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REVIEW

Inflammatory aspects of Alzheimer's disease

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Abstract

Alzheimer´s disease (AD) stands out as the most common chronic neurodegenerative disorder. AD is characterized by progressive cognitive decline and memory loss, with neurodegeneration as its primary pathological feature. The role of neuroinflammation in the disease course has become a focus of intense research. While microglia, the brain's resident macrophages, have been pivotal to study central immune inflammation, recent evidence underscores the contributions of other cellular entities to the neuroinflammatory process. In this article, we review the inflammatory role of microglia and astrocytes, focusing on their interactions with AD's core pathologies, amyloid beta deposition, and tau tangle formation. Additionally, we also discuss how different modes of regulated cell death in AD may impact the chronic neuroinflammatory environment. This review aims to highlight the evolving landscape of neuroinflammatory research in AD and underscores the importance of considering multiple cellular contributors when developing new therapeutic strategies.

Keywords Innate immunity · Activation · Cytokine · Immune mediator · Neurodegeneration · Neuroinflammation · Alzheimer's disease

Abbreviations

ACT	Antichymotrypsin
AD	Alzheimer disease
Aβ	Amyloid-β
APOE	Apolipoprotein E
ApoJ/Clusterin	Apolipoprotein J
ALS	Amyotrophic lateral sclerosis
ASC	Apoptosis-associated Speck-like protein containing a CARD
APP	Amyloid precursor protein
BAMs	Border-associated macrophages
BBB	Blood–brain barrier
Bcl	B-cell lymphoma
BECs	Brain endothelial cells
C	Complement component
C1q	Subcomponent q
CCL	C–C motif chemokine ligand
CD40L	CD40 ligand
CDK	Cyclin-dependent kinase
CNS	Central nervous system
CN	Calcineurin
COX	Cyclooxygenase
DAMPs	Damage-associated molecular patterns
EOAD	Early onset familial alzheimer disease
FERMT	Fermitin family homolog
GFAP	Glial fibrillary acidic protein
GMF	Glia maturation factor
GBP	Guanylate binding protein
GSK	Glycogen synthase kinase
GWAS	Genome-wide association studies
HSPs	Heat shock proteins
HSPGs	Heparan sulfate proteoglycans
HMGB	High mobility group box
ICAM-1	Intercellular adhesion molecule 1
IDE	Insulin-degrading enzyme
IFN	Interferon
IL	Interleukin
iPS	Induced pluripotent stem
JAK	Janus kinase
MAPK	Mitogen-activated protein kinase
MMP9	Matrix metalloprotease 9
MLKL	Mixed lineage kinase domain-like
MMP	Matrix metalloproteinase

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NADPH	Nicotinamide adenine dinucleotide phosphate
NDDs	Neurodegenerative diseases
NEP	Neprylisin
NFAT	Nuclear factor of activated T cells
NFκB	Nuclear factor-κB
NLRs	Nucleotide-binding oligomerization domain-like receptors
NFTs	Neurofibrillary tangles
NO	Nitric oxide
NOS	Nitric oxide synthase
NOD	Nucleotide-binding oligomerization domain
PAR	Protease-activated receptors
PAMPs	Pathogen-associated molecular patterns
PD	Parkinson's disease
PDGFRβ	Platelet-derived growth factor receptor β
PG	Prostaglandin
PKs	Protein kinases
PFFs	Preformed fibrils
PRRs	Pattern recognition receptors
PSEN	Presenilin
PVMs	Perivascular macrophages
RIPK	Receptor-interactive protein kinases
RAGE	Receptor for advanced glycation end products
RB	Retinoblastoma
ROS	Reactive oxygen species
RNS	Reactive nitrogen species
RCD	Regulated cell death
SAM	Senescent-associated microglia
SASP	Senescence-associated secretory phenotype
SAHF	Senescence-associated heterochromatin foci
SORL	Sortilin-related receptor
SP	Substance P
STAT	Signal transducer and activator of transcription
SRs	Scavenger receptors
TNTs	Tunnelling nanotubes
TNF	Tumor necrosis factor
TRAIL	TNF-related apoptosis-inducing ligand
TREM	Triggering receptor expressed on myeloid cells
TGF	Transforming growth factor
TLRs	Toll-like receptors
VEGF	Vascular endothelial growth factor

Alzheimer's disease and neurodegeneration

Aging is a global phenomenon, with projections indicating that by 2050, 16% of the world's population will be aged 65 or older, compared to 9% in 2019 [235]. This demographic shift poses a significant challenge, as aging is a major risk factor for dementia, imposing an estimated economic cost exceeding 2.8 trillion dollars. Alzheimer's disease (AD) is the most prevalent form of dementia affecting 50 million people at present. AD cases are expected to double every 20 years [26, 163]

AD patients experience progressive cognitive decline, notably in episodic memory and executive functions, leading to interference with their daily activities. This cognitive impairment manifests as short-term memory deterioration, visuospatial processing issues, executive problems, and expressive speech difficulties. Together, this results in a growing burden on patients, caregivers, and families, impacting patients and relatives independence [118]. Despite extensive efforts, current treatments for AD are mainly symptomatic with limited efficacy, stressing the urgent development of therapies capable of halting the pathogenic process [110, 146]. Alois Alzheimer first reported AD in 1906 based on the examination of a single patient's brain, identifying key neuropathological features including deposition of so-called senile plaques composed of extracellular amyloid-β (Aβ) peptide aggregates and the formation of intraneuronal neurofibrillary tangles (NFTs) consisting mainly of hyperphosphorylated tau protein [5, 6]. He also depicted and described a massive glial reaction; however, it took several decades until the role of immune processes, such as microglial and astroglial reactivity, have become a major focus of research [92].

The predominant hypothesis for AD pathogenesis is the amyloid cascade hypothesis, proposed by Hardy and Higgins (1992) and supported by Selkoe and Hardy (2002) and others subsequently. Mutations in the amyloid precursor protein (APP), Presenilin-1 (PSEN1), and Presenilin-2 (PSEN2) genes, associated with early onset familial AD (EOAD), cause AD in individuals as young as their 30s and 40s [88, 89]. EOAD mutations in APP and PS1/2 alter Aβ biogenesis, resulting in an altered formation of amyloidogenic Aβ peptides [43, 52, 91, 152, 172, 240, 249]. In EOAD, symptoms follow the development of Aβ pathology by up to a decade, marked by the aggregation and deposition of Aβ peptides [13, 89, 104, 105]. This hypothesis suggests that accumulating Aβ peptides initiate a cascade of pathological events involving neuroinflammation, synaptic loss, tau pathology, and neuronal loss, leading to progressive symptoms, cerebral atrophy, and ultimately death.

Neurodegenerative diseases (NDDs), including AD, can be distinctively identified by characteristics such as

brain region susceptibility or protein aggregate composition [70]. Interestingly, they also share important commonalities like pathological protein aggregation, synaptic and neuronal network dysfunction, aberrant proteostasis, cytoskeletal abnormalities, altered energy metabolism, DNA and RNA defects, inflammation, and neuronal cell death [257]. These commonalities do not arise from a single dominant molecular pathway. Instead, the neurodegenerative process seems to result from the synergistic action of various interrelated mechanisms including abnormal protein dynamics, increased production of reactive oxygen species (ROS), defective autophagy, mitochondrial dysfunctions, impairment of axonal transport, and, notably, neuroinflammation [106].

