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Decoding the Dialogue: Immunity and central nervous system interactions in neurodegenerative diseases

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Abstract

This review article aims to discuss neuroimmune interactions by emphasizing the role of central and peripheral immunities in central nervous system (CNS) protection and function, as well as how abnormalities in this relationship may be implicated in the genesis of neurodegenerative diseases (NDDs). Immune elements that play roles within the CNS both during stable and infectious states are described. Innate CNS immunity is explored as a distinct entity comprised of the brain blood barrier, CNS parenchyma, and resident immune cells-microglia and astrocytes, whose roles in antigen recognition and clearance and neuromodulation are further enumerated. Due to the inability of the CNS to independently initiate an adaptive immune response, the necessary recruitment and regulation of elements from the peripheral immune system (PIS) are described in a process that, in chief, utilizes resident antigen-presenting cells to prime naïve T-cells, which later enter the CNS through areas of access to the cerebrospinal fluid. The previous modes of interaction especially enable microglia, astrocytes, and T-cells to play part in neurodevelopment and plasticity, and the proposed mechanisms by which they participate in synaptic pruning, neurogenesis, and memory are examined. In addition to its protective role, the PIS has also been shown to play a regulatory role in the CNS, where it drives responses that optimize immune function, such as fever and sickness behavior. Due to the high level of involvement of the immune system within the CNS, dysregulations of the immune system are thought to be implicated in numerous NDD pathogeneses, where neuroinflammation both causes and is caused by immune reactions. Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis are particularly discussed.

Keywords: CNS, PIS, Innate immunity, Adaptive immunity, Neuroplasticity, NDDS.

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Introduction

Research in neuroimmune interaction reveals that both immune and nervous systems can regulate each other, despite initial compartmentalized investigations.[1] In brief, the central nervous system (CNS), which consists of the brain and spinal cord, functions to perceive,

integrate, and respond to stimuli. These processes are greatly aided by the peripheral nervous system (PNS), as its sensory division serves to collect external and internal stimuli and pass them to the CNS for the generation of commands to motor efferent fibers.[2]

The broadest functional divisions of the immune system are the innate and adaptive immunities. Innate immunity is a "non-specific," in-built first line of defense against foreign antigens; it includes anatomic, physiologic, cellular, and inflammatory barriers. Adaptive immunity is an acquired immunity that develops as B- and T-lymphocytes, which are exposed to antigens to which they form specialized responses and an immunologic memory that aids in faster, more efficient immune reactions upon reinfection.[3,4]

However, this classification of the immune system may be further modified when considering its interaction with the CNS: the central immune system (CIS) is a term rarely used to describe the sum of immune cells within the CNS working to protect it, while the peripheral immune system (PIS) constitutes elements of the immune system outside the CNS. In line with the rising evidence of the involvement of the PIS in the regulation of CNS function and immunity, the contemporary view of the CNS no longer remains one of complete immune privilege.[5]

This review article aims to demonstrate how physiological interactions between the immune system and CNS are necessary for normal body function and homeostasis by tackling the most relevant effects of the central and peripheral immune systems on the central nervous system, as well as highlight the neurodegenerative diseases (NDD) that may stem from dysregulations in that interaction.

Methods

The authors searched PubMed/Midline, Connected Papers, National Library for Medicine, Clinical trials.gov, and Google Scholar for case reports and series, retrospective case-control, cohort, or cross-sectional studies. The search focused on the studies relevant to CNS immune privilege, interplay between innate or peripheral immunity and the CNS, role of immune system components in neurodevelopment and plasticity, and role of immune system components in the pathogenesis of NDD namely Alzheimer's, Parkinson's, Huntington's, and amyotrophic lateral sclerosis. The search was limited to articles published in English.

