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Innate Immunity and Neurodegeneration

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Abstract

The innate immune system plays diverse roles in health and disease. It represents the first line of defense against infection and is involved in tissue repair, wound healing, and clearance of apoptotic cells and cellular debris. Excessive or nonresolving innate immune activation can lead to systemic or local inflammatory complications and cause or contribute to the development of inflammatory diseases. In the brain, microglia represent the key innate immune cells, which are involved in brain development, brain maturation, and homeostasis. Impaired microglial function, either through aberrant activation or decreased functionality, can occur during aging and during neurodegeneration, and the resulting inflammation is thought to contribute to neurodegenerative diseases. This review highlights recent advances in our understanding of the influence of innate immunity on neurodegenerative disorders such as Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease, and Huntington's disease.

INTRODUCTION

Neurodegenerative diseases are generally characterized by synaptic loss and neuronal death, resulting in cognitive decline, dementia, and loss of motor function. Neuronal loss is attributed to the formation, spread, and deposition of pathogenic protein aggregates, which can arise either spontaneously or due to inherited mutations. Histologically, neurodegenerative diseases can be classified according to the pathologic protein aggregate that is deposited in distinct brain regions. These include the amyloidoses, with prion protein and beta-amyloid (Aβ) plaques manifesting in Creutzfeldt-Jakob disease and Alzheimer's disease (AD), respectively; the tauopathies, with the characteristic neurofibrillary tangles of the hyperphosphorylated microtubule-binding protein tau, which is also present in AD; the synucleinopathies, such as Parkinson's disease, with aggregates of α-synuclein (α-syn) forming Lewy bodies; and the transactivation response DNA binding protein (TDP)-43 proteinopathies, including amyotrophic lateral sclerosis (ALS) (1).

Protein aggregate deposition and neuron loss typically start in a specific region of the brain and subsequently spread to other regions, though how this occurs remains controversial. Spread of these aggregates—particularly of tau and α-syn, which form intracellular aggregates—may proceed in a prion-like manner, where uptake of aggregates into neighboring cells seeds the aggregation of the soluble protein in new cells (2). This seeding effect could also explain how soluble fibrils can be more neurotoxic than other large aggregates (as in the case of Aβ). However, it is also possible that aggregation of these intracellular proteins occurs in a cell-autonomous manner and that the affected neurons are in a microenvironment that makes them vulnerable to increased protein aggregation (3). Whereas mutations that predispose proteins to misfolding likely drive aggregation in familial inherited disease, defects in proteostasis, such as dysfunctional protein chaperoning and defective lysosomal clearance, may promote protein aggregation in sporadic disease (4). Another key factor is age; risk for developing neurodegenerative disease increases as we get older. This review considers the role of the innate immune system in aggregate formation, deposition, and clearance; how these aggregates can trigger inflammation; and how inflammation affects central nervous system (CNS) function.

NEURODEGENERATIVE DISEASE HALLMARKS

AD is the most common cause of dementia, with >46 million people worldwide estimated to be affected (5). Sporadic AD, which occurs in 10–30% of the population aged over 65, is characterized by extracellular Aβ plaques and accumulation of the microtubule-binding protein tau in neurons as neurofibrillary tangles (6). Aβ is processed from the amyloid precursor protein (APP) by multiple enzymes including the gamma secretase complex, a multiprotein complex mediating intramembrane proteolysis whose enzymatic subunits presenilin 1 (PS1, encoded by *PSEN1*) and presenilin 2 (PS2, encoded by *PSEN2*) are mutated in familial forms of AD (6). Pathologic mutations in APP, PS1, or PS2 can be inherited in an autosomal dominant manner and manifest as early-onset AD, which, in terms of disease progression and pathology, is comparable to sporadic, late-onset AD (6). Although mutations in the gene encoding tau (*MAPT*) produce tauopathies, they do not produce AD. This observation suggests that hyperphosphorylation of tau and neurofibrillary tangles results from Aβ-related pathology, in agreement with the amyloid cascade hypothesis (3).

Parkinson's disease (PD) is the second most common neurodegenerative disease, estimated to affect 1–2% of the population aged over 60 (7). PD symptoms include the classic motor triad of tremor, rigidity, and bradykinesia, as well as dementia (7). The characteristic motor impairment in PD is a result of dopamine deficiency due to loss of dopaminergic neurons in the substantia nigra pars compacta (8). Like AD, PD is a complex disease with both genetic and environmental components, including the aggregation of α-syn.

