach to unraveling epigenetics. *Trends Genet* 2011;27(3):116–125. doi:10.1016/j.tig.2010.12.005, PMID:21257220.
- [193] Sampson TR, Debelius JW, Thron T, Janssen S, Shastri GG, Ilhan ZE, *et al*. Gut Microbiota Regulate Motor Deficits and Neuroinflammation in a Model of Parkinson's Disease. *Cell* 2016;167(6):1469–1480. e12. doi:10.1016/j.cell.2016.11.018, PMID:27912057.
- [194] Ordoñez-Rodríguez A, Roman P, Rueda-Ruzafa L, Campos-Rios A, Cardona D. Changes in Gut Microbiota and Multiple Sclerosis: A Systematic Review. *Int J Environ Res Public Health* 2023;20(5):4624. doi:10.3390/ijerph20054624, PMID:36901634.
- [195] Jowaed A, Schmitt I, Kaut O, Wüllner U. Methylation regulates alpha-synuclein expression and is decreased in Parkinson's disease patients' brains. *J Neurosci* 2010;30(18):6355–6359. doi:10.1523/JNEUROSCI.6119-09.2010, PMID:20445061.
- [196] Krzyzanowski B, Searles Nielsen S, Turner JR, Racette BA. Fine Particulate Matter and Parkinson Disease Risk Among Medicare Beneficiaries. *Neurology* 2023;101(21):e2058–e2067. doi:10.1212/WNL.0000000000207871, PMID:37903644.
- [197] Hirsch EC, Hunot S. Neuroinflammation in Parkinson's disease: a target for neuroprotection? *Lancet Neurol* 2009;8(4):382–397. doi:10.1016/S1474-4422(09)70062-6.
- [198] Lassmann H, van Horsen J, Mahad D. Progressive multiple sclerosis: pathology and pathogenesis. *Nat Rev Neurol* 2012;8(11):647–656. doi:10.1038/nrneurol.2012.168, PMID:23007702.
- [199] Perry VH, Teeling J. Microglia and macrophages of the central nervous system: the contribution of microglia priming and systemic inflammation to chronic neurodegeneration. *Semin Immunopathol* 2013;35(5):601–612. doi:10.1007/s00281-013-0382-8, PMID:23732506.
- [200] Mosley RL, Benner EJ, Kadiu I, Thomas M, Boska MD, Hasan K, *et al*. Neuroinflammation, Oxidative Stress and the Pathogenesis of Parkinson's Disease. *Clin Neurosci Res* 2006;6(5):261–281. doi:10.1016/j.cnr.2006.09.006, PMID:18060039.
- [201] Virolainen SJ, VonHandorf A, Viel KCMF, Weirauch MT, Kottyan LC. Gene-environment interactions and their impact on human health. *Genes Immun* 2023;24(1):1–11. doi:10.1038/s41435-022-00192-6, PMID:36585519.
- [202] Qin J, Ma Z, Chen X, Shu S. Microglia activation in central nervous system disorders: A review of recent mechanistic investigations and development efforts. *Front Neurol* 2023;14:1103416. doi:10.3389/fneur.2023.1103416, PMID:36959826.
- [203] Kwon HS, Koh SH. Neuroinflammation in neurodegenerative disorders: the roles of microglia and astrocytes. *Transl Neurodegener* 2020;9(1):42. doi:10.1186/s40035-020-00221-2, PMID:33239064.
- [204] Gao C, Jiang J, Tan Y, Chen S. Microglia in neurodegenerative diseases: mechanism and potential therapeutic targets. *Signal Transduct Target Ther* 2023;8(1):359. doi:10.1038/s41392-023-01588-0, PMID:37735487.
- [205] Dias de Sousa MA, Desidério CS, da Silva Catarino J, Trevisan RO, Alves da Silva DA, Rocha VFR, *et al*. Role of Cytokines, Chemokines and IFN- γ (+) IL-17(+) Double-Positive CD4(+) T Cells in Patients with Multiple Sclerosis. *Biomedicines* 2022;10(9):2062. doi:10.3390/biomedicines10092062, PMID:36140164.
- [206] Hsu RJ, Yu WC, Peng GR, Ye CH, Hu S, Chong PCT, *et al*. The Role of Cytokines and Chemokines in Severe Acute Respiratory Syndrome Coronavirus 2 Infections. *Front Immunol* 2022;13:832394. doi:10.3389/fimmu.2022.832394, PMID:35464491.
- [207] Elemam NM, Talaat IM, Maghazachi AA. CXCL10 Chemokine: A Critical Player in RNA and DNA Viral Infections. *Viruses* 2022;14(11):2445. doi:10.3390/v14112445, PMID:36366543.
- [208] Gąssowska-Dobrowolska M, Chlubek M, Kolasa A, Tomasiak P, Korbecki J, Skowrońska K, *et al*. Microglia and Astroglia-The Potential Role in Neuroinflammation Induced by Pre- and Neonatal Exposure to Lead (Pb). *Int J Mol Sci* 2023;24(12):9903. doi:10.3390/ijms24129903, PMID:37373050.
- [209] Van Zeller M, Dias D, Sebastião AM, Valente CA. NLRP3 Inflammation: A Starring Role in Amyloid- β - and Tau-Driven Pathological Events in Alzheimer's Disease. *J Alzheimers Dis* 2021;83(3):939–961. doi:10.3233/JAD-210268, PMID:34366341.
- [210] Simpson DSA, Oliver PL. ROS Generation in Microglia: Understanding Oxidative Stress and Inflammation in Neurodegenerative Disease. *Antioxidants (Basel)* 2020;9(8):743. doi:10.3390/antiox9080743, PMID:32823544.
- [211] Teleanu DM, Niculescu AG, Lungu II, Radu CI, Vladăncenco O, Roza E, *et al*. An Overview of Oxidative Stress, Neuroinflammation, and Neurodegenerative Diseases. *Int J Mol Sci* 2022;23(11):5938. doi:10.3390/ijms23115938, PMID:35682615.
