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Microglia efferocytosis: an emerging mechanism for the resolution of neuroinflammation in Alzheimer's disease

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Abstract

Alzheimer's disease (AD) is a complex neurodegenerative disorder characterized by significant neuroinflammatory responses. Microglia, the immune cells of the central nervous system, play a crucial role in the pathophysiology of AD. Recent studies have indicated that microglial efferocytosis is an important mechanism for clearing apoptotic cells and cellular debris, facilitating the resolution of neuroinflammation. This review summarizes the biological characteristics of microglia and the mechanisms underlying microglial efferocytosis, including the factors and signaling pathways that regulate efferocytosis, the interactions between microglia and other cells that influence this process, and the role of neuroinflammation in AD. Furthermore, we explore the role of microglial efferocytosis in AD from three perspectives: its impact on the clearance of amyloid plaques, its regulation of neuroinflammation, and its effects on neuroprotection. Finally, we summarize the current research status on enhancing microglial efferocytosis to alleviate neuroinflammation and improve AD, as well as the future challenges of this approach as a therapeutic strategy for AD.

Keywords Microglia, Efferocytosis, Neuroinflammation, Alzheimer's disease, Neurodegenerative disease

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease that is a leading cause of dementia worldwide and overwhelms global health care systems given its high burden of care. Currently, it is estimated that around 44 million people worldwide have AD, and this number is expected to rise, especially given the continuing trend of an aging population. Projections show that by 2050, the number of people affected could nearly double [1]. AD is characterized by cognitive decline and memory loss, accompanied by pathological features such as amyloid plaque buildup, neuronal apoptosis, and pronounced neuroinflammation. Microglia are the main immune cells of the central nervous system (CNS) and play a vital role in maintaining homeostasis, especially in the context of neuroinflammation associated with neurodegenerative diseases such as AD [2]. Soliman et al. revealed that microglia can clear apoptotic cells (ACs) and cell debris through efferocytosis, regulate neuroinflammation and promote recovery in the neural environment [3]. Recent studies have highlighted the importance of understanding the mechanisms by which microglia perform efferocytosis, particularly in the context of AD, as this knowledge could inform the development of novel

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therapeutic strategies aimed at mitigating neuroinflammation and its detrimental effects on cognitive function [4].

Efferocytosis refers to the phagocytic clearance of ACs by professional phagocytes, including microglia. This mechanism is crucial for preventing secondary necrosis, which can trigger the release of pro-inflammatory molecules and exacerbate neuroinflammation [5]. In AD, microglia fail to effectively perform efferocytosis, leading to the accumulation of ACs and debris, which further intensifies inflammatory responses and neuronal damage. Research indicates that microglial efferocytosis is influenced by various cytokines and signaling pathways, including milk fat globule epidermal growth factor 8 (MFG-E8) and cathepsin B, which play roles in regulating microglial activation and phagocytic activity [6]. Understanding the specific cytokines and pathways that regulate efferocytosis could provide potential interventions to enhance microglial function and promote the resolution of neuroinflammation.

Microglia play a crucial role in the CNS, not only by clearing ACs but also by forming a complex network of interactions with other cell types, such as neurons and astrocytes. These interactions are essential for the effective process of efferocytosis. Specifically, while microglia remove ACs, they also communicate with surrounding cells by releasing anti-inflammatory cytokines, facilitating a phenotypic shift [7]. This shift allows microglia to transition from a pro-inflammatory state to a more reparative one, which is vital for tissue repair and regeneration following neuroinflammatory damage. Under healthy conditions, these intercellular interactions help maintain immune balance within the CNS, ensuring that inflammatory responses remain appropriate and effective. However, in neurodegenerative diseases like AD, this delicate balance is severely disrupted. Microglia become persistently activated in a pro-inflammatory state, leading to chronic inflammatory responses [8]. This sustained inflammation not only impairs the efferocytosis function of microglia but may also exacerbate neuronal damage and death, creating a vicious cycle [9]. Therefore, it is imperative to delve deeper into the interactions between microglia and other cell types, such as neurons and astrocytes, and to understand how these interactions influence the efferocytosis mechanisms of microglia. This research is not only critical for elucidating the pathogenesis of AD and similar conditions but also holds promise for identifying new therapeutic targets aimed at restoring immune balance in affected patients, ultimately promoting recovery and regeneration within the nervous system.

In conclusion, microglial efferocytosis emerges as a vital mechanism for the resolution of neuroinflammation in AD. A deeper understanding of the molecular pathways and cellular interactions involved in this process could provide important directions for developing novel targeted therapeutic strategies aimed at inhibiting the progression of neurodegenerative diseases, promoting neurological recovery, and improving cognitive outcomes for patients. Future research should focus on identifying specific therapeutic agents that can enhance microglial efferocytosis and restore the balance of neuroinflammation in AD.

Biological characteristics of microglial cells

Origin and development of microglial cells

Microglial cells play a crucial role in the CNS as the resident immune cells, originating from yolk sac progenitors during early embryonic development. This distinct lineage not only sets them apart from other macrophages but also underscores their unique functionality within the CNS. The migration and colonization of microglial cells are tightly regulated by various factors, including the neurogenic state of the surrounding environment and the presence of blood vessels. For instance, recent studies in zebrafish have demonstrated that microglial precursors utilize intraocular hyaloid blood vessels as pathways to infiltrate the developing retina, emphasizing the critical role of vascular structures in guiding microglial migration [10]. In addition to their migratory pathways, microglial cells exhibit dynamic changes throughout development. Research has shown that these cells are involved in critical processes such as synaptic pruning, neuronal survival, and the regulation of neuroinflammation [11]. Notably, their migration patterns are influenced by interactions with the extracellular matrix and signaling molecules present in the microenvironment. For example, integrin receptors on microglia mediate their interactions with fibronectin, which has been found to facilitate or inhibit their migration depending on the developmental stage [12]. Furthermore, microglial cells are not merely passive observers, they actively contribute to the maturation of neuronal networks by modulating synaptic connections and responding to developmental cues [13].