Characterized by the activation of microglia and astrocytes, neuroinflammation has garnered attention in recent years due to the early presence in the disease course, even before histopathological and pathological features of degeneration can be detected, representing an attractive therapeutic approach [92, 93, 257]. This immune activation was detected in close proximity to areas of neuronal damage and degeneration, leading to the obvious yet simplistic conclusion that it was a consequence of neuronal death. Now, a growing body of evidence challenge this assumption, demonstrating that neuroinflammation may also play an active role in the disease. (1) In many NDDs, signs of neuroinflammation are often detected prior to the appearance of neurodegenerative biomarkers and clinical symptoms [63], suggesting a driving role for disease pathogenesis rather than a pure bystander reaction [124]. (2) This view is further supported by the correlation between inflammatory markers, such as soluble TREM2 (sTREM2), YKL-40 or glial fibrillary acidic protein (GFAP), and disease severity [46, 47, 97]. (3) Genome-wide association studies (GWAS) and next-generation sequencing approaches have identified over 80 independent genetic loci modulating the risk of AD. Notably, many of these risk loci are located in genes that encode for proteins which form integral parts of microglia key signaling pathways including immunoreceptors (TREM2, SPI1, CD33) [250], agonistic ligands (IL34 and APOE) or effector mechanisms (ABI3 and EPHA1), suggesting a connection of inflammation to disease pathogenesis [16, 120, 168]. (4) Furthermore, preclinical in vivo models of extracellular Aβ accumulation or intraneuronal formation of NFTs show widespread innate immune activation that correlates with neuropathology. In keeping with this, inflammation-targeting genetic modifications greatly impact disease outcome in rodent models of neurodegenerative disease in general [21, 261] and AD in particular [94, 258]. (5) Persistent activation of CNS glial cells, such as microglia and astrocytes, results in elevated levels of inflammatory cytokines (IL-1β, TNFα, and IL-6) for prolonged periods of time. This, in turn, prompts the upregulation of matrix metalloprotease 9 (MMP9) in brain endothelial cells (BECs). MMP9 targets components of the endothelial basal layer and tight junctions (TJs), thereby possibly affecting blood–brain barrier (BBB) integrity [18, 262]. (6) Neurons exposed to microglia-derived pro-inflammatory cytokines, such as IL-1β, IL-2, IL-6, or TNFα, show enhanced spine loss and reduced hippocampal long-term potentiation (LTP) [48, 161]. (7) Epidemiological data suggest that individuals with chronic inflammatory conditions are at a higher risk of developing neurodegenerative diseases [72, 199, 227]. Taken together, current evidence strongly supports the idea that neuroinflammation represents an influential player able to contribute to the progression of pathological processes.

The intricate interplay between neuroinflammation and neurodegeneration emerges as a future target for therapeutics. Interrupting the mutual interaction between both components may be exceedingly complex; but offer the opportunity to develop effective therapies. This undertaking, however, requires a deep understanding of all the implicated players in the brain and the periphery. In this review, we aim to highlight the inflammatory contribution to AD neurodegenerative process throughout the lens of the different major cells types involved, including microglia, astrocytes, and neurons, but also others, such as T cells, oligodendrocytes, pericytes, and border-associated macrophages.

The neuroinflammatory disease component

Inflammation is an evolutionarily conserved process involving the activation of both immune and non-immune cells. This response protects the host from bacteria, viruses, toxins, and infections by eliminating pathogens and facilitating tissue repair and recovery [30]. Neuroinflammation refers to the inflammatory process in the CNS in response to injury, infection, mental illness, ROS and RNS, redox iron, and different oligomers of τ- and β-amyloid [75]. Despite the negative connotations, inflammation per se is neither harmful nor maladaptive, but a survival response aimed to reinstate the cellular homeostasis upon an inflammatory challenge. This response usually includes four different components: inflammatory triggers, sensors, inflammatory mediators, and the affected tissues [153]. In classical NDDs, such as AD, Parkinson's disease (PD), or amyotrophic lateral sclerosis (ALS), the neuroinflammatory process translates into increased reactivity of glia cells, like astrocytes and microglia, together with the elevated production and release of pro-inflammatory molecules.

Besides Aβ plaques and intracellular NFTs, neuroinflammation has been identified as the third core feature in AD pathogenesis [92, 129] that may serve a link between the pathologies [78, 225, 268]. The old prevailing belief of "immune privilege" excluded the capacity of brain cells to initiate an immune response [36, 207]. Evidence

demonstrated that the brain indeed is not privileged, but rather specialized [28, 138]. By now, multiple lines of research have established the presence of reactive microglia in AD brains as well as its unequivocal interaction with amyloid plaques and NFTs, both AD pathological hallmarks. Likewise, biomarker studies have widely demonstrated that this reactive phenotype results in increased levels of immune mediators, such as cytokines, chemokines, inflammasomes, and ROS [27, 37]. Latter publications have not only validated the profound immune alterations under AD conditions but have also confirmed the implication of other cellular entities, such as astrocytes, oligodendrocytes, and even neurons, in the inflammatory equation [84, 179]. While in the early phase of the pathogenic process, tissue repair and control of the inflammatory response is attempted through the release of anti-inflammatory interleukins like IL-10, IL-4, IL-13, and transforming growth factor β, later stages are characterized by chronic inflammation in which microglia switches to an activated phenotype, releasing ROS, NO, and producing pro-inflammatory cytokines, including IL-1β, IL-6, IL-12, IL-23, and TNF-α [40].

Naturally, evolution has provided "protein quality control systems" to maintain the proteostasis. Mechanisms, such as proteasome degradation, autophagy or the unfolded protein response, and specialized proteins such as chaperones or heat shock proteins (HSPs), work together serving that purpose. In AD, Aβ dyshomeostasis may arise from an imbalance between Aβ neuronal production and extracellular clearance of Aβ [89, 202]. As this imbalance persists over time, it leads to the accumulation of Aβ deposits, marking a critical transition from a state of balanced proteostasis to one of pathological aggregation. These toxic Aβ aggregates are detected as danger or pathogen associated molecular patterns (DAMPs/PAMPs) by a group of receptors collectively known as pattern recognition receptors (PRRs) [23]. PRRs comprise a number of different surface receptors which can sense bacterial or viral products, neurodegenerative proteins, DNA, and neuronal debris [276]. Aβ activates microglia through multiple receptors including the receptor for advanced glycation end products (RAGE), nucleotide-binding oligomerization domain-like receptors (NLRs), or Toll-like receptors (TLRs) [125]. Microglial Aβ phagocytosis can take place via CD36, involving the formation of a TLR2–TLR6 heterodimer and subsequent NFKB activation [221]. Additionally, it can occur through CD14, which acts as a coreceptor for TLR4, TLR6, TLR9, α6β1 integrin, and SCARAq [66, 136, 247]. PRRs ligation triggers different inflammatory signaling cascades leading to the production and release of inflammatory mediators, such as complement factors, cytokines IL-1β, IL-6, IL-18, and TNF-α, chemokines such as C–C and C-X-C motif chemokine ligand 1 (CCL1, CXCL1), CCL5, small-molecule messengers, prostaglandins, nitric oxide (NO), and ROS [57, 92, 95].

NFTs, AD's other core pathology, are made of hyperphosphorylated tau protein [4, 101]. Under normal physiological conditions, tau plays important roles in a wide range of biological processes spanning from control of microtubule dynamics and stability, to glucose metabolism, and extending to phenomena such as hibernation [8, 58, 145]. Tau protein undergoes multiple posttranslational modifications (PTMs), among them phosphorylation, glycation, ubiquitination, or truncation [265], which critically contribute to tau proteostasis, dysfunction, and aggregation. In AD, multiple protein kinases (PKs) are known to phosphorylate tau at nearly 40 AD-relevant epitopes. Glycogen synthase kinase (GSK-3β) and cyclin-dependent kinase (CDK5) are the two most studied kinases involved in tau hyperphosphorylation, while PP2A is the main phosphatase related with tau dephosphorylation [12]. When hyperphosphorylated, tau reduces its affinity for microtubules, detaches, and aggregates in the neuronal cytoplasm and extracellular spaces, later propagating through the brain in a prion-like manner [160]. Accumulation of toxic tau forms is considered to lead to impairment of intraneuronal processes, specifically protein degradation, energy metabolism, membrane integrity, intracellular transport, and signal transmission [165]. Pathological tau not only disrupts microtubule stability but also instigates an immune response. Interestingly, NLRP3 inflammasome, one of the most important immune pathways in microglia, can also be activated by tau, and indeed, elevated levels can be found in brain tissue and CSF of tauopathy cases [107]. In line, NLRP3 loss of function leads to reduced tau hyperphosphorylation and aggregation by regulating tau kinases and phosphatases [102].