Various proteins have been suggested to be misfolded and prion-like in ALS. The disease is characterized by progressive deterioration of the upper and lower motor neurons, resulting in rapid loss of muscle function, with 50% of patients dying within 1.5 years of disease onset (9). In both ALS and frontotemporal lobar degeneration, protein aggregates of TDP-43, gain-of-function mutant superoxide dismutase 1 (SOD1), and hexanucleotide repeated expansion of C9Orf72 are all associated with neuronal death and disease progression (1). Like α-syn and tau, misfolded SOD1 displays prion-like properties and is capable of seeding new aggregates in neighboring cells (9).

Huntington's disease (HD) is a rare, autosomal dominant inherited disease with a prevalence of 1 in ~7,500 in Western populations and an age of onset of ~45 years (10). An expanded CAG repeat in the *HTT* gene, which encodes the protein huntingtin, corresponds to an abnormally long polyglutamine sequence in the protein, giving it pathologic properties (10). In HD, the aggregation of mutant huntingtin to form so-called huntingtin-rich inclusions culminates in neuronal dysfunction and death (10).

MICROGLIAL FUNCTION DURING HOMEOSTASIS

Microglia are the main innate immune cells present in the CNS and are considered the resident brain macrophages (11), although recent studies employing single-cell transcriptomic profiling have revealed that microglia are epigenetically and transcriptionally distinct from other tissue macrophages or bone marrow–derived macrophages (12). Microglia, unlike other tissue-resident macrophages, do not arise from bone marrow precursors but are generated from a yolk sac–derived pool of progenitors in the CNS (13). In addition, microglia can self-renew in situ upon receiving an activation stimulus (14). Although the blood–brain barrier keeps the CNS immune privileged, influx of peripheral immune cells is also possible. This occurs beneficially during infection and pathogenically during autoimmune diseases such as multiple sclerosis. The function of microglia is multifaceted: They are important for normal brain development, maturation, and homeostasis as well as for responding to and clearing CNS infections. For instance, microglia are required for complement C1q- and C3-dependent synaptic pruning in neuronal development (15, 16) and support proper functioning of neuronal networks. Microglia furthermore phagocytose apoptotic cells during neurogenesis via the anti-inflammatory receptors Axl and Mer (17), and they may also support learning-dependent synapse formation by releasing brain-derived neurotrophic factor (18).

In the healthy CNS, resting microglia have multi-branched, long processes that are constantly in contact with neurons, astrocytes, and endothelial cells, monitoring local synapses and surveying for injury or infection. Upon detecting such a disturbance in homeostasis, activated microglia change their morphology to become more rounded and "amoeboid" in shape, reflecting their increased phagocytic capacity and production of proinflammatory cytokines (19). During aging and neurodegeneration, there is evidence for both microgliosis, i.e., a total increase in the number of microglia present in the CNS (20), and changes in microglial function.

MICROGLIAL ACTIVATION IN NEURODEGENERATION

High levels of proinflammatory cytokines, including tumor necrosis factor (TNF), interleukin (IL)-1β, and IL-6, are expressed in the brains, cerebrospinal fluid, and serum of patients with AD, PD, and HD (21). However, in contrast to the neuroinflammation that occurs in bacterial or viral infection or in multiple sclerosis, in these neurodegenerative disorders there is no accompanying infiltration of adaptive immune cells into the CNS (22). The source of these proinflammatory cytokines in the brain is therefore primarily microglia and other infiltrating peripheral myeloid cells. In addition to detecting and responding to CNS infection by recognizing pathogen

associated molecular patterns (PAMPs), microglia can also respond to sterile triggers, such as protein aggregates or danger associated molecular patterns (DAMPs).

Identifying the precise DAMPs that activate microglia in the context of neurodegeneration is difficult. There is extensive evidence that fibrillar Aβ and α-syn can act as DAMPs within the CNS, but dying neurons can give rise to a multitude of other DAMPs, including ATP (23), high-mobility group box protein 1 (HMGB1), and lysophosphatidylcholine (24). Hence, numerous physicochemically diverse DAMPs can be recognized by different receptors, culminating in a neuroinflammatory response (25). **Figure 1** gives an overview.