Activation state of microglia and efferocytosis

Microglia exhibits remarkable plasticity that enables them to adapt to the diverse stimuli encountered within the complex environment of the CNS. Under normal homeostatic conditions, these multifunctional cells maintain overall brain health and function by clearing ACs and cellular debris, preventing unnecessary inflammation, and preserving the integrity of surrounding tissues, thus ensuring a stable and healthy neural environment [14]. However, in pathological contexts such as neurodegeneration or physical injury, microglia undergo complex activation processes, displaying a continuum of functional states rather than simplistic binary classifications (e.g., the traditional M1/M2 paradigm) [15].

Recent studies emphasize that microglial activation states are determined by specific stimuli (e.g., Aβ oligomers, ATP, pathogen-associated molecular patterns) and distinct genetic-proteomic response profiles. For example, during acute neuroinflammation, microglia exposed to IFN-γ or LPS upregulate pro-inflammatory-related genes (e.g., IL-1β, TNF-α, iNOS) and release reactive oxygen species (ROS), exacerbating neuronal damage [16]. In tissue repair phases, microglia stimulated by IL-4 or IL-13 highly express homeostatic regulatory genes (e.g., Arg1, Ym1, CD206), promoting synaptic remodeling and myelin regeneration [17]. Single-cell RNA sequencing has identified novel subpopulations such as disease-associated microglia (DAM), characterized by genes (e.g., ApoE, TREM2, LPL) linked to neurodegenerative disease progression [18].

The phagocytic capacity of microglia is closely tied to their activation state. During efferocytosis, microglia may differentiate into a pro-resolving phenotype, secreting anti-inflammatory mediators like TGF-β and IL-10 to suppress secondary inflammation and maintain tissue homeostasis. Conversely, impaired efferocytosis (e.g., due to defective TAM receptor signaling or reduced MerTK expression) leads to the accumulation of cellular debris and release of damage-associated molecular patterns (DAMPs), driving microglia toward an inflammation-dominant phenotype and resulting in chronic neuroinflammation and CNS dyshomeostasis. This dynamic regulation involves synergistic interactions among multiple signaling pathways. Interleukin-33 activates the MAPK/NF-κB pathway via the ST2 receptor, enhancing microglial phagocytic activity [19]. The NLRP3 inflammasome regulates inflammation-repair balance through Caspase-1-mediated IL-1β maturation [20]. HDAC inhibitors induce the expression of pro-resolving genes, reprogramming microglial function. Studies further demonstrate that microglial activation states directly influence synaptic plasticity and neuronal survival [21]. In peripheral nerve injury models, pro-resolving microglia promote axonal sprouting via the release of brain-derived neurotrophic factor (BDNF) [22].

Mechanisms of microglial efferocytosis

Molecular basis of efferocytosis

Efferocytosis primarily involves four stages: recruitment of microglia ("Find-Me"), identification ("Eat-Me" and "Don't-Eat-Me"), phagocytosis, and digestion of ACs [23].

Recruitment of microglia

During the "Find-Me" phase, ACs release a variety of soluble mediators, including nucleotides, proteins, lipids, and various lipid products, to recruit microglia. These "Find-Me" signals mainly consist of adenosine triphosphate (ATP), uridine triphosphate (UTP), sphingosine-1-phosphate (S1P), CX3C motif chemokine ligand 1 (CX3CL1), and lysophosphatidylcholine (LPC) (Fig. 1). Among these, ATP and UTP signals can be released through pannexin channels, which are activated by the cleavage of caspases 3/7 during apoptosis, and they bind to purinergic P2Y receptors on the surface of microglia to induce their migration [24, 25]. S1P, CX3CL1, and LPC interact with their respective receptors—S1P receptor subtypes 1–5, C-X3-C motif chemokine receptor 1, and G protein-coupled receptor G2A—to recruit microglia, upregulate anti-inflammatory/pro-resolving gene expression, and regulate the cytoskeleton [26–28]. These signals not only attract microglia but also prepare them for "battle" by enhancing the expression of phagocytic

