Lipid metabolism in microglia: Emerging mechanisms and therapeutic opportunities for neurodegenerative diseases (Review)

YUNLONG SUN[1,2], KAIFANG WEI[1], XUDONG LIAO[2], JIAN'AN WANG[1], LI'NA GAO[1] and BO PANG[1]

[1]College of Pharmacy, Jining Medical University, Rizhao, Shandong 276826, P.R. China; [2]Gao Shixian National Famous Chinese Medicine Expert Inheritance Studio, Changchun University of Chinese Medicine, Changchun, Jilin 130117, P.R. China

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Abstract. Neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis, are characterized by progressive neuronal loss and neuroinflammation, with microglial dysfunction emerging as a central driver of pathogenesis. Microglia, the central nervous system-resident immune cells, exhibit dual pro-inflammatory and anti-inflammatory phenotypes, dynamically regulated by lipid metabolic reprogramming. Chronic activation of M1 microglia exacerbates neuronal damage, while M2 microglia promote tissue repair via phagocytic clearance and neurotrophic factor secretion. Lipid dysregulation-marked by ceramide accumulation, cholesterol esterification defects and oxidized lipid-driven neuroinflammation-critically modulates microglial polarization. Mechanistic studies reveal that mitochondrial dysfunction, lysosomal stress and ferroptosis intersect with lipid metabolic pathways to amplify neurotoxicity. Therapeutic strategies targeting lipid homeostasis, such as TREM2 agonism, demonstrate efficacy in preclinical models by restoring microglial function and mitigating pathology. This review synthesizes emerging evidence linking microglial lipid metabolism to NDD progression, highlighting novel biomarkers and therapeutic avenues to disrupt the lipid-neuroinflammation axis in neurodegeneration.

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Correspondence to: Professor Li'na Gao or Dr Bo Pang, College of Pharmacy, Jining Medical University, 669 Xueyuan Road, Rizhao, Shandong 276826, P.R. China
E-mail: linagao448@126.com
E-mail: pbb1996@126.com

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1. Introduction

Neurodegenerative diseases (NDDs) represent a group of disorders characterized by progressive degeneration and neuronal death within the nervous system. With accelerating global population aging, NDDs have emerged as a critical public health concern, imposing substantial burdens on individual health outcomes and societal healthcare resources (1). Alzheimer's disease (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS) constitute the most prevalent and clinically severe representatives within this category (2). AD manifests as progressive cognitive decline accompanied by β-amyloid aggregation and neurofibrillary tangles (3). PD primarily presents with motor symptoms including tremor, rigidity and bradykinesia, with degeneration of dopaminergic neurons in the substantia nigra representing its core pathological hallmark (4). ALS features progressive muscular weakness and atrophy resulting from extensive upper and lower motor neuron degeneration (5). Despite distinct clinical presentations, these disorders share common pathological mechanisms involving neuronal damage, apoptosis and neuroinflammation, with disease pathogenesis intricately linked to gene-environment interactions (6,7).

Microglia, the resident immune cells of the central nervous system (CNS), play pivotal roles in maintaining neural homeostasis and responding to pathological perturbations (8,9). Under physiological conditions, quiescent microglia continuously surveil the neural microenvironment through dynamic process extension, participating in neurodevelopmental processes and synaptic pruning (10). However, in neurodegenerative contexts-particularly in AD, PD and ALS-microglial functions undergo significant alterations (11-13). Activated microglia proliferate and secrete cytokines, chemokines and immune mediators, initiating neuroinflammatory cascades that exacerbate neuronal damage (14). Studies demonstrate

that chronic microglial activation correlates with sustained neuroinflammation, potentially accelerating neurodegeneration through oxidative stress induction, immune dysregulation and apoptotic pathway activation (15,16).

Lipid metabolism maintains fundamental importance in preserving cellular structural and functional integrity (17). Lipids not only serve as fundamental structural components of cellular membranes but also participate in signal transduction, energy storage and various cellular regulatory processes. Of note, dysregulated lipid metabolism in microglia may critically influence neurodegenerative pathogenesis through neuroinflammatory modulation (12,18,19). Research indicates that fatty acid metabolites, particularly oxidized lipids, can regulate microglial immune responses by activating specific receptor pathways (20,21). Accumulation of lipid peroxidation products, especially oxidized long-chain fatty acids, induces microglial hyperactivation and pro-inflammatory cytokine release, thereby initiating or amplifying neural damage (18). Furthermore, lipid metabolic disturbances may contribute to neuronal membrane deterioration and functional decline, suggesting their potential utility as biomarkers and therapeutic targets in NDDs.

2. Microglial activation in NDDs

Pattern recognition and phenotypic transition of microglia. As the principal immune effector cells in the CNS, microglial activation constitutes a central event in neurodegenerative pathogenesis. In NDDs, microglia detect pathological signals through pattern recognition receptors (PRRs), including damage-associated molecular patterns (DAMPs) such as amyloid-β (Aβ) aggregates, hyperphosphorylated Tau proteins, neuronal debris and mitochondrial DNA (mtDNA) in AD (22,23). Disease-specific DAMP activation mechanisms also operate across other NDDs: For instance, α-synuclein (α-syn) oligomers in PD activate the NF-κB signaling pathway via Toll-like receptor (TLR)2/4 receptors (24), while myelin fragments in multiple sclerosis (MS)-which is primarily an autoimmune demyelinating disease-trigger inflammation through TLR4/MYD88 innate immune signal transduction adaptor (MyD88) pathways (25,26). These endogenous signals induce microglial transition from resting (M0) to activated states, manifesting as somatic hypertrophy, process retraction and enhanced motility (27,28). Notably, microglial activation exhibits high heterogeneity, with phenotypes dynamically regulated by local microenvironmental cues. For instance, Aβ oligomers bind CD36/TLR4/TLR6 receptor complexes to activate MyD88-dependent signaling, driving nuclear translocation of NF-κB and interferon regulatory factors, thereby initiating transcription of pro-inflammatory cytokines (e.g., IL-1β, TNF-α) and chemokines [e.g., C-C motif chemokine ligand (CCL)2, CXCL10] (29,30). Similarly, α-syn in PD activates the NLR family pyrin domain containing 3 (NLRP3) inflammasome via caspase-1-dependent pyroptosis, promoting gasdermin D cleavage (31), while TAR DNA binding protein-43 aggregates in ALS trigger calcium influx-dependent NLRP3 activation through P2X7 receptors (32,33). These mechanisms amplify inflammatory signaling and facilitate NLRP3 inflammasome assembly (34,35).

Aberrant microglial endocytosis critically modulates neurodegenerative microenvironments. In AD pathology, abnormally modified Tau proteins regulate microglial activation: Hyperphosphorylated Tau enters microglia via CX3CR1 receptor-mediated endocytosis, activating Syk tyrosine kinase signaling to induce phagolysosomal dysfunction and pro-inflammatory mediator release (36,37). This receptor-mediated endocytic mechanism demonstrates cross-disease conservation: In Huntington's disease (HD), mutant huntingtin upregulates complement C1q-mediated synaptic tagging of PSD-95 sites, activating CR3-dependent synaptic pruning (38-40), while progranulin deficiency in frontotemporal dementia exacerbates Tau propagation through lysosomal dysfunction (41). In addition, ATP released from injured neurons activates P2X7 purinergic receptors to induce calcium oscillations, enhancing NLRP3 inflammasome activity and caspase-1-dependent IL-1β maturation (35,42). In traumatic brain injury and neuroinflammation, triggering receptor expressed on myeloid cells 1 (TREM-1) receptors mediate microglia-neutrophil crosstalk via SYK signaling, amplifying dopaminergic neuron degeneration in the substantia nigra (43). Such multi-signal synergy sustains microglial activation, establishing self-reinforcing inflammatory loops. Importantly, aging-associated microglial senescence elevates activation thresholds: TREM2 downregulation in aged individuals reduces Aβ clearance efficiency, while senescence-associated secretory phenotype factors (e.g., IL-6, MMP-9) impair homeostatic maintenance (44,45).