Reactive microglia is observed in the vicinity of NFTs [56] and tau internalization by microglia has been demonstrated in vitro and in vivo [22], but the underlying mechanisms are still elusive [273]. Likewise, microglia implication in tau pathology and propagation has been extensively demonstrated in multiple tau-transgenic mouse lines. Virginia Lee's group observed that treatment of P301S Tg mice with FK506 immunosuppressant inhibited microglial activation and attenuated tau pathology [266]. Also, in another study, microglia depletion through two independent approaches (PLX3397&CSF1R) in two independent tauopathy models significantly suppressed the propagation of tau measured by AT8 + [9]. The activation of microglia and the subsequent propagation of tau pathology could potentially be driven by the joint action of several agents like pro-inflammatory cytokines (IL-1β) [117], transcription factors (NF-κB) [248], and signaling pathways (CX3CL1/CX3CR1) [19]. Taken together, these studies demonstrate that tau can serve as DAMP, activating microglia, and triggering and immune response.

Here, we offer a comprehensive review of the inflammatory processes that contribute to the neurodegenerative

progression in AD from a cellular perspective. Our focus centers on the principal cellular contributors, notably microglia, astrocytes, and neurons, while also examining the intricate interactions among them. Specifically, we delve into the inflammatory response of microglia and astrocytes within the context of AD's core pathologies, amyloid, and tau pathology. Additionally, we explore the inflammatory contribution of neurons, considering the various modes of programmed cell death, as well as other cells types, including T cells, oligodendrocytes, pericytes, and border-associated macrophages. This cellular-centric approach aims to provide deeper insights into the complex interplay between neuroinflammation and the neurodegenerative process in AD.

Microglia

Microglia are the resident macrophages and represent the major component of the innate immune system of the CNS. They are unique in their origin, deriving from embryonic yolk sac precursors, similar to perivascular, meningeal, and retinal macrophages [79, 180]. Before the formation of the BBB, myeloid progenitor cells migrate to the neuroepithelium, proliferate, and spread throughout the CNS, where they differentiate into microglia [254]. They account for 0.5–16.6% [156] of the total number of cells in the human brain and slowly renew at a yearly median rate of 28% [184]. Microglia are highly dynamic cells whose states depend on their location and neighboring entities, translating into epigenomic, transcriptomic, proteomic, metabolomic, and functional changes. The combination of single-cell multiomics technologies and protein expression analysis has allowed the identification of multiple of these states such as disease-associated microglia (DAMs), interferon response microglia (IRM), antigen-presenting response (HLA), or ribosomal microglia (RM), among others [142, 179, 245]. Importantly, evidence suggest that these states are fluid and highly context dependent [223]. Microglia play an essential role maintaining brain homeostasis. They provide neurotrophic factors, scale, and prune synapses, thereby contributing to neuronal plasticity. Further, they engulf and degrade excess metabolic byproducts and damaged tissues, promote development and myelination of oligodendrocytes, and perform fundamental housekeeping functions [32]. These functions are tightly regulated by genes encoding chemokine and chemoattractant receptors, phagocytosis, and synaptic pruning and remodeling.

In basal physiological conditions, homeostatic microglia are highly motile by nature, with multiple ramifications that constantly extend and retract, enabling active surveillance of their immediate microenvironment [166]. In AD, Aβ accumulation induces a sustained microglia activation, leading to a continuous release of inflammatory elements that impair their phagocytic and degrative capacities. This aggravates Aβ accumulation, promoting tau propagation, and leading to neuronal death in vivo and in vitro [173, 220], ultimately advancing the progression of the disease [98, 154]. This central role of microglia in AD pathogenesis has been extensively demonstrated from different angles. Genome-wide association studies (GWAS) have shown that mutations in key microglia genes, such as TREM2, dramatically increase AD risk [222]. Furthermore, Aβ clearance seems to be impaired not only in late but early onset forms of AD [149, 178], and its regulation and effectiveness may depend on factors such as age or stage of the disease [122]. In line, mouse models of Aβ deposition have repeatedly shown impaired microglia phagocytic capacity [98, 201, 255]. Finally, in vitro experiments have robustly demonstrated that exposure of microglia cultures to Aβ leads to the production of neurotoxic ROS and RNS, NLRP3 (NOD-, LRR-, and pyrin domain-containing protein 3) inflammasome activation [69], and production of pro-inflammatory cytokines, such as pro-IL-1β, IL-6, or TNF-α [134, 140, 246].

Ineffective microglia clearance of Aβ leads to the sustained release of the pro-inflammatory mediators mentioned above. Over time, this inflammatory activation turns into a chronic, deleterious process. This unbridled microglia activity not only creates a pro-neurodegenerative environment but also promotes the initial Aβ pathology. Different Aβ species can trigger microglia activation through a wide variety of cell receptors, such as CD40, CD36/TLR4/6, CD33, TREM2, and RAGE [61, 221]. CD40 and CD36/TLR4/6 activate the nuclear factor-κB (NFκB) transcription factor, resulting in the expression of auto-inhibited NLRP3, as well as the release of ROS/NOS [17, 204]. Internalized Aβ damages mitochondria and lysosomes, causing the release of ROS and Cathepsin B (CatB). CatB in turn serves as the triggering signal for NLRP3 inflammasome formation [41]. After NLRP3 activation, the adaptor protein known as apoptosis-associated speck-like protein containing a CARD (ASC) is mobilized to assemble ASC helical fibrils specks. ASC recruits procaspase-1, followed by cleavage and activation of caspase-1 through induced proximity autocatalysis [139]. Active caspase-1 cleaves Gasdermin D (GSDMD) which releases its N-terminal domain (NT-GSDMD) to form membrane pores. Lytic cell death, or pyroptosis, occurs when the extent of pore formation exceeds the cell's capacity to repair its membrane [137]. Upon cell membrane rupture, intracellular content gets released including recently formed ASC specks as well as inflammatory cytokines such as IL-1β and IL-18 [183]. Released extracellular ASC specks not only propagate inflammation to surrounding cells [68] but bind Aβ acting like "seeds", accelerating the ongoing amyloidogenic process [69, 239] (Fig. 1). In line, microglia depletion in experimental models of AD has shown numerous benefits including reduction of both intraneuronal amyloid as well as neuritic plaque deposition [215], neuronal loss, and mitigation of neuritic dystrophy [143, 216].