The search was for free-text words and medical subject headings' terms related to central nervous system, peripheral immune system, innate immunity, adaptive immunity, neuroplasticity, neurodegenerative diseases, microglia, astrocytes, pathogen-associated molecular patterns, damage-associated molecular patterns, toll-like receptors, NOD-like receptors, immunosurveillance, neuro-modulation, immune recruitment, boarder-associated macrophages, neurodevelopment, neurogenesis, dorsolateral geniculate nucleus of the thalamus, neurogenesis, synaptogenesis, synaptic stripping, homeostasis, thermo-regulation, neurobehavior, sickness behavior, Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis.

Immunity within the CNS

1. Innate Immunity

Innate immune reactions within the CNS are usually secluded from those that may occur in the periphery; however, the interaction of microglia and astrocytes, protective glial cells of the CNS, with CNS-infiltrating T-cells is essential for immune surveillance.[6] This ensures that the CNS receives sufficient immune protection, while simultaneously being protected from peripheral inflammation. As such, the first component of the innate CIS is the brain-blood barrier (BBB) that plays a major role in restraining CNS inflammation by blocking the entry of peripheral immune cells and inflammatory mediators.[7] The second component is the anti-inflammatory environment of the CNS parenchyma itself, as it contains high concentrations of transforming growth factor β (TGF-β), interleukin 10 (IL-10), and gangliosides (molecules immuno-suppressive to T-cells) that dull CNS inflammatory responses.[8]

Microglia and astrocytes play key roles in innate CNS immunity through recognition of foreign antigens, protection against them, recruitment of peripheral immune cells in case of failure, and restoration of damaged tissues.[5] Though their methods of operation are mostly distinct, they could both be activated similarly through the recognition of pathogen-associated molecular patterns (PAMPs), which are pathogenic products, and damage-associated molecular patterns (DAMPs), which are products of cellular death, damage, or stress.[9] These molecules bind to toll-like or nucleotide-binding oligomerization domain (NOD)-like receptors (Toll like Receptors [TLRs] and Nod like Receptors [NLRs], respectively): their binding to TLRs activates nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) pathways that will transcribe IL-1 family precursors (namely, pro IL-1β and pro IL-18), while their binding to NLRs will trigger inflammasomes to assemble, activating caspase-1 that will prompt the release of IL-33 alarmin and cleave the IL precursors into their active forms. IL-33 alarmin exacerbates the aforementioned process by signaling tissue damage, and IL-1β and IL-18 will initiate a secondary inflammatory cytokine cascade of tumor necrotic factor α (TNF α), IL-6, and IL-17 that work to enhance recruitment of peripheral immune cells (macrophages, natural killer cells, and lymphocytes) by increasing BBB permeability.[10]

1.1. Microglia

1.1.1. Role of Microglia in Neurodevelopment and Neuroplasticity

During neurodevelopment, the CNS produces an excessive number of neurons whose axons partake in a quantity of synapses disproportionate to that required for efficient postnatal brain function and organization.[11] Microglia, the most widely studied immune cell regarding neurodevelopment, aids in shaping the brain through a multitude of ways. Generally, they modulate rates of neurogenesis by phagocytosing neural progenitor cells, a process that peaks during late-stage brain development. They also participate in synaptic pruning by inducing cell death and/or phagocytosing inactive synaptic elements.[12]

This is studied heavily in the dorsolateral geniculate nucleus (dLGN) of the thalamus, where visual information is processed and relayed from the retina to the visual cortex. Initially, the dLGN receives excessive, overlapping synapses from both eyes; redundant synapses eventually grow inactive and, with the help of astrocytes that secrete TGF-β, express complement component 1q (C1q) that then triggers the classical compliment pathway, enabling recognition by compliment receptor 3 (CR3) on microglia for phagocytosis.[13,14]

Conversely, microglia also possess the ability to promote the formation and myelination of neuronal circuits. For instance, they induce neuro- and oligodendrogenesis through releasing insulin-like growth factor 1 (IGF-1) and cytokines (as TNF-α, IL-1β, IL-6, and interferon [INF]-γ) and aid in dendritic spine and synapse formation and maturation by secreting brain-derived neurotrophic factor (BDNF), prostaglandin E2 (PGE2), and IL-10.[14,15]