Microglial activation exhibits stage-dependent characteristics in neurodegenerative progression. During early AD, localized Aβ deposits recruit microglia via chemokine gradients to form barrier-like structures constraining plaque spread, with microglia predominantly exhibiting M2-like anti-inflammatory phenotypes that secrete insulin-degrading enzyme and apolipoprotein E (APOE) to facilitate Aβ clearance (46,47). Similar spatial heterogeneity occurs in MS lesions: Peri-plaque microglia overexpress APOE and secreted phosphoprotein 1 (SPP1), displaying enhanced phagocytosis but impaired repair capacity (48,49), while C1q complement inhibition rescues aberrant synaptic pruning (50,51). However, chronic inflammatory microenvironments drive phenotypic shifts toward M1-like proinflammatory states as pathology advances. Transcriptomic studies reveal that disease-associated microglia in AD brains upregulate APOE, TREM2 and SPP1 while downregulating phagocytic pathways [e.g., liver X receptor (LXR)/retinoid X receptor (RXR) signaling], suggesting functional transition from protective clearance to pathological promotion (44). In HD, this phenotypic shift involves cyclic GMP-AMP synthase (cGAS)-stimulator of interferon response cGAMP interactor (STING) pathway activation: Mutant Huntingtin (mHTT) induces mtDNA leakage, triggering chronic neuroinflammation via type I interferon responses (52-54). Such transitions correlate with mitochondrial dysfunction: Aβ-induced loss of mitochondrial membrane potential reduces ATP synthesis, while leaked mtDNA activates cGAS-STING signaling to exacerbate type I interferon production and neuroinflammation (55,56).

Balancing act: Pro-inflammatory injury vs. anti-inflammatory repair. Microglia exhibit dual paradoxical functions in NDDs: Their pro-inflammatory (M1) phenotype exacerbates

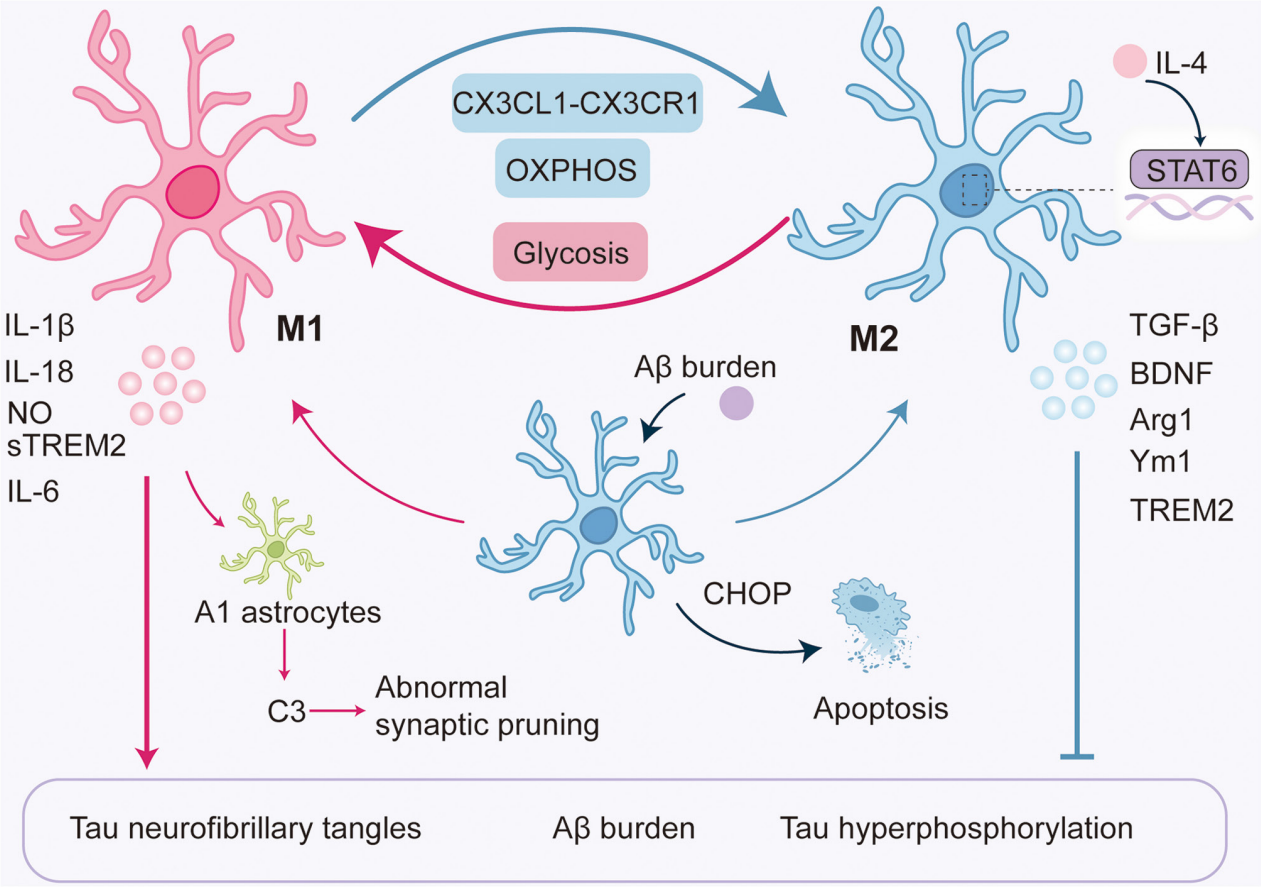

Figure 1. Dual pro-inflammatory and anti-inflammatory roles of microglia. M1 microglia secrete pro-inflammatory factors such as IL-1β, IL-18, sTREM2 and IL-6. These mediators cause neuronal injury and concurrently promote the transformation of astrocytes into the neurotoxic A1 phenotype, which secretes complement component C3 and mediates aberrant synaptic pruning. In addition, M1 microglia produce NO, which modifies Tau protein, thereby enhancing its phosphorylation and facilitating the formation of neurofibrillary tangles. Upon IL-4 stimulation, microglia activate the STAT6 signaling pathway to secrete Arg1 and Ym1, promoting polarization toward the M2 phenotype. M2 microglia, in turn, secrete cytokines such as BDNF and TGF-β to enhance synaptic plasticity and mitigate Aβ burden via TREM2 signaling. TREM2, triggering receptor expressed on myeloid cells 2; NO, nitric oxide; BDNF, bone-derived neurotrophic factor; sTREM2, soluble triggering receptor expressed on myeloid cells 2; IL-6, interleukin-6; CX3CL1, C-X3-C motif chemokine ligand 1; CX3CR1, C-X3-C motif chemokine receptor 1; OXPHOS, oxidative phosphorylation; C3, complement component 3; STAT6, signal transducer and activator of transcription 6; TGF-β, transforming growth factor β; Arg1, arginase 1; Ym1, chitinase-like protein 3.

neuronal damage through cytotoxic mediator release, while the anti-inflammatory (M2) phenotype exerts neuroprotection via pathological protein clearance and neurotrophic factor secretion (as shown in Fig. 1). This functional dichotomy is dynamically regulated by cytokine networks, disease stages and aging status. During early AD, M2-polarized microglia clear soluble Aβ through TREM2-dependent phagocytosis and secrete brain-derived neurotrophic factor and TGF-β to enhance synaptic plasticity (46,47,57). Furthermore, IL-4 stimulation promotes M2 polarization via STAT6 signaling-mediated upregulation of arginase-1 (Arg1) and chitinase-like molecule 1, enhancing Aβ degradation capacity while suppressing neuroinflammation (58,59).

However, during advanced AD stages, chronic inflammatory microenvironments induce microglial dysfunction with M1 phenotype predominance. Activated M1 microglia release IL-1β and IL-18 through NLRP3 inflammasome-dependent mechanisms. These pro-inflammatory cytokines not only directly damage neurons but also drive astrocyte transformation into neurotoxic A1 phenotypes (35,60). Concurrent C3 complement secretion mediates aberrant synaptic pruning via C3aR-C3a axis activation, significantly reducing hippocampal synaptic density (60,61). Reactive nitrogen species such as nitric oxide (NO) produced by M1 microglia modify Tau proteins, increasing phosphorylation levels and neurofibrillary tangle formation (62,63). Neuropathological analyses reveal positive correlations between cerebrospinal fluid (CSF) M1 markers (e.g., TREM2, IL-6) and Tau-PET signal intensity in patients with AD, suggesting pro-inflammatory microglia accelerate Tau pathology propagation (37,64). In late-stage disease, aging-associated lysosomal acidification defects prevent effective Aβ degradation, leading to intracellular lipofuscin-like inclusion accumulation and autophagic-lysosomal pathway suppression (45,65). Sustained Aβ oligomer exposure induces endoplasmic reticulum stress, activating the unfolded protein response and triggering CHOP-dependent apoptosis, thereby depleting protective microglial populations (66,67). Transcriptomic profiling reveals functional exhaustion characterized by downregulated NFE2 like bZIP transcription factor 2 antioxidant and peroxisome proliferator activated receptor (PPAR)γ pathways (44).

