



Review article

Microglial dysfunction and NLRP3 inflammasome signalling in Alzheimer's disease: mechanistic insights into neuroinflammation and neurodegeneration

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ABSTRACT

Alzheimer's disease (AD) is a progressively debilitating neurodegenerative condition characterized by the accumulation of amyloid- β (A β), tau pathology, synaptopathy, and neuron loss. Recent studies suggest that Neuroinflammation is a critical part of the disease process rather than an accompanying feature of the mentioned pathological changes. Microglia, the immune cells of the central nervous system, respond to amyloid-beta and pathological tau and exhibit functional alterations leading to the transition from their initial anti-inflammatory and neuroprotective function to chronic inflammation. Persistent activation of microglia is linked with the inability to clear abnormal proteins, excessive complement-dependent synaptic loss, secretion of cytokines, activation of astrocytes, and neuronal damage. Various inflammatory pathways play their roles, and one of the most prominent is the NOD-like receptor pyrin domain-containing protein 3 (NLRP3) inflammasome. The activation of the NLRP3 inflammasome leads to the recruitment of apoptosis-associated speck-like protein containing CARD (ASC) and caspase-1 activation, followed by interleukin-1 β (IL-1 β) and IL-18 maturation and gasdermin D (GSDMD) cleavage, contributing to pyroptosis and inflammatory processes. The current review will cover the changing role of microglia in AD progression, interactions between A β , tau, and inflammatory signaling pathways, as well as molecular mechanisms of NLRP3 Inflammasome activation. Furthermore, it will discuss new approaches that could be used for modulations of NLRP3 inflammasome signaling, including selective small molecule inhibition, caspase-1 targeting, natural compound use, repurposed drugs, and new drug delivery systems. Specifically, the ability to cross the blood-brain barrier (BBB), safety, translational challenges, and dissimilarity between animal models and humans' AD will be discussed in this context. Overall, targeting dysregulated Neuroinflammation, including NLRP3 inflammasome activation, could serve as an alternative approach to existing protein-directed treatment methods.

Keywords: Alzheimer's disease, Neuroinflammation, Microglia, NLRP3 inflammasome, Amyloid- β , Tau pathology, Synaptic pruning, Caspase-1, Pyroptosis, Neurodegeneration, Therapeutic targeting, Disease-modifying therapy.

INTRODUCTION

Brief overview of Alzheimer's disease pathology

Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized pathologically by the accumulation of extracellular amyloid-beta (A β) plaques and intracellular neurofibrillary tangles of hyperphosphorylated tau protein. These typical features lead to synaptic dysfunction, neuronal loss and cognitive decline observed in AD patients. Also, chronic neuroinflammation, largely driven by the brain's innate immune cells, microglia, is a major contributor to disease progression [1, 2].

In the core of AD pathology, A β plaques accumulate in the extracellular space, causing microglial activation. Subsequently, hyperphosphorylated tau aggregates into neurofibrillary tangles inside neurons, impairing neuronal function and survival. Importantly, studies suggest that tau pathology develops downstream of amyloid-beta induced microglial activation, suggesting a mechanistic cascade linking these pathologies [3].

Microglial cells are the resident immune sentinels of the brain and respond with an immune response to accumulating A β and tau aggregates. One key molecular actor in this response is the

NLRP3 inflammasome, a multiprotein complex in microglia that senses danger signals like A β plaques and tau tangles that serve as damage-associated molecular patterns (DAMPs). The activation of NLRP3 inflammasome induces the cleavage of caspase-1 that promotes the maturation and secretion of the pro-inflammatory cytokines IL-1 β and IL-18. This cascade leads to neuroinflammation, neuronal death, and aggravated AD pathology.

Activation of the NLRP3 inflammasome not only sustains microglial inflammatory responses but also impairs the clearance of amyloid-beta, thus creating a vicious cycle of inflammation and protein aggregation that accelerates neurodegeneration. Importantly, systemic inflammation may aggravate this situation by altering microglial morphology and function, hence impairing their ability to clear A β deposits, an effect that may be attenuated by NLRP3 inflammasome inhibition.

NLRP3 has a role beyond the brain's parenchymal environment linking peripheral immune challenges with central neuroinflammation. Misfolded proteins in AD trigger innate immune responses mediated by glial cells and promote the recruitment of peripheral macrophages, which aggravates chronic inflammation in the brain. NLRP3 activation also crosstalks with various receptor signalling pathways, including Toll-like receptors (TLRs), triggering receptor expressed on myeloid cells 2 (TREM2), purinergic receptors such as P2X7 and key kinases such as MINK. Together, these pathways regulate inflammasome activation and augment inflammatory signalling in AD. Mitochondrial dysfunction also causes oxidative stress, which further promotes the activation of the NLRP3 inflammasome, thus worsening the neuroinflammatory milieu and neuronal damage that are essential in AD pathogenesis [5].

Rationale for targeting neuroinflammation

The rationale for targeting neuroinflammation as a therapeutic strategy for Alzheimer's disease (AD) is supported by a growing body of evidence demonstrating that inflammatory processes are not merely passive, secondary consequences of the disease, but active, early, and central drivers of its pathogenesis.

The primary reasons for targeting neuroinflammation include: It is a Core Pathological Hallmark and Early Indicator. Historically, AD research has focused on amyloid- β (A β) plaques and neurofibrillary tangles (NFTs) of hyperphosphorylated tau. However, neuroinflammation is now broadly recognised as the third major hallmark of AD.

Importantly, neuroinflammation is one of the earliest detectable events in AD, with alterations in the brain's immune profile occurring decades before clinical symptoms or significant plaque and tangle accumulation. It propagates a "Vicious Cycle" of Pathology (The Feedback Loop). Neuroinflammation serves as a bridge linking and amplifying both A β and tau pathologies through a self-perpetuating feedback loop [6].