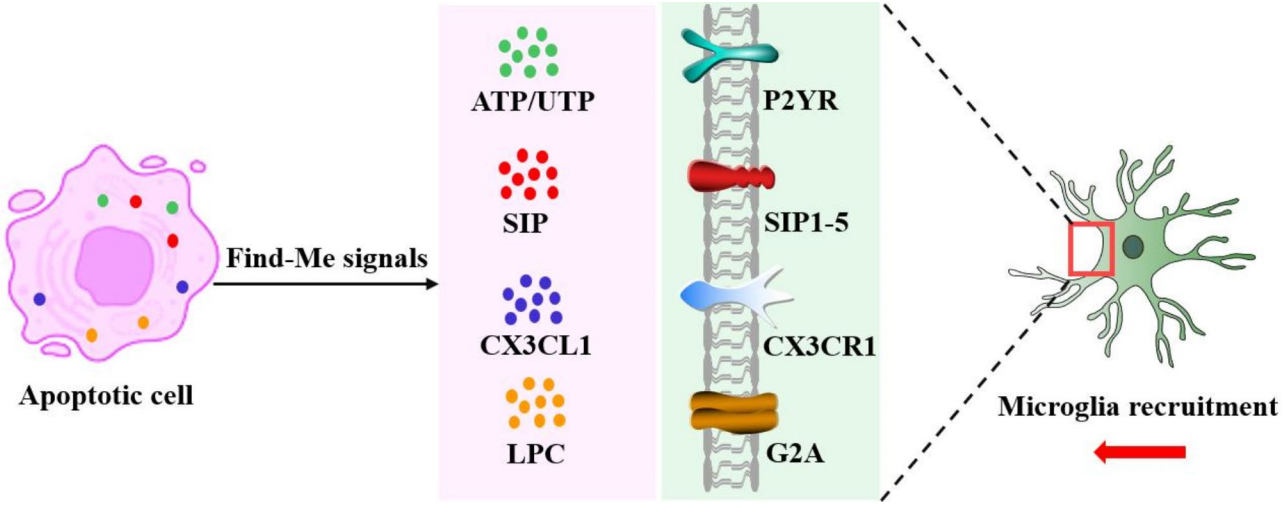

Fig. 1 Recruitment of microglia by ACs. Abnormal activation of nuclear ACs recruit microglia by releasing a large number of "Find-Me" signals. "Find-Me" signals mainly consist of adenosine triphosphate (ATP), uridine triphosphate (UTP), sphingosine-1-phosphate (S1P), CX3C motif chemokine ligand 1 (CX3CL1), and lysophosphatidylcholine (LPC). The receptors corresponding to the above "Find-Me" signals are P2YR, SIP1-5, CX3CR1 and G2A, respectively

receptors and digestive mechanisms. When the integrity of the lipid membrane of non-ACs is compromised, inflammatory signals are directly released into the extracellular space. Pathogen-infected cells release pathogen-associated molecular patterns, which can bind to pattern recognition receptors on microglia, influencing their function and immune activation. Additionally, non-ACs can release damage-associated molecular patterns, triggering inflammatory responses and acting as chemotactic factors for microglia. Moreover, nucleotides can modulate the immune mechanisms of microglia. For instance, ATP or AMP released from ACs can be converted into adenosine, which subsequently inhibits inflammation through adenosine receptors, upregulating the expression of anti-inflammatory and pro-resolution genes, including Nr4a1 and platelet-activating factor [29].

Identification of microglia

Although "Find-Me" signals enable microglia to reach the vicinity of ACs, the specific recognition of ACs among neighboring viable cells relies on the exposure of "Eat-Me" signals. The "Eat-Me" signals are crucial for identifying ACs and triggering efferocytosis through the activation of phagocytic receptors and subsequent signaling cascades. These "Eat-Me" signals include phosphatidylserine (PS), calreticulin (CRT), and oxidized low-density lipoproteins, with PS being the most effective and evolutionarily conserved signaling molecule. A common feature of all forms of cell death is the loss of phospholipid asymmetry in the plasma membrane, leading to the exposure of PS on the cell surface, which facilitates the engulfment of dying cells. During apoptosis, PS, which is normally located on the inner leaflet of the membrane, translocates to the outer surface in the early stages [30].

PS can directly bind to phagocytic receptors on the surface of microglia, such as T cell immunoglobulin and mucin domain-containing protein 4 (TIM4), brain angiogenesis inhibitor 1 (BAI1), receptor for advanced glycation end products (RAGE), and stabilin-2 (Stab2) [31] (Fig. 2). It can also indirectly couple with TAM family receptors through bridging molecules like growth arrest-specific 6 (Gas6) and Protein S, activating the expression of ELMO and DOCK proteins, which in turn activate the GTPase RAC1, enhancing actin remodeling and the formation of phagocytic cups [32]. The TAM family