- [212] Korovesis D, Rubio-Tomás T, Tavernarakis N. Oxidative Stress in Age-Related Neurodegenerative Diseases: An Overview of Recent Tools and Findings. *Antioxidants (Basel)* 2023;12(1):131. doi:10.3390/antiox12010131, PMID:36670993.
- [213] Juan CA, Pérez de la Lastra JM, Plou FJ, Pérez-Lebeña E. The Chemistry of Reactive Oxygen Species (ROS) Revisited: Outlining Their Role in Biological Macromolecules (DNA, Lipids and Proteins) and Induced Pathologies. *Int J Mol Sci* 2021;22(9):4642. doi:10.3390/ijms22094642, PMID:33924958.
- [214] Li Y, Li S, Wu H. Ubiquitination-Proteasome System (UPS) and Autophagy Two Main Protein Degradation Machineries in Response to Cell Stress. *Cells* 2022;11(5):851. doi:10.3390/cells11050851, PMID:35269473.
- [215] Barmaki H, Nourazarian A, Khaki-Khatibi F. Proteostasis and neurodegeneration: a closer look at autophagy in Alzheimer's disease. *Front Aging Neurosci* 2023;15:1281338. doi:10.3389/fnagi.2023.1281338, PMID:38020769.
- [216] Sonninen TM, Goldsteins G, Laham-Karam N, Koistinaho J, Lehtonen Š. Proteostasis Disturbances and Inflammation in Neurodegenerative Diseases. *Cells* 2020;9(10):2183. doi:10.3390/cells9102183, PMID:32998318.
- [217] Zhang W, Xu C, Sun J, Shen HM, Wang J, Yang C. Impairment of the autophagy-lysosomal pathway in Alzheimer's diseases: Pathogenic mechanisms and therapeutic potential. *Acta Pharm Sin B* 2022;12(3):1019–1040. doi:10.1016/j.apsb.2022.01.008, PMID:35530153.
- [218] Eshraghi M, Adlimoghaddam A, Mahmoodzadeh A, Sharifzad F, Yasavoli-Sharahi H, Lorzadeh S, *et al*. Alzheimer's Disease Pathogenesis: Role of Autophagy and Mitophagy Focusing in Microglia. *Int J Mol Sci* 2021;22(7):3330. doi:10.3390/ijms22073330, PMID:33805142.
- [219] Adamu A, Li S, Gao F, Xue G. The role of neuroinflammation in neurodegenerative diseases: current understanding and future therapeutic targets. *Front Aging Neurosci* 2024;16:1347987. doi:10.3389/fnagi.2024.1347987, PMID:38681666.
- [220] He J, Zhu G, Wang G, Zhang F. Oxidative Stress and Neuroinflammation Potentiate Each Other to Promote Progression of Dopamine Neurodegeneration. *Oxid Med Cell Longev* 2020;2020:6137521. doi:10.1155/2020/6137521, PMID:32714488.
- [221] Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, *et al*. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020;395(10229):1033–1034. doi:10.1016/S0140-6736(20)30628-0, PMID:32192578.
- [222] Solomon IH, Normandin E, Bhattacharyya S, Mukerji SS, Keller K, Ali AS, *et al*. Neuropathological Features of COVID-19. *N Engl J Med* 2020;383(10):989–992. doi:10.1056/NEJMc2019373, PMID:32530583.
- [223] Toscano G, Palmerini F, Ravaglia S, Ruiz L, Invernizzi P, Cuzzoni MG, *et al*. Guillain-Barré Syndrome Associated with SARS-CoV-2. *N Engl J Med* 2020;382(26):2574–2576. doi:10.1056/NEJMc2009191, PMID:32302082.
- [224] Ellul MA, Benjamin L, Singh B, Lant S, Michael BD, Easton A, *et al*. Neurological associations of COVID-19. *Lancet Neurol* 2020;19(9):767–783. doi:10.1016/S1474-4422(20)30221-0, PMID:32622375.
- [225] Varatharaj A, Thomas N, Ellul MA, Davies NWS, Pollak TA, Tenorio EL, *et al*. Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study. *Lancet Psychiatry* 2020;7(10):875–882. doi:10.1016/S2215-0366(20)30287-X, PMID:32593341.
- [226] Alqahtani MS, Abbas M, Alshahrani MY, Alabdullh K, Alqarni A,

- Alqahtani FF, *et al.* Effects of COVID-19 on Synaptic and Neuronal Degeneration. *Brain Sci* 2023;13(1):131. doi:10.3390/brainsci13010131, PMID:36672112.
- [227] Puelles VG, Lütgehetmann M, Lindenmeyer MT, Spherhake JP, Wong MN, Allweiss L, *et al.* Multiorgan and Renal Tropism of SARS-CoV-2. *N Engl J Med* 2020;383(6):590–592. doi:10.1056/NEJMc2011400, PMID:32402155.
- [228] Moriguchi T, Harii N, Goto J, Harada D, Sugawara H, Takamino J, *et al.* A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. *Int J Infect Dis* 2020;94:55–58. doi:10.1016/j.ijid.2020.03.062, PMID:32251791.
- [229] Zubair AS, McAlpine LS, Gardin T, Farhadian S, Kuruvilla DE, Spudich S. Neuropathogenesis and Neurologic Manifestations of the Coronavirus in the Age of Coronavirus Disease 2019: A Review. *JAMA Neurol* 2020;77(8):1018–1027. doi:10.1001/jamaneurol.2020.2065, PMID:32469387.
- [230] Heneka MT, Golenbock D, Latz E, Morgan D, Brown R. Immediate and long-term consequences of COVID-19 infections for the development of neurological disease. *Alzheimers Res Ther* 2020;12(1):69. doi:10.1186/s13195-020-00640-3, PMID:32498691.