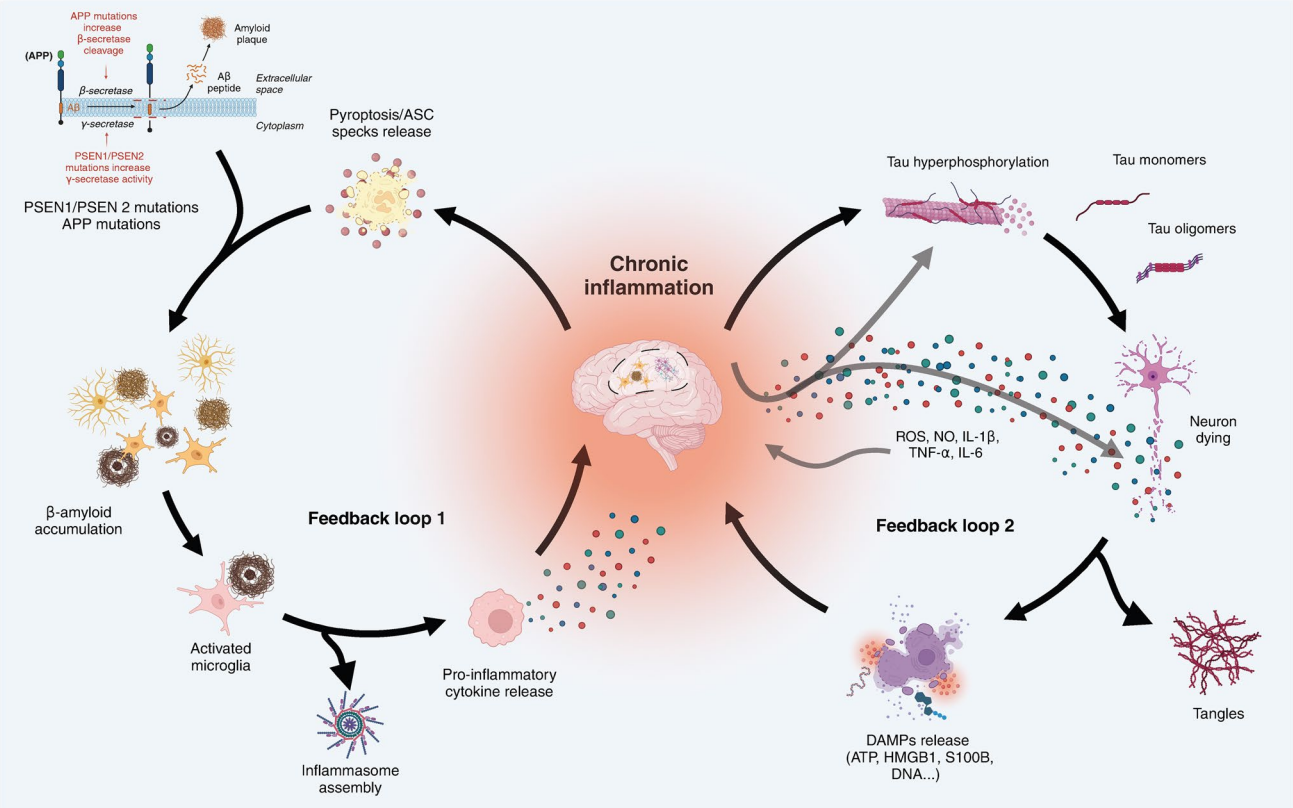

Fig. 1 Microglia-mediated inflammation in AD. In the earliest stages of AD, the abnormal cleavage of APP by β- and γ-secretases leads to the formation of Aβ. Aβ monomers are inherently disordered and tend to aggregate into plaques, a process further promoted by genetic mutations in APP or PSEN1/PSEN2 genes. These Aβ aggregates activate microglia, which initially attempt to clear Aβ through phagocytosis and proteolysis. Upon failure, microglia become persistently activated, leading to Inflammasome activation and the release of pro-inflammatory components. This process culminates with the membrane rupture and release of the intracellular contents through pyroptosis. The release of ASC specks will further promote Aβ aggregation, closing the first inflammatory loop. Activated microglia in a chronic state release inflammatory cytokines along with detrimental substances like reactive ROS and NO, heightening the immune response and contributing to neuronal damage. Moreover, the release of DMAPs from dying neurons, including ATP, HMGB1, S100B, and DNA, exacerbates inflammation, creating a reinforcing loop. This inflammatory environment leads to the excessive phosphorylation of tau protein, its detachment from microtubules, and subsequent formation of tau tangles within neurons. Hence, inflammation acts as a pivotal intermediary linking Aβ aggregation to the accumulation of tau tangles in AD pathology. (Figure created using BioRender.com)

Interestingly, tau pathology is also amplified by these same Aβ-induced cytokines, with tau kinases like CDK5, GSK-3β, and p38-Mitogen-activated protein kinase (MAPK), increasing their activity, and, consequently, tau hyperphosphorylation [59]. Increased hyperphosphorylation is associated with microtubule disruption and tau polymerization into filaments and NFTs [4]. Moreover, tau monomers and oligomers also operate as DAMPs, resulting in NRLP3-ASC activation [102]. In parallel to this inflammatory cascade of events, microglia serve as a mobile carrier for the propagation of protein aggregates with several mechanisms proposed, including heparan sulfate proteoglycans (HSPGs)-mediated endocytosis, exosome fusion, receptor-mediated endocytosis, phagocytosis, and, more recently, tunneling nanotubes (TNTs) [38, 237]. Astrocytes are also indirectly affected by activated microglia. Through the release of IL-1α, TNF and complement component 1 (C1), subcomponent q (C1q) by microglia, astrocytes transition into the A1 astrocytic state where basic functions such promotion of neuronal survival, outgrowth, synaptogenesis, and phagocytosis get compromised, further contributing to the ongoing neurodegenerative process [132]. In a similar manner, the TNF-Signal Transducer and Activator of Transcription 3 (STAT3)-α1-antichymotrypsin (α1ACT) signaling axis can also induce Guanylate Binding Protein 2^{+} ($GBP2^{+}$) astrocytic activation, leading to BBB dysfunction through increased levels of Serpina3n/α1ACT [112] (Fig. 1).

Age is the primary risk factor for most NDDs [100]. Microglia have been identified as remarkably long-lived cells [71]. Aging microglia can enter a senescent state displaying modified surveillance phenotype, reduced branching and motility, and persistent inflammatory response upon damage [49]. Senescence markers include an irreversible cell-cycle arrest induced by the activation of p53/p21 and $p16^{INK4a}$/

Retinoblastoma (Rb) pathways, and the formation of Senescence-associated heterochromatin foci (SAHF) [82]. Senescent-associated microglia (SAM) might substantially contribute to the AD neurodegenerative process through different mechanisms. First, an important characteristic of SAM is the Senescence-associated secretory phenotype (SASP) which involves the activation of cGAS–cGAMP–STING pathway and the successive release of type I interferons (IFN), MMPs, High mobility group box 1 (HMGB1) protein, and other pro-inflammatory mediators, including IL1β, IL-6, and IL-8 [126, 209]. Through a process called paracrine senescence, SASP can propagate to neighboring cells via NF-κB and IL-1 signaling, contributing to the inflammatory process [3]. Second, cell-cycle arrest impose substantial constrains on cell functionality like clearance of cellular debris. APP/PS1 mice have a twofold-to-fivefold decrease in expression of the Aβ-binding scavenger receptors scavenger receptor A (SRA), CD36, and RAGE, and the Aβ-degrading enzymes insulysin, neprilysin, and MMP9, compared with their littermate controls [98]. Moreover, characterization post-mortem AD brain tissue revealed senescent microglia associated with inflammatory activation and downregulated phagocytic capacity [65]. Finally, senolytic therapy consistently decreases neuroinflammation in AD, tau and aging mouse models [81, 169, 269]. Taken together, these data demonstrate the interplay of cellular senescence between inflammation and AD.

Astrocytes

Astrocytes are integral for neuronal survival and function of CNS and are involved in multiple fundamental processes, such as synaptic pruning and remodeling, blood flow regulation, neural metabolism, clearance of synaptic and neuronal debris, or circadian rhythms [238]. Interestingly, changes in the transcriptomic and functional characteristics of astrocytes occur in both the aging brain [171] and NDDs [85, 241]. In the past years, the role of astrocytes as key regulators of innate and adaptative immune responses has been demonstrated in multiple in vivo and in vitro studies [31, 44, 90, 253]. Reactive astrogliosis is a common feature in neurodegenerative disorders which encompasses morphological, transcriptional, biochemical, metabolic, and physiological changes as a result of a pathological insult. Typically, these alterations manifest as elevated levels of Glial Fibrillary Acidic Protein (GFAP) and vimentin, along with heightened production of pro-inflammatory cytokines, such as INF-γ, IL-1β, IL-6, and TNFα [24, 214]. Additionally, there is an upregulation in the expression of innate immune-related genes like Lipocalin 2 (Lcn2) and the protease inhibitor 1-antichymotrypsin (Serpina3n) [274].