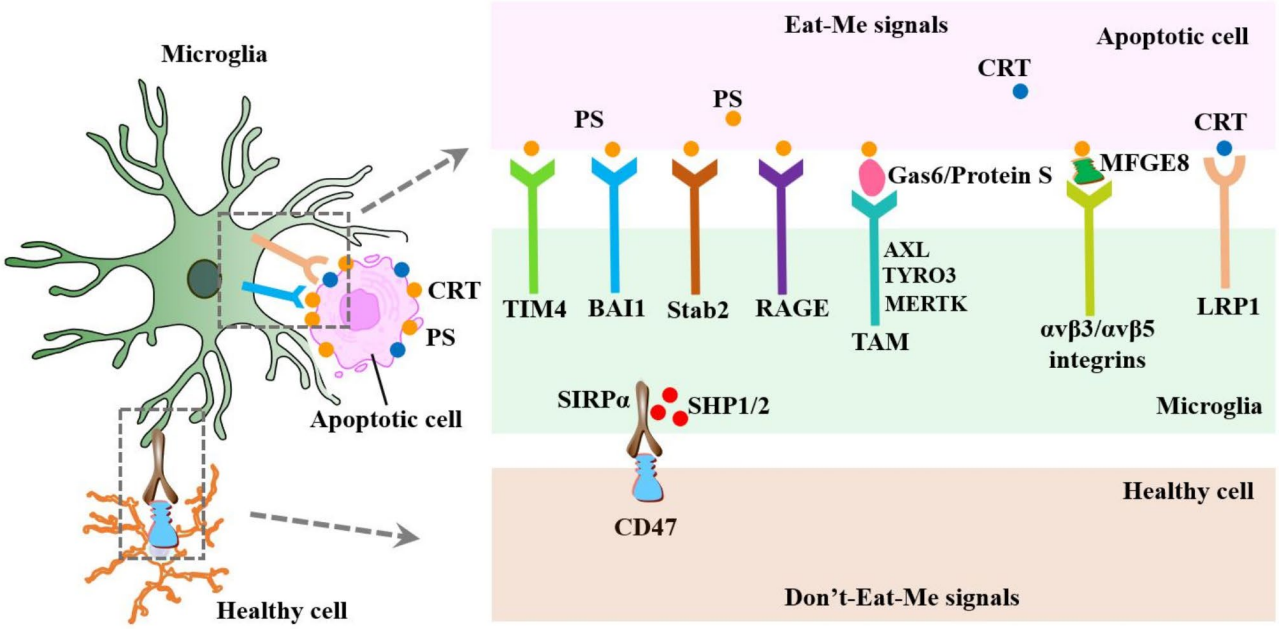

Fig. 2 Microglia recognize apoptotic cell processes. Microglia are recruited to the vicinity of ACs, where they recognize "Eat-Me" signals displayed on the membranes of these cells, initiating phagocytosis through direct or indirect interactions. Following apoptosis, "Eat-Me" signals such as phosphatidylserine (PS) and calreticulin (CRT) become exposed on the cell surface, interacting with receptors on microglia either directly or indirectly. Receptors that interact directly with PS include T cell immunoglobulin and mucin domain-containing protein 4 (TIM4), brain angiogenesis inhibitor 1 (BAI1), receptor for advanced glycation end products (RAGE), and stabilin-2 (Stab2). The TAM receptor tyrosine kinases, which include TYRO3, AXL, and Mer receptor tyrosine kinase (MERTK), recognize PS through specific bridging ligands such as growth arrest-specific 6 (Gas6) and Protein S. Additionally, integrins αvβ3 and αvβ5 recognize ACs via the bridging molecule milk fat globule-epidermal growth factor 8 (MFGE8). Activated microglia also express low-density lipoprotein receptor-related protein 1 (LRP1), which directly interacts with calreticulin on the surface of ACs. In contrast, healthy cells display "Don't-Eat-Me" signals, such as CD47, on their surfaces. CD47 binds to the regulatory protein alpha (SIRPα) on microglia, leading to the tyrosine phosphorylation of the cytoplasmic domain of SIRPα and the recruitment of SHP1/2, which inhibits phagocytosis. TYRO3: TYRO3 protein tyrosine kinase. AXL: AXL protein tyrosine kinase. MERTK: Mer receptor tyrosine kinase. Gas6: growth arrest-specific 6

includes TYRO3 protein tyrosine kinase, AXL protein tyrosine kinase (AXL), and Mer receptor tyrosine kinase (MERTK). Additionally, MFG-E8 serves as another bridging molecule that connects to αvβ3/αvβ5 integrins on phagocytes [33]. Annexin I, an intracellular protein under normal conditions, translocates to the outer membrane surface of PS-containing cells during apoptosis, functioning as a bridging molecule [34]. Upon binding to PS, BAI1 initiates intracellular signaling through the ELMO1-DOCK complex, inducing Rac1-mediated actin cytoskeletal rearrangements to prepare for the "eating" of ACs [35]. CRT, a membrane-associated protein, exerts its "Eat-Me" signaling role by binding to and activating lipoprotein receptor-related protein 1 on phagocytes, thereby ensuring the successful engulfment of ACs [36]. In contrast, healthy cells display "Don't-Eat-Me" signals on their surfaces, including CD47. CD47 binds to the signal regulatory protein α (SIRPα) on the surface of phagocytes, leading to the tyrosine phosphorylation of SIRPα's cytoplasmic domain. This event recruits SHP1/2, which subsequently inhibits phagocytosis through non-muscle myosin IIA [37, 38]. These signals enable healthy cells to evade clearance by phagocytes.

Phagocytosis of microglia

Phagocytes upregulate corresponding surface receptors and bridging molecules, facilitating direct or indirect interactions between ACs and phagocytes. This interaction occurs via the CRKII/DOCK180/ELMO pathway, ultimately resulting in the activation of Rac1, which promotes cytoskeletal changes and the formation of phagocytic cups in phagocytes [39]. Members of the Rho/RAS family of GTPases, which are small signaling proteins within the Ras superfamily, play a crucial role in this process by driving actin cytoskeletal rearrangements during efferocytosis and facilitating the engulfment of ACs. Notable members of this family include RhoA, Cdc42, and Rac [40]. Research indicates that the activation of Rac1 leads to changes in the actin cytoskeleton, further promoting the engulfment of ACs, while the activation of RhoA has the opposite effect [41].

Digestion of ACs

Once ACs are engulfed by macrophages, phagosome formation occurs, leading to the release of a range of hydrolytic and degradative enzymes. These enzymes induce the fusion of the phagosome with lysosomes and promote further acidification of the resulting phagolysosome. Concurrently, the expression of glucose transporter protein type 1 and monocarboxylate transporter 1 from the solute carrier family is upregulated, facilitating the release of lactate and driving the intracellular pH toward approximately 4. This acidic environment is crucial for the degradation of the engulfed ACs, effectively completing the digestion process [42]. Additionally, the aerobic glycolytic reactions that occur during digestion further promote actin polymerization, sustaining the phagocytic activity of macrophages as they continue to clear ACs.