- [231] Pajo AT, Espiritu AI, Apor ADAO, Jamora RDG. Neuropathologic findings of patients with COVID-19: a systematic review. *Neurol Sci* 2021;42(4):1255–1266. doi:10.1007/s10072-021-05068-7, PMID:33483885.
- [232] Marshall M. How COVID-19 can damage the brain. *Nature* 2020;585(7825):342–343. doi:10.1038/d41586-020-02599-5, PMID:32934351.
- [233] Boldrini M, Canoll PD, Klein RS. How COVID-19 Affects the Brain. *JAMA Psychiatry* 2021;78(6):682–683. doi:10.1001/jamapsychiatry.2021.0500, PMID:33769431.
- [234] Meinhardt J, Radke J, Dittmayer C, Franz J, Thomas C, Mothes R, *et al.* Olfactory transmucosal SARS-CoV-2 invasion as a port of central nervous system entry in individuals with COVID-19. *Nat Neurosci* 2021;24(2):168–175. doi:10.1038/s41593-020-00758-5, PMID:33257876.
- [235] Fotuhi M, Mian A, Meysami S, Raji CA. Neurobiology of COVID-19. *J Alzheimers Dis* 2020;76(1):3–19. doi:10.3233/JAD-200581, PMID:32538857.
- [236] Vandenbark AA, Offner H, Matejuk S, Matejuk A. Microglia and astrocyte involvement in neurodegeneration and brain cancer. *J Neuroinflammation* 2021;18(1):298. doi:10.1186/s12974-021-02355-0, PMID:34949203.
- [237] Alghamri MS, McClellan BL, Hartlage CS, Haase S, Faisal SM, Thalla R, *et al.* Targeting Neuroinflammation in Brain Cancer: Uncovering Mechanisms, Pharmacological Targets, and Neuropharmaceutical Developments. *Front Pharmacol* 2021;12:680021. doi:10.3389/fphar.2021.680021, PMID:34084145.
- [238] Zhang T, Ma C, Zhang Z, Zhang H, Hu H. NF- κ B signaling in inflammation and cancer. *MedComm* 2021;2(4):618–653. doi:10.1002/mco2.104, PMID:34977871.
- [239] Uddin MS, Kabir MT, Mamun AA, Sarwar MS, Nasrin F, Emran TB, *et al.* Natural Small Molecules Targeting NF- κ B Signaling in Glioblastoma. *Front Pharmacol* 2021;12:703761. doi:10.3389/fphar.2021.703761, PMID:34512336.
- [240] Tao JC, Yu D, Shao W, Zhou DR, Wang Y, Hou SQ, *et al.* Interactions between microglia and glioma in tumor microenvironment. *Front Oncol* 2023;13:1236268. doi:10.3389/fonc.2023.1236268, PMID:37700840.
- [241] Sharma P, Aroee A, Liang J, Puduvali VK. Tumor microenvironment in glioblastoma: Current and emerging concepts. *Neurooncol Adv* 2023;5(1):vdad009. doi:10.1093/oaajnl/vdad009, PMID:36968288.
- [242] Menna G, Mattogno PP, Donzelli CM, Lisi L, Olivi A, Della Pepa GM. Glioma-Associated Microglia Characterization in the Glioblastoma Microenvironment through a ‘Seed-and Soil’ Approach: A Systematic Review. *Brain Sci* 2022;12(6):718. doi:10.3390/brainsci12060718, PMID:35741603.
- [243] Lin C, Wang N, Xu C. Glioma-associated microglia/macrophages (GAMs) in glioblastoma: Immune function in the tumor microenvironment and implications for immunotherapy. *Front Immunol* 2023;14:1123853. doi:10.3389/fimmu.2023.1123853, PMID:36969167.
- [244] Yu W, Tu Y, Long Z, Liu J, Kong D, Peng J, *et al.* Reactive Oxygen Species Bridge the Gap between Chronic Inflammation and Tumor Development. *Oxid Med Cell Longev* 2022;2022:2606928. doi:10.1155/2022/2606928, PMID:35799889.
- [245] Crivii CB, Boşca AB, Melincovici CS, Constantin AM, Mărginean M, Dronca E, *et al.* Glioblastoma Microenvironment and Cellular Interactions. *Cancers (Basel)* 2022;14(4):1092. doi:10.3390/cancers14041092, PMID:35205842.
- [246] Groblewska M, Mroczko B. Pro- and Antiangiogenic Factors in Gliomas: Implications for Novel Therapeutic Possibilities. *Int J Mol Sci* 2021;22(11):6126. doi:10.3390/ijms22116126, PMID:34200145.
- [247] Puebla M, Tapia PJ, Espinoza H. Key Role of Astrocytes in Postnatal Brain and Retinal Angiogenesis. *Int J Mol Sci* 2022;23(5):2646. doi:10.3390/ijms23052646, PMID:35269788.
- [248] Mosteiro A, Pedrosa L, Ferrés A, Diao D, Sierra À, González JJ. The Vascular Microenvironment in Glioblastoma: A Comprehensive Review. *Biomedicines* 2022;10(6):1285. doi:10.3390/biomedicines10061285, PMID:35740307.
- [249] Wang Y, Zhang F, Xiong N, Xu H, Chai S, Wang H, *et al.* Remodeling and Treatment of the Blood-Brain Barrier in Glioma. *Cancer Manag Res* 2021;13:4217–4232. doi:10.2147/CMAR.S288720, PMID:34079374.
- [250] Cabral-Pacheco GA, Garza-Veloz I, Castruita-De la Rosa C, Ramirez-Acuña JM, Perez-Romero BA, Guerrero-Rodriguez JF, *et al.* The Roles of Matrix Metalloproteinases and Their Inhibitors in Human Diseases. *Int J Mol Sci* 2020;21(24):9739. doi:10.3390/ijms21249739, PMID:33419373.