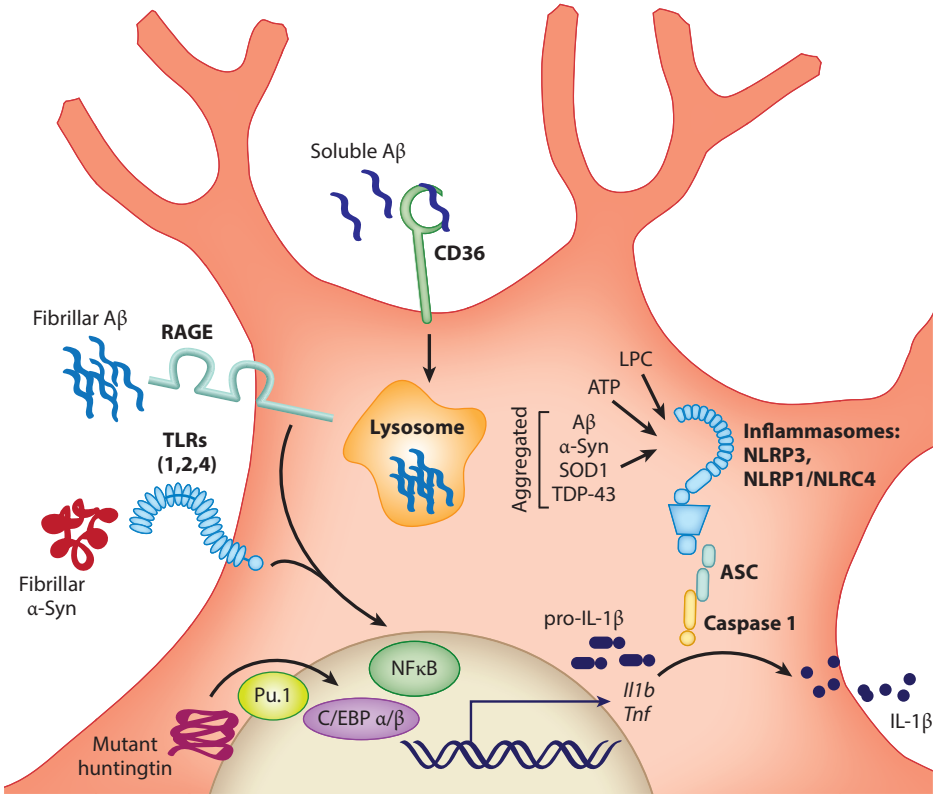

Figure 1

PRR activation by protein aggregates in neurodegeneration. Soluble fibrillary Aβ or α-syn can be recognized by cell surface receptors such as RAGE, TLR2, and TLR4, triggering NF-κB-dependent proinflammatory gene expression and upregulating components of the inflammasome pathway. Uptake of soluble Aβ mediated by CD36 can increase cellular Aβ concentrations such that Aβ aggregates. Fibrillar and aggregated Aβ, α-syn, TDP-43, and SOD1, along with other DAMPs released by dying neurons such as ATP and LPC, can trigger NLRP3 and NLRP1/NLRC4 inflammasome activation, which in turn triggers IL-1β release. Aggregation-prone mutant huntingtin triggers Pu.1- and C/EBPα/β-dependent upregulation of proinflammatory gene expression. Abbreviations: ASC, apoptosis-associated speck-like protein containing a carboxy-terminal CARD; PRR, pattern recognition receptor; Aβ, beta-amyloid; α-syn, α synuclein; RAGE, receptor for advanced glycation end products; TLR, Toll-like receptor; NF-κB, nuclear factor κB; TDP, transactivation response DNA binding protein; SOD1, superoxide dismutase 1; LPC, lysophosphatidylcholine; DAMP, danger-associated molecular pattern; ATP, adenosine triphosphate; C/EBPα/β, CCAAT/enhancer binding protein alpha/beta.