The pathogenesis of Alzheimer's disease is multifactorial and involves several interacting processes. Some of the key processes in the development of the disease will be discussed below.

Induction of inflammation: Soluble oligomers, fibrils and aggregates of Amyloid-beta (A β) and tau are known as damage-associated molecular patterns or DAMPs. They activate microglial pattern-recognition receptors such as Toll-like receptors (TLR2/4) and CD36, which activate NF- κ B and the NLRP3 inflammasome.

Impaired Clearance: Activated microglia in acute inflammation have a neuroprotective role in clearing A β and tau via phagocytosis. However, chronic neuroinflammation compromises this protective response, resulting in reduced microglial capacity to clear such pathological proteins and thus reduced elimination of protein aggregates.

Increased plaque and tangle formation: Proinflammatory cytokines such as IL-1 β , TNF-alpha and IL-6 via p38 MAPK activation contribute to increased tau phosphorylation and A β production. Moreover, microglia-derived ASC specks (released upon inflammasome activation) bind to A β and serve as a "seed" to accelerate amyloid aggregation.

Direct mediation of synaptic loss and neurotoxicity

Chronic neuroinflammation causes disease by directly damaging neurons and leads to cognitive decline independent of plaques.

Synaptic Pruning: Synapses are lost in excess because of overly aggressive microglial phagocytosis of synapses through complement-dependent pathways (e.g., C1q and C3). This impairs synaptic plasticity and circuit function, contributing to cognitive deficits.

A1 Astrocyte Activation: Hyperactive microglia secrete proinflammatory cytokines (e.g. TNF-alpha, IL-1 beta, and C1q) that cause astrocytes to become neurotoxic "A1" astrocytes that contribute to cognitive decline. These A1 astrocytes lose their normal homeostatic functions and secrete factors that directly promote neuronal death and oligodendrocyte damage.

Damage to the blood-brain barrier (BBB): Cytokines damage the integrity of the BBB. This disaggregation permits infiltration of peripheral immune cells and inflammatory mediators into the brain, further amplifying the central neuroinflammation.

Limitations of existing amyloid and tau therapies

The clinical results of conventional therapies targeting A β or tau pathology are mostly disappointing as they rarely prevent or reverse cognitive decline despite reducing pathological burden. Furthermore, monoclonal antibodies have poor pharmacological properties, including limited brain penetration, short half-lives, and induction of amyloid-related imaging abnormalities (ARIA) [7].

Therefore, the opportunity to modulate microglial function and dampen aberrant neuroinflammation may represent a valuable disease-modifying strategy and/or a needed adjunct to anti-

amyloid therapies, given the intimate link between neuroinflammation and neurodegeneration.

Scope and objectives of the review

This review work focuses on the role of glial cells in chronic neuroinflammation that accompanies the development of Alzheimer's disease (AD). The article highlights the significant contribution of this process to the pathophysiology of the disease, despite the traditionally predominant attention to amyloid plaques and tau proteins.

While traditional research has long focused on amyloid- β (A β) plaques and tau-associated neurofibrillary tangles as the primary initiating hallmarks of AD, this work examines how the persistent activation of microglial and astrocytic immune responses acts as an active mediator of synaptic loss, neuronal damage, and cognitive decline.

Specifically, the scope of this article is to explore the mechanism of the NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3) inflammasome, including the composition of the complex, the activation of the receptor by non-infectious danger-associated molecular patterns such as A β oligomers and tau aggregates, and the downstream effects including the activation of caspase-1 and the production of interleukin-1 β (IL-1 β) and IL-18, with a focus on gasdermin D and pyroptosis and their implication in Alzheimer's disease [8].

The purpose of this review is to assess the feasibility of targeting these inflammatory pathways for disease-modifying treatment of AD. By focusing on the mechanisms of regulation of the NLRP3 activity and its contribution to the pathogenesis of the disease, this article highlights the ways by which the progression of the condition could be interrupted by targeting specific elements of the immune response. The multifactorial nature of the regulation of NLRP3, including the involvement of such diverse mechanisms as autophagy, the ubiquitin system, and the gut microbiota, is discussed in detail.

Furthermore, we provide an overview of the emerging anti-inflammatory therapies now in preclinical and clinical development, with an emphasis on the relative therapeutic, safety, and blood-brain barrier penetration profile of selective small-molecule NLRP3 inhibitors, caspase-1 antagonists, natural compounds, and repositioned clinical candidates.

Additionally, we discuss the major translational impediments and safety considerations, including those related to the consequences of chronic suppression of innate immunity and the challenge of optimal CNS drug delivery, and identify future research directions. Specifically, we highlight the therapeutic potential of innovative approaches, such as nano-based carriers for targeted delivery of microRNA and therapeutic molecules, and combination strategies, targeting both proteinopathic and neuroinflammatory processes. Overall, this review aims to serve as a comprehensive cross-cutting discussion of the field, with an emphasis on the shift

in paradigm in immunomodulatory approaches to targeting AD, providing mechanistic insights into the disease process while supplying practical guidance in the identification of optimal therapeutic strategies for clinical translation and effective treatment of dementia.

Neuroinflammation in Alzheimer's disease: conceptual framework

Within the conceptual framework of Alzheimer's disease (AD), neuroinflammation is characterised as a chronic non-infectious immunological response that preferentially involves the central nervous system (CNS), which manifests as glial activation, peripheral invasion by immune cells, and production of proinflammatory molecules leading to neuronal damage.

The main cells that participate in the described processes are microglial cells. They are responsible for detecting foreign substances, such as A β and pathological tau proteins, and initiating an immune response. Upon their recognition, microglia become activated and secrete pro-inflammatory cytokines and other factors that are harmful to neurons. Moreover, microglia play a major role in the response to pathological proteins by altering their activation state toward a disease-associated one. The cells mentioned above also affect astrocytes, which are essential for neuron survival and function.