- [251] Giles B, Nakhjavani M, Wiesa A, Knight T, Shigdar S, Samarasinghe RM. Unravelling the Glioblastoma Tumour Microenvironment: Can Aptamer Targeted Delivery Become Successful in Treating Brain Cancers? *Cancers (Basel)* 2023;15(17):4376. doi:10.3390/cancers15174376, PMID:37686652.
- [252] Lin H, Liu C, Hu A, Zhang D, Yang H, Mao Y. Understanding the immunosuppressive microenvironment of glioma: mechanistic insights and clinical perspectives. *J Hematol Oncol* 2024;17(1):31. doi:10.1186/s13045-024-01544-7, PMID:38720342.
- [253] Prinz M, Priller J. The role of peripheral immune cells in the CNS in steady state and disease. *Nat Neurosci* 2017;20(2):136–144. doi:10.1038/nn.4475, PMID:28092660.
- [254] Glass CK, Saijo K, Winner B, Marchetto MC, Gage FH. Mechanisms underlying inflammation in neurodegeneration. *Cell* 2010;140(6):918–934. doi:10.1016/j.cell.2010.02.016, PMID:20303880.
- [255] Ransohoff RM. How neuroinflammation contributes to neurodegeneration. *Science* 2016;353(6301):777–783. doi:10.1126/science.aag2590, PMID:27540165.
- [256] McGeer PL, McGeer EG. Glial reactions in Parkinson’s disease. *Mov Disord* 2008;23(4):474–483. doi:10.1002/mds.21751.
- [257] Passaro AP, Lebos AL, Yao Y, Stice SL. Immune Response in Neurological Pathology: Emerging Role of Central and Peripheral Immune Crosstalk. *Front Immunol* 2021;12:676621. doi:10.3389/fimmu.2021.676621, PMID:34177918.
- [258] Baik SH, Kang S, Lee W, Choi H, Chung S, Kim JJ, *et al.* A Breakdown in Metabolic Reprogramming Causes Microglia Dysfunction in Alzheimer’s Disease. *Cell Metab* 2019;30(3):493–507.e6. doi:10.1016/j.cmet.2019.06.005, PMID:31257151.
- [259] Schwartz M, Baruch K. Breaking peripheral immune tolerance to CNS antigens in neurodegenerative diseases: boosting autoimmunity to fight-off chronic neuroinflammation. *J Autoimmun* 2014;54:8–14. doi:10.1016/j.jaut.2014.08.002.
- [260] Wang C, Zong S, Cui X, Wang X, Wu S, Wang L, *et al.* The effects of microglia-associated neuroinflammation on Alzheimer’s disease. *Front Immunol* 2023;14:1117172. doi:10.3389/fimmu.2023.1117172, PMID:36911732.
- [261] Gate D, Saligrama N, Leventhal O, Yang AC, Unger MS, Middeldorp J, *et al.* Clonally expanded CD8 T cells patrol the cerebrospinal fluid in Alzheimer’s disease. *Nature* 2020;577(7790):399–404. doi:10.1038/s41586-019-1895-7, PMID:31915375.
- [262] Heppner FL, Ransohoff RM, Becher B. Immune attack: the role of inflammation in Alzheimer disease. *Nat Rev Neurosci* 2015;16(6):358–372. doi:10.1038/nrn3880, PMID:25991443.
- [263] Miao J, Ma H, Yang Y, Liao Y, Lin C, Zheng J, *et al.* Microglia in Alzheimer’s disease: pathogenesis, mechanisms, and therapeutic po-

- tentials. *Front Aging Neurosci* 2023;15:1201982. doi:10.3389/fnagi.2023.1201982, PMID:37396657.
- [264] Darwish SF, Elbadry AMM, Elbokhomy AS, Salama GA, Salama RM. The dual face of microglia (M1/M2) as a potential target in the protective effect of nutraceuticals against neurodegenerative diseases. *Front Aging* 2023;4:1231706. doi:10.3389/fragi.2023.1231706, PMID:37744008.
- [265] Zhang W, Tian T, Gong SX, Huang WQ, Zhou QY, Wang AP, *et al*. Microglia-associated neuroinflammation is a potential therapeutic target for ischemic stroke. *Neural Regen Res* 2021;16(1):6–11. doi:10.4103/1673-5374.286954, PMID:32788440.
- [266] Zhang X, Chen F, Sun M, Wu N, Liu B, Yi X, *et al*. Microglia in the context of multiple sclerosis. *Front Neurol* 2023;14:1157287. doi:10.3389/fneur.2023.1157287, PMID:37360338.
- [267] Mado H, Adamczyk-Sowa M, Sowa P. Role of Microglial Cells in the Pathophysiology of MS: Synergistic or Antagonistic? *Int J Mol Sci* 2023;24(3):1861. doi:10.3390/ijms24031861, PMID:36768183.
- [268] Cai Y, Liu J, Wang B, Sun M, Yang H. Microglia in the Neuroinflammatory Pathogenesis of Alzheimer's Disease and Related Therapeutic Targets. *Front Immunol* 2022;13:856376. doi:10.3389/fimmu.2022.856376, PMID:35558075.
- [269] Long HZ, Zhou ZW, Cheng Y, Luo HY, Li FJ, Xu SG, *et al*. The Role of Microglia in Alzheimer's Disease From the Perspective of Immune Inflammation and Iron Metabolism. *Front Aging Neurosci* 2022;14:888989. doi:10.3389/fnagi.2022.888989, PMID:35847685.
- [270] Kuntzel T, Bagnard D. Manipulating Macrophage/Microglia Polarization to Treat Glioblastoma or Multiple Sclerosis. *Pharmaceutics* 2022;14(2):344. doi:10.3390/pharmaceutics14020344, PMID:35214076.
- [271] Zenaro E, Piacentino G, Constantini G. The blood-brain barrier in Alzheimer's disease. *Neurobiol Dis* 2017;107:41–56. doi:10.1016/j.nbd.2016.07.007, PMID:27425887.