Similar to peripheral innate immune cells, microglia express all classes of innate immune signaling receptors, also called pattern recognition receptors (PRRs). The best-characterized PRRs, especially in regard to neurodegeneration, are the Toll-like receptors (TLRs) and inflammasomes. TLRs are activated after engaging ligands that cause TLRs to dimerize and undergo conformational changes leading to the recruitment of the adaptor proteins MyD88 or TRIF (Tir-domain containing adaptor inducing interferon-β). Downstream signaling cascades result in activation and nuclear translocation of transcription factors, including nuclear factor κB (NF-κB) and members of the interferon regulatory factor family, and subsequent induction of proinflammatory cytokines (26). Inflammasomes are cytosolic multimeric signaling platforms that are required for processing the inactive proforms of IL-1β and IL-18 into their mature active forms. This requires oligomerization of the inflammasome "sensor" protein upon recognition of the trigger, followed by recruitment of the adaptor ASC (apoptosis-associated speck-like protein containing a carboxyterminal CARD), and the subsequent activation of caspase-1. Active caspase-1 proteolytically activates IL-1β and IL-18 cytokines and promotes an inflammatory cell death termed pyroptosis. NLRP3 inflammasome activation is tightly regulated, and one of the key mechanisms is that both pro-IL-1β and NLRP3 expression need to be induced (priming) before the second stimulus can induce inflammasome activation (27). Exactly how NLRP3 is activated is still not understood, although for particulate, crystalline, and aggregated ligands (such as the protein aggregates in neurodegeneration), lysosomal damage and release of lysosomal proteases is proposed to trigger NLRP3 oligomerization (27). The NLR proteins (nucleotide-binding domain, leucine-rich repeat containing) are the best-characterized inflammasomes in neurodegeneration. The DNA sensing AIM2 (absent in melanoma 2) inflammasome is also expressed in astrocytes and microglia and is further upregulated during gliosis, a model of neurodegenerative disease (28).

Pattern Recognition Receptor Activation in Alzheimer's Disease

One of the earliest receptors described for Aβ is the receptor for advanced glycation end products (RAGE), which triggers microglial activation and secretion of proinflammatory cytokines (29, 30). Fibrillar Aβ has also been shown to bind to and elicit proinflammatory signaling in murine microglia through the B-class scavenger receptor CD36 (31), which can form complexes with TLRs 4 and 6 (32). While soluble (prefibrillar) Aβ does not directly induce inflammation in microglia, CD36 also mediates the uptake of soluble Aβ, where it can then aggregate in the lysosome (33). This intracellular, fibrillar Aβ is then able to activate the NLRP3 inflammasome, resulting in IL-1β release (34). This uptake and activation is summarized in **Figure 1**. The pathogenic role of the NLRP3 inflammasome and IL-1β in AD pathogenesis was confirmed in vivo as NLRP3- or caspase-1-deficient mice in the APP/PS1 model showed improved spatial memory and decreased Aβ plaque load in the brain (35). Of note, increased caspase-1 cleavage was also seen in brain lysates isolated from either the frontal cortex or hippocampal cortex of patients with AD compared to healthy control subjects, suggesting inflammasome pathway engagement in human AD (35). Of note, monocytes from AD patients have more NLRP3 and NLRP1 expression than healthy control subjects, concomitant with an increased release of IL-1β upon stimulation with Aβ fibrils (36), whereas MCC950, a specific NLRP3 inhibitor, blocks Aβ- induced IL-1β release from microglia and improves cognitive function in murine models (37). Aβ has also been described to activate NLRP1 in neurons, triggering IL-1β release and neuronal pyroptosis (38). A recent study demonstrated that the neuronal NLRP1 inflammasome was activated in response to stress (serum starvation) to release IL-1β and even Aβ in a caspase-1- and -6-dependent manner (39). Because IL-1β is a potent modulator of microglial responses, and IL-1 is known to have a pathogenic role in neurodegenerative diseases (40), deciphering the exact contributions of the NLRP1 and

NLRP3 inflammasomes in their respective cell types is of great interest. Recently described roles for the AIM2 (41) and NLRC4 inflammasomes in mediating the inflammatory response in acute brain injury (42) suggest that these inflammasomes could also play pathogenetic roles in AD.