Specifically, microglia-derived factors such as TNF- α , IL-1 β , and C1q drive astrocytes toward a highly neurotoxic "A1" reactive state, in which the astrocytes lose homeostatic supportive functions and acquire cytotoxic properties against neurons and oligodendrocytes.

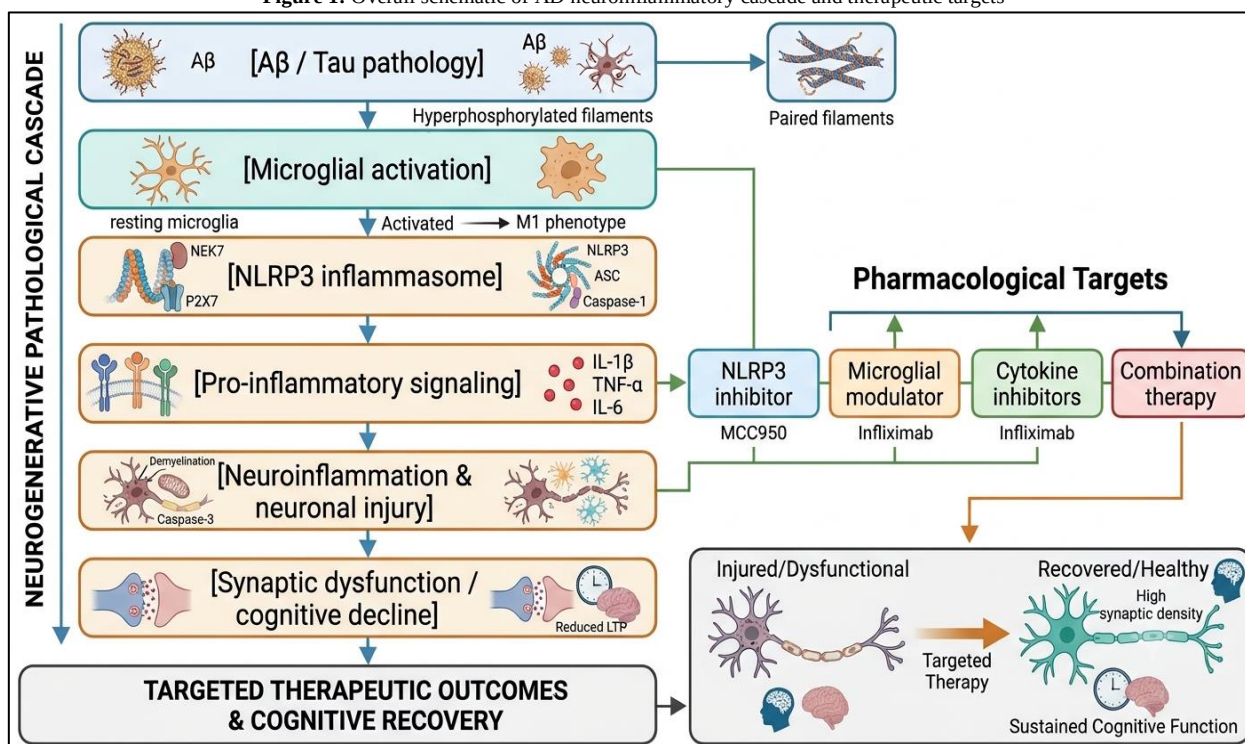
The most important characteristic of this condition is reactive gliosis, which, together with the disruption of the blood-brain barrier (BBB), leads to the fact that peripheral immune cells such as monocytes, neutrophils, and T cells enter the brain parenchyma, where they colonize and lead to a continuing degenerative cycle of the central nervous system by interacting with astrocytes and other glial cells that secrete additional inflammatory factors [9].

Interaction between amyloid- β , Tau, and inflammatory cascades

Alzheimer's disease progresses through multiple phases and is now recognized as a tripartite vicious cycle in which amyloid- β (A β) deposits, tau phosphorylation, and neuroinflammation mutually reinforce each other. The first step in this cycle involves the production of various soluble oligomers and fibrils of A β that act as endogenous damage-associated molecular patterns (DAMPs) by binding to toll-like receptors (TLR2, TLR4), and other microglial receptors, such as CD36, leading to NF- κ B transcription factor activation and upregulated production of NLRP3, and pro-IL-1 β . In addition to this transcriptional priming, the microglial phagocytosis of insoluble β -amyloid fibrils leads to lysosomal distension and subsequent membrane rupture, resulting in the release of active cathepsin B into the cytosol. Meanwhile, microglial internalization

of soluble β -amyloid oligomers induces mitochondrial dysfunction with resultant overproduction of reactive oxygen species (ROS) and release of mitochondrial DNA (mtDNA) [10].

Figure 1: Overall schematic of AD neuroinflammatory cascade and therapeutic targets



These intracellular events are together referred to as secondary activation signals that lead to the formation of the multi-protein complex called NLRP3 inflammasome that activates ASC and caspase-1, resulting in the processing of pro-IL-1 β and pro-IL-18 into their mature and more neurotoxic forms [13].

Once activated, this microglial inflammasome promotes tau pathology by triggering a progression from a restricted proteinopathy to a systemic neurodegenerative disease. The persistent release of mature IL-1 β into the parenchyma not only activates microglia but also binds to the neuronal receptor, inducing the activation of downstream effector kinases, including glycogen synthase kinase-3 β (GSK-3 β), cyclin-dependent kinase 5 (CDK5), and p38 mitogen-activated protein kinase (p38 MAPK), which phosphorylate tau. Hyperphosphorylated tau, in turn, detaches from microtubules and aggregates into neurotoxic soluble oligomers and intracellular neurofibrillary tangles (NFTs).