Synaptogenesis and synaptic stripping of neural circuits persist in adulthood to aid in synaptic plasticity, a property of the brain that allows for memory and learning. Both microglia and T-cells are implicated in the upkeep of plasticity due to their involvement in spatial learning, memory, emotional behavior, and stress responsiveness.[16] Although studies showed that released TNF-α, IL-1, IL-4, and IL-6 are involved, the specific roles that microglia and T-cells play in plasticity are still mostly ambiguous.[6,16]

1.1.2. Role of Microglia in Nervous System Innate Immunity

During the states of homeostasis, microglia assume the role of immunosurveillance, due to their high motility and sensitivity, and neuromodulation. They prevent neuronal overexcitation by breaking down adenosine triphosphate produced during neuronal activation into adenosine that binds to adenosine receptors on neurons and causes negative feedback inhibition. The microglial

ability to interact with cells of the CNS makes them adept at dealing with states of CNS injury or infection.[5] They phagocytose and destroy apoptotic, injured, or infected cells as well as pathogens through complement and Fc gamma receptors, opsonic receptors that bind complement proteins and immunoglobulins, respectively, and detect and remove myelin debris (neuronal corpse clearance) through three homologous tyrosine-protein kinase, TYRO3, AXL and MER (TAM) receptors. They also induce inflammation by producing cytokines, chemokines (for peripheral recruitment), and nitric oxide.[7,17]

2. Astrocytes

2.1. Role of Astrocytes in Neurodevelopment and Neuroplasticity

Astrocytes aid in memory formation by regulating and fortifying long-term potentiation (LTP) in the hippocampus.[18] LTP normally occurs as a presynaptic neuron rapidly releases glutamate that binds to α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-d-aspartate (NMDA) receptors on a postsynaptic neuron, allowing for a prolongated excitatory postsynaptic potential (EPSP) and dendritic modifications. Seeing as they express NMDA receptors, astrocytes can react to presynaptic glutamate and further augment LTP by releasing more glutamate themselves.[19] Further, in the thalamus and spinal cord, IL-33 released by astrocytes guides synaptic pruning by microglia.[15]

2.2. Role of Astrocytes in Nervous System Innate Immunity

Although other modes of activation exist, reactive astrocytes are said to have two general states: A1 and A2. Stimulated by IL-1α, TNF-α, and C1q, A1 astrocytes promote inflammation and are neurotoxic. A2 astrocytes, on the other hand, release anti-inflammatory cytokines. Consequently, astrocytic activation during states of CNS inflammation could be both beneficial and harmful, as the neurotoxic effects of A1 astrocytes may stimulate the excessive death of neurons and oligodendrocytes and are implicated in the pathogenesis of neurodegenerative diseases.[5] Generally, astrocytes also play an important role in the maintenance of a healthy metabolic environment within the CNS through regulation of potassium, glutamate, and water levels, among others. This function is disrupted in inflammatory conditions where excess levels of TNF-α produced by microglia prevent astrocytes from recycling harmful glutamate, leading to neuronal death via overexcitation.[10]

3. Specific Immunity

CNS cannot generate adaptive immune responses de novo and instead depends on immune surveillance for the recruitment of a peripheral adaptive immune response, if necessary. This means that while the CNS maintains a highly regulated, cautious interaction with the PIS, it does not completely restrict the entry of peripheral immune cells into the CNS.[17]