Astroglial pathological changes can be broadly grouped into three categories: (i) astrodegeneration, involving astroglial atrophy and functional loss; (ii) the pathological remodeling of astrocytes; and (iii) reactive astrogliosis. The first two categories, representing non-reactive pathological transformations of astrocytes, can be collectively referred to as astrocytopathies, distinguishing them from reactive astrogliosis [242]. Other documented altered functions in reactive astrocytes include impaired phagocytosis, decreased glutamate uptake, loss of astrocyte foot processes accompanied by the loss of polarized localization of AQP4, and release of neurotoxic compounds [132]. From a phenotypic perspective, recent single-cell and single-nucleus RNAseq analysis in human brains and mouse models of chronic neurodegenerative pathologies have shown multiple stage dependent transcriptomes [195, 212]. Similar to microglia, astrocytes can adopt multiple intermediate states, undergoing morphological, molecular, and functional changes, thus moving beyond outdated classical polarization views [181]. In AD, astrocytes display an upregulation of monoaminoxidase-B, translating into increased levels of GABA and H_2O_2 [42]. The classical neurocentric view of AD attributed these changes to a nonspecific secondary response to the disease process [164]. An increasing body of evidence indicates that astrocytes, not solely due to the impairment of their inherent homeostatic functions, but also through active processes, might play a role in the advancement of AD pathology.

Several astrocytic functional processes like glutamate removal, extracellular potassium regulation, calcium signaling [133], and energetic metabolism are known to be impaired in AD [2]. Moreover, genetic studies also suggest a pivotal role of astroglia in AD, with several risk factor genes, such as Apolipoprotein E (APOE), Sortilin-related receptor 1 (SORL1), clusterin (ApoJ), and Fermitin family homolog 2 (FERMT2), primarily expressed by astrocytes. Post-mortem tissue studies in humans with mild cognitive impairment or preclinical AD have confirmed the presence of reactive astrocytes even before the formation of amyloid plaques [60, 189, 243], aspect that has been extensively demonstrated in animal models [7, 96, 229]. Reactive astrogliosis can be also visualized in later stages of the disease (assessed by the expression of GFAP and neurotrophic factor S100β) where astrocytes can be found in the plaques vicinity, with a marked upregulation of intermediate filament proteins, such as synemin, vimentin, nestin [64, 224], and adopting different pathological phenotypes [113]. In addition to exhibiting astroglial reactivity, AD also features atrophic astrocytes characterized by reduced volume and thinner processes. These atrophic astrocytes have been confirmed in post-mortem brains of AD patients [188], mouse models of AD [217], and induced pluripotent stem (iPS) cells derived from patients with both familial and sporadic forms of the disease [108]. Noteworthily, both phenomena seem to be spatial dependent, with cells surrounding the plaques undergoing gliosis but those distant from them becoming atrophied [187]. Furthermore, different signaling pathways

have been implicated in AD astrogliosis among them the cyclic Adenosine monophosphate (cAMP) pathway [177], the Janus Kinase (JAK) /STAT3 pathway [86], the NF-κB pathway, the calcineurin/nuclear factor of activated T cells (CN/NFAT) pathway [1], and the MAPK pathways [196].

While robust data support the interaction of astrocytes with Aβ, there is no substantial evidence yet to confirm a significant role in Aβ production by astrocytes under physiological conditions [127, 272]. Reactive astrocytes seem to cluster around neuritic plaques forming a barrier and isolating them from the surrounding neuropil [103]. Whether the final outcome of this mechanism is detrimental or neuroprotective is still under debate. The creation of physical limits around the aggregate could limit its growth, reducing its neurotoxicity for neighboring cells [176]. Conversely, it is well documented that astrocytes can phagocytose Aβ [80, 228] and synapses [128]. Under normal physiological conditions, astrocytes uptake and transport Aβ from the brain into the perivascular space through the BBB. Aβ degradation occurs via neprylisin (NEP), insulin-degrading enzyme (IDE) and MMP-9 [10]. However, during AD, accumulation of Aβ forms resistant to degradation, such as N-terminally truncated forms [51], alongside heightened synaptic pruning activity [232], could potentially exacerbate the neurodegenerative process. Ablation of astrocytes in AD transgenic mice models aggravates amyloid pathology and leads to an increase in the expression of pro-inflammatory markers such as IL-6 and Il-1β [50, 111]. These data suggest a dual role of reactive astrocytes in AD. At first, they might play a significant role in Aβ uptake and degradation [11], as well as containing inflammation through glia-scar formation [213, 244]. As inflammation perpetuates, the sustained release of inflammatory mediators might hamper this capacity, leading to the formation of secondary deposits through the death of Aβ-loaded astrocytes [162]. Astrocytes can sense Aβ in the TLR/RAGE-dependent manner leading to morphological changes and increased levels of GFAP and S100β [162]. Aβ-reactive astrocytes provide neuroprotection through the release of neurotrophic factors, but they also participate in the inflammatory process via the afore stated signaling pathways with the release of ROS, NO, cytokines (e.g., IL-1β, IL-6, TNF-α, IFN-α, granulocyte–macrophage colony-stimulating factor), and chemokines (e.g., MCP-1, MIP1-α, CCL4, IL-8, IFN-γ-inducible protein-10) [135]. The synthesis of pro-inflammatory mediators contributes to Aβ pathology by disturbing APP processing equilibrium and boosting β- and γ-secretases activity by astrocytes [10]. In a similar manner, activated microglia can also activate astrocytes through the release of cytokines, such as IL-1α, IL-1β, IL-6, TNF-α, and C1q, stimulating again astrocytic β-amyloid production [132, 271] (Fig. 2).

The levels of tau in healthy astrocytes have been reported very low [175]; however, hyperphosphorylated tau has been observed in astrocytes in AD [185]. Astrocytes can internalize different forms of tau including monomers, tau preformed fibrils (PFFs), and aggregates [62, 147, 158]. Astrocytes may play as well a dual role during the disease course; while the uptake of tau from the extracellular environment might help mitigate the direct neurotoxic impacts of tau on neurons, the internalization and release of pathological tau species by astrocytes could potentially exert adverse effects on astrocytic function and propagate tau pathology [67]. Tau accumulation within astrocytes could also elicit an inflammatory response, further contributing to the neurodegenerative process. The available data regarding tau-mediated inflammation by astrocytes are limited. In one of the few reports available, Wang and Ye triggered an astrocytic inflammatory reaction using αV/β1 integrin by exposing them to tau monomers and PFFs. The administration of PFFs resulted in a robust elevation of numerous pro-inflammatory cytokines (IL1α, IL1β, IL6, and TNFα) and chemokines (CCL2, CCL3, CCL4, and CXCL10). Conversely, exposure to monomeric tau elicited a decreased inflammatory response [251]. In another paper, Ungerleider and colleagues exposed human astrocytes to tau monomers, PFFs, or a combination of both. All 3 treatments increased expression of IL-1β and IL-8 mRNA at 24 h. Also, a delayed increased in TNFα levels and Nitric oxide synthase 2 (NOS2), indicating an increase in oxidative stress following the initial inflammatory response [234]. Uptake of pathological tau by cells could potentially modify the secretion of cytokines by astrocytes, indicating a feedback loop where tau and inflammation mutually exacerbate the neurodegenerative process. The inflammatory state will also lead to a sustained astrogliosis, with trophic and metabolic support functions potentially comprised (Fig. 2). Tau-mediated astrocytic dysfunction has been demonstrated both in vivo and in vitro, resulting in a reduced neurosupportive capacity and increased neuronal loss [208]. Interestingly, this phenomenon seems to be an early event in the pathogenic process of AD that may serve as a bridge between Aβ pathology and early tau phosphorylation [15].