When these degenerating neurons undergo cell death or release extracellular tau, the hyperphosphorylated form of tau is recognized by the microglial TLRs, thus promoting the NF- κ B pathway (TLR). Moreover, the uptake of tau aggregates by the neighboring microglia causes lysosomal destabilization and further release of cathepsin B, thus locking the microglia in a chronic and hyperactivated state for an excessively prolonged period of time [14].

This pathological crosstalk forms a self-sustaining circuit in which both activation of microglia by A β and subsequent tau pathology drive each other. The Proinflammatory effects of activated microglia may be potent enough to cause chronic neuroinflammation that in turn leads to further tau pathology.

Moreover, this interaction can take place via a prion-like mechanism involving extracellular spread of pathological assemblies of apoptosis-associated speck-like protein containing a CARD (ASC).

This pathological crosstalk establishes a positive feedback loop in which both A β -induced microglial activation drives tau pathology and, conversely, tau aggregates sustain neuroinflammation. This tripartite interaction is reinforced through a prion-like mechanism, which probably involves extracellular transmission of misfolded, aggregated proteins. It was shown that upon microglial activation or pyroptosis, activated NLRP3 complexes release large ASC specks, which are highly resistant to protease treatment and can be detected in the supernatants of activated cells.

These extracellular ASC specks showed an extremely high affinity for A β peptides and acted as seeds or nucleation sites for A β oligomerization and dense core plaque formation. Moreover, ASC-A β complexes were strongly pro-inflammatory and more toxic than either ASC or A β alone, driving additional inflammasome formation and release of cytokines by activated microglia and ultimately leading to pyroptotic cell death via gasderin D expression.

This self-propagating loop means that neuroinflammation does not simply contribute to the progression of protein aggregationopathies, but rather drives the spatial spread of both A β and tau pathologies; thus, individual therapies targeting each pathology are insufficient, and combination approaches are needed to interrupt the pathological loop at multiple nodes [15].

Acute vs. Chronic neuroinflammation and impact on disease progression

In the initial phases of Alzheimer's disease, acute neuroinflammation is a protective response mounted by the brain's innate immune system. The acute response occurs when microglia sense very early, "sterile" insults, such as A β monomers and oligomers. In the early preclinical Alzheimer's disease stages, microglia-mediated neuroinflammation is beneficial and resolves pathology by removing A β deposits and preventing further accumulation and spread of pathological proteins. Indeed, in early mild cognitive impairment and preclinical Alzheimer's disease, microglia are strongly activated and migrate to the sites of injury to clear A β by phagocytosis. Furthermore, they surround the core of the senile plaques and restrict their expansion.

During this preclinical or the mild phase of cognitive decline, acute microglial activation is highly beneficial. The main reason is that such activation leads to the cells' migration to the sites of damage, where they perform their main function – phagocytosis and degradation of pathological protein aggregates. Moreover, activated microglia forms a protective barrier around senile plaques, reducing their ability to compact, becoming more toxic, and spread.

Meanwhile, if the disease progresses, such beneficial responses are no longer effective. The reason for this is the fact that the persistent and intense innate immune response leads to the transformation of the microglial cells into a chronically activated state. The trigger for this step is the accumulation of dense-core A β plaques and hyperphosphorylated tau aggregates. As a result, microglia become incapable of adequately responding to pathological changes in the brain, decreasing the ability to clear protein deposits^[16].

At the same time, microglia switch to a phenotype that permanently produces neurotoxic reactive oxygen species, nitric oxide, and pro-inflammatory cytokines, including IL-1 β , TNF- α , and IL-6. This response further promotes the pathological process by creating a positive feedback loop that leads to increased phosphorylation of tau protein, amyloid accumulation, and neuron death.

The persistent release of pro-inflammatory cytokines and chemokines severely impairs synaptic plasticity and leads to synaptic pruning defects, as hyperactivated microglia aberrantly target and phagocytose synapses in a complement-dependent manner.

Furthermore, microglia-induced astrogliosis leads to the transition of neighboring astrocytes into a highly neurotoxic "A1" reactive state that directly contributes to decreased neuronal and oligodendrocyte survival. As a result, whereas acute neuroinflammation serves as a protective response, chronic neuroinflammation is an important component of synaptic loss, blood-brain barrier breakdown, and rapid cognitive decline^[17].

Microglial biology in health and Alzheimer's disease

Homeostatic functions of microglia in the healthy brain

In the healthy CNS, they constitute 5–20% of all glial cells and arise from primitive yolk-sac-derived myeloid progenitors during earliest embryogenesis. In the steady state, that is, in the absence of pathological challenges, they constantly patrol the CNS parenchyma as highly motile cells with numerous thin processes, which makes them distinct from other immune cells.

They are generally nonactivated, resting cells. However, homeostatic microglia are far from being inert; they are the most active cells in the healthy brain, continuously extending and retracting their processes into and from the parenchyma.

This perpetual immune surveillance is executed by a variety of pattern-recognition receptors (PRRs) that allow a microglial cell to detect subtle deviations from the homeostatic state so as to recognize both pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) for the purpose of protecting neighboring tissue.

In addition to surveillance, homeostatic microglia contribute to the essential physiological functions that are responsible for the proper development of neuronal circuits and synapses. It is reported that microglia play an important role in the postnatal period because they "sculpt" developing circuits by the removal of specific presynaptic and postsynaptic proteins. It is necessary to remove these proteins to ensure normal synaptic activity. This activity is regulated by complement-dependent mechanisms that include C1q, C3, and complement receptor 3, as well as neuron-microglia communication through fractalkine ligand-receptor (CX3CL1/CX3CR1). The latter is important for the control of microglia activation state. Microglia are important for proper homeostasis since they can engulf apoptotic cells and cellular debris. In addition, they contribute to the proper survival and proliferation of neurons and neural progenitor cells. Microglia are important producers of neurotrophic factors. In particular, homeostatic microglia release brain-derived neurotrophic factor (BDNF), which is critical for the normal functioning of the adult brain and for supporting learning and memory.