The meninges, cerebrospinal fluid (CSF), perivascular areas, and choroid plexuses are common areas of communication with the PIS and contain resident immune sentinels (boarder-associated macrophages (BAMs) and microglia) whose function in immunosurveillance enables them to regulate communication and be the first to respond to immunological threats. Other cells within the aforementioned areas are dendritic cells (DCs), T-cells, and B-cells. Upon availability of a malicious antigen, antigen-presenting cells (APCs), including BAMs, microglia, and DCs, present the antigen to local T-cells and exit through lymphatic vessels in the dura matter to prime naïve peripheral immune cells in deep cervical lymph nodes as the BBB does not permit entry to naïve cells. The activated peripheral immune cells, both innate and adaptive, will then travel to subarachnoid veins and choroid plexuses, where they can access the CSF to commence pathogen containment and clearance.[6] Their journey within the CNS is mainly guided by varying concentrations of CXCL2, a chemokine least present in brain parenchyma, and their action on pathogens, which may be cytopathic or non-cytopathic, happens through the secretion of TNF-α, INF-γ, granzyme, perforin, and Fas ligand, among others.[7]

Role of Peripheral Immunity in CNS Homeostasis

1. Thermoregulation

In addition to its standard immune function, the PIS also plays a regulatory role in CNS, as it relays bodily information necessary to establish homeostasis.[20] The connection between the PIS and CNS has long been associated with fever, a hyperthermic response that necessitates the brain to receive chemical signals from the peripheral immune cells to prevent microbial growth.[1]

Upon detecting certain PAMPs or DAMPs, TLRs of peripheral innate immune cells, such as macrophages/monocytes, release proinflammatory cytokines such as IL-1β, IL-6, TNF-α, and chemokines to the CNS which is especially seen in lipopolysaccharide (LPS)-TLR4 interactions.[21,22] This is naturally complicated by the BBB's impermeability to cytokines, and as such these cytokines target the organum vasculosum laminae terminalis (OVLT), a circumventricular organ; an area of the brain lacking a BBB.[23] Activated, innate immune cells of the CNS release pyrogenic molecules, notably IL-6 and IL-1β, that will induce central PGE2 production by cyclooxygenase-2 (COX-2). PGE2 will then bind to its EP3 receptor on thermosensitive neurons present in the median preoptic nucleus of the hypothalamus, influencing the release of norepinephrine from the thermoregulatory center of the hypothalamus to increase thermogenesis in brown adipose tissue and preserve heat via vasoconstriction.[22,24] Acetylcholine is also released to muscles to increase their metabolic rates, and thus thermal energy, which is outwardly perceived as shivering.[25,26]

IL-1β is also one of the key proinflammatory cytokines that indirectly activate the hypothalamus-pituitary-adrenal (HPA) axis by inducing PGE2 production.[27,28] In this context, PGE2 has a paracrine effect on the EP1 and 3 receptors of catecholaminergic neurons in the ventrolateral medulla, whose fibers project to the paraventricular nucleus of the hypothalamus.[20] This prompts the release of corticotropin-releasing hormone (CRH) that, upon acting on the pituitary gland, triggers the release of adrenocorticotropic hormone (ACTH).[21] Once activated by ACTH, the adrenal cortex releases glucocorticoids that act on a multitude of immune cell types, increasing the phagocytic potential of monocytes and macrophages and promoting foreign body clearance.[1,29]

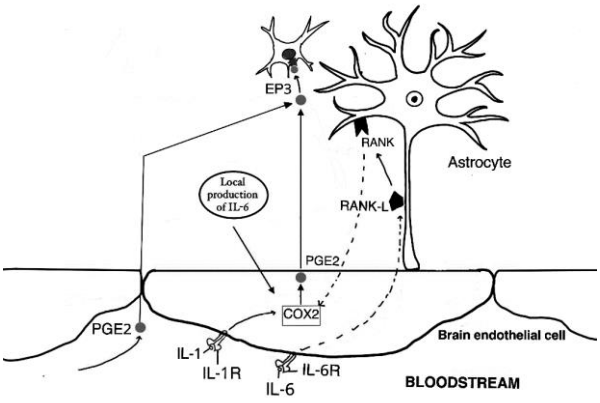

Figure 1. How fever is induced in response to infections in the median preoptic nucleus. *Abbreviations:* COX2: Cyclooxygenase-2, EP3: Prostaglandin E2 Receptor 3, IL-1: Interleukin-1, IL-6: Interleukin-6, IL-1R: Interleukin-1 Receptor, IL-6R: Interleukin-6 Receptor, PGE2: Prostaglandin E2, RANK: Receptor Activator of Nuclear factor Kappa beta, RANKL: Receptor Activator of Nuclear factor Kappa beta Ligand.