Pattern Recognition Receptor Activation in Parkinson's Disease

Microglial TLR2, which can heterodimerize with TLR1, binds to misfolded, fibrillar α-syn released from neurons, triggering TNF and IL-1β production via MyD88 and NF-κB (43, 44). A similar study in a human monocytic cell line (THP1) confirmed that fibrillar α-syn, but not oligomeric α-syn, could trigger TNF and IL-1β upregulation in a TLR1/2-dependent manner (45). TLR4 may also play a role in α-syn microglial responses as α-syn uptake, proinflammatory cytokine release, and reactive oxygen species production were all TLR4 dependent in microglial cultures (46). Moreover, in an MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridin)–induced murine model of PD, TLR4-deficient mice were protected, suggesting a detrimental role for TLR4 in PD pathogenesis (47). The involvement of the NLRP3 inflammasome in α-syn-induced inflammatory responses is also not completely elucidated. Fibrillar α-syn induced pro-IL-1β and NLRP3 mRNA expression in human monocytes, and it induced IL-1β release in monocytes and THP1 cells in an NLRP3- and caspase-1-dependent manner (45, 48). In contrast, Gustin and colleagues (49) found that NLRP3 is not activated by α-syn in primary mouse microglia, although a recent study demonstrated increased NLRP3 expression in a mouse microglial cell line upon α-syn treatment, which correlated with caspase-1-dependent IL-1β release (50). Finally, NLRP3-deficient mice were protected from MPTP-induced loss of nigral dopaminergic neurons and had decreased MPTP-induced caspase-1 activation and IL-1β release (51), suggesting a role for NLRP3 in PD development. Interestingly, dopamine itself was described to inhibit the NLRP3 inflammasome (51); however, whether inflammasome activation precedes the loss of dopaminergic neurons, or is a result of that loss, remains to be determined.

Pattern Recognition Receptor Activation in Amyotrophic Lateral Sclerosis

The DAMPs contributing to neuroinflammation in ALS are less well characterized than those underlying AD and PD. Recombinant TDP-43 protein triggered TNF and IL-1β induction when added to microglia and was cytotoxic to motor neurons in coculture with microglia (52). This release was due to NF-κB and AP-1 activation downstream of CD14 (52), and although the nature of the aggregates and their uptake was not characterized, TDP-43 with gain-of-function mutations was able to activate microglia more effectively than wild-type protein at lower doses (52). Similarly, recombinant mutant (G39A) SOD1 triggered IL-1β release from primary murine microglia, whereas wild-type SOD1 did not (53). Treating G39A SOD1 transgenic mice with an IL-1R antagonist (IL-1Ra), or genetically deleting IL-1β or caspase-1, slowed disease progression and modestly improved cognitive function (53). Anakinra, a recombinant form of IL-1Ra, was recently tested in a pilot study for ALS, and although lower cytokine levels were observed in the first 24 weeks of treatment, this observation did not extend to the full 52 weeks of the study (54). However, the drug was well tolerated, and further studies will answer whether targeting IL-1β in ALS is therapeutically desirable.

Pattern Recognition Receptor Activation in Huntington's Disease

To date there is little evidence that mutant huntingtin acts as an extracellular DAMP to induce inflammation in CNS cells. Huntingtin is, however, highly expressed in both neurons and microglia, and a recent study determined that overexpression of mutant huntingtin in primary murine

microglia led to increased expression of inflammatory genes in the absence of any activating stimuli (55). This was associated with increased expression and activity of the key myeloid transcription factors Pu.1 and C/EBPα/β (CCAAT/enhancer binding protein alpha/beta). Furthermore, microglia overexpressing mutant huntingtin induced more neuronal cell death than their counterparts expressing wild-type huntingtin, suggesting a mechanism whereby mutant huntingtin expression results in basally hyperinflammatory microglia, which can then be further activated by other DAMPs released by dying neurons (55). Whether aggregation-prone huntingtin also triggers inflammasome activation and how mutant huntingtin activates Pu.1 and C/EBP activity in microglia remain to be determined.

MICROGLIAL DYSFUNCTION IN NEUROINFLAMMATION

There is evidence that IL-1β and IL-6 can contribute to tau hyperphosphorylation, a prerequisite for the formation of neurofibrillary tangles (56). Moreover, reactive oxygen species and nitric oxide produced by activated microglia can be directly cytotoxic to neurons (57). One of the most intriguing possibilities is that these inflammatory cytokines cause microglia to be dysfunctional, particularly by modulating their phagocytic capacity (**Figure 2**). Indeed, an emerging consensus is that the microglia surrounding Aβ plaques or Lewy bodies are not activated, as originally and commonly interpreted, but are instead nonfunctional (58, 59). Proinflammatory cytokines were shown to downregulate the expression of microglial receptors involved in phagocytosis, resulting