- [272] Rodríguez-Giraldo M, González-Reyes RE, Ramírez-Guerrero S, Bonilla-Trilleras CE, Guardo-Maya S, Nava-Mesa MO. Astrocytes as a Therapeutic Target in Alzheimer's Disease-Comprehensive Review and Recent Developments. *Int J Mol Sci* 2022;23(21):13630. doi:10.3390/ijms232113630, PMID:36362415.
- [273] Tan R, Hong R, Sui C, Yang D, Tian H, Zhu T, *et al*. The role and potential therapeutic targets of astrocytes in central nervous system demyelinating diseases. *Front Cell Neurosci* 2023;17:1233762. doi:10.3389/fncel.2023.1233762, PMID:37720543.
- [274] Chen Y, Qin C, Huang J, Tang X, Liu C, Huang K, *et al*. The role of astrocytes in oxidative stress of central nervous system: A mixed blessing. *Cell Prolif* 2020;53(3):e12781. doi:10.1111/cpr.12781, PMID:32035016.
- [275] Valenza M, Facchinetti R, Menegoni G, Steardo L, Scuderi C. Alternative Targets to Fight Alzheimer's Disease: Focus on Astrocytes. *Biomolecules* 2021;11(4):600. doi:10.3390/biom11040600, PMID:33921556.
- [276] LaFerla FM, Green KN. Animal models of Alzheimer disease. *Cold Spring Harb Perspect Med* 2012;2(11):a006320. doi:10.1101/cshperspect.a006320, PMID:23002015.
- [277] Verghese JP, Terry A, de Natale ER, Politis M. Research Evidence of the Role of the Glymphatic System and Its Potential Pharmacological Modulation in Neurodegenerative Diseases. *J Clin Med* 2022;11(23):6964. doi:10.3390/jcm11236964, PMID:36498538.
- [278] Lynch MA. Exploring Sex-Related Differences in Microglia May Be a Game-Changer in Precision Medicine. *Front Aging Neurosci* 2022;14:868448. doi:10.3389/fnagi.2022.868448.
- [279] VanRyzin JW, Marquardt AE, Pickett LA, McCarthy MM. Microglia and sexual differentiation of the developing brain: A focus on extrinsic factors. *Glia* 2020;68(6):1100–1113. doi:10.1002/glia.23740.
- [280] Gildawie KR, Orso R, Peterzell S, Thompson V, Brenhouse HC. Sex differences in prefrontal cortex microglia morphology: Impact of a two-hit model of adversity throughout development. *Neurosci Lett* 2020;738:135381. doi:10.1016/j.neulet.2020.135381.
- [281] Kadlecova M, Freude K, Haukedal H. Complexity of Sex Differences and Their Impact on Alzheimer's Disease. *Biomedicines* 2023;11(5):1261. doi:10.3390/biomedicines11051261, PMID:37238932.
- [282] Lopez-Lee C, Kodama L, Gan L. Sex Differences in Neurodegeneration: The Role of the Immune System in Humans. *Biol Psychiatry* 2022;91(1):72–80. doi:10.1016/j.biopsych.2021.01.002, PMID:33715827.
- [283] Reed EG, Keller-Norrell PR. Minding the Gap: Exploring Neuroinflammatory and Microglial Sex Differences in Alzheimer's Disease. *Int J Mol Sci* 2023;24(24):17377. doi:10.3390/ijms242417377, PMID:38139206.
- [284] Kang S, Ko EY, Andrews AE, Shin JE, Nance KJ, Barman PK, *et al*. Microglia undergo sex-dimorphic transcriptional and metabolic rewiring during aging. *J Neuroinflammation* 2024;21(1):150. doi:10.1186/s12974-024-03130-7, PMID:38840206.
- [285] Villa A, Vegeto E, Poletti A, Maggi A. Estrogens, Neuroinflammation, and Neurodegeneration. *Endocr Rev* 2016;37(4):372–402. doi:10.1210/er.2016-1007, PMID:27196727.
- [286] Vegeto E, Benedusi V, Maggi A. Estrogen anti-inflammatory activity in brain: a therapeutic opportunity for menopause and neurodegenerative diseases. *Front Neuroendocrinol* 2008;29(4):507–519. doi:10.1016/j.yfrne.2008.04.001, PMID:18522863.
- [287] Giallongo S, Longhitano L, Denaro S, D'Aprile S, Torrissi F, La Spina E, *et al*. The Role of Epigenetics in Neuroinflammation-Driven Diseases. *Int J Mol Sci* 2022;23(23):15218. doi:10.3390/ijms232315218, PMID:36499544.
- [288] Petralia S, De Chirico F, Miti A, Tartagni O, Massenzio F, Poeta E, *et al*. Epigenetics and Communication Mechanisms in Microglia Activation with a View on Technological Approaches. *Biomolecules* 2021;11(2):306. doi:10.3390/biom11020306, PMID:33670563.
- [289] Zang X, Chen S, Zhu J, Ma J, Zhai Y. The Emerging Role of Central and Peripheral Immune Systems in Neurodegenerative Diseases. *Front Aging Neurosci* 2022;14:872134. doi:10.3389/fnagi.2022.872134, PMID:35547626.
- [290] Chen X, Holtzman DM. Emerging roles of innate and adaptive immunity in Alzheimer's disease. *Immunity* 2022;55(12):2236–2254. doi:10.1016/j.immuni.2022.10.016, PMID:36351425.
- [291] Russillo MC, Andreozzi V, Erro R, Picillo M, Amboni M, Cuoco S, *et al*. Sex Differences in Parkinson's Disease: From Bench to Bedside. *Brain Sci* 2022;12(7):917. doi:10.3390/brainsci12070917, PMID:35884724.
- [292] Reekes TH, Higginson CI, Ledbetter CR, Sathivadivel N, Zweig RM, Disbrow EA. Sex specific cognitive differences in Parkinson disease. *NPJ Parkinsons Dis* 2020;6:7. doi:10.1038/s41531-020-0109-1, PMID:32284961.