2. Neurobehavior

Sickness behavior is defined as the set of behavioral changes that develop during the course of an infection, such as reduction in motor activity, sleepiness, anorexia, anhedonia, and defects in learning and/or memory.[30] This set of behaviors is orchestrated in order to efficiently maximize metabolic resources to target and remove pathogens, support recovery, and promote tissue repair. Inflammatory signals reach the CNS in a fashion either similar to the pathway previously described in the initiation of fever or through site-specific sensory afferents of the autonomic nervous system.[1,28] For example, proinflammatory cytokines released in the viscera may be sensed by the vagus nerve and then transmitted to the brain stem.[21]

Though behaviors characteristic of sickness and their relevant physiologies are numerous, IL-1β has been shown to play an important role in the manifestation of many symptoms, as anorexia and decreased motility.[21,28] In the hippocampus, IL-1β causes reactive oxidative damage that impedes learning and memory by repressing LTP.[30] Moreover, IFN-α has been linked to malaise and anhedonia, which (in cases of viral infection) may last even after the infection has been resolved.[21] Other effects of IFN-α include changes in serotonin levels and rising quinolinic acid associated with depression, as well as alterations to the overall metabolic activity of the cingulate cortex responsible for processing of reward and punishment.[1,31]

Immune System Dysfunction and Neurodegenerative diseases

1. Alzheimer's Disease

Known for its manifestation as cognitive decline in the elderly, Alzheimer's disease (AD) is the most prevalent NDD. AD is characterized by accumulations of extracellular β-amyloid (Aβ)/senile plaques, and intracellular neurofibrillary tangles (NFTs).[32] Despite copious research, the pathogenesis of AD is still poorly understood but includes neuroinflammation due to aberrant microglia and astrocyte activity.[33]

Microglia assume a physiological role in clearing Aβ-plaques, especially in earlier stages of AD; therefore, any mutation in transmembrane receptors as triggering receptor expressed on myeloid cells 2 (TREM2) and cluster of differentiation 33 (CD33) that decreases rates of phagocytosis may predispose and progress AD.[5,33] AD itself may also impact normal microglia activity, as persistent stimulation of microglia by DAMPs and cytokines facilitates neurotoxicity via chronic inflammation. Concurrently, excessive stimulation may transform active microglial states into dysfunctional senescence as they gradually lose the ability to sense and phagocytose Aβ peptides. As Aβ continues to accumulate, it triggers microglia to promote tau hyperphosphorylation, forming NFTs, and activates NLRP3 (Nucleotide-binding oligomerization domain, Leucine rich Repeat and Pyrin domain) inflammasomes that release IL-1β and IL-18 that further exacerbate microglial dysfunction and Aβ aggregation.[13,34]

Astrocytes have also been speculated to play a role in neurodegeneration through the production of hydrogen peroxide, and current studies are investigating the correlation of the age-related increase of TGF-β/C1q expression with AD predisposition, as they drive rates of synaptic pruning.[7,13]