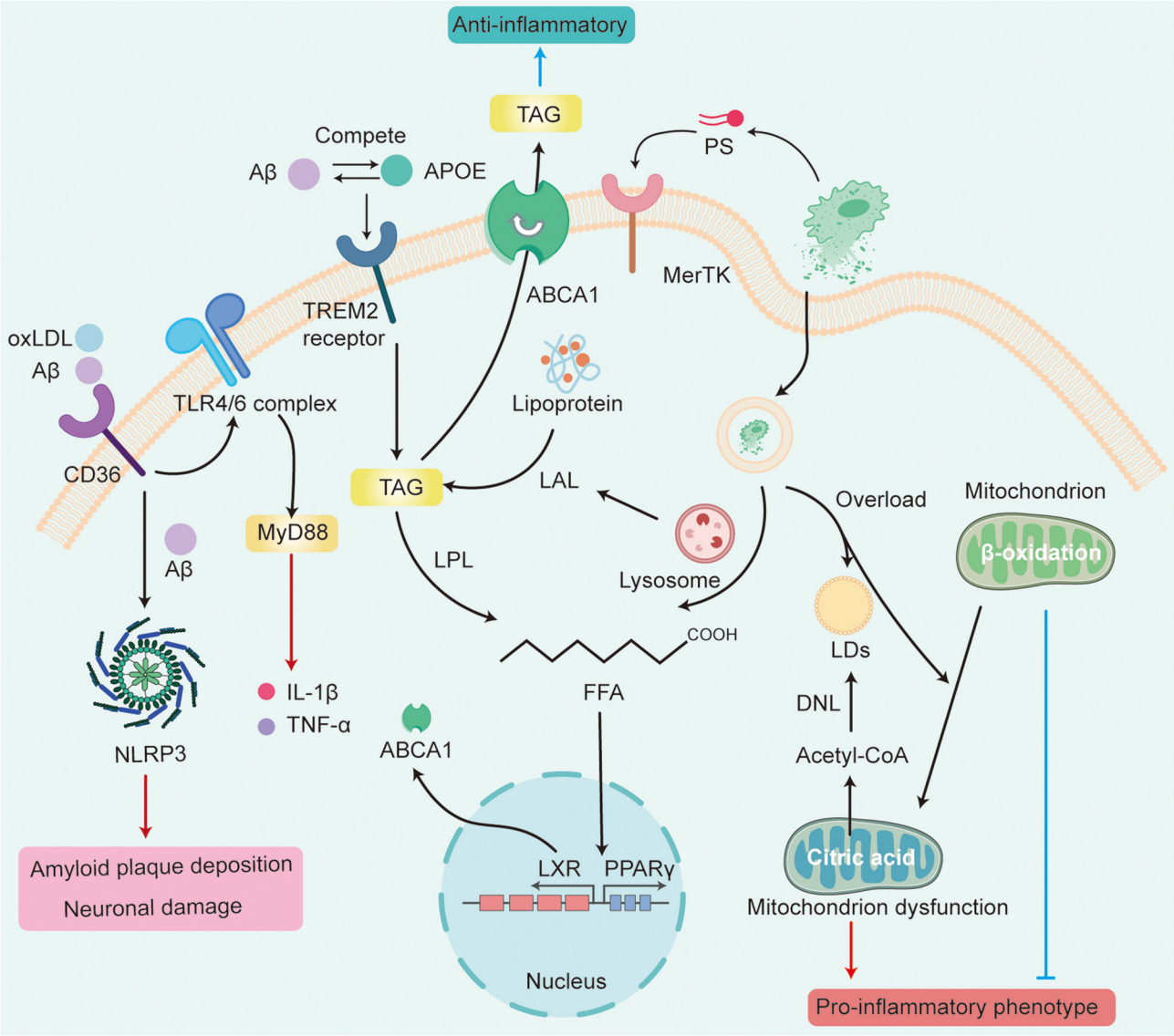

Figure 2. Link between lipid metabolism and the pro-inflammatory and anti-inflammatory phenotypes of microglia. CD36 recognizes oxLDL and Aβ; its binding with Aβ drives the assembly of the NLRP3 inflammasome, accelerating amyloid plaque deposition and neuronal injury. Furthermore, activation of CD36 can trigger a MyD88-dependent signaling cascade via the TLR4/6 complex, promoting the release of pro-inflammatory cytokines IL-1β and TNF-α. Aβ and APOE competitively bind to TREM2, thereby regulating microglial lipid uptake. LAL degrades lipoproteins in lysosomes to release cholesterol, while intracellular cholesterol is hydrolyzed into FFA by LPL. Myelin debris is internalized and degraded in lysosomes to produce FFAs, which further activate nuclear receptors LXR and PPARγ, inducing the expression of the lipid efflux transporter ABCA1. This promotes reverse cholesterol transport and suppresses inflammatory responses. Under pathological conditions, excessive accumulation of myelin debris leads to lipid droplet formation and mitochondrial dysfunction. Normally, mitochondria generate ATP via β-oxidation, which is associated with the anti-inflammatory phenotype; however, in pathological states, abnormal accumulation of citrate in the TCA cycle occurs within mitochondria, followed by its transport to the cytosol where it is converted into acetyl-CoA. This drives DNL, leading to abnormal lipid droplet accumulation and excessive release of inflammatory mediators. oxLDL, oxidized LDL; LAL, lysosomal acid lipase; LPL, lipoprotein lipase; FFA, free fatty acids; DNL, *de novo* lipogenesis; NLRP3, NOD-like receptor family, pyrin domain-containing 3; MyD88, myeloid differentiation primary response 88; TLR4/6, toll-like receptor 4/6; IL-1β, interleukin-1β; TNF-α, tumour necrosis factor α; APOE, apolipoprotein E; LXR, liver x receptor; PPARγ, peroxisome proliferator-activated receptor γ; ABCA1, ATP-binding cassette transporter A1; TAG, triacylglycerol; PS, phosphatidylserine; MerTK, MER tyrosine-protein kinase; LDs, lipid droplets.

Lipid metabolism as a regulator of microglial function. As illustrated in Fig. 2, microglial functional states critically depend on dynamic lipid metabolic homeostasis. Lipids not only constitute fundamental membrane structures but also act as signaling molecules, energy substrates and inflammatory mediators, deeply engaging in phagocytosis, inflammatory responses and tissue repair processes (48,68). Lipid metabolic dysregulation is closely associated with neurodegenerative pathologies, such as AD (48,68). Microglia sense extracellular lipid microenvironmental changes through specialized receptors, integrating lipid signals via endocytic, oxidative, synthetic and storage pathways to modulate functional phenotypes (69,70).

Microglia detect parenchymal lipid composition changes through multiple PRRs. CD36, a class B scavenger receptor, recognizes oxidized low-density lipoprotein and Aβ while facilitating fatty acid transmembrane transport (70,71). CD36 activation triggers MyD88-dependent signaling via TLR4/6 complexes, promoting pro-inflammatory cytokine release (e.g., IL-1β, TNF-α) and enhancing phagocytic activity (72,73). In

AD models, CD36-Aβ interactions drive NLRP3 inflammasome assembly, accelerating amyloid deposition and neuronal damage (30,74). APOE regulates microglial lipid/Aβ uptake through TREM2 receptor binding. The APOE4 isoform exhibits impaired lipid-loading capacity, causing cholesterol clearance defects that elevate AD risk (20,75). Of note, APOE competes with Aβ for TREM2 binding, with APOE dysfunction synergistically promoting Tau pathology spread (76,77).

Microglial lipid handling involves intricate enzymatic cascades and organelle crosstalk. Lipoprotein lipase maintains membrane phospholipid homeostasis and supports phagocytosis by hydrolyzing triacylglycerols to release free fatty acids (FFAs) (78,79). Lysosomal acid lipase (LAL) degrades internalized lipoproteins, with LAL deficiency causing cholesteryl ester (CE) accumulation and lysosomal storage disorders (80). During myelin clearance, microglia recognize phosphatidylserine on apoptotic cells via MER proto-oncogene, tyrosine kinase receptors, initiating phagolysosomal pathways (81,82). Myelin-derived FFAs activate nuclear receptors LXR and PPARγ, inducing cholesterol efflux transporter ATP binding cassette subfamily A member 1 (ABCA1) expression to promote reverse cholesterol transport and suppress inflammation (83,84). However, aging or chronic pathology induces myelin debris overload exceeding microglial clearance capacity, leading to lipid droplet (LD) formation and mitochondrial dysfunction that drive pro-inflammatory polarization (85,86). Preclinical studies have shown that the PPARγ agonist pioglitazone exhibits reproducible neuroprotective effects in tissue culture and animal models (87). However, clinical trials of Pioglitazone in early PD have indicated that it is ineffective, possibly due to toxin-induced animal models not reflecting the pathogenesis of PD or pioglitazone failing to reach the target nigral neurons and not achieving sufficient drug exposure in clinical trials (88). Peroxisomal β-oxidation degrades very-long-chain fatty acids, with its dysfunction causing lipotoxic mediator accumulation (e.g., ceramides) that induce oxidative stress and aberrant inflammatory signaling (89,90). Multifunctional protein-2-deficient mice exhibit microglial metabolic reprogramming characterized by enhanced glycolysis, reactive oxygen species (ROS) bursts and pro-inflammatory cytokine hypersecretion (91,92). Mitochondrial β-oxidation correlates with anti-inflammatory phenotypes, showing significant upregulation in alternatively activated microglia to support tissue repair through ATP generation (93). However, pro-inflammatory stimuli disrupt mitochondrial TCA cycling, causing the accumulation of citrate, which is exported to the cytoplasm for acetyl-CoA conversion, driving *de novo* lipogenesis (DNL) and LD biogenesis (94,95). This metabolic shift provides precursors for inflammatory mediator synthesis (e.g., prostaglandins) while altering membrane fluidity to affect receptor signaling (96,97).