- [293] Harms AS, Cao S, Rowse AL, Thome AD, Li X, Mangieri LR, *et al*. MH-CII is required for α -synuclein-induced activation of microglia, CD4 T cell proliferation, and dopaminergic neurodegeneration. *J Neurosci* 2013;33(23):9592–9600. doi:10.1523/JNEUROSCI.5610-12.2013, PMID:23739956.
- [294] Sommer A, Marxreiter F, Krach F, Fadler T, Grosch J, Maroni M, *et al*. Th17 Lymphocytes Induce Neuronal Cell Death in a Human iPSC-Based Model of Parkinson's Disease. *Cell Stem Cell* 2018;23(1):123–131.e6. doi:10.1016/j.stem.2018.06.015, PMID:29979986.
- [295] Reynolds AD, Banerjee R, Liu J, Gendelman HE, Mosley RL. Neuroprotective activities of CD4+CD25+ regulatory T cells in an animal model of Parkinson's disease. *J Leukoc Biol* 2007;82(5):1083–94. doi:10.1189/jlb.0507296, PMID:17675560.
- [296] Appel SH, Beers DR, Henkel JS. T cell-microglial dialogue in Parkinson's disease and amyotrophic lateral sclerosis: are we listening? *Trends Immunol* 2010;31(1):7–17. doi:10.1016/j.it.2009.09.003, PMID:19879804.
- [297] Folke J, Bergholt E, Pakkenberg B, Aznar S, Brudek T. Alpha-Synuclein Autoimmune Decline in Prodromal Multiple System Atrophy and Parkinson's Disease. *Int J Mol Sci* 2022;23(12):6554. doi:10.3390/ijms23126554, PMID:35742998.
- [298] Scott KM. B Lymphocytes in Parkinson's Disease. *J Parkinsons Dis* 2022;12(s1):S75–S81. doi:10.3233/JPD-223418, PMID:35938259.
- [299] Li X, Koudstaal W, Fletcher L, Costa M, van Winsen M, Siregar B, *et al*. Naturally occurring antibodies isolated from PD patients inhibit synuclein seeding in vitro and recognize Lewy pathology. *Acta Neuropathol* 2019;137(5):825–836. doi:10.1007/s00401-019-01974-5, PMID:30805666.
- [300] Xu K, Li Y, Zhou Y, Zhang Y, Shi Y, Zhang C, *et al*. Neuroinflammation in Parkinson's disease: focus on the relationship between miRNAs and microglia. *Front Cell Neurosci* 2024;18:1429977. doi:10.3389/fncel.2024.1429977.

- [301] Araújo B, Caridade-Silva R, Soares-Guedes C, Martins-Macedo J, Gomes ED, Monteiro S, *et al.* Neuroinflammation and Parkinson's Disease-From Neurodegeneration to Therapeutic Opportunities. *Cells* 2022;11(18):2908. doi:10.3390/cells11182908, PMID:36139483.
- [302] Han J, Zhu K, Zhang XM, Harris RA. Enforced microglial depletion and repopulation as a promising strategy for the treatment of neurological disorders. *Glia* 2019;67(2):217–231. doi:10.1002/glia.23529, PMID:30378163.
- [303] Cossu D, Hatano T, Hattori N. The Role of Immune Dysfunction in Parkinson's Disease Development. *Int J Mol Sci* 2023;24(23):16766. doi:10.3390/ijms242316766.
- [304] Tansey MG, Wallings RL, Houser MC, Herrick MK, Keating CE, Jowers V. Inflammation and immune dysfunction in Parkinson disease. *Nat Rev Immunol* 2022;22(11):657–673. doi:10.1038/s41577-022-00684-6.
- [305] Marrella V, Facoetti A, Cassani B. Cellular Senescence in Immunity against Infections. *Int J Mol Sci* 2022;23(19):11845. doi:10.3390/ijms231911845, PMID:36233146.
- [306] Saleh M, Markovic M, Olson KE, Gendelman HE, Mosley RL. Therapeutic Strategies for Immune Transformation in Parkinson's Disease. *J Parkinsons Dis* 2022;12(s1):S201–S222. doi:10.3233/JPD-223278, PMID:35871362.
- [307] Fargiuele A, Pereira FC, Martini S, Marino F, Cosentino M. Dopaminergic regulation of inflammation and immunity in Parkinson's disease: friend or foe? *Clin Transl Immunology* 2023;12(10):e1469. doi:10.1002/cti2.1469, PMID:37781343.
- [308] Zhang Y, Chen H, Li R, Sterling K, Song W. Amyloid β -based therapy for Alzheimer's disease: challenges, successes and future. *Signal Transduct Target Ther* 2023;8(1):248. doi:10.1038/s41392-023-01484-7, PMID:37386015.
- [309] Zhao Z, Liu Y, Ruan S, Hu Y. Current Anti-Amyloid- β Therapy for Alzheimer's Disease Treatment: From Clinical Research to Nanomedicine. *Int J Nanomedicine* 2023;18:7825–7845. doi:10.2147/IJN.S444115, PMID:38144511.
- [310] Pöyhönen S, Er S, Domanskyi A, Airavaara M. Effects of Neurotrophic Factors in Glial Cells in the Central Nervous System: Expression and Properties in Neurodegeneration and Injury. *Front Physiol* 2019;10:486. doi:10.3389/fphys.2019.00486.
- [311] de Pins B, Cifuentes-Díaz C, Farah AT, López-Molina L, Montalban E, Sancho-Balsells A, *et al.* Conditional BDNF Delivery from Astrocytes Rescues Memory Deficits, Spine Density, and Synaptic Properties in the 5xFAD Mouse Model of Alzheimer Disease. *J Neurosci* 2019;39(13):2441–2458. doi:10.1523/JNEUROSCI.2121-18.2019, PMID:30700530.