The contribution of peripheral immune cells to the pathogenesis of AD remains obscure. Postmortem specimens of brains of AD patients have long since confirmed elevated CD4+ and CD8+ concentrations in brain parenchyma and CSF; however, it is unclear how this observation manifests. Increased BBB permeability, due to decreased expression of tight junction molecules ZO-1 and occludin in vascular endothelial cells, has been hypothesized to play a role.[7] Similarly, observations of increased peripheral T-cell activation, perhaps due to increased chemokine receptor expression as chemokine receptor type 2 (CCR2), CCR5, and CXCR2, may also aid in T-cell recruitment to the CNS. Research shows that antibodies against Aβ can initial a humoral immune response through the presentation of the Aβ self-antigen to T-cells in the periphery or directly in the brain parenchyma via APCs. Within CNS parenchyma, T-cells may help with Aβ clearance, but mostly assume a neurotoxic state: they may trigger neuronal apoptosis through Fas ligand- LFA-1, and CD40 and initiate crosstalk with microglia and astrocytes that enhances their proliferation and neuroinflammatory activation. The direct interaction of T-cells with neurons may furthermore cause upset neuronal calcium homeostasis, aiding the manifestations of AD.[35]

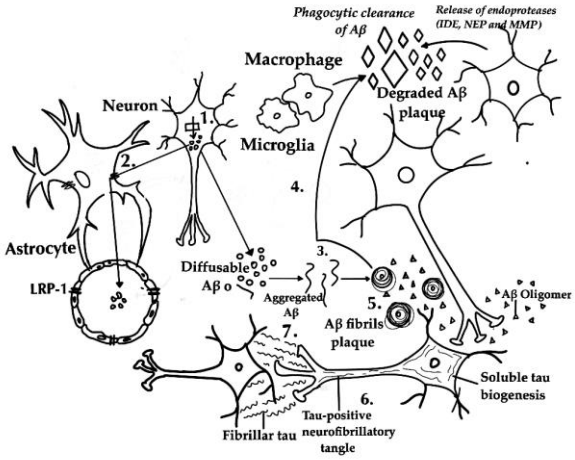

Figure 2. The pathway leading to the formation of senile plaques and neurofibrillary tangles (NFTs) based on the amyloid-beta theory of Alzheimer's disease (AD). *Abbreviations:* Aβ: Amyloid Beta, APP: Amyloid Precursor Protein, LRP-1: Low-density lipoprotein Receptor–related Protein-1.

Table 1. The different roles of inflammatory mediators in Alzheimer's disease (AD) pathogenesis.

Mediator	Function
IL-1α	Increases α-secretase and increases sAPPα Decreases amyloidogenic processing
IL-1β	Increases APP mRNA, α-secretase and γ -secretase, upregulates TAU mRNA, downregulates β-secretase,
IL-6	Upregulates APP mRNA, increases p-TAU
IL-10	Favors β deposition
TNF-α	Upregulates APP mRNA, upregulates both β-secretase and γ-secretase
IFN-γ	upregulates β-secretase and γ-secretase, increases Aβ-deposition
TGF-β	Increases APP mRNA, increases Aβ deposition

Abbreviations: Aβ: Amyloid Beta, APP: Amyloid Precursor Protein, IFN-γ: Interferon-gamma, IL-1α: Interleukin-1 Alpha, IL-1β: Interleukin-1 Beta, IL-6: Interleukin-6, IL-10: Interleukin-10, mRNA: Messenger Ribonucleic Acid, sAPPα: Secreted Amyloid Precursor Protein Alpha, TAU: Tubulin Associated Unit, TGF-β: Transforming Growth Factor Beta, TNF-α: Tumor Necrosis Factor Alpha.