Microglia–astrocyte crosstalk has recently become a central focus in glial research. New evidence shows that signals originating from microglia and astrocytes are crucial in determining the functions and fates of each other [141, 192, 256]. In the AD context, neurons release self-antigens or aberrant protein forms that activate homeostatic microglia. Upon migration to the damaged site, microglia exhibit beneficial phagocytic activity by clearing toxic Aβ forms [210]; however, their involvement becomes deleterious when chronic activation occurs, leading to unresolved inflammation and acceleration of the neurodegenerative process. In this state, secretion of TNF-α, TNF-related apoptosis-inducing ligand (TRAIL), IL1α, and C1q by microglia is sufficient to induce A1 astrocytes with impaired support of synaptogenesis, reduced phagocytosis,

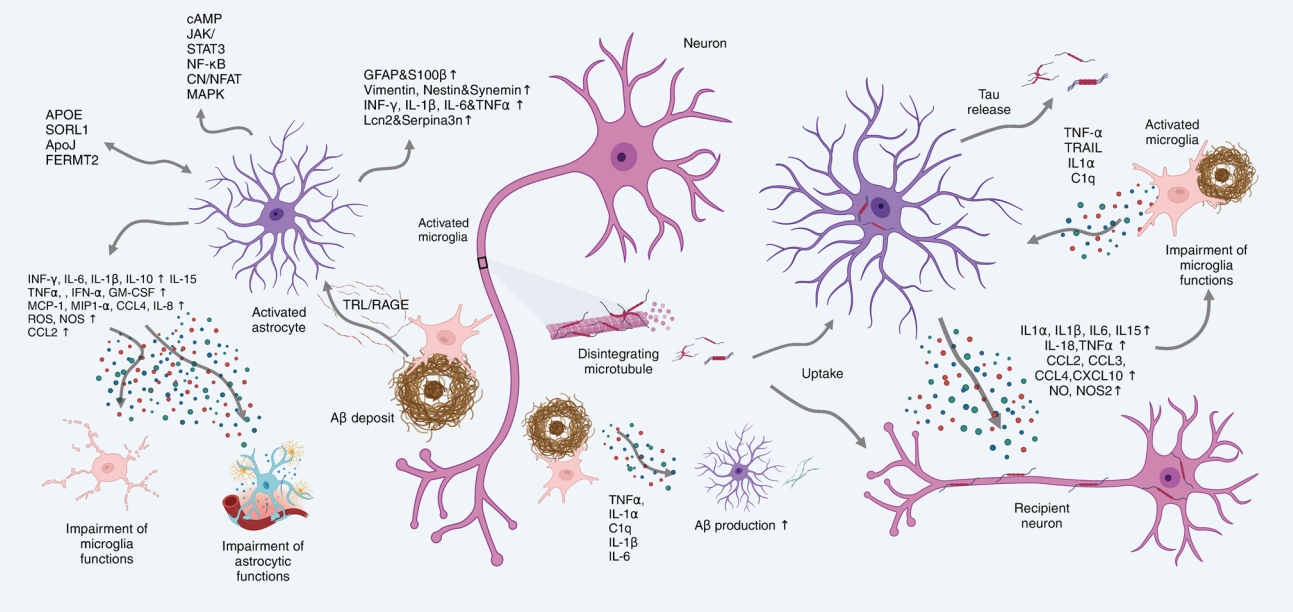

Fig. 2 Astrocytes-mediated inflammation in AD. Upon sensing Aβ plaques in a TLR/RAGE manner, astrocytes become activated and undergo significant changes in gene expression and signaling pathways. Activated astrocytes exhibit elevated levels of GFAP, S100β, and intermediate filament proteins, such as synemin, vimentin, and nestin, indicating their reactive state. Furthermore, there is an upregulation of pro-inflammatory cytokines, such as INF-γ, IL-1β, and IL-6, along with increased expression of Lcn2 and Serpina3n. Multiple signaling pathways have been implicated including cyclic Adenosine monophosphate (cAMP) pathway, the Janus Kinase (JAK)/STAT3 pathway, the NF-κB pathway, the calcineurin/nuclear factor of activated T cells (CN/NFAT) pathway, and the MAPK pathway. Additionally, microglia can further activate astrocytes by releasing neuroinflammatory contents, such as TNF-α, IL-1α, complement component 1q (C1q), IL-1β, and IL-6, leading to increased production of Aβ by astrocytes. In parallel, aggregated and hyperphosphorylated forms of tau are released by dying neurons. These forms could be uptake by another recipient neuron or by glial cells. The activation of astrocytes leads to the release of pro-inflammatory cytokines (IL1α, IL1β, IL6, and TNFα), chemokines (CCL2, CCL3, CCL4, and CXCL10), and nitric oxide. This pro-inflammatory milieu increases neurotoxicity, but also affects microglia, leading to the release of TNF-α, IL-1α, complement component 1q (C1q), IL-1β, further activating astrocytes. Additionally, the release of aggregated tau forms by astrocytes might also enhance the propagation of tau in a prion-like manner. (Figure created using BioRender.com)

and decreased expression of neurotrophic factors [29, 132]. Crosstalk between microglia and astrocytes is reciprocal, and therefore, microglia functions are also influenced by different cytokines and chemokines, such as IL-1β, IL-10, IL-15, TNF-α, nitric oxide, and CCL2 that are secreted by astrocytes [20] (Fig. 2). Data from animal models suggest that these functional alterations might significantly influence AD progression. Using an APP transgenic mouse model, Lian et al. showed that Aβ acts as an upstream activator of astroglial NF-κB, leading to the release of C3. The interaction of C3 with microglial C3a receptor leads to impaired Aβ phagocytosis [131]. In another report, McAlpine et al. utilized a 3D microfluidic triculture system comprising microglia derived from human iPS cells and the 5xFAD transgenic mouse model. Their study demonstrated that astrocyte-produced IL-3 plays a central role in directing microglial activity, leading to increased mobility and enhanced capability to cluster around and eliminate Aβ and tau aggregates [151]. Another important route of cross talk is the gut–brain axis. Through the metabolites of dietary tryptophan, commensal and pathogenic enteric bacteria may impact the production of Vascular Endothelial Growth Factor-β (VEGF-β) and transforming growth factor alpha (TGFα) by microglia, thereby regulating astrocyte pathogenic processes during inflammation and neurodegeneration [193]. Recently, several other routes of activation have been identified including complement protein C3 [259] and C8γ [114], human antimicrobial peptide LL-37 [39], extracellular vesicles [190], or TNTs [191].

Neurons

Neurodegeneration defines as an irreversible detrimental process for neurons that presents in NDDs, and to a lesser extent, during aging. Neurons themselves do not possess a pro-inflammatory machinery, and therefore, the classical unidirectional relation is that neuroinflammation acts upon neurons. However, neurons can also contribute to the inflammatory process through the different modes of programmed cell death [144]. Apoptosis is a form of regulated cell death (RCD) that can be initiated by various perturbations in both

the intracellular [DNA damage, endoplasmic reticulum (ER) stress, ROS overload, replication stress, microtubular alterations, etc.] and extracellular microenvironments (through plasma membrane receptors)[73]. Among all RCD implicated in AD, apoptosis is the least detrimental with the production of anti-inflammatory factors, such as lactate, IL-10, and TGF-β, and with a cellular clearance without release of the intracellular components. However, accumulating evidence also suggest that the catalytic activity of caspases implicated in the apoptotic process may influence AD neuroinflammatory process. Caspase 3, for instance, has the capacity to cleave both APP and tau, producing additional cytotoxic APP fragments and disrupting synaptic communication, respectively [170, 174] (Fig. 3). Solid evidence of the presence of apoptosis is AD post-mortem tissue remains elusive [231], with few reports showing neurons with morphological features of apoptosis [218, 219]. Several reasons could explain this absence. First, apoptotic cells are usually degraded by microglia; hence, accumulation of them is only possible if microglia functions are severely impaired. Also, upregulation of anti-apoptotic B-cell lymphoma 2 (Bcl-2) family proteins and down-regulation of both the pro-apoptotic protein Bax and several pro-apoptotic BH3-only proteins, confer mature neurons natural resistant to apoptotic