- [312] Edison P. Astroglial activation: Current concepts and future directions. *Alzheimers Dement* 2024;20(4):3034–3053. doi:10.1002/alz.13678, PMID:38305570.
- [313] Goenaga J, Araque A, Kofuji P, Herrera Moro Chao D. Calcium signaling in astrocytes and gliotransmitter release. *Front Synaptic Neurosci* 2023;15:1138577. doi:10.3389/fnsyn.2023.1138577, PMID:36937570.
- [314] Merighi S, Nigro M, Travagli A, Gessi S. Microglia and Alzheimer's Disease. *Int J Mol Sci* 2022;23(21):12990. doi:10.3390/ijms232112990, PMID:36361780.
- [315] Wong-Guerra M, Calfio C, Maccioni RB, Rojo LE. Revisiting the neuroinflammation hypothesis in Alzheimer's disease: a focus on the druggability of current targets. *Front Pharmacol* 2023;14:1161850. doi:10.3389/fphar.2023.1161850, PMID:37361208.
- [316] Abdi S, Javanmehr N, Ghasemi-Kasman M, Bali HY, Pirzadeh M. Stem Cell-based Therapeutic and Diagnostic Approaches in Alzheimer's Disease. *Curr Neuropharmacol* 2022;20(6):1093–1115. doi:10.2174/1570159X20666211231090659, PMID:34970956.
- [317] Dijk JM, Espay AJ, Katzenschlager R, de Bie RMA. The Choice Between Advanced Therapies for Parkinson's Disease Patients: Why, What, and When? *J Parkinsons Dis* 2020;10(s1):S65–S73. doi:10.3233/JPD-202104, PMID:32651333.
- [318] Gouda NA, Elkamhaway A, Cho J. Emerging Therapeutic Strategies for Parkinson's Disease and Future Prospects: A 2021 Update. *Biomedicines* 2022;10(2):371. doi:10.3390/biomedicines10020371, PMID:35203580.
- [319] Saramowicz K, Siwecka N, Galita G, Kucharska-Lusina A, Rozpędek Kamińska W, Majsterek I. Alpha-Synuclein Contribution to Neuronal and Glial Damage in Parkinson's Disease. *Int J Mol Sci* 2023;25(1):360. doi:10.3390/ijms25010360, PMID:38203531.
- [320] Du XY, Xie XX, Liu RT. The Role of α -Synuclein Oligomers in Parkinson's Disease. *Int J Mol Sci* 2020;21(22):8645. doi:10.3390/ijms21228645, PMID:33212758.
- [321] Sulzer D, Alcalay RN, Garretti F, Cote L, Kanter E, Agin-Lieb J, *et al.* T cells from patients with Parkinson's disease recognize α -synuclein peptides. *Nature* 2017;546(7660):656–661. doi:10.1038/nature22815, PMID:28636593.
- [322] Pierce S, Coetzee GA. Parkinson's disease-associated genetic variation is linked to quantitative expression of inflammatory genes. *PLoS One* 2017;12(4):e0175882. doi:10.1371/journal.pone.0175882, PMID:28407015.
- [323] Schaser AJ, Osterberg VR, Dent SE, Stackhouse TL, Wakeham CM, Boutros SW, *et al.* Alpha-synuclein is a DNA binding protein that modulates DNA repair with implications for Lewy body disorders. *Sci Rep* 2019;9(1):10919. doi:10.1038/s41598-019-47227-z, PMID:31358782.
- [324] Cummings J. The Role of Biomarkers in Alzheimer's Disease Drug Development. *Adv Exp Med Biol* 2019;1118:29–61. doi:10.1007/978-3-030-05542-4_2, PMID:30747416.
- [325] Kandiah N, Choi SH, Hu CJ, Ishii K, Kasuga K, Mok VCT. Current and Future Trends in Biomarkers for the Early Detection of Alzheimer's Disease in Asia: Expert Opinion. *J Alzheimers Dis Rep* 2022;6(1):699–710. doi:10.3233/ADR-220059, PMID:36606209.
- [326] Hnilicova P, Kantorova E, Sutovsky S, Grofik M, Zelenak K, Kurca E, *et al.* Imaging Methods Applicable in the Diagnostics of Alzheimer's Disease, Considering the Involvement of Insulin Resistance. *Int J Mol Sci* 2023;24(4):3325. doi:10.3390/ijms24043325, PMID:36834741.
- [327] Wu Y, Eisel ULM. Microglia-Astrocyte Communication in Alzheimer's Disease. *J Alzheimers Dis* 2023;95(3):785–803. doi:10.3233/JAD-230199, PMID:37638434.
- [328] Bouter C, Hennings P, Franke TN, Irwin C, Sahlmann CO, Sichler ME, *et al.* (18)F-FDG-PET Detects Drastic Changes in Brain Metabolism in the Tg4-42 Model of Alzheimer's Disease. *Front Aging Neurosci* 2018;10:425. doi:10.3389/fnagi.2018.00425, PMID:30670962.
- [329] Bonomi CG, Chiaravalloti A, Camedda R, Ricci F, Mercuri NB, Schilacci O, *et al.* Functional Correlates of Microglial and Astrocytic Activity in Symptomatic Sporadic Alzheimer's Disease: A CSF/(18)F-FDG-PET Study. *Biomedicines* 2023;11(3):725. doi:10.3390/biomedicines11030725, PMID:36979704.
- [330] Zhou R, Ji B, Kong Y, Qin L, Ren W, Guan Y, *et al.* PET Imaging of Neuroinflammation in Alzheimer's Disease. *Front Immunol* 2021;12:739130. doi:10.3389/fimmu.2021.739130, PMID:34603323.
- [331] Wang Q, Xie C. Microglia activation linking amyloid- β drive tau spatial propagation in Alzheimer's disease. *Front Neurosci* 2022;16:951128. doi:10.3389/fnins.2022.951128, PMID:36033617.