2. Parkinson's Disease

Parkinson's disease (PD) is an NDD involving the demise of dopaminergic neurons in the substantia nigra pars compacta (SNpC) and the presence of aggregated α-synuclein (α-syn) deposits in Lewy vesicles, termed Lewy bodies, that drive neurodegeneration. It manifests as motor defects including bradykinesia, impaired gait, resting tremors, and rigidity, as well as non-motor and neuropsychiatric symptoms including dementia, depression, anxiety, constipation, and sleep disturbances.[36] The activation of microglia and astrocytes, and thus increased cytokine levels and oxidative stress, plays a vital role in the pathogenesis of PD.[37]

As in AD, microglia, which are densely populated in the substantia nigra, may play a role in clearing α-syn, but excessive aggregation of α-syn also leads to activation of NLRP3 inflammasomes and release of elevated levels

of TNF-α, IL-1β, IL-2, IL-6, reactive oxygen species (ROS), and pro-apoptotic proteins typically found in the CSF of PD patients.[38] This subsequently drives greater loss of dopaminergic neurons and aggregation of α-syn.[5,39,40]

Astrocytes are speculated to typically play a preventative role in PD pathogenesis due to their ability to regulate glutamate levels. Studies showed that dopaminergic neurons in areas normally less populated with astrocytes tend to degenerate. Additionally, A2 astrocytes play a generally neuroprotective role again ROS, nitric oxide, and inflammatory cytokines.[41] On the other hand, A1 astrocytes could be activated by TNF-α, IL-1, and C1q released by microglia to become neurotoxic, inducing death in neurons and oligodendrocytes. Excessive stimulation by inflammatory cytokines may also impede astrocytic glutamate regulation and cause neuronal excitotoxicity via glutamate accumulation, thereby augmenting mitochondrial dysfunction and the death of dopaminergic neurons.[42]

Additionally, studies have implicated the PIS in PD through the discovery of T-cells within the brains of PD patients (suggesting BBB dysfunction) and serum levels of INF-γ and TNF-α that increased with the severity of non-motor and psychiatric symptoms. Peripheral T-helper (Th) 17 cells have also been shown to secrete IL-17 which plays an important role in the death of dopaminergic neurons.[5,39]

3. Huntington's Disease

Huntington's disease (HD) is characterized by the demise of neurons in the neostriatum and the cortex, which explains the cognitive and behavioral disturbances with involuntary movements seen in patients.[43] It results from the alteration and accumulation of huntingtin protein in the form of nuclear and cytoplasmic inclusions within neurons.

Postmortem studies have revealed remarkable amounts of activated microglial cells and gliosis in brain regions relevant to HD, the cortex, globus pallidus, and neostriatum, which correlate with the severity of neuronal demise in a fashion like AD and PD.[44] TNF-α and IL-10 are particularly increased in the striatum, while levels of IL-6 and IL-8 were seen in the cortex and cerebellum of patients with HD.[45] Interestingly, a study has noted a significant increase in plasma levels of IL-6 in pre-symptomatic HD mutation carriers sixteen years before the predicted onset of the disease, which may denote that inflammatory changes occur very early in the disease process.[46] Generally, reactive astrocytes are also present in pre-symptomatic HD patients and become dysfunctional as the disease progresses, which contributes to neuroinflammation and toxicity. Similarly, microglia are hyperactivated during diseased states, as they are both affected by and aiding in neurodegeneration.[47]

The role of peripheral inflammatory changes in HD is still poorly understood and the infiltration of peripheral immune cells into brain parenchyma is insignificant compared to other NDDs. Whether inflammatory changes result from neurodegeneration or are an independent pathological mechanism in HD is unclear.[46,48]

4. Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a fatal, severe NDD characterized by progressive degeneration of upper and lower motor neurons in the brain and spinal cord, leading to muscle weakness, complete loss of muscle control, and, ultimately, death.[49]

Abnormalities of the immune system and injuries to motor neurons lead to the activation of immune cells. Modes of microglia activation are similar to the aforementioned states, as the anti-inflammatory, neuroprotective phenotypes they assume in the early onset of the disease shift to pro-inflammatory, neurotoxic states in later stages.[39,50] In the pre-symptomatic disease, microglial cells have been shown to overexpress IL-10 which blocks accelerated clinical onset of ALS by decreasing inflammation. Transactive response (TAR) DNA-binding protein 43 (TDP-43) found in the brains of ALS patients is thought to be the reason behind increased BBB permeability, allowing peripheral immune cells to travel from neuromuscular junctions, up motor nerves, and into the CNS.[51,52]