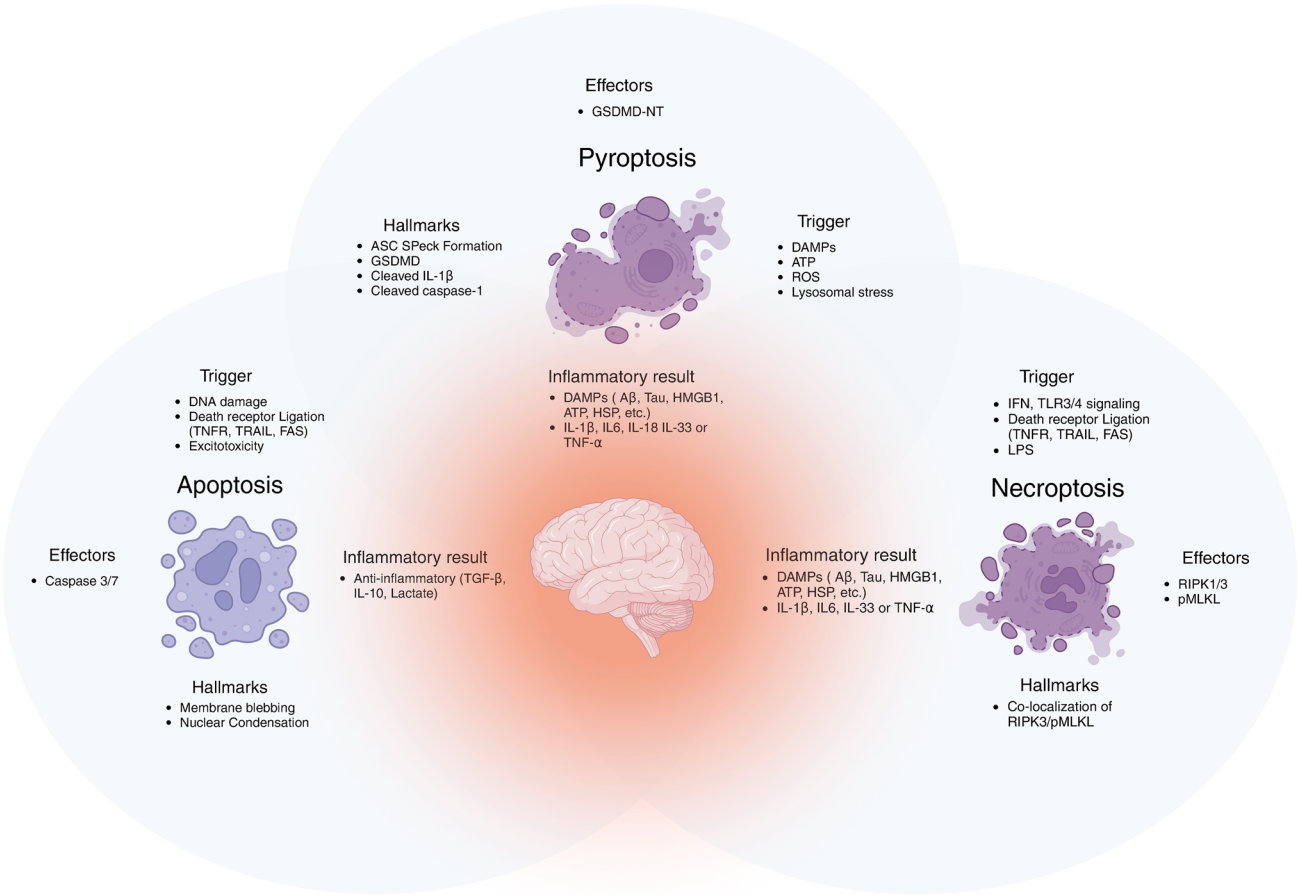

Fig. 3 Regulated cell death (RCD) & Inflammation. RCD modes (Apoptosis, Pyroptosis, and Necroptosis) and their relationship with inflammation in AD are outlined here, focusing on triggers, effectors, hallmarks, and inflammatory outcomes. Apoptosis, distinguished by its quiet nature and lack of inflammation, coordinates the removal of cells without releasing intracellular contents. It can be induced by various stimuli, culminating in Caspase-3 cleavage. Apoptotic death entails nuclear condensation and membrane blebbing, while also exerting an anti-inflammatory effect through the release of TGF-β, IL-10, and Lactate. Necroptosis occurs in the absence of Caspase-8 and after the activation of death receptors, such as TNFR, TRAIL, and FAS. This process involves RIPK1 autophosphorylation, RIPK3 activation, and subsequent MLKL phosphorylation, leading to oligomerization of phosphorylated MLKL at the plasma membrane, disrupting cell polarity, and ultimately resulting in lysis. Necroptosis incites inflammation by releasing intracellular contents as DAMPs together with pro-inflammatory cytokines. Pyroptosis is an inherently inflammatory RCD that induces cell lysis via membrane pore formation with two signals required for initiation. The first one primes the inflammasome, while the second activates intracellular pattern recognition receptors (e.g., NLRP3, NLRP1, and AIM2), forming inflammasome complexes. This cascade triggers Caspase-1 activation, cleaving substrates including pro-IL-1b, pro-1L-18, and GSDM. Active GSDM forms pores resulting in membrane integrity loss, cell lysis, and release of pro-inflammatory cytokines and intracellular DAMPs. (Figure created using BioRender.com)

cell death [99]. Some lines of evidence indicate the presence of apoptotic markers in AD, but to what extend apoptosis contributes to neuron death in the disease course remains under debate [144].

Necroptosis, on the contrary, represents an inflammatory RCD characterized by the loss of membrane integrity and the release of intracellular content including pro-inflammatory cytokines, such as IL-1β, IL6, IL-33 or TNF-α, and DAMPs. Necroptosis is usually triggered by pro-inflammatory cytokines and death signaling ligands released by inflammatory cells like astrocytes and microglia. This process leads to the autophosphorylation of receptor-interacting protein kinase 1 (RIPK1) and the latter recruitment of RIPK3 to form a large molecular complex named necrosome. Activated RIPK3 then phosphorylates and activates the pseudokinase mixed lineage kinase domain-like protein (MLKL), which oligomerizes and translocates to the plasma membrane, disrupting its integrity and causing cell death [252] (Fig. 3). Different studies point toward a prominent role for necroptosis in AD. Caccamo and colleagues provided direct evidence for the activation of necroptosis in human AD brains, as well as in a mouse model of AD. Necroptosis levels positively correlated with Braak stages, and inversely correlated with brain weight and cognitive scores [33]. In another study, Salvadores et al. using post-mortem human AD brain tissue showed that Aβ oligomers correlates with the expression of key markers of necroptosis activation. Furthermore, pharmacological or genetic inhibition of necroptosis resulted in reduced neurodegeneration and memory impairment triggered by Aβ oligomers in mice [197]. Finally, in human post-mortem AD brains, Koper and colleagues demonstrated the presence of all three activated necrosome components when granulovacuolar degeneration (GVD) neuronal lesions were analyzed, suggesting an AD specific form of necroptosis [119]. Necroptosis machinery (RIPK1, RIPK3, and MLKL) promotes a robust and sustained pro-inflammatory response [45, 275]. Upon membrane rupture, released DAMPs might get recognized by nearby bystander glia (microglia and astrocytes) serving as pro-inflammatory triggers. However, in the context of AD, the situation might be even more detrimental, due to the release of pathological intraneuronal tau forms. These forms could not only act as DAMPs, but also have the potential to spread tau pathology within the local environment [25].