Microglial activation states (m1/m2 and contemporary frameworks)

Historically, microglial activation in neurodegenerative diseases has been framed through a binary polarisation model adapted from peripheral macrophages, classifying microglia into either the classical pro-inflammatory (M1) or the alternative anti-inflammatory (M2) state. The M1 macrophage phenotype is induced by pro-inflammatory stimuli such as lipopolysaccharide (LPS) and interferon-gamma (IFN- γ). It exhibits an amoeboid morphology characterised by the translocation of NF- κ B into the nucleus and the production of cytotoxic substances. These substances include tumor necrosis factor- α (TNF- α), IL-1 β , IL-6, and reactive oxygen species (ROS). Macrophages with the M2 phenotype are generally activated by anti-inflammatory cytokines IL-4, IL-13, and IL-10 to

mediate neuroprotection or tissue repair and clear cellular debris by increasing Arg-1, CD206, and FIZZ1 expression. However, this dichotomous division largely overlooks the continuous spectrum of intermediate activation states often found in the pathophysiological milieu of the diseased brain. Modern approaches to microglial classification, including single-cell RNA sequencing (scRNA-seq) and single-nucleus RNA sequencing (snRNA-seq) analyses, have therefore uncovered a diverse range of transcriptionally distinct microglial subsets with complex expression profiles.

Within this classification, it is possible to distinguish several specialized microglial reactive states, driven by specific metabolic and genetic programs. For instance, Disease-Associated Microglia (DAM) represent a type of reactive microglia associated with A β plaques and characterized by a two-stage TREM2-dependent response. During the first stage, a number of homeostatic genes, including P2RY12, TMEM119, CX3CR1, are downregulated, while stage two is marked by the induction of genes coding for phagocytosis, lysosomal, and lipid metabolism, for instance, APOE, LPL, CST7, TREM2. Microglial Neurodegenerative Phenotype (MGnD) is another type of disease-associated microglia, associated with apoptotic neurons and TREM2-APOE signaling. Genes characteristic of MGnD include Clec7a, Lgals3 (Galectin-3), Gpnmb, Itgax, Ccl2^[18].

Other key specialized microglia subtypes are White Matter-Associated Microglia (WAM) (white matter aging; expressing ApoE, CD63, Clec7a, and CSF1R), Lipid Droplet-Accumulating Microglia (LDAM) (with severe impairment in phagocytosis, high levels of ROS production, and increased cytokine release), and Dark Microglia (DM) (identified by ultrastructural features of the cytoplasm and nucleus rich in electron density, associated with oxidative stress, down-regulated homeostatic receptors IBA1, CX3CR1, and P2RY12, and excessive synaptic pruning). Notably, microglia can also exhibit intermediate morphophysiological phenotypes, ranging from bipolar or rod-shaped microglia to amoeboid forms, observed predominantly during the early stages of activation. This subset demonstrates increased proliferative potential and neuroprotective activity, attributed to the production of anti-inflammatory cytokines IL-10 and TGF- β ^[10].

To translate such microglial phenotypes into therapeutic strategies, there is a need to overcome critical challenges associated with the study, including the gap between established rodent models of disease and manifestations of AD pathology in patients. Transcriptome analysis of human brains identified a human homolog of rodent DAMs termed Human AD Microglia (HAM), which demonstrated significant differences from its murine counterpart. The HAM cells demonstrated an enhanced expression of the IRF8 transcription factor following A β insult, which is

typically downregulated in the wake of peripheral nerve injury in mice.

Moreover, human AD brains exhibit altered subpopulation-specific patterns of gene expression associated with homeostatic antigen presentation (decreased CD74) and an age-related increase in senescence-associated transcripts, including CDKN2A and GIL1, and lipid droplets in microglia that express APOE4/4. Thus, immunomodulatory therapeutic strategies are being refined to converge on specific manipulations of signaling pathways, bioenergetics, or transition-state programs to reset dysfunctional homeostasis in a temporally resolved manner.

Disease-associated microglia (DAM) and transcriptional states

Homeostatic microglia express signature genes, including P2RY12, TMEM119, CX3CR1, SALL1, and TGFBR1, and possess a characteristic finely branched cell body to probe the parenchyma and ensure central nervous system (CNS) homeostasis. Under normal physiological conditions, surveilling microglia are inactive and poised to respond to any changes in the microenvironment due to a strong TGF- β receptor signalling cascade and CX3CL1–CX3CR1-dependent neuron–microglia crosstalk. Upon pathological insults, for instance, exposure to amyloid- β (A β) and tau proteins, microglia undergo two-stage dynamic functional transitions towards disease-associated microglia (DAM). The first stage, which is TREM2 independent, is linked to decreased expression of homeostatic genes, whereas the second stage entails induction of various transcripts, including TREM2, APOE, LPL, CST7, and genes associated with lipid metabolism and lysosomal function. Morphologically, microglia with upregulated DAM signatures were found as clusters ensheathing dense-core plaques of aggregated A β .

Recent advances in single-cell and single-nucleus RNA sequencing (scRNA-seq and snRNA-seq) have mapped a highly dynamic continuum of other transcriptional states that coexist during AD progression. Prominent among these is the Microglial Neurodegenerative Phenotype (MGnD), which is upregulated by apoptotic neurons via the TREM2-APOE pathway. MGnD is characterized by specific markers such as Clec7a, Lgals3 (Galectin-3), Gpnmb, Itgax, app1, Fabp5, and Ccl2. Although MGnD displays reduced responsiveness to homeostatic TGF- β signaling, it plays a protective role in the initial response to early neuronal injury. Other distinct subsets include White Matter-Associated Microglia (WAM), which are observed in aged and AD-afflicted brains. WAM express ApoE, CD63, Clec7a, TMEM119, CX3CR1, P2RY12, and CSF1R through a TREM2-dependent pathway.