In the CNS, astrocytes regulate crosstalk between the peripheral immune cells and microglia, a process mediated by the inflammatory molecules and attractants released by microglia but still poorly understood, thereby promoting neurodegeneration.[51,53] Astrocytes are also responsible for the upregulation of TGF-β1; overexpression of TGF-β1 accelerates disease progression by disrupting the protective effects of T-cells and microglia.[51,54]

T-regulatory cells (Tregs) are hypothesized to play an important role in ALS. In the early stages of the disease, patients tend to show increased concentrations in peripheral CD4+ and CD25+ that then significantly decrease as the disease progresses. This may be due to the increased need of recruitment to the inflamed CNS.[55] Along with Tregs, early ALS also exhibits more activity of Th2, with both secreting IL-4 that inhibits microglial activation. With more inflammation, exposure to nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) oxidase 2 (NOX2), IL-1β, IL-12, INF-γ, and IL-6 inhibits the action of Tregs, which promotes further inflammation. Studies also show that Tregs are not only inhibited by dysfunction, as components important for their action like genes, such as forkhead box protein P 3 (FOXP3), and cytokines like IGF-β, IL-10, and IL-4, are down-regulated. Overall, Tregs may be helpful prognostic factors for the progression of ALS.[56]

Current Therapeutic Prospects of Immunomodulators in Neurodegenerative Disease

Studies are currently investigating ways to incorporate the neuroinflammatory nature of NDDs into therapeutic strategies that aim to dampen the driving forces that make that inflammation possible. For example, clinical trials for small-molecule inhibitors or viral overexpression of TNF-α, NLRP3, and ILs as well as passive and active and passive vaccines against α-syn, Aβ, and tau are currently being run.[57,58] With a similar intention, some studies suggest utilizing Tregs in the treatment of NDDs to invoke their immunomodulatory effects without the immunosuppression associated with drugs. Experimentation of Tregs is, however, highly particular to the nature of the NDD being studied and is, as such, preliminary and subjective.[59]

Conclusion and Future Prospects

All in all, there are many ways in which the immune system is involved within the structure and function of the CNS, and, as such, its normal functioning is integral to the maintenance of CNS homeostasis. As discussed, the CNS heavily relies on its innate immunity for immune surveillance and action, but in the case that the cause of irritation grows unmanageable, it may recruit heavily regulated PIS elements to initiate adaptive immunity. Due to their roles in phagocytosis and high sensitivity to neuronal activities, microglia, astrocytes, and T-cells have been further implicated in shaping the CNS through their respective roles in neurodevelopment and plasticity. Generally, the PIS not only responds to CNS distress but also communicates the current immunological status and needs of the body to the CNS to maintain homeostasis and ensure optimal immune responses. Finally, because of their inextricable functions and overlapping regulatory effects, disruptions of the immune system have been shown to have cardinal roles in NDD pathogenesis.

Overall, gaps in neuroimmune research are many due to the breadth of the topic. Still, filling those gaps would provide opportunities on multiple fronts. For instance, further research on the involvement of the central and peripheral immune systems in the early stages of NDDs may provide a means of better tracking disease trajectory and creating preventative measures; likewise, a more detailed observation of NDD causative pathophysiology throughout the disease as it relates to the immune system may enhance treatment options. Additionally, a better understanding of the involvement of innate and adaptive immune cells in neurodevelopment and plasticity may offer a more comprehensive look into the genesis of neuropsychiatric disorders, such as autism spectrum disorder, schizophrenia, and

depression, lending to current knowledge of their etiology and management.

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Author Contributions

All authors made significant contributions to this research in the form of study design, acquisition of information, drafting, revising, and critically reviewing the manuscript. All the authors approve the publication of the final version of the manuscript.

Declaration of Conflicting Interests

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