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Fueling neurodegeneration: metabolic insights into microglia functions

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Abstract

Microglia, the resident immune cells of the central nervous system, emerge in the brain during early embryonic development and persist throughout life. They play essential roles in brain homeostasis, and their dysfunction contributes to neuroin□ammation and the progression of neurodegenerative diseases. Recent studies have uncovered an intricate relationship between microglia functions and metabolic processes, o□ering fresh perspectives on disease mechanisms and possible treatments. Despite these advancements, there are still signi□cant gaps in our understanding of how metabolic dysregulation a□ects microglial phenotypes in these disorders. This review aims to address these gaps, laying the groundwork for future research on the topic. We speci□cally examine how metabolic shifts in microglia, such as the transition from oxidative phosphorylation and mitochondrial metabolism to heightened glycolysis during proin□ammatory states, impact the disease progression in Alzheimer's disease, multiple sclerosis, Parkinson's disease, amyotrophic lateral sclerosis, and Huntington's disease. Additionally, we explore the role of iron, fatty and amino acid metabolism in microglial homeostasis and repair. Identifying both distinct and shared metabolic adaptations in microglia across neurodegenerative diseases could reveal common therapeutic targets and provide a deeper understanding of disease-speci□c mechanisms underlying multiple CNS disorders.

Keywords Microglia, Neuroin□ammation, Immunometabolism, Neurodegenerative diseases, Therapeutic strategies

Microglia, the resident mononuclear phagocytes of the central nervous system (CNS), are essential components of the brain's immune system. Derived from erythromyeloid progenitors in the yolk sac, microglia populate the brain and spinal cord during the early embryonic period and constitute 5–15% of the total glial cell population within the CNS parenchyma [1, 2]. ese highly specialized cells exhibit unique characteristics during homeostasis, including a slower proliferation rate and a 'rami ed' morphology, characterized by highly branched processes [3, 4]. During in ammation, microglia rapidly assume 'hypertrophic morphology', often referred to as being "activated", a phenotype characterized by clonal proliferation, an enlarged cell body, and shortened cellular processes [5, 6]. Microglia play two primary roles in the CNS: providing immune defense and maintaining CNS homeostasis. As sentinels, microglia detect signs of pathogenic invasion or tissue damage, playing a crucial role in maintaining the immune integrity of the brain [7]. Simultaneously, they balance the immune response with the ability to moderate potential CNS damage and support tissue repair. In the context of neurodegenerative disorders, however, abnormal activation of microglia exacerbates

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pathological processes, ultimately resulting in neuronal impairment and neurodegeneration.

Neurodegeneration, which refers to the progressive loss of neural tissues and the function of neurons, is associated with a wide range of symptoms, including cognitive impairment, motor de cits, and dementia [8]. Alzheimer's disease (AD), multiple sclerosis (MS), Parkinson's disease (PD), and Huntington's disease (HD) are among the most prevalent neurodegenerative disorders and a ect millions of people, resulting in substantial mortality and morbidity worldwide [9, 10]. While genetic and environmental factors contribute to the etiology of neurodegenerative disorders, age stands out as the most signi cant risk factor for neurodegeneration. As life expectancy increases, the prevalence of neurodegenerative disorders is expected to rise substantially [11]. Management of such disorders, which are deemed incurable owing to the inability of neurons to self-regenerate after cell death, is limited by a lack of therapies that prevent disease progression.

Chronic neuroin ammation underlying the neurodegeneration is often associated with 'dysfunctional' microglia [12–14]. As e ector cells, microglia are sensitive to pathological stimuli and changes in the microenvironment of the CNS, and their response impacts neuronal networks and contributes to the development of neurodegenerative disorders. As microglia engage in immune responses, they undergo concurrent metabolic changes that closely link these cells to their activation, di erentiation, and overall function. is has resulted in growing evidence that highlights the importance of investigating immunometabolism to inform future research and treatments for neurodegenerative diseases [16, 17]. Here, we provide a comprehensive review of the metabolic characteristics of microglia and their importance in driving pathology across di erent neurodegenerative disorders. By recognizing shared and distinct metabolic adaptations in microglia across neurodegenerative diseases, this review will o er critical insights into how common metabolic dysregulation drives neurodegeneration. ese discoveries could pave the way for potentially common therapeutic strategies, advancing both disease-speci c and pan-neurodegenerative treatments.

Alzheimer's disease (AD)

As a widely occurring neurodegenerative disorder, AD manifests in both genetic and sporadic forms. From a biological and pathological perspective, AD is characterized by the accumulation of extracellular plaques composed of amyloid-β (Aβ), followed by the formation of intracellular neuro brillary tangles made up of tau protein (Fig. 1) [19, 20]. ese pathological processes gradually lead to the loss of synapses, the connection between di erent neurons. e current understanding acknowledges that microglia play a dual role in the development of AD. Initially, microglia are recruited to sites of pathological Aβ plaque deposition to facilitate Aβ clearance and constitute a protective barrier against the neurotoxic