As pathology progresses into end-stage AD, interferon-responsive and senescent microglia become more prevalent amongst microglia subpopulations. Compared to other microglia subsets, Interferon-Responsive Microglia exhibit upregulated expression of interferon-inducible genes, such as IFITM3, IRF7, and STAT1, leading to dysregulated antigen presentation and T cell responses that contribute to synaptic loss^[20].

Simultaneously with the changes described above, microglia exhibit features of cellular aging (senescence). This process is associated with a dystrophic phenotype, reduced motility, and accumulation of age-associated pigments, such as lipofuscin. Senescent microglia demonstrate decreased expression of homeostatic genes, reduced phagocytic capacity, and induction of an innate immune response typically associated with “inflammaging.” This proinflammatory state is mediated by the persistent activation of the NLRP3 inflammasome and upregulation of senescence-associated genes, including CDKN2A and GIL1. It is noteworthy that while most of the described microglial features have been extensively characterized in rodents, human AD microglia (HAM) exhibit considerable differences compared to their murine counterparts. For instance, upon A β treatment, human microglia display an IRF8-dependent transcriptional program that is not observed in rodent models. Moreover, in human AD brains, CD74, a gene encoding for an antigen-presenting molecule typically associated with homeostasis and inflammation, was found to be depleted from microglia in AD enriched-synapse clusters (54).

Microglia-synapse interactions and synaptic pruning

The ways microglia cells communicate with synapses are essential for maintaining normal functioning in the CNS. Specifically, there occurs synaptic pruning which is achieved through complement-dependent receptor signaling by eliminating synapses. It is well established that interactions between microglia and synapses take place throughout postnatal development and adulthood. However, there are alterations in the interactions between microglia and neurons by A β oligomers in Alzheimer’s disease (AD).

The engagement of these oligomers leads to the dysregulation of complement pathways, particularly C1q/C3 and CR3, causing aberrant synaptic pruning via microglia-mediated engulfment. There is evidence that there is a connection between increased microglia synaptic pruning and altered long-term potentiation in AD. Additionally, synaptic pruning is promoted by A β through complement activation, as shown by increased C3 protein levels around the synapses.

Furthermore, there are other receptors that control microglia synaptic connectivity, including CX3CR1–CX3CL1 and CD200–CD200R. Chronic neuroinflammation is another key contributor to synaptic loss and cognitive impairment in Alzheimer’s disease. Inflammatory cytokines, such as tumor necrosis factor- α , cause synaptic dysfunction, whereas activated microglia promote the production of neurotoxic astrocytes, which accentuate neuronal damage and the loss of synapses. Thus, it is significant to target complement signaling, microglia, and specific checkpoints that control synaptic pruning, such as TREM2 and CD33, to treat AD.

Molecular mechanisms of microglia in neurodegeneration Pattern recognition receptors (TLRs, RAGE, CD36 etc.)

Pattern Recognition Receptors (PRRs) of microglia are key innate immune sentinels for detecting the presence of misfolded protein aggregates and triggering downstream neurodegenerative cascades and pro-inflammatory transcriptional processes. Examples of sterile danger-associated molecular patterns (DAMPs) that are increased in AD brains and are recognised by toll-like receptors TLR2 and TLR4 are amyloid- β (A β) and hyperphosphorylated tau.

Specifically, TLR4 and its co-receptor CD14 engage MyD88, IRAK1 and IRAK4 to activate NF- κ B and prime the NLRP3 inflammasome, while TLR2 ligation by extracellular A β stimulates transcription of pro-inflammatory genes via NF- κ B and c-Jun N-terminal kinase (JNK) pathways. CD36-mediated endocytosis of A β leads to lysosomal destabilisation, leakage of cathepsin B and subsequent assembly of the multiprotein NLRP3 complex. The scavenger receptor CD36 cooperates with TLR4/TLR6 heterodimer to bind aggregated A β resulting in nuclear translocation of NF- κ B. Additionally, the Receptor for Advanced Glycation Endproducts (RAGE) is a high affinity cell-surface receptor for both soluble and oligomeric A β . Microglial RAGE ligation induces sustained glutamate release, nitric oxide (NO) production, and NF- κ B-driven cytokine amplification, all of which directly mediate progressive blood-brain barrier (BBB) degradation, persistent excitotoxicity, and neuronal damage.

The complement system and synapse elimination

In physiologically normal conditions, resident microglia actively shape postnatal neural circuits and potentiate mature neuronal networks through activity-dependent synaptic pruning. In this developmental process of opsonisation, the complement cascade regulates opsonisation or “tagging” of inappropriate, redundant or immature synapses by complement proteins C1q and C3. Microglia then use the complement receptor 3 (CR3) pathway to specifically tag, phagocytise and remove these tagged synapses.

In the AD brain, this highly coordinated process aberrantly reactivates; soluble A β oligomers bind to synaptic density and work in concert with complement proteins C1q and C3 to mark viable, functional synapses for excessive and inappropriate removal by phagocytic microglia. This complement-dependent misdirected synaptic tagging and pruning leads to profound disruption of long term potentiation (LTP) and neural network activity and is the main cause of early cognitive impairments and hippocampal synaptic loss.

Importantly, genetic deletion or knockdown of complement factors C1q or C3 in AD mice models protects against progressive cognitive decline and spatial memory deficits, and maintains dendritic spine shape and rescues synaptic connections [21].

Cytokine and chemokine signaling (IL-1 β , TNF- α , IL-6, etc.)