Global lipidome remodeling drives microglial phenotypic switching. Pro-inflammatory activation enhances glycolysis and mitochondrial fragmentation, inducing citrate efflux that activates ATP-citrate lyase to promote acetyl-CoA production and DNL initiation (94,98). Endoplasmic reticulum-resident fatty acid elongases [e.g., ELOVL fatty acid elongase 5 (ELOVL5)] and desaturases (e.g., stearoyl-CoA desaturase) modify nascent FFAs for membrane phospholipid integration or triacylglycerol (TAG) storage (97,99). LDs serve dual roles as neutral lipid reservoirs sequestering arachidonic acid to limit peroxidation, while functioning as prostaglandin synthesis platforms regulating inflammatory cascades (100,101). In aged brains, lipid droplet-accumulating microglia exhibit TAG enrichment, phagocytic impairment and pro-inflammatory mediator hypersecretion, emerging as neurodegenerative drivers (102). Conversely, anti-inflammatory phenotypes activate LXR/PPARγ signaling to enhance cholesterol efflux and restore remyelination capacity (103,104).

3. Dysregulated lipid metabolism in neurodegeneration

AD. The human brain, being the most lipid-rich organ, maintains complex lipid composition with exquisite homeostatic regulation. Patients with AD exhibit significant lipidomic alterations across multiple brain regions (105-109). Fatty acid metabolic dysregulation-observed even in early AD-manifests as elevated total FFAs in CSF with subtype-specific variations: ω-3 polyunsaturated fatty acids (PUFAs) like docosahexaenoic acid decrease markedly in vulnerable regions, while pro-inflammatory arachidonic acid levels rise abnormally (110-112). This PUFA/saturated fatty acid ratio imbalance not only reduces membrane fluidity but may also disrupt amyloid precursor protein (APP) processing via lipid raft structural modifications, thereby promoting Aβ generation (113-115). Notably, decreased ω-3 PUFAs/monounsaturated fatty acids and reduced desaturation indices in lipid rafts emerge early in entorhinal and frontal cortices, suggesting lipid microenvironment alterations precede classical pathological deposition (116).

Sphingolipid dysregulation constitutes another core feature of AD lipid abnormalities, with ceramide accumulation strongly correlating with neurodegeneration. Patients with AD show elevated ceramide levels alongside decreased sphingomyelin in prefrontal and temporal cortices, associated with enhanced sphingomyelinase activity and downregulated synthetic enzymes (117-121). Ceramide accumulation exacerbates neuronal damage through mitochondrial oxidative stress and apoptosis while directly promoting Aβ production via β-secretase activation (122-124). Myelin-specific lipids (e.g., sulfatides, galactosylceramides) exhibit early depletion in AD, potentially linked to oligodendrocyte dysfunction and white matter integrity loss-pathological changes confirmed to correlate with cognitive decline (125-127). Despite blood-brain barrier restrictions, AD brains demonstrate elevated cholesterol levels positively correlating with pathological severity (118,128-130). Enhanced acetyl-CoA acetyltransferase 1 (ACAT1) activity in the entorhinal cortex promotes CE accumulation, which exacerbates Aβ deposition through APP amyloidogenic cleavage and alters γ-secretase localization via lipid raft modulation (131-133). Notably, astrocyte-specific cholesterol synthesis inhibition significantly alleviates Aβ and Tau pathology in AD mice, indicating glial cholesterol metabolism exerts transcellular regulatory effects (134).

Genetic studies underscore the central role of lipid metabolism genes in AD risk. APOEε4-the strongest genetic risk factor-impairs lipid transport alongside Aβ clearance: APOEε4 carriers exhibit reduced lipoprotein lipidation compared to APOEε3, leading to defective neuronal lipid clearance and mitochondrial dysfunction (135,136). Risk genes like TREM2

and ABCA1/ABCA7 influence AD progression by regulating microglial lipid phagocytosis/efflux. The TREM2 R47H variant loses CE recognition capacity, causing lipid droplet dysmetabolism and impaired remyelination (15,76,137,138). These findings collectively implicate lipid trafficking defects as multi-mechanism drivers of AD pathology. AD brains show reduced pro-resolving mediators like DHA-derived resolvins alongside elevated pro-inflammatory prostaglandin E2, perpetuating chronic neuroinflammation through pro-/anti-inflammatory mediator imbalance (139-143). Aberrant lipid sensing in glial cells exacerbates this dysregulation: APOE4 astrocytes exhibit impaired fatty acid β-oxidation, causing intracellular lipid accumulation and pro-inflammatory cytokine release (135). Ceramides directly activate NLRP3 inflammasomes, establishing lipid-inflammation positive feedback loops that accelerate neuronal injury (144,145).

PD. The neuropathological hallmark of PD is the formation of Lewy bodies (LBs), proteinaceous inclusions composed of abnormally aggregated α-syn. Studies have revealed that dysregulated lipid metabolism not only modulates α-syn pathology but also interacts with mitochondrial dysfunction, endoplasmic reticulum stress and inter-organelle communication, collectively forming a complex pathogenic network in PD. Notably, lipid metabolic disturbances-particularly the dyshomeostasis of PUFAs, cholesterol and cardiolipin-play pivotal roles in driving dopaminergic neurodegeneration.

Lipid accumulation observed in patients with PD is closely linked to α-syn aggregation (146). Mutations in the glucosylceramidase β1 (GBA1) gene represent one of the most significant genetic risk factors for PD. These mutations impair lysosomal function, leading to intracellular cholesterol and PUFA accumulation (147). Elevated PUFAs not only upregulate α-syn gene expression but also directly induce oligomerization of α-syn monomers into neurotoxic intermediates (148). Lipid-mediated conformational changes in α-syn may involve interactions with cellular membranes: Binding to cholesterol-rich lipid rafts accelerates the transition of soluble α-syn monomers into insoluble fibrils, providing a molecular basis for LB formation (149,150). Furthermore, elevated ApoE levels in the cerebrospinal fluid of patients with early-stage PD suggest that α-syn exploits ApoE-mediated lipid transport systems for interneuronal pathological propagation, amplifying the impact of lipid dysregulation in PD progression (151).

Mitochondrial-ER crosstalk emerges as a critical pathological axis in PD. Excessive fatty acid accumulation triggers mitochondria-cytoplasmic stress responses, generating ROS that preferentially oxidize PUFAs. This lipid peroxidation cascade alters mitochondrial membrane permeability and disrupts electron transport chain function (152). Loss of ER-localized very-long-chain fatty acid elongase Elovl2 disrupts fatty acid synthesis, leading to short-chain fatty acid accumulation within the ER lumen. This metabolic perturbation induces sustained ER stress through unfolded protein overload, culminating in mitochondrial decompensation, exacerbating ROS production and establishing a vicious cycle of mitochondrial decline (153,154). Cardiolipin (CL), a signature phospholipid of mitochondrial inner membranes, exhibits complex pathological interactions in PD. Misfolded α-syn directly binds CL, compromising mitochondrial membrane integrity and impairing oxidative phosphorylation (155). Critically, CL governs mitophagy quality control: Aberrant CL levels impair selective clearance of damaged mitochondria while activating NLRP3 inflammasomes and the cGAS-cGAMP-STING-TBK1-interferon regulatory factor 3 pathway, synergistically exacerbating dopaminergic neuron degeneration (156,157).

Microglia bridge lipid dysregulation and neurodegeneration in PD by sensing metabolic disturbances. Oxidized lipids and glycosphingolipids activate microglia, triggering TNF-α and IL-1β release and establishing chronic neuroinflammation, particularly in GBA1-mutant PD models (158-160). Elevated glycoprotein NMB protein levels in PD substantia nigra microglia correlate with cerebral lipid accumulation, indicating lipid metabolic stress directly drives neuroimmune responses (161). The ApoE ε4 allele exacerbates microglial clearance deficits by impairing lipid transport, facilitating α-syn pathology spread (162,163). Notably, lipopolysaccharide (LPS)-induced microglial activation enhances neuronal susceptibility to α-syn aggregation (164,165). Dysregulated neuron-astrocyte lipid metabolic coupling further contributes to PD: Neurons export toxic fatty acids via ApoE-positive lipid droplets to astrocytes for mitochondrial β-oxidation. However, α-syn-induced astrocytic mitochondrial dysfunction disrupts this detoxification pathway, leading to toxic lipid reaccumulation in neurons and establishing a PD-accelerating feedback loop (166,167).

Other diseases. In HD, synaptic membrane cholesterol dyshomeostasis precedes myelin structural alterations. Mutant huntingtin directly disrupts cholesterol biosynthesis by suppressing sterol regulatory element-binding proteins, leading to significantly reduced total cholesterol levels in neurons and brain tissues of patients with HD and transgenic animal models (168-172). Dynamic changes in 24-hydroxycholesterol (24-OHC) reveal stage-specific metabolic imbalances: Transient elevation in early disease stages reflects compensatory mechanisms, while progressive decline in later stages correlates with neuronal degeneration and attenuated LXR signaling, with plasma 24-OHC levels strongly associated with disease progression (171,173,174). Gene expression analyses demonstrate sustained downregulation of key cholesterol synthesis enzymes (e.g., 3-hydroxy-3-methylglutaryl-CoA reductase, cytochrome P450 family 51) in cortical tissues of patients with HD and in animal models of HD, positively correlating with CAG repeat length and mHTT burden (172,175-177). Astrocytic dysfunction exacerbates metabolic disturbances, characterized by reduced ApoE secretion, while LXR agonists partially rescue these phenotypes, highlighting the central role of glia-neuron crosstalk (171,178,179). Patients with HD also exhibit sphingolipid dysregulation, including elevated total ceramides but marked reductions in myelin-critical dihydroceramide species (e.g., C18:0). Regional deficiencies in ganglioside GM1 and sulfatides further indicate impaired synthesis pathways, destabilizing myelination across brain regions (180).

ALS is intricately linked to systemic lipid metabolic disturbances. Blood profiling reveals significant elevations in plasma sphingomyelins, ceramides and triglycerides in patients with ALS, with a 32-metabolite panel (including 11

lipid species) effectively distinguishing patients from healthy controls (181-185). Blood-brain barrier permeability alterations may exacerbate central-peripheral lipid exchange abnormalities (186,187). Elevated phosphatidylcholine (PC 36:4) in CSF and its recapitulation in superoxide dismutase 1 (SOD1)-G93A mouse brain tissues suggest direct involvement of central lipid remodeling in ALS pathogenesis (188,189).

Postmortem studies demonstrate pronounced lipid abnormalities in ALS spinal cords, including increased triglycerides and lysophosphatidylcholine in gray matter, with ceramide, sphingomyelin and complex sphingolipids accumulating in correlation with disease severity (190-192). Animal models mirror these findings: SOD1 mutant mice exhibit progressive ceramide and CE accumulation in spinal tissues, while fused in sarcoma-overexpressing mice display cardiolipin downregulation and altered nuclear membrane lipid composition (190,192-195). Aberrant ceramide accumulation in ALS correlates with oxidative stress-driven enhancement of *de novo* sphingolipid synthesis, with dysregulated serine palmitoyltransferase activity due to SPTLC1 variants implicated in familial ALS (190,196,197). CE accumulation in ALS patient spinal cords and SOD1 models positively correlates with disease progression, and its byproduct lysoPC directly damages motor neurons (191). Although serum cholesterol levels show inconsistent associations with ALS prognosis, CNS-specific oxysterols (e.g., 25-OHC) exhibit validated neurotoxicity in cellular and animal models (198,199).

4. Lipid homeostasis and microglial-mediated neuroinflammation

Lipid droplet accumulation and microglial dysfunction. Cerebral metabolism is tightly regulated to ensure precise neuronal function (200). Although the brain primarily relies on circulating glucose for energy, lipids also support neuronal activity through metabolic crosstalk with astrocytes (166,201). A study has revealed lipid-laden vesicles in glial cells of patients with dementia, with lipid-accumulating microglia exhibiting functional impairments, suggesting a critical link between microglial function and lipid dynamics (202). Abnormal lipid accumulation, particularly lipid droplets-cytoplasmic organelles enriched in lipids that regulate cellular lipid metabolism and immune responses-is a key driver of myeloid cell immune dysfunction (203). LDs are bounded by a monolayer membrane decorated with structural proteins, including perilipin family proteins and lipid-metabolizing enzymes, which are essential for maintaining LD morphology and function. Microglial LDs are strongly implicated in neurodegenerative disease pathogenesis (204). In aged mouse models, LD-rich microglia display functional dysregulation, characterized by elevated ROS, increased pro-inflammatory cytokine production and impaired phagocytosis (102). Research in *Grn* (progranulin-encoding gene) knockout mice demonstrated that 9-month-old mice exhibit pronounced LD accumulation in hippocampal microglia. Transcriptomic profiling revealed that LD-enriched microglia in *Grn*-/-mice share gene network signatures with 20-month-old wild-type aged mice, indicating conserved lipid-associated dysfunction in neurodegeneration and aging (205). In a cerebral ischemia rat model, Lin *et al* (206) observed that serum glucose-oxygen deprivation significantly increases microglial LD accumulation, concurrent with elevated release of inflammatory mediators TNF-α and IL-1β. Pharmacological inhibition of LD formation not only reduced microglial inflammatory activation and mortality but also attenuated cerebral infarct volume and motor deficits in ischemic rats (206). Similarly, in a kainic acid-induced hippocampal CA1 injury model, perilipin-2 (an LD surface protein) colocalized with the microglial marker Iba1. These LD-laden microglia exhibited Apoc2 (a neutral lipid-associated apolipoprotein) deposits colocalized with lysosomal marker Lamp1, accompanied by phagocytic impairment and ROS-mediated neuronal damage (207). Collectively, these studies demonstrate that aberrant LD accumulation in microglia represents a hallmark of dysfunctional, pro-inflammatory microglial states in the aging brain and is a consistent feature across neuroimmune-associated neurodegenerative pathologies.

Cholesterol dynamics and microglial functional impairments. Early neuropathological studies identified cytoplasmic neutral lipid inclusions within glial cells in AD patient brains (202). Subsequent investigations have delineated the pathological significance of CE accumulation, observed in AD postmortem specimens (208) and recapitulated across multiple neurodegenerative disease models (208). *In vitro* evidence demonstrates that ACAT1-mediated cholesterol esterification converts myelin-derived cholesterol into CE for storage within LDs (as shown in Fig. 3). Pharmacological or genetic inhibition of this enzyme exerts neuroprotective effects in Aβ and tau pathology models through autophagy activation (209), indicating ACAT1's regulatory role in disease progression via CE metabolism. Endolysosomal cholesterol accumulation has been observed in APOE4-homozygous human induced pluripotent stem cell (iPSC)-derived astrocytes (210), implicating APOE4-induced glial cholesterol dyshomeostasis in late-onset AD pathogenesis. Three human APOE isoforms (APOE2, APOE3, APOE4), encoded by distinct alleles on chromosome 19 (211), exhibit differential lipid-binding capacities. APOE4 demonstrates reduced cholesterol efflux efficiency, predisposing to intracellular LD accumulation (212). Comparative analyses reveal more pronounced LD deposition in APOE4-expressing microglia vs. APOE3 counterparts (213). iPSC studies further show APOE4 upregulates sterol regulatory element-binding protein 2 to drive *de novo* cholesterol synthesis while disrupting cholesterol trafficking via lysosomal sequestration of free cholesterol (214). Emerging data indicate APOE4 downregulates mitochondrial oxidative phosphorylation genes and activates lipogenic pathways, exacerbating microglial LD accumulation (215). Reduced cholesterol uptake by APOE4 microglia increases extracellular cholesterol incorporation into neuronal membranes, enhancing lipid-gated potassium channel activity (212). Pharmacological inhibition of acyl-CoA synthetase 1 (ACSL1) to modulate LD levels restores purinergic signaling and sustains microglial homeostasis, supporting neural network integrity (215).

Oxysterols, cholesterol-derived metabolites, impair microglial clearance of cellular debris and neurotoxic molecules through direct cytotoxicity or downstream pathway modulation. Deficient Aβ monomer clearance promotes oligomerization and plaque formation-cardinal AD pathological

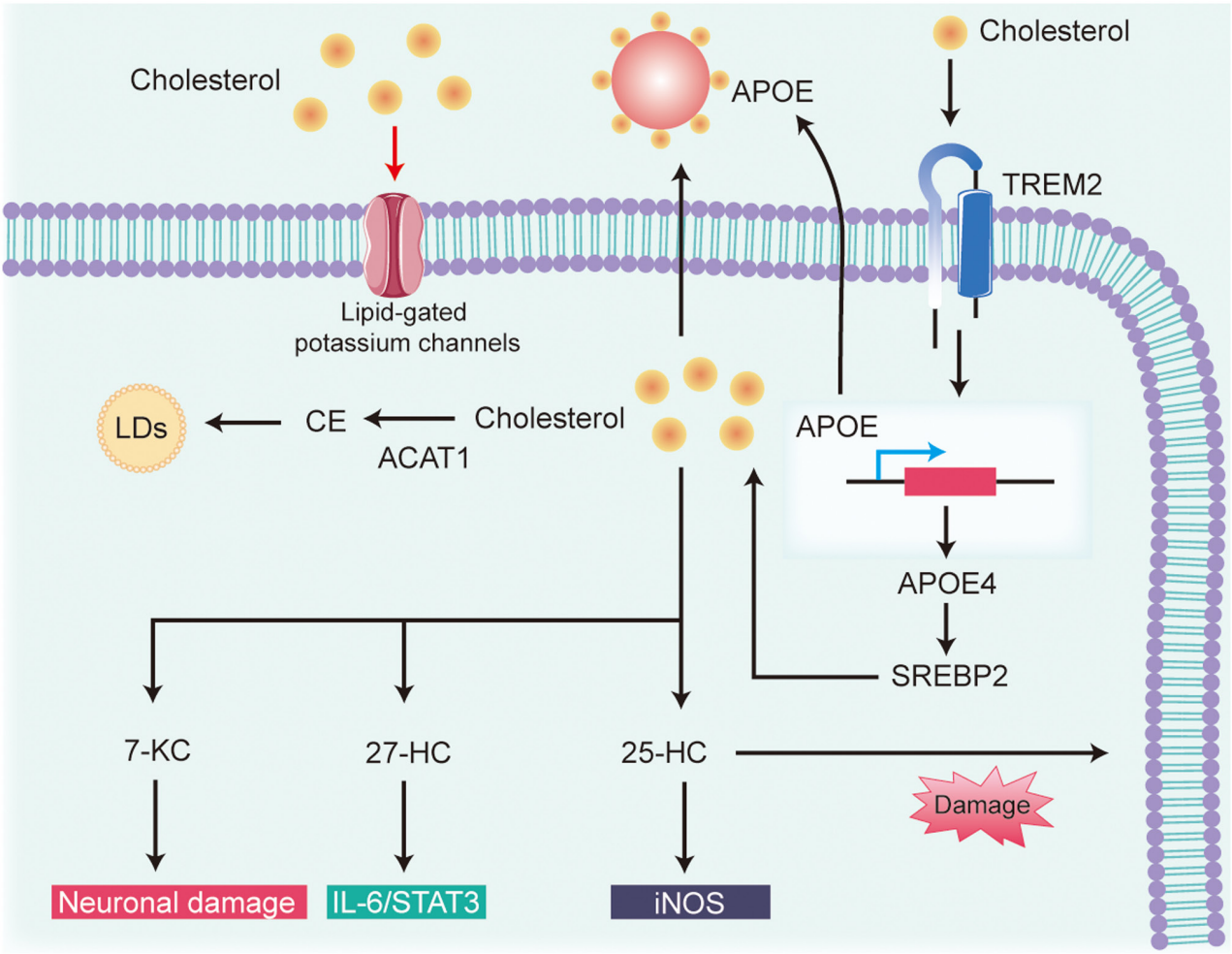

Figure 3. Impact of cholesterol and its metabolites on microglial function. ACAT1 catalyzes the esterification of myelin-derived cholesterol into CE, which are stored in lipid droplets. Loss of TREM2 signaling leads to reduced APOE expression, thereby decreasing cholesterol efflux and resulting in intracellular CE accumulation and axonal degeneration. Increased cholesterol levels enhance the activity of lipid-gated potassium channels. The cholesterol metabolite 25-HC can induce iNOS, disrupting membrane permeability. Additionally, 27-HC activates the IL-6/STAT3 pathway, leading to cellular senescence, while 7-KC mediates neuronal injury by inhibiting peroxisomes through the action of ROS. CE, cholesterol esters; ROS, reactive oxygen species; TREM2, triggering receptor expressed on myeloid cells 2; LDs, lipid droplets; 7-KC, 7-ketocholesterol; 25-HC, 25-hydroxycholesterol; IL-6, interleukin-6; STAT3, signal transducer and activator of transcription 3; iNOS, inducible nitric oxide synthase; ACAT1, acyl-CoA cholesterol acyltransferase 1; SREBP2, sterol regulatory element-binding protein 2.

hallmarks (216,217). Enzymatic conversion of cholesterol by 25-hydroxylase and 27-hydroxylase generates 25-OHC and 27-OHC, respectively, while 7-ketocholesterol arises via ROS-mediated non-enzymatic oxidation (218). Experimental data demonstrate that 25-OHC synergizes with LPS to induce inducible NO synthase (iNOS) mRNA expression (219), and 27-OHC activates the IL-6/STAT3 pro-inflammatory axis (220). ROS-driven accumulation of non-enzymatic oxysterols sustains chronic disease-associated microglial activation (221). Mechanistically, 25-OHC increases membrane permeability through lipid bilayer disorganization, triggering cell death (222-224). Concurrently, 27-OHC induces senescence via oxidative damage (225), while 7-ketocholesterol disrupts peroxisomal activity and mediates activated microglia-induced neuronal injury through oxidative stress (226).

LD accumulation driven by cholesterol dysmetabolism correlates with pro-inflammatory lipidomic signatures (227). LXR activation suppresses CNS inflammation, enhances lipid recycling and improves microglial function in rodent models (228). Cholesterol-enriched membranes promote lipid raft assembly, facilitating TLR dimerization and amplifying LPS-induced pro-inflammatory signaling (229). Chronic LPS exposure exacerbates Aβ deposition (230), while a 3% high-cholesterol diet induces inflammasome activation and blood-brain barrier disruption via pro-inflammatory microglial polarization (231). APOE4 carriers exhibit heightened neuroinflammation under hypercholesterolemic conditions due to impaired cholesterol efflux (232), highlighting genetic susceptibility to chronic microglial activation. Elevated CNS cholesterol levels inhibit phagocytic capacity (75), whereas methyl-β-cyclodextrin-mediated cholesterol depletion enhances phagocytosis (233). Of note, CE accumulation caused by TREM2 deficiency does not impair phagocytic function (20), underscoring the primacy of cholesterol transport efficiency over total cholesterol load. ABCA1-deficient microglia exhibit increased TNF-α secretion and reduced phagocytosis (234), while ABCA7 loss accelerates amyloid precursor protein processing and impairs Aβ clearance (235).

Translocator protein knockout AD models display exacerbated Aβ deposition alongside diminished phagocytic microglia (236), validating functional phagocytosis as a critical preventive mechanism in AD.

Microglial regulation of demyelination and remyelination. Demyelination contributes to neuronal dysfunction and cognitive decline in AD (237). Clinical studies demonstrate oligodendrocyte degeneration and reduced/damaged phospholipid content in AD brains (238,239). Single-cell transcriptomic analyses reveal significant gene expression alterations in oligodendrocyte lineage cells during early AD stages (240), with myelination-related pathways consistently disrupted across multiple cell types in prefrontal cortical tissues, underscoring myelination's pivotal role in AD pathophysiology (240). Microglia critically maintain myelin integrity. Under homeostatic conditions, axonal myelination is dynamically regulated by a demyelination-remyelination equilibrium requiring coordinated interactions between oligodendrocyte progenitor cells (OPCs) and microglia (241). Microglia clear myelin debris and secrete signaling factors to promote OPC differentiation into oligodendrocytes (242). However, aging and neuropathological accumulation accelerate remyelination decline, impairing myelin maintenance and causing myelin debris accumulation (85). Excessive debris disrupts OPC recruitment to axons and suppresses microglia-derived factors essential for OPC differentiation, further compromising remyelination (241). While microglia protectively degrade phagocytosed myelin debris via autophagy and secrete pro-remyelination cytokines (9,243), their clearance capacity is finite. Pathological myelin overload exceeding lysosomal degradation capacity induces lysosomal damage, triggering microglial senescence and pro-inflammatory cytokine release-termed the senescence-associated secretory phenotype (SASP) (85). SASP microglia exacerbate pathology through dual mechanisms: Impaired phagocytosis amplifies amyloid plaque and myelin debris accumulation, while debris-activated microglia directly drive neuroinflammation, damaging neurons, oligodendrocytes and OPCs (241).

Similar to astrocytes, microglia/macrophages exhibit context-dependent dual activation states: Pro-inflammatory classical (M1; marked by iNOS, TNF, CD16/CD32) and anti-inflammatory pro-regenerative (M2; expressing Arg1, insulin-like growth factor 1, CD206). Focal lysolecithin-induced corpus callosum demyelination models demonstrate M1-to-M2 phenotypic switching during remyelination initiation, involving necroptosis of pro-inflammatory subsets and repopulation by regenerative phenotypes (244,245). *In vitro*, M2-conditioned media enhances OPC differentiation, abolished by M2 depletion in lesions. Heterochronic parabiosis (a surgical model that connects the circulatory systems of young and old mice) shows aged mice exhibit increased lesion M2 cells with enhanced remyelination, blocked by inhibiting M2-derived activin-A (244). Microglial activation transcends simplistic M1/M2 dichotomies, encompassing broader phenotypic spectra. In Theiler's virus-induced demyelination, endocannabinoid 2-arachidonoylglycerol induces microglial phagocytosis and OPC differentiation without altering classical M1/M2 markers (246). Myelin debris induces novel foamy macrophage phenotypes with ABCA1 deficiency, impairing apoptotic/necrotic cell clearance and exacerbating secondary injury (247). Single-cell RNA sequencing in experimental autoimmune encephalomyelitis (EAE) mice reveals shared activation markers (CD44, CD86, programmed cell death ligand 1) alongside Major histocompatibility complex class II/stem cell antigen-1 upregulation and CD14 downregulation (248). Lysolecithin lesion microglia form distinct subsets expressing APOE but diverging in CCL4/CXCL10 expression (249). Demyelination models identify APOE-dependent molecular signatures overlapping with those of microglia from patients with MS (48,250). Real-time imaging captures dynamic microglial/macrophage shifts from pro-inflammatory to immunoregulatory states in EAE lesions (251). CD11c+ microglia-critical for postnatal myelination-expand in EAE and cuprizone models. Colony stimulating factor 1 receptor activation drives CD11c+ expansion via C-C motif chemokine ligand 2 chemotaxis, ameliorating EAE and reducing demyelination (252). The homeobox gene *muscle segment homeobox 3* regulates polarization by oppositely modulating PPARγ/STAT6/JAK3 in M2/M1 cells, influencing disease progression across models (253). During EAE recovery, pro-regenerative microglia upregulate purinergic receptor P2X4R, whose activation enhances debris clearance and suppresses inflammation-effects abolished by receptor blockade (254).

5. Ferroptosis linking lipid metabolism and neuroinflammation

The interplay between dysregulated lipid metabolism in microglia and ferroptosis constitutes a critical pathological mechanism underlying neurodegenerative disorders (255). Ferroptosis, an iron-dependent form of regulated cell death driven by lipid peroxidation, particularly depends on the aberrant oxidation of phospholipids enriched with PUFAs (256). As resident immune sentinels in the CNS, microglial susceptibility to ferroptosis and their involvement in neuroinflammatory processes are fundamentally regulated by their polarization states through lipid metabolic reprogramming (102). At the molecular level, the 15-lipoxygenase (15-LOX)/phosphatidylethanolamine-binding protein 1 complex serves as a pivotal driver of ferroptosis (257). This enzymatic complex specifically catalyzes the peroxidation of arachidonoyl-phosphatidylethanolamine to generate 15-hydroperoxy-eicosatetraenoyl-phosphatidylethanolamine (15-HpETE-PE) (as shown in Fig. 4), a potent ferroptosis-inducing lipid species (258). This process requires both redox-active iron-generated ROS and precise enzymatic regulation. Of note, structural studies revealed that 15-LOX contains specific 'oxygen channels' permitting competitive access of molecular oxygen and NO radicals (NO•), thereby dynamically modulating lipid peroxidation kinetics (259). Polarization status critically determines microglial ferroptosis susceptibility. Pro-inflammatory M1 microglia exhibit ferroptosis resistance through iNOS-mediated NO• production, which directly binds to the Fe^{2+} catalytic center of 15-LOX to inhibit 15-HpETE-PE synthesis (260). Conversely, anti-inflammatory M2 microglia lacking iNOS expression demonstrate impaired 15-LOX inhibition, leading to progressive lipid peroxide accumulation and eventual ferroptotic death (260). Beyond

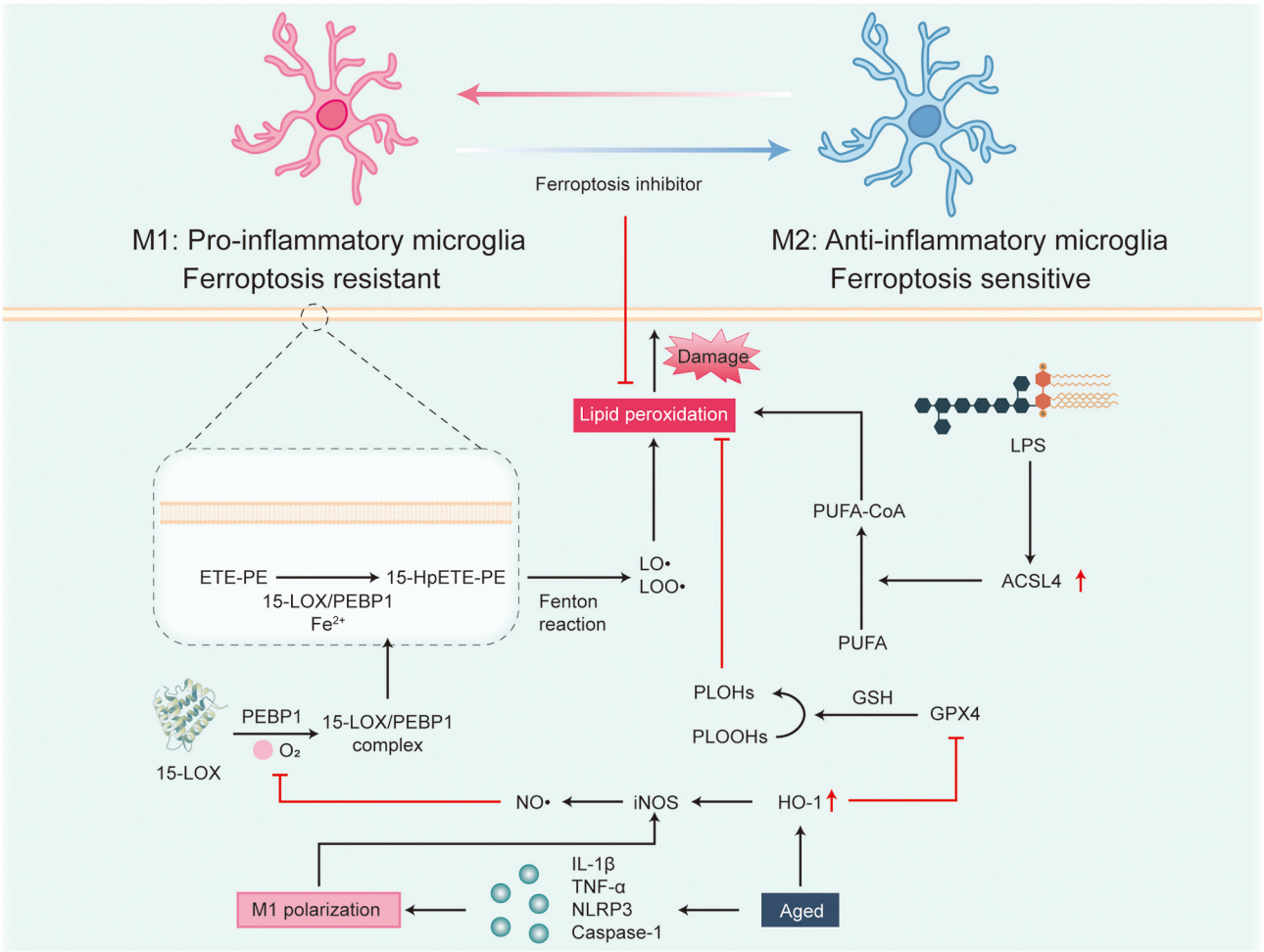

Figure 4. Regulatory network of ferroptosis in microglia and its association with neuroinflammation. The complex formed by 15-LOX and PEBP1 catalyzes the conversion of ETE-PE into the pro-ferroptotic signal 15-HpETE-PE via its 'oxygen channel'. This process relies on the redox activity of iron and the competitive binding of oxygen and NO•. In M1 microglia, the high levels of NO• produced by iNOS inhibit 15-LOX activity, thereby preventing ferroptosis; by contrast, M2 microglia, due to their lack of iNOS, accumulate lipid peroxides, which trigger ferroptosis. ACSL4 facilitates ferroptosis by esterifying PUFAs into PUFA-CoA, increasing the oxidative sensitivity of the cell membrane. LPS stimulation upregulates ACSL4 expression via NF-κB, exacerbating neuroinflammation, whereas propofol can dose-dependently inhibit ACSL4, thereby alleviating neuronal injury in a sepsis-associated encephalopathy model. Overexpression of HO-1 depletes GSH and inhibits GPX4 activity, resulting in the accumulation of lipid peroxides and iron deposition. This process drives microglia toward a pro-inflammatory M1 phenotype, characterized by upregulated expression of inflammatory mediators including iNOS, IL-1β, TNF-α, NLRP3 and caspase-1. Ferroptosis inhibitors can reverse this phenotypic transition by scavenging free radicals. 15-LOX, 15-lipoxygenase; PUFAs, polyunsaturated fatty acids; GSH, glutathione; ETE-PE, eicosatetraenoyl-phosphatidylethanolamine; 15-HpETE-PE, 15-hydroperoxy-eicosatetraenoyl-phosphatidylethanolamine; PEBP1, phosphatidylethanolamine-binding protein 1; PLOHs, phospho-lipid hydroxides; PLOOHs, phospho-lipid hydroperoxides; ACSL4, acyl-CoA synthetase long-chain family member 4; HO-1, heme oxygenase-1; NO, nitric oxide; GPX4, glutathione peroxidase 4.

the LOX system, Acyl-coA synthetase long chain family member 4 (ACSL4) exacerbates ferroptotic vulnerability by esterifying PUFAs into membrane phospholipids, increasing oxidizable substrate availability (261). Experimental evidence from sepsis-associated encephalopathy models demonstrates that ACSL4 upregulation mediates neuroinflammation through NF-κB pathway activation, while pharmacological inhibition with propofol attenuates hippocampal ferroptosis by ACSL4 downregulation, preserving neuronal viability, as evidenced by Nissl staining and reduced Fluoro-Jade C positivity (262,263). These findings position ACSL4 as a key regulator of microglial membrane lipid composition and neurodegeneration progression. The glutathione peroxidase 4 (GPX4) antioxidant system provides crucial protection against ferroptosis by reducing lipid peroxides to non-toxic alcohols using reduced glutathione (264). Importantly, experimental models of sepsis-associated encephalopathy have revealed significant GPX4 downregulation in affected brain regions (265). Notably, aging-associated microglial dysfunction involves heme oxygenase-1 upregulation, which suppresses GPX4 expression and promotes iron accumulation, driving M1 polarization and neurotoxic cytokine production (IL-1β, TNF-α, NLRP3, caspase-1) (266). Therapeutic interventions with ferroptosis inhibitors demonstrate dual benefits by scavenging free radicals, suppressing lipid peroxidation and promoting microglial phenotype switching from pro-inflammatory M1 to neuroprotective M2 states, accompanied by enhanced phagocytic capacity and reduced inflammatory mediator secretion (267). Collectively, these mechanisms establish microglial lipid metabolic dysregulation as a central hub integrating ferroptotic cell death with neuroinflammatory cascades in neurodegenerative pathogenesis.

6. Therapeutic advances targeting lipid metabolism

TREM2 as a lipid metabolism regulatory target in NDDs. Modulating lipid metabolism pathways shows therapeutic potential for AD, with dietary interventions attracting particular attention. Preclinical studies confirm that ω-3 PUFA supplements DHA and eicosapentaenoic acid ameliorate AD pathology in postmenopausal women and older individuals with mild cognitive impairment (268,269). Statins, which inhibit cholesterol synthesis, improve cognitive deficits in patients with AD or amnestic mild cognitive impairment and hypercholesterolemia by targeting TLR4 signaling (270,271). The upregulation of TLR4 in TREM2-deficient models (272) suggests statins may specifically regulate neuroinflammation in patients with AD carrying TREM2 mutations. Mechanistically, TREM2-deficient myeloid cells exhibit pathological CE accumulation, reversible via inhibition of ACAT1 (20), providing a potential therapeutic target for TREM2 mutation carriers (209). Given the loss-of-function nature of most pathogenic TREM2 variants, agonistic antibodies AL002a or engineered TREM2-expressing myeloid cell transplantation are emerging therapeutic approaches (15). Price *et al* (273) demonstrated that AL002a antibody treatment significantly reduces Aβ pathology and improves cognition in 5XFAD mice. TREM2 also modulates APOE isoform-specific effects: TREM2 deficiency exacerbates microglial Aβ clearance deficits in APOE ε4 mice (274), supporting TREM2-targeted therapies for APOE ε4-associated AD. The RXR agonist bexarotene exhibits multi-target efficacy by enhancing microglial phagocytosis and regulating the TREM2-TYRO protein tyrosine kinase binding protein-CD33 network (275). Transcriptomic analyses reveal bexarotene's dual actions in APP/PS1 mice: Activating immune pathways for Aβ clearance while suppressing neuroinflammation (276). Notably, bexarotene corrects lipoprotein metabolism and cognitive deficits in humanized APOE4 mice (277), suggesting TREM2-mediated APOE isoform regulation underlies its therapeutic effects, though mechanistic details require further elucidation.

Therapeutic potential of fatty acid synthase inhibitors. CMS121, a flavonoid derivative of fisetin, combines neuroprotective and metabolic regulatory properties (278). This compound concurrently inhibits two programmed cell death pathways: Glutathione depletion-associated oxytosis and iron-dependent ferroptosis (279,280). *In vitro* studies demonstrate CMS121's selective protection against diverse cytotoxic agents: It blocks RSL3-induced lipid peroxidation in HT22 neurons and mitigates glutamate-and erastin-induced cell death in AD mice (280). CMS121 broadly modulates LPS-stimulated microglial responses in BV2 cells, suppressing lipid peroxidation and downregulating pro-inflammatory mediators, including iNOS, TNF-α and cyclooxygenase 2 (280). These effects phenocopy fatty acid synthase (FASN) gene silencing, confirming target specificity. In AD mouse models, CMS121 significantly reduces hippocampal 4-hydroxynonenal, a lipid peroxidation marker linked to neuronal damage (281), while decreasing glial fibrillary acidic protein expression, indicating attenuated glial activation (282). CMS121 exerts multi-directional lipid metabolic regulation by lowering endocannabinoids, free fatty acids and PUFAs in AD mice (280). However, it paradoxically elevates ceramide levels-a consequence of FASN inhibition-induced malonyl-CoA accumulation, which blocks carnitine palmitoyltransferase 1-mediated fatty acid β-oxidation and diverts metabolic flux toward ceramide synthesis in brains from patients who suffered from neuropathological disorders (117).

7. Conclusions and future perspectives

NDDs, including AD, PD and ALS, present significant global health challenges due to progressive neuronal degeneration and associated cognitive and functional impairments. Despite differences in clinical manifestations, these disorders share common pathological mechanisms characterized by neuroinflammation, microglial dysfunction and disrupted lipid metabolism. Microglia, as resident immune cells in the CNS, play critical roles in neurodegenerative disease progression through their dynamic polarization into pro-inflammatory and anti-inflammatory phenotypes (8,9). The M1 phenotype exacerbates neuronal injury through the secretion of inflammatory cytokines, lipid peroxidation and promotion of ferroptosis (44), whereas the M2 phenotype mediates neuroprotective effects by enhancing pathological protein clearance, secreting neurotrophic factors and supporting synaptic plasticity (46,47). Lipid metabolism has emerged as a pivotal factor influencing microglial function and neuroinflammatory processes. Dysregulated cholesterol metabolism and fatty acid oxidation, mediated by key molecules such as TREM2 and ACAT1, lead to lipid droplet accumulation and pro-inflammatory activation in microglia (138,209). Furthermore, lipid peroxidation products and ferroptotic pathways, driven by altered lipid metabolism, establish crucial mechanistic links between microglial dysfunction and neuronal cell death (261). Targeting lipid metabolic pathways represents an innovative therapeutic approach for NDDs. Pharmacological agents including TREM2 agonists, ACAT1 inhibitors and fatty acid synthase inhibitors like CMS121 have demonstrated promising efficacy in preclinical studies by reducing neuroinflammation, restoring lipid homeostasis and improving cognitive outcomes (15,281). Future research directions should focus on clarifying the molecular interactions between lipid metabolism and microglial polarization, identifying reliable lipid biomarkers for disease progression and developing optimized lipid-targeted therapeutic interventions. Advances in this field hold significant potential for improving treatment efficacy and establishing novel therapeutic strategies for NDDs.

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Authors' contributions

YS and LG provided the theoretical foundation and wrote the manuscript. YS generated the figures. XL performed the literature search. KW and JW categorized and organized the literature. BP reviewed the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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