Pyroptosis represents an alternative type of inflammatory RCD characterized by DNA fragmentation, cellular swelling, and membrane disruption that is triggered by inflammasomes. Neuronal pyroptosis seems to be highly dependent on caspase-1 activation although recent reports have shown that other caspases, including caspase-3/4/5/6/8/9/11, may also cause pyroptosis [267]. The cleavage of GSDMD by caspase-1 results in the formation of membrane pores, leading to membrane rupture and subsequent release of cellular contents into the extracellular environment. Most pyroptosis-related AD research has focused on glial cells, but recent evidence suggests activation of the neuronal NLRP1 inflammasome may play an important role [264]. Increased levels of neuronal pyroptosis caused by NLRP1/caspase-1 activation were found in cultured cortical neurons exposed to Aβ. In the same study, NLRP1 or caspase-1 deficiency resulted in significantly lower levels of neuronal pyroptosis and reversed cognitive impairments [226]. The presence of other pyroptosis-related proteins has been also demonstrated in AD. In a recent paper analyzing human AD samples, Moonen and colleagues demonstrated the presence of cleaved GSDM in neurons. Interestingly, caspase-8 and non-canonical inflammasome protein caspase-4 were also detected, suggesting novel mechanisms for GSDMD cleavage [157]. Another set of experiments showed increased levels of GSDMD p30, NLRP3 protein, and cleaved caspase-1 following the incubation of mouse cortical neurons with $A\beta_{1\text{-}42}$ [87]. The relation between phosphorylated tau (p-tau) and neuronal pyroptosis is barely explored. In one of the few reports available, hyperphosphorylated tau induced pyroptosis and release of IL-1β and IL-18 in PC12 cells treated with forskolin [130]. Additionally, increased concentrations of GSDMD, total tau (t-tau), and tau181p have been detected in the CSF of AD patients in comparison to both, the overall population and individuals with vascular dementia [205](Fig. 3).

Other cell types

While the involvement of the aforementioned cellular types in the neuroinflammatory phenomena of AD is well documented, increasing evidence is introducing new players into the field. The adaptive immune system is increasingly acknowledged for its role in the pathogenesis of AD. Integrity loss of the BBB in AD has been extensively investigated [123] and allows peripheral lymphocytes such as B and T cells, access to the brain parenchyma. This has been demonstrated in brains of transgenic AD mice, where the presence of mature B cells led to immunoglobulin deposits which were often colocalized with Aβ plaques and activated microglia. Moreover, loss of B cells was significantly reduced Aβ burden and behavioral impairments [115]. In line, individuals with mild cognitive impairment and AD exhibited elevated levels of inflammatory CD8 + CD45RA + T effector memory (TEMRA) cells in peripheral blood, along with their clonal expansion in the CSF [77]. Recently, these results have been confirmed using a novel a 3D human neuroimmune axis model [109].

Brain pericytes are key constituent cells of the neurovascular unit playing various functions including angiogenesis, vascular remodeling, regulation of microcirculation, and the

formation and maintenance of the BBB itself. Pericyte loss and/or degeneration has also been reported in AD [155, 206], which results in BBB disruption. This allows the extravasation of toxic-blood derived products leading to immune response and secondary neuronal degenerative changes [14]. Interestingly, pericyte reduction has been shown to correlate not only with BBB dysfunction but also amyloid plaque load [203]. Brain pericytes can internalize and clear Aβ via an LRP1/APOE [35]. In AD, aberrant deposition of Aβ leads to progressive capillary constriction [167], decreasing oxygen and blood levels, leading to neuronal loss. Indeed, exposure to $A\beta_{1-40/42}$ promoted membrane release of key pericyte proteins, including proteoglycan NG2 and platelet-derived growth factor receptor β (PDGFRβ) [200]. Perivascular cells are also involved in immune regulation [194]. Through the release of diverse immunomodulators, such as IL-1β, TNF-α, IFN-γ, or IL-6, pericytes can induce pro-inflammatory states in microglia, astrocytes, and endothelial cells [148]. Lipopolysaccharide immune activation have been shown in human and mice pericytes cultures, resulting in significant release of pro-inflammatory factors, such as L-1α, TNF-α, IL-3, IL-9, IL-10, IL-13, iNOS, and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 4 [83, 121]. Finally, anti-inflammatory roles have also been proven in mouse models, with the release of CX3CL1 and IL-33, decreasing microglia activation and promoting their anti-inflammatory phenotype [34, 263].

While AD is often viewed primarily as a gray-matter disease, white-matter changes are also frequently reported [76, 150]. Remarkably, these lesions have also been shown in preclinical AD [53, 186], indicating a role in the disease etiology. In this regard, the group of Klaus-Armin Nave demonstrated in AD mice models, that myelin defects upstream amyloid deposition, recruit away plaque-corralling microglia, leading to a less efficient Aβ clearance. Additionally, RNA-seq analysis revealed a more inflammatory profile of microglia with upregulation of classical DAM signature genes, such as Clec7a, Gpnmb, APOE, Spp1, Axl, and Itgax [54]. Downstream amyloid deposition, the exact mechanisms leading to myelin loss in AD remain unknown but are likely to include cytotoxicity, RNA metabolism disruption, and neuroinflammation [74, 116, 260]. Additionally, independent lines of evidence suggest that oligodendrocytes might be active contributors in the disease development. Indeed, amyloidogenic-processing machinery is abundant in oligodendrocytes [198], generating detectable Aβ levels in vitro [211] and possible contributing to the Aβ burden. Aligned, another recent study showed that suppression of oligodendrocyte-derived Aβ rescued neuronal dysfunction in vivo [182]. Finally, both in AD patients and an AD mouse model, oligodendrocytes exhibited NLRP3-dependent GSDMD-associated inflammatory injury, concomitant with demyelination and axonal degeneration [270].

Recently, another population of tissue-resident macrophages was identified [159]. Border-associated macrophages (BAMs) are defined and resident macrophages in non-parenchymal tissues. They play critical roles in maintaining CNS homeostasis and differ phenotypically and functionally from microglial cells [55]. Also, several subgroups of BAMs have been identified based on their anatomical site: subdural/leptomeningeal macrophages (sdMΦ), dural macrophages (dmMΦ), stromal choroid plexus macrophages (cpMΦ), choroid epiplexus macrophages (cp^{epi}MΦ), and perivascular macrophages (PVMs) [236]. Owing to their recent discovery, BAMs role in AD needs further research. In one recent study, Tg2576 mice perivascular and leptomeningeal compartments were repopulated through $CD36^{-/-}$ or $CD36^{+/+}$ bone marrow transplantation. Deletion of CD36 in BAMs suppressed ROS production and improved neurovascular function, with complete rescue of cognitive function [233]. In another paper, immune responses induced by amyloid-targeting antibodies and CAA-induced microhemorrhages were analyzed using mouse models of AD. Anti-Aβ (3D6) immunotherapy lead to increased occurrences of microhemorrhages, altered cerebrovascular structure, and the formation of an antibody immune complexes with vascular amyloid deposits associated with perivascular macrophage [230].

Conclusion

Neuroinflammation is a conserved immune response aimed to protect neurons from a deleterious stimulus and resolve the homeostatic disbalance. In AD, chronic neuroinflammation emerges as a central driver for the neurodegenerative process due to the orchestrated interaction among multiple cell types including but not only, microglia, astrocytes, and neurons. Persistent ligand–receptor interactions in the CNS microenvironment overactivate cells for sustained periods of time causing chronic NDDs. The concept of microglia as the sole instigators of inflammation oversimplifies the complex interplay within the neuroinflammatory landscape. It is crucial to acknowledge and explore the contribution of other cellular entities such as astrocytes or neurons. Microglia and astrocytes, crucial components of the brain's immune system, are activated by pathological forms of proteins such as Aβ and tau, initiating a cascade of inflammatory responses that self-sustain over the disease course. An over-extended inflammatory status then translates into increased cytokine and chemokine production, systemic stress, and, eventually, neural damage. In AD, neuronal damage sets off a subsequent harmful cycle, wherein multiple DAMPs, including toxic protein aggregates, and additional pro-inflammatory molecules are discharged into the extracellular space through the different RCD modes. This closes an iterative loop where

neuroinflammation leads to neurodegeneration and neurodegeneration boost neuroinflammation. The complex interplay between cellular types makes the breaking point identification a formidable challenge. Therapies aimed to stop or halt this loop are urgently required.

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