In AD, further release of pro-inflammatory cytokines and chemokines from microglia maintains chronic neuroinflammation,

which directly affects neuronal survival and synaptic plasticity. Assembly of the NLRP3 inflammasome leads to the recruitment of the adaptor ASC and the effector pro-caspase-1 that mediate the maturation and secretion of IL-1 β (IL-1 β) and IL-18. Mature IL-1 β binds to neuronal IL-1 receptors and activates intracellular kinases such as p38 MAPK, GSK-3 β , and CDK5, which are actively involved in tau hyperphosphorylation, microtubule collapse and the formation of neurofibrillary tangles (NFTs). Similarly, tumor necrosis factor- α (TNF- α), which is present at much higher concentrations in the serum and CSF of AD patients, inhibits long-term potentiation (LTP) at hippocampal glutamatergic synapses and enhances BACE1 expression, favoring the deposition of A β plaques. TNF- α also cooperates with JNK and NF- κ B pathways to induce expression of inducible nitric oxide synthase (iNOS) resulting in neurotoxic reactive nitrogen species (RNS) and neuronal apoptosis.

IL-6 classical and trans-signalling cascades can boost tau hyperphosphorylation through CDK5 pathways, but IL-6 also has context-dependent roles, e.g., causing massive reactive gliosis that can limit A β deposition under specific circumstances. These signaling events are potentiated by upregulation of chemokines (such as CCL2, CCR3 and CCR5) orchestrating local inflammatory niches and recruiting peripheral immune cells ^[22].

Crosstalk with astrocytes and neurons

In AD, the progression of neurodegeneration is driven by complex, bidirectional crosstalk between microglia, astrocytes and neighboring neurons. A triad of pro-inflammatory mediators, namely TNF- α , IL-1 β and complement component C1q, are secreted by hyperactive microglia and act in concert to induce neighboring quiescent astrocytes to adopt a highly neurotoxic, reactive “A1” phenotype.

These reactive A1 astrocytes lose their homeostatic functions, such as regulation of synaptogenesis and trophic support, and instead secrete neurotoxic factors that actively induce death of neurons and oligodendrocytes. Conversely, homeostatic communication between neurons and microglia is mediated by inhibitory checkpoints including neuronal fractalkine (CX3CL1) binding to microglial CX3CR1 and CD200 binding to CD200R, which maintain microglia in a surveying, non-neurotoxic state.

Disruption of such homeostatic pathways (e.g. CX3CR1 deletion) results in microglial hyperreactivity, excessive synaptic pruning and tau hyperphosphorylation at an accelerated rate. In addition, microglia-derived sTREM2 can interact with neuronal transgelin-2 (TG2), inactivating the RhoA-Rock-GSK3 β pathway and providing protection from tau pathology. Injured or degenerating neurons release intracellular danger signals including adenosine triphosphate (ATP), a powerful chemotactic ligand that stimulates microglial purinergic P2X7 and P2Y12 receptors to promote directional microglial migration, MyD88/NF- κ B-dependent cytokine secretion, and NLRP3 inflammasome

formation, thereby trapping the brain parenchyma in a destructive neurodegenerative feedback cycle.

The NLRP3 inflammasome in Alzheimer's disease Structure and activation mechanisms of NLRP3

The NOD-, LRR- and pyrin domain containing protein 3 (NLRP3) is a 118 kDa cytosolic pattern recognition receptor (PRR) protein which consists of three distinct functional segments: A C-terminal leucine-rich repeat (LRR) domain, a central ATPase containing NACHT domain that regulates oligomerization and an N-terminal pyrin (PYD) domain responsible for recruiting downstream adapters. In its inactive, auto-inhibited state, ADP is bound to the nucleotide-binding domain (NBD) of the NACHT region and the protein adopts a closed, cage-like, double-ring structure with 10 protomers in humans or 12 to 16 protomers in mice.

The canonical activation of the NLRP3 inflammasome is a tightly controlled two-step biological process characterized by a priming and an activation signal. The priming step (Signal 1) is triggered by the recognition of extracellular DAMPs or PAMPs by cell-surface TLRs or cytokine receptors, leading to the activation of MyD88-dependent transcription factors that upregulate the transcription of NLRP3, IL1B, and IL18 genes. Concurrently, non-transcriptional priming allows for NLRP3 activation through post-translational modifications (PTMs) including phosphorylation and deubiquitination.

Signal 2 or activation occurs when a secondary homeostatic stress signal (e.g. ion fluxes, mitochondrial injury or lysosomal rupture) promotes the exchange of ADP for ATP at the Walker motifs of the NACHT domain. This conformational change to an open, disc-like conformation allows for direct binding of NIMA-related kinase 7 (NEK7) to NACHT and LRR domains. The active NEK7-NLRP3 complex exposes the pyrin domain of the adapter protein apoptosis-associated speck-like protein containing a CARD (ASC) that polymerises in a prion-like fashion to form a large, macromolecular assembly known as the ASC speck, which initiates homotypic PYD-PYD interactions ^[23].

Evidence of NLRP3 activation in AD models and patient tissue

There is a large body of preclinical and clinical data directly linking aberrant activation of the microglial NLRP3 inflammasome in the brain parenchyma in Alzheimer's disease (AD). Post-mortem cortical and hippocampus tissues from AD patients had significantly higher levels of cleaved caspase-1, active interleukin-1 β (IL-1 β), mature IL-18, cleaved gasdermin D (GSDMD) and assembled ASC specks than age-matched, non-demented controls. Additionally, circulating peripheral blood monocytes of AD and mild cognitive impairment (MCI) patients are transcriptomically primed and hyperresponsive to secondary NLRP3-activating stimuli, while cerebrospinal fluid (CSF) from patients exhibits strikingly increased levels of IL-1 β and GSDMD.