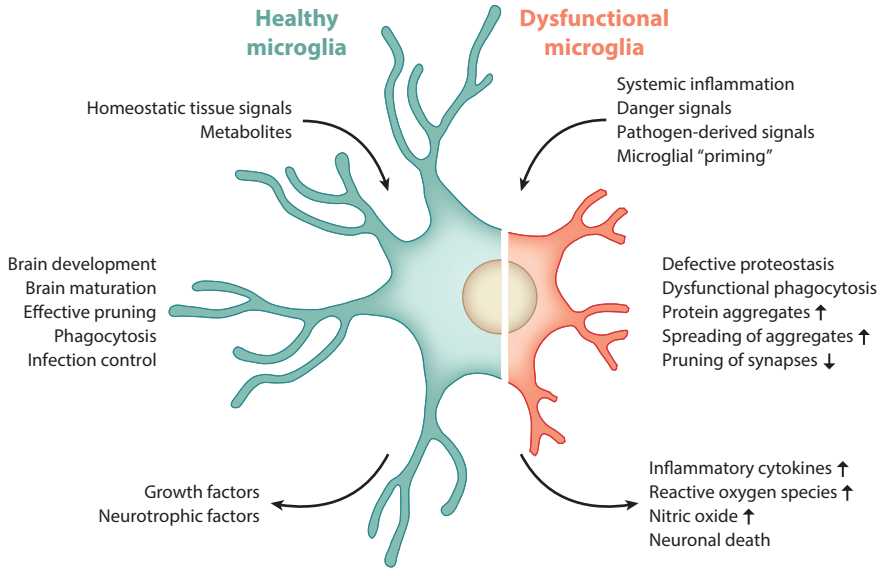

Figure 2

Microglial function in homeostasis and dysfunction in neurodegeneration. Healthy microglia are maintained by homeostatic tissue signals from surrounding cells in the microenvironment and play key roles in brain development, maturation, synaptic pruning, phagocytosis, and infection control. Additionally, healthy microglia support neurons by secreting growth factors and neurotrophic factors. Age, local and systemic inflammation, and other factors can cause microglia to become dysfunctional. Microglia can recognize both pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs), leading to an amplification in inflammation and a "primed" state. This, coupled with defects in proteostasis and dysfunctional phagocytosis, can lead to an increase in pathogenic aggregates, as well as a hyperinflammatory state that is neurotoxic.

in impaired Aβ clearance in murine AD models (60). This concept has been supported by genetic studies that identified rare variants in immune receptor genes involved in phagocytosis as conferring increased risk of sporadic AD, including TREM2 (triggering receptor expressed on myeloid cells 2), inhibitory receptor myeloid cell surface antigen CD33, and the complement component 3b/4b receptor 1 (CR1) (58). In keeping with this, a recent study showed that Aβ increased complement C1q levels, which may aberrantly activate the developmental synaptic pruning process by microglia, leading to synapse loss in AD (61).

Of these receptors, TREM2 has received the most interest (reviewed in Reference 62). TREM2 is a receptor expressed highly in microglia and other myeloid cells that signals through the adaptor Dap12 (also known as TYROBP) to initiate a multitude of functions. These include phagocytosis, survival, and proliferation and secretion of cytokines (62), as well as an immunosuppressive role in TLR-induced inflammation in macrophages (63, 64). A systems-analysis study on post mortem brain tissue from patients with late-onset AD identified a key role for Dap12/TYROBP and inflammatory gene networks in AD progression (65). In vitro studies suggested TREM2 could be directly involved in Aβ clearance (66), but the function of TREM2 in AD in vivo is still being fully elucidated. In two recent studies, TREM2 deficiency also reduced neuroinflammation in the brain tissue of mice with either APP/PS1 (67) or 5XfAD mutations (68). In one study (68), the overall outcome of TREM2 deficiency was increased Aβ accumulation and neuronal loss, but another (67) found that TREM2 deficiency improved disease outcome, suggesting that TREM2 is detrimental in AD pathology. The differences between these studies were reconciled by a further study that investigated TREM2 involvement in AD pathogenesis in vivo at several time points; it suggested that TREM2 is required for early microglial expansion around Aβ plaques (68), which limits diffusion of plaques and ensuing neuronal damage to Aβ (69). A number of ligands for TREM2 have also been recently described, including phospholipids that are associated with fibrillar Aβ (68) and apolipoprotein E, of which the variant ApoE4 is encoded by a well-established AD risk gene (70, 71). Whether microglial TREM2 binding of these DAMPs results in increased inflammation or increased Aβ clearance, and how this affects AD pathogenesis, remain intriguing questions.