- [332] Padovani A, Canale A, Schiavon L, Masciocchi S, Imarisio A, Risi B, *et al.* Is amyloid involved in acute neuroinflammation? A CSF analysis in encephalitis. *Alzheimers Dement* 2022;18(11):2167–2175. doi:10.1002/alz.12554, PMID:35084105.
- [333] Temmerman J, Engelborghs S, Bjerke M, D'haeseleer M. Cerebrospinal fluid inflammatory biomarkers for disease progression in Alzheimer's disease and multiple sclerosis: a systematic review. *Front Immunol* 2023;14:1162340. doi:10.3389/fimmu.2023.1162340, PMID:37520580.
- [334] Mallah K, Couch C, Borucki DM, Toutonji A, Alshareef M, Tomlinson S. Anti-inflammatory and Neuroprotective Agents in Clinical Trials for CNS Disease and Injury: Where Do We Go From Here? *Front Immunol* 2020;11:2021. doi:10.3389/fimmu.2020.02021, PMID:33013859.
- [335] Gouda NA, Elkamhaway A, Cho J. Emerging Therapeutic Strategies for Parkinson's Disease and Future Prospects: A 2021 Update. *Biomedicines* 2022;10(2):371. doi:10.3390/biomedicines10020371.
- [336] Entsie P, Kang Y, Amofo EB, Schöneberg T, Liverani E. The Signaling Pathway of the ADP Receptor P2Y₁₂ in the Immune System: Recent Discoveries and New Challenges. *Int J Mol Sci* 2023;24(7):6709. doi:10.3390/ijms24076709, PMID:37047682.
- [337] Preman P, Alfonso-Triguero M, Alberdi E, Verkhatsky A, Arranz AM. Astrocytes in Alzheimer's Disease: Pathological Significance and Molecular Pathways. *Cells* 2021;10(3):540. doi:10.3390/cells10030540.

- [338] Lopes CR, Cunha RA, Agostinho P. Astrocytes and Adenosine A(2A) Receptors: Active Players in Alzheimer's Disease. *Front Neurosci* 2021;15:666710. doi:10.3389/fnins.2021.666710, PMID:34054416.
- [339] Strzelec M, Detka J, Mieszczak P, Sobocińska MK, Majka M. Immunomodulation-a general review of the current state-of-the-art and new therapeutic strategies for targeting the immune system. *Front Immunol* 2023;14:1127704. doi:10.3389/fimmu.2023.1127704, PMID:36969193.
- [340] Mortada I, Farah R, Nabha S, Ojcius DM, Fares Y, Almawi WY, *et al*. Immunotherapies for Neurodegenerative Diseases. *Front Neurol* 2021;12:654739. doi:10.3389/fneur.2021.654739, PMID:34163421.
- [341] Knecht L, Folke J, Dodel R, Ross JA, Albus A. Alpha-synuclein Immunization Strategies for Synucleinopathies in Clinical Studies: A Biological Perspective. *Neurotherapeutics* 2022;19(5):1489–1502. doi:10.1007/s13311-022-01288-7, PMID:36083395.
- [342] Makkar R, Behl T, Bungau S, Zengin G, Mehta V, Kumar A, *et al*. Nutraceuticals in Neurological Disorders. *Int J Mol Sci* 2020;21(12):4424. doi:10.3390/ijms21124424, PMID:32580329.
- [343] Huang LK, Kuan YC, Lin HW, Hu CJ. Clinical trials of new drugs for Alzheimer disease: a 2020-2023 update. *J Biomed Sci* 2023;30(1):83. doi:10.1186/s12929-023-00976-6, PMID:37784171.
- [344] Chopade P, Chopade N, Zhao Z, Mitragotri S, Liao R, Chandran Suja V. Alzheimer's and Parkinson's disease therapies in the clinic. *Bioeng Transl Med* 2023;8(1):e10367. doi:10.1002/btm2.10367, PMID:36684083.
- [345] Khalaf NEA, El Banna FM, Youssef MY, Mosaad YM, Daba MY, Ashour RH. Clopidogrel combats neuroinflammation and enhances learning behavior and memory in a rat model of Alzheimer's disease. *Pharmacol Biochem Behav* 2020;195:172956. doi:10.1016/j.pbb.2020.172956.
- [346] Quintana D, Ren X, Hu H, Corbin D, Engler-Chiurazzi E, Alvi M, *et al*. IL-1 β Antibody Protects Brain from Neuropathology of Hypoperfusion. *Cells* 2021;10(4):855. doi:10.3390/cells10040855, PMID:33918659.
- [347] MacKenzie G, Subramaniam S, Caldwell LJ, Fitzgerald D, Harrison NA, Hong S, *et al*. Research priorities for neuroimmunology: identifying the key research questions to be addressed by 2030. *Wellcome Open Res* 2021;6:194. doi:10.12688/wellcomeopenres.16997.1, PMID:34778569.
- [348] Chen X, Jiang S, Wang R, Bao X, Li Y. Neural Stem Cells in the Treatment of Alzheimer's Disease: Current Status, Challenges, and Future Prospects. *J Alzheimers Dis* 2023;94(s1):S173–S186. doi:10.3233/JAD-220721, PMID:36336934.
- [349] Loh JS, Mak WQ, Tan LKS, Ng CX, Chan HH, Yeow SH, *et al*. Microbiota-gut-brain axis and its therapeutic applications in neurodegenerative diseases. *Signal Transduct Target Ther* 2024;9(1):37. doi:10.1038/s41392-024-01743-1, PMID:38360862.
- [350] Yadav H, Jaldhi, Bhardwaj R, Anamika, Bakshi A, Gupta S, Maurya SK. Unveiling the role of gut-brain axis in regulating neurodegenerative diseases: A comprehensive review. *Life Sci* 2023;330:122022. doi:10.1016/j.lfs.2023.122022, PMID:37579835.