Cytokines and signaling pathways affecting efferocytosis

Efferocytosis is not merely a passive process; it is significantly influenced by various cytokines and signaling pathways that regulate the efficiency of apoptotic cell clearance. Cytokines such as transforming growth factor-β (TGF-β) have been shown to enhance efferocytosis by upregulating the expression of efferocytosis receptors and promoting a pro-resolving macrophage phenotype [43, 44]. In contrast, pro-inflammatory cytokines like IL-17 A can activate the JAK/STAT signaling pathway, leading to increased expression of recombinant A disintegrin and metalloprotease 17 (ADAM17), a disintegrin and metalloproteinase that cleaves the MERTK receptor, thereby inhibiting efferocytosis [45]. Additionally, the presence of neutrophil extracellular traps under inflammatory conditions has been associated with a reduction in efferocytosis, as they can suppress the functional capabilities of phagocytes [46].

Recent studies have highlighted the role of mitochondrial reactive oxygen species (mtROS) in maintaining efferocytosis, particularly within macrophages [47]. Oxidized low-density lipoprotein has been shown to disrupt this process by excessively generating mtROS, thereby impairing the effective clearance of ACs. This disruption is mediated through the CD36-PKM2 signaling pathway, which affects the internalization mechanisms related to efferocytosis [47]. TAM receptors (MERTK, AXL, TYRO3) are critical for this recognition, as they facilitate the clearance of ACs by promoting cytoskeletal rearrangement and phagosome formation. The activation of these receptors triggers downstream signaling pathways, including phosphoinositide 3-kinase (PI3K), Akt, and mitogen-activated protein kinases (MAPKs), which coordinate the phagocytic process [48]. Furthermore, the roles of the aryl hydrocarbon receptor (AhR) and indoleamine 2,3-dioxygenase (IDO1) in regulating macrophage metabolism during efferocytosis have been identified, indicating a complex relationship between metabolic pathways and the efferocytosis response [49]. Gas6 has been shown to promote microglial efferocytosis, thereby improving neurological function following subarachnoid hemorrhage [50]. Additionally, Sigma-1 receptors have been found to be regulators of microglia efferocytosis, enhancing the phagocytosis of microglia, thereby preventing secondary neuronal damage during ischemic stroke [51, 52]. This intricate balance of cytokine signaling emphasizes the potential for therapeutic interventions targeting these pathways to enhance efferocytosis

and improve outcomes in chronic inflammatory diseases characterized by impaired clearance of ACs.

Influence mechanism of interaction between microglia and other cells on efferocytosis

The interactions of microglia with other cell types in the CNS, such as neurons, astrocytes, and macrophages, are crucial for maintaining neural homeostasis and functionality. These interactions influence the efferocytosis capacity of microglia through various mechanisms. Firstly, the communication between microglia and neurons is primarily regulated by signaling molecules released by neurons. When neurons undergo apoptosis or are damaged, they release ATP, adenosine, and pro-inflammatory cytokines, which activate microglia and promote their migration to the site of injury. Microglia enhance their phagocytic capabilities by sensing these signals through the expression of specific receptors, such as P2Y receptors [53]. Additionally, neurons can facilitate a phenotypic shift in microglia by releasing anti-inflammatory cytokines, transitioning them from a pro-inflammatory state to a reparative state [54]. This transformation is essential for an effective efferocytosis process, as reparative microglia are better equipped to clear ACs and promote tissue repair. Macrophages also play a role in modulating the efferocytosis capacity of microglia by secreting cytokines and chemokines, thereby influencing the clearance of apoptotic neurons. Studies have shown that signaling molecules released by macrophages, such as MFG-E8, can enhance the phagocytic activity of microglia and promote the clearance of ACs [55]. The interactions between microglia and astrocytes are equally significant. Astrocytes play a supportive role during neuroinflammation and injury; they can release pro-inflammatory factors that activate microglia while also secreting anti-inflammatory factors to regulate their activity [56]. This bidirectional regulatory mechanism allows microglia to exhibit different functions under varying environmental conditions, ensuring the immune balance within the nervous system.

At the mechanistic level, the efferocytosis of microglia is regulated by multiple signaling pathways that play crucial roles in the interactions between microglia and other cell types, including neurons, astrocytes, and macrophages. The TREM2/Rac1 pathway is a key signaling route for microglia in recognizing and engulfing ACs. TREM2, a receptor on the surface of microglia, when activated, enhances their migratory and phagocytic capabilities [57]. Research has shown that signaling molecules released by neurons can activate TREM2, thereby improving microglial recognition and engulfment of ACs [58]. Additionally, the transcription 6 (STAT6)/arginase-1 (Arg1) pathway is significant for the reparative functions of microglia. When astrocytes release anti-inflammatory factors such as IL-4 and IL-13, they can activate the transcription factor STAT6 in microglia, promoting the expression of Arg1 and further enhancing the reparative functions of microglia [59]. The Axl/Rac1 pathway also contributes to regulating the phagocytic activity of microglia, as Axl, a receptor tyrosine kinase, when activated, facilitates the engulfment of ACs by microglia [60]. Moreover, Annexin A1, as a regulatory factor, has been shown to enhance microglial phagocytic capacity during efferocytosis by influencing the PPARγ signaling pathway [61]. EphA4, on the other hand, limits microglial efferocytosis by inhibiting the activity of MERTK, thereby affecting the resolution of inflammation [62]. Furthermore, after engulfing ACs, microglia release anti-inflammatory cytokines, creating a feedback mechanism that helps maintain immune balance within the nervous system and promotes a reparative phenotype in microglia. Through the interplay of these mechanisms, microglia effectively clear ACs, facilitate tissue repair, and uphold the health of the CNS. However, in neurodegenerative diseases such as AD, dysregulation of these interactions may lead to microglial dysfunction, exacerbating neuroinflammation and neuronal damage.