During aging, microglia may become hyperresponsive—with increased proinflammatory cytokine output and upregulated cell surface receptor expression—and/or assume a dysfunctional state with loss of phagocytic functionality and the ability to degrade excess proteins (72). The phenomenon of microglial priming, whereby primed microglia have an exaggerated or heightened response to a second inflammatory stimulus compared to naïve microglia, was proposed to explain microglial dysfunction in aging (73). Microglial priming is similar to the newly emerging concept of "trained immunity" or "innate immune memory," in which peripheral innate immune cells such as monocytes undergo epigenetic and metabolic changes upon an initial challenge by a stimulatory trigger. This acquired cellular programming results in an intensified adapted (or maladapted) response to a secondary challenge (74). Epigenetic changes modulate gene expression by variably acetylating or methylating the histone proteins in the region of interest and thus altering the accessibility of transcription factors and transcriptional machinery to target promoters. For example, the histone H3K27me3 demethylase JMDJ3 (Jumonji domain containing 3) was required for polarizing microglia toward an anti-inflammatory phenotype (75). Consistent with this, JMDJ3 knockdown promoted microglia-mediated neuronal cell death in microglia/neuron cocultures, and in vivo knockdown of JMDJ3 exacerbated dopaminergic neuron loss in a MPLT-induced model of PD (75). Similarly, in a murine model of AD, profiling the epigenetic changes in the hippocampus by comparing H3K4 methylation or H3K27 acetylation states showed increased transcription factor accessibility to immune genes and their enhancer regions, suggesting increased immune gene expression, and a concomitant decrease in genes associated with synaptic plasticity (76). This supports the idea that microglial priming could indeed be mediated by epigenetic changes.

The source of the initial stimulus that primes microglia in aging remains unclear. Local factors within the CNS, lack of inhibitory signals from surrounding neurons, and factors triggered during systemic inflammation are all possibilities, and not mutually exclusive. Indeed, many studies have documented that induction of systemic inflammation can trigger increased disease pathology in murine models of AD, PD, and ALS (77). A recent study found that effective microglial function is dependent on microbiome-derived short-chain fatty acids, suggesting that the microbiome and nutrition could also have an impact on innate immune function in neurodegeneration (78). This is consistent with a study suggesting that gut microbiota can influence blood–brain barrier permeability (79). With the advance of single-cell analyses at the epigenetic, transcriptional, proteomic, and metabolomic levels, it will be interesting to systematically define the changes in microglia during aging, discern whether they are indeed primed during neurodegeneration, and determine whether this is reminiscent of peripheral trained immunity.

CONCLUSIONS

In the last two decades, it has been appreciated that innate immune cells, including microglia, are equipped with a broad range of germ-line encoded signaling receptors allowing them to respond to microbes or damage to tissues. We have started to understand under which conditions these pathways play beneficial or pathogenic roles in the brain, but we are still far from a clear picture of the breadth of innate immune function in brain homeostasis and disease. Only a fraction of these innate immune receptors and signaling pathways have been studied in the context of neuroinflammatory or neurodegenerative diseases.

Future work needs to better decipher the contribution of other pathways, such as the nucleic acid–sensing pathways, to the inflammatory response in the brain. Indeed, aberrant cytokine production due to gain-of-function mutations in nucleic acid–sensing receptors or their regulatory pathways triggers autoinflammatory syndromes in people with type I interferonopathies. Many of these diseases present with CNS defects (80).

There is also evidence that type I interferon (IFN) signaling is associated with aging in the choroid plexus, and that blocking type I IFN activity may improve cognitive function (81). Whether this type I IFN signaling in aging arises from increased sensing of damaged DNA or cellular senescence by cytosolic DNA and RNA sensors remains to be determined.

It is well known that neurodegenerative diseases are associated with cell demise. As the activation of many innate immune pathways can cause inflammatory forms of cell death, such as pyroptosis, it is important to better understand how inflammatory cell death pathways contribute to neuroinflammation or neurodegenerative diseases.

The quantity and quality of innate immune cell responses are profoundly influenced by cellular metabolism and the epigenetic status of the cell. It would be beneficial to better define how microglial function can be tuned by changes in cellular metabolism or innate immune training induced by local or systemic triggers, and how diet, lifestyle, and aging impact this. As innate immune pathways are amenable to pharmacologic interference, there is a great prospect that a better understanding of the contribution of different pathways to neurodegenerative diseases could lead to future development of targeted therapies.

DISCLOSURE STATEMENT

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