In the transgenic mouse models of AD, such as APP/PS1 and 5xFAD lines, the assembly of NLRP3 inflammasome complexes directly mirrors the temporal appearance of early amyloid- β (A β) deposition. Importantly, genetic deletion or knockdown of Nlrp3 or Casp1 in APP/PS1 mice restores spatial memory impairments, maintains hippocampus long-term potentiation (LTP) and reduces neuroinflammation.

Additionally, this genetic ablation causes microglia to shift from a pro-inflammatory classical state to an anti-inflammatory, neuroprotective "M2" phenotype, which greatly increases microglial phagocytosis and the removal of parenchymal A β plaques [24].

Downstream effectors: caspase-1, il-1 β , il-18, and pyroptosis

The ASC speck functions as a highly concentrated molecular platform that attracts pro-caspase-1 via homotypic CARD–CARD domain interactions once the NLRP3 inflammasome is fully assembled. Pro-caspase-1 is forced into its active, enzymatically functional form by proximity-induced dimerization and autolytic cleavage due to structural clustering. The major protease that cleaves the inactive cytoplasmic precursors pro-IL-1 β and pro-IL-18 into mature, physiologically active cytokines is active caspase-1. At the same time, the pyroptotic substrate gasdermin D (GSDMD) is cleaved by active caspase-1, which separates its autoinhibitory C-terminal domain and releases the active N-terminal fragment (GSDMD-NT).

The release of mature IL-1 β and IL-18 by GSDMD-NT is facilitated by rapid translocation and embedding into the inner leaflet of plasma membrane where it oligomerizes to form symmetrical, membrane-disrupting holes. Cell swelling, membrane rupture, and pyroptosis—a highly inflammatory programmed cell death pathway—are caused by the gradual growth in GSDMD membrane holes, which modifies cellular osmotic potential. Importantly, huge, insoluble ASC specks are released into the extracellular space by the pyroptotic lysis of microglia. These persistent extracellular ASC specks have an exceptionally high binding affinity for A β peptides, acting as physical “seeds” or nucleation platforms that cross-seed A β oligomerisation and accelerate the formation of thick, deadly amyloid plaques.

NLRP3 as a hub integrating amyloid, tau, and metabolic stress signals

The NLRP3 inflammasome constitutes a major pathogenic hub, linking intracellular aggregation, cellular metabolic stress and biochemical assaults from exogenous proteinopathies. While the endocytosis of A β fibrils destabilizes microglial lysosomes, resulting in membrane rupture and the leakage of active cathepsin B into the cytosol, soluble and fibrillar species of A β prime and activate the inflammasome through cell-surface multi-receptor complexes consisting of CD36, TLR4, and TLR6, which trigger MyD88/NF- κ B-dependent transcriptional upregulation. Tau pathology is directly linked to this A β -induced inflammasome

activation; extracellular IL-1 β derived from NLRP3 binds to neuronal IL-1R1 receptors, activating intracellular kinases like p38 MAPK, glycogen synthase kinase-3 β (GSK-3 β), and cyclin-dependent kinase 5 (CDK5) that hyperphosphorylate tau, causing it to separate from microtubules and self-assemble into neurofibrillary tangles (NFTs). After neuronal death, these intracellular tau clumps are reciprocally identified by microglial receptors, which triggers further lysosomal cathepsin B leakage and NF- κ B priming to intensify the chronic inflammatory cycle. Microglial metabolic reprogramming and mitochondrial stress further speed up this proteopathic feedback loop.

Microglia experience a metabolic transition from oxidative phosphorylation to glycolysis under A β -mediated pathogenic stress, which lowers ATP generation and directly promotes NLRP3 complex assembly. While extracellular ATP released from degenerating neurons engages microglial purinergic P2X7 receptors to drive rapid K⁺ efflux and VRAC-mediated Cl[−] efflux, completing the activation cascade, soluble A β oligomers disrupt mitochondrial respiration, producing excessive reactive oxygen species (ROS) and causing the cytosolic leakage of oxidized mitochondrial DNA (mtDNA), which directly binds the NLRP3 LRR domain to initiate oligomerization [25].

CONCLUSION

Current research recognizes Alzheimer's disease as a multi-faceted condition where amyloid- β accumulation, tauopathy, microglial dysregulation and neuroinflammation are mutually connected through all stages of its development. The data mentioned above demonstrates the ability of microglia to possess either protective or damaging functions according to the particular stage and inflammatory environment of AD. At early disease stages, microglia may be helpful to clear abnormal proteins and preserve tissue homeostasis; however, their excessive activation may lead to reduction of phagocytosis, excessive synaptic elimination, secretion of pro-inflammatory substances and finally – neuron injury. The cooperation of microglia, astrocytes, neurons and peripherally induced inflammation enhances these processes.

The activity of NLRP3 inflammasome appears to be a key factor of this network of interactions. A β and tau-induced stress conditions, lysosomal damage, mitochondria dysfunction and changes in metabolic signaling pathways activate NLRP3, followed by recruitment of ASC into a complex, activation of caspase-1, secretion of mature cytokines and initiation of pyroptosis by gasdermin D. These steps appear to amplify protein misfolding and Neuroinflammation, providing a self-propelling loop of neuronal damage. Therefore, selective regulation of the NLRP3 inflammasome and associated inflammatory pathways is a promising therapeutic target.

Nevertheless, modulating neuroinflammation cannot be regarded as blocking microglial activation, since microglia are responsible for certain physiological functions in the brain. Thus,

future therapy must focus on restoration of microglia functions rather than complete immune response inhibition. The difficulties associated with such therapy are related to insufficient drug delivery to the brain due to the blood-brain barrier, long-term safety, determination of proper treatment time and transition of results obtained in animal models to humans. Combination treatment directed both at protein aggregation and inflammation inhibition might be especially effective. Further research of selective NLRP3 inhibitors, microglial regulation, biomarkers and drug delivery systems appears to help develop disease-modifying strategies for Alzheimer's disease.

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