Neuroinflammation in AD

Neuroinflammation is a critical component in the pathogenesis of AD, with various triggers contributing to its onset and progression. The accumulation of amyloid-β (Aβ) plaques and neurofibrillary tangles, hallmark features of AD, is closely associated with neuroinflammatory responses. These pathological accumulations activate microglia, the resident immune cells of the CNS, leading to a pro-inflammatory environment characterized by the release of cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) [63]. Genetic factors also play a significant role; for instance, polymorphisms in immune-related genes such as CD33 have been identified as risk factors for AD, influencing microglial function and neuroinflammatory responses [64]. Additionally, environmental factors, including chronic stress and lifestyle factors such as diet and exercise, can exacerbate neuroinflammation. Chronic stress has been shown to elevate levels of glucocorticoids, which can modulate the activity of neuroinflammatory pathways, further contributing to neuronal damage [65]. The interplay of these triggers creates a vicious cycle where neuroinflammation not only contributes to neuronal loss but also perpetuates the pathological processes characteristic of AD.

Neuroinflammation significantly impacts the progression of AD, influencing both the severity of symptoms and the rate of cognitive decline. Activated microglia and astrocytes release a variety of pro-inflammatory mediators that can lead to neuronal injury and synaptic

dysfunction. This inflammatory response is not merely a byproduct of neurodegeneration but a driving force that exacerbates the disease process. Studies have shown that sustained neuroinflammation correlates with increased levels of Aβ and tau pathology, suggesting that inflammatory cytokines may facilitate the aggregation of these proteins [66]. Furthermore, neuroinflammation has been linked to the impairment of neurogenesis and synaptic plasticity, crucial processes for maintaining cognitive function [14]. The dual role of neuroinflammation—both protective and detrimental—highlights its complexity; while it serves to clear damaged cells and pathogens, excessive or chronic activation can lead to further neuronal damage and cognitive decline. Emerging therapeutic strategies are focusing on modulating neuroinflammation to slow the progression of AD, with the aim of restoring homeostasis in the neuroimmune environment [67]. Targeting specific inflammatory pathways, such as the JAK/STAT signaling pathway, has shown promise in preclinical models, indicating that a better understanding of neuroinflammatory mechanisms could lead to effective interventions [68]. Thus, neuroinflammation is not only a marker of AD but also a potential therapeutic target that could alter the course of the disease.

Role of efferocytosis of microglia in AD

Impact of efferocytosis on amyloid plaque clearance

Amyloid plaques are one of the pathological hallmarks of AD, primarily formed by the aggregation of Aβ peptides. The accumulation of Aβ is considered a major driver of neurotoxicity and neuroinflammation, leading to neuronal damage and cognitive decline. Microglia, through the process of efferocytosis, can recognize and clear these harmful Aβ aggregates, thereby reducing neuroinflammation and protecting neurons [69]. Research has shown that the efferocytosis capability of microglia is closely related to their role in clearing amyloid plaques [70]. When microglia detect Aβ aggregates, they initiate the phagocytic process by binding to specific receptors such as MerTK and Axl. Once engulfed, Aβ is not only degraded but also aids in the activation and functional enhancement of microglia, promoting the release of anti-inflammatory factors and further suppressing neuroinflammation.

However, in AD patients, microglia often exhibit a state of "chronic activation" due to prolonged exposure to the pathological environment, resulting in a decline in their efferocytosis capacity. This leads to reduced clearance efficiency of Aβ and exacerbates neuroinflammation, creating a vicious cycle [71]. This phenomenon may be associated with the activation state of microglia, changes in the microenvironment, and the influence of inflammatory factors. Studies have found that the activation of TREM2 can enhance microglial phagocytosis of Aβ, improving their efficiency in clearing amyloid plaques, which further suppresses neuroinflammation and facilitates neuroprotection [72]. Additionally, the activation of the TRPV2 ion channel is considered an important regulatory mechanism that can affect calcium ion influx in microglia and promote their phagocytosis of Aβ. Changes in calcium signaling not only influence the functional state of the cells but may also modulate their interactions with other immune cells in the microenvironment [73].

Regulation of neuroinflammation by efferocytosis

Microglial efferocytosis plays a crucial role in the regulation of neuroinflammation. By clearing ACs and cellular debris, microglia can effectively suppress the release of inflammatory factors. Studies have shown that efferocytosis can reduce the release of pro-inflammatory cytokines, such as TNF-α and IL-1β, by inhibiting the activation of microglia and monocytes, thereby alleviating the extent of neuroinflammation [74]. In AD models, the impaired phagocytic capacity of microglia is associated with a persistent state of neuroinflammation, leading to further neuronal damage and functional impairment [75]. Additionally, efferocytosis can enhance the anti-inflammatory response of microglia by modulating intracellular signaling pathways, such as extracellular signal-regulated kinase (ERK), promoting the maintenance of tissue homeostasis [76].

Efferocytosis not only inhibits the release of pro-inflammatory factors but also promotes the production of anti-inflammatory cytokines. Research has found that during the process of efferocytosis, microglia can significantly increase the expression of anti-inflammatory cytokines, such as IL-10 and TGF-β [77]. These anti-inflammatory factors play a critical role following neural injury, as they can suppress inflammatory responses and promote neuroprotection. Furthermore, efferocytosis enhances the anti-inflammatory response through the regulation of relevant signaling pathways, such as PPARγ, facilitating the repair and regeneration of neural tissue [78].

The nuclear factor kappa B (NF-κB) signaling pathway is the core pathways regulating the efferocytosis of microglia, playing a crucial role in maintaining neuroimmune homeostasis by balancing inflammatory responses and the clearance of ACs. Studies have shown that abnormal activation of NF-κB can bidirectionally regulate microglial function: on one hand, it exacerbates the inflammatory microenvironment by upregulating the secretion of pro-inflammatory cytokines such as IL-6 and TNF-α; on the other hand, it directly weakens the phagocytic capacity of microglia by inhibiting the expression of efferocytosis-related receptors like MerTK and AXL [79]. During the pathological process of brain injury,

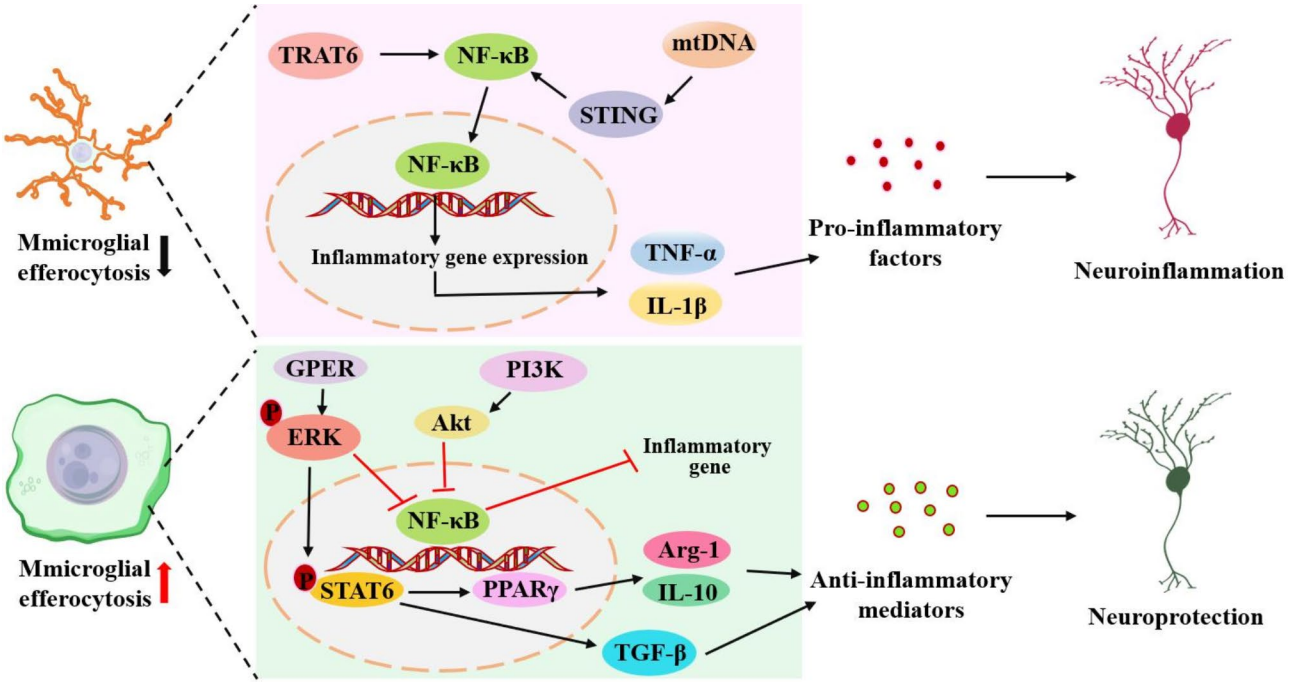

Fig. 3 Regulatory mechanism of efferocytosis on microglial neuroinflammation. Abnormal activation of nuclear factor kappa B (NF-κB) drives the transcriptional expression of inflammatory factors upon nuclear translocation, leading to the release of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β). This dysregulation impairs the efferocytosis function of microglia, thereby exacerbating neuroinflammatory responses. Once mitochondrial DNA (mtDNA) is released into the cytoplasm of microglia, it can activate the STING signaling pathway, driving the translocation of NF-κB and subsequently inducing the excessive production of pro-inflammatory mediators. Exogenous stimuli can promote the sustained activation of the NF-κB pathway by activating TRAF6, further amplifying the neuroinflammatory cascade. However, the G protein-coupled estrogen receptor (GPER) can increase the phosphorylation of extracellular signal-regulated kinase (ERK), thereby blocking the nuclear translocation of NF-κB. Activation of the PI3K/Akt pathway reduces NF-κB activity, inhibiting neuroinflammation. Furthermore, ERK can activate signal transducer and activator of transcription 6 (STAT6), leading to its phosphorylation and nuclear translocation, which increases the expression of PPARγ. This, in turn, further promotes the expression and release of anti-inflammatory mediators such as arginase-1 (Arg-1) and interleukin-10 (IL-10), thereby enhancing microglial efferocytosis and facilitating neuroprotection

mitochondrial DNA (mtDNA) released into the cytoplasm of microglia can activate the STING-cGAS signaling pathway, driving the nuclear translocation of the NF-κB p65 subunit and inducing excessive production of pro-inflammatory mediators such as IL-6 and TNF-α, leading to microglial overactivation [80, 81]. Additionally, external stimuli (such as β-amyloid and LPS) bind to TLR4, promoting the sustained activation of the NF-κB pathway through TRAF6-dependent phosphorylation of the IKK complex, further amplifying the neuroinflammatory cascade [82]. Notably, other signaling pathways can cross-regulate NF-κB activity and influence microglial function: the G protein-coupled estrogen receptor (GPER) activates ERK1/2, inhibiting the degradation of IκBα, thus blocking NF-κB nuclear translocation [83]; the PI3K/Akt pathway phosphorylates and inhibits IKKβ, reducing the DNA binding activity of NF-κB [84]. Inhibiting the NF-κB signaling pathway can significantly enhance the phagocytic capacity of microglia and improve the neuroinflammatory microenvironment (Fig. 3). Therefore, modulating the NF-κB signaling pathway could represent a potential strategy for the treatment of neuroinflammatory-related diseases.

Impact of efferocytosis on neuroprotection

The influence of microglial efferocytosis on neuroprotection in AD is multifaceted. Microglia not only participate in the clearance of ACs and debris but also help prevent the release of potentially harmful intracellular components that could trigger further inflammation and neuronal damage. Additionally, the process of efferocytosis is associated with the release of anti-inflammatory cytokines, which can promote neuronal survival and repair mechanisms. Specific signaling pathways, such as those involving the S100A9 protein, have been shown to enhance the efferocytosis activity of macrophages, thereby improving functional recovery following cerebral ischemia [85]. Therapeutic strategies aimed at enhancing efferocytosis, such as the use of soluble proteins derived from omega-3 fatty acids, have demonstrated promise in promoting neuroprotective effects and facilitating the resolution of inflammation [86]. Furthermore, microglial efferocytosis is crucial for the remodeling of neural

circuits during development and in response to injury, indicating that these cells play a vital role in maintaining homeostasis and facilitating recovery from neurodegenerative processes. However, excessive or dysregulated phagocytosis can lead to detrimental effects. Studies have observed the removal of healthy synapses in AD patients, which may contribute to cognitive decline [87]. Thus, while microglial efferocytosis fundamentally serves a protective role, its regulation is essential to ensure that neuroprotection is achieved without inadvertently exacerbating neurodegenerative changes.

Conclusions and perspectives

In conclusion, the role of microglial efferocytosis in resolving neuroinflammation in AD represents a critical area of exploration that bridges multiple research perspectives. Microglia, as the resident immune cells of the CNS, have demonstrated their significance in clearing ACs and cellular debris. This function not only mitigates neuroinflammation but also facilitates the restoration of the neural environment, highlighting the dual role of microglia in both defense and repair mechanisms. Microglial activity and the pathophysiology of AD is complex and multifaceted. On one hand, enhanced microglial clearance is associated with protective outcomes that may delay the progression of neurodegeneration. Conversely, dysregulated microglial activation can exacerbate inflammatory responses, suggesting that the state of microglial activity is a critical determinant of disease trajectory.

Despite the promising potential of targeting microglial efferocytosis as a therapeutic approach, several challenges must be addressed to translate these strategies into clinical practice. A major obstacle is the complexity of microglial biology, including their heterogeneity and dynamic responses to various stimuli. Understanding the specific microglial phenotypes and their functional states in different disease contexts is crucial for developing targeted therapies. Current imaging techniques, such as positron emission tomography, provide insights into microglial activation states but have limitations regarding specificity and sensitivity. Therefore, developing more refined imaging tools and biomarkers to accurately assess microglial activity in vivo is essential for monitoring therapeutic efficacy. Additionally, translating findings from animal models to human conditions poses another challenge, as many studies rely on rodent models that may not fully replicate human microglial responses. Establishing human-derived microglial models, such as those developed from induced pluripotent stem cells, could enhance the relevance of preclinical research. Overall, while targeting microglia offers a hopeful avenue for treating neuroinflammation and neurodegenerative diseases, overcoming these challenges will require interdisciplinary collaboration among neuroscience, pharmacology, and imaging technologies. Future research should focus on elucidating the precise roles of microglia in various disease states, developing targeted therapeutic strategies, and improving methods for assessing microglial function in clinical settings. By addressing these challenges, we can unlock the full potential of microglia as therapeutic targets in the quest for effective treatments for CNS disorders.

Abbreviations

AD	Alzheimer's disease
CNS	Central nervous system
ACs	Apoptotic cells
STAT6	Transcription 6
Arg1	Arginase-1
ATP	Adenosine triphosphate
UTP	Uridine triphosphate
S1P	Sphingosine-1-phosphate
CX3CL1	CX3C motif chemokine ligand 1
LPC	Lysophosphatidylcholine
PS	Phosphatidylserine
BAI1	Brain angiogenesis inhibitor 1
Gas6	Growth arrest-specific 6
AXL	AXL protein tyrosine kinase
MERTK	Mer receptor tyrosine kinase
SIRPα	Signal regulatory proteinα
CRT	Calreticulin
TGF-β	Transforming growth factor-β
ADAM17	Metalloprotease 17
MFG-E8	Milk fat globule epidermal growth factor 8
TIM4	T cell immunoglobulin and mucin domain-containing protein 4
BAI1	Brain angiogenesis inhibitor 1
RAGE	Receptor for advanced glycation end products
Stab2	Stabilin-2
mtROS	Mitochondrial reactive oxygen species
PI3K	Phosphoinositide 3-kinase
MAPKs	Mitogen-activated protein kinases
AhR	Aryl hydrocarbon receptor
IDO1	Indoleamine 2,3-dioxygenase
Aβ	Amyloid-β
IL-1β	Interleukin-1β
IL-6	Interleukin-6
TNF-α	Tumor necrosis factor-alpha
NF-κB	Nuclear factor kappa B
ERK	Extracellular signal-regulated kinase
mtDNA	Mitochondrial DNA
DAM	Disease-associated microglia
DAMPs	Damage-associated molecular patterns

Author contributions

YPC drafted the manuscript and created the Figs. 1, 2 and 3, while YHK and YN conducted the literature search and organized the data. HTY and CLX contributed to the manuscript's conceptualization, and HGF and HQL revised the manuscript and conducted the final review.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication
All authors approved the final version of the manuscript.

Competing interests
The authors declare no competing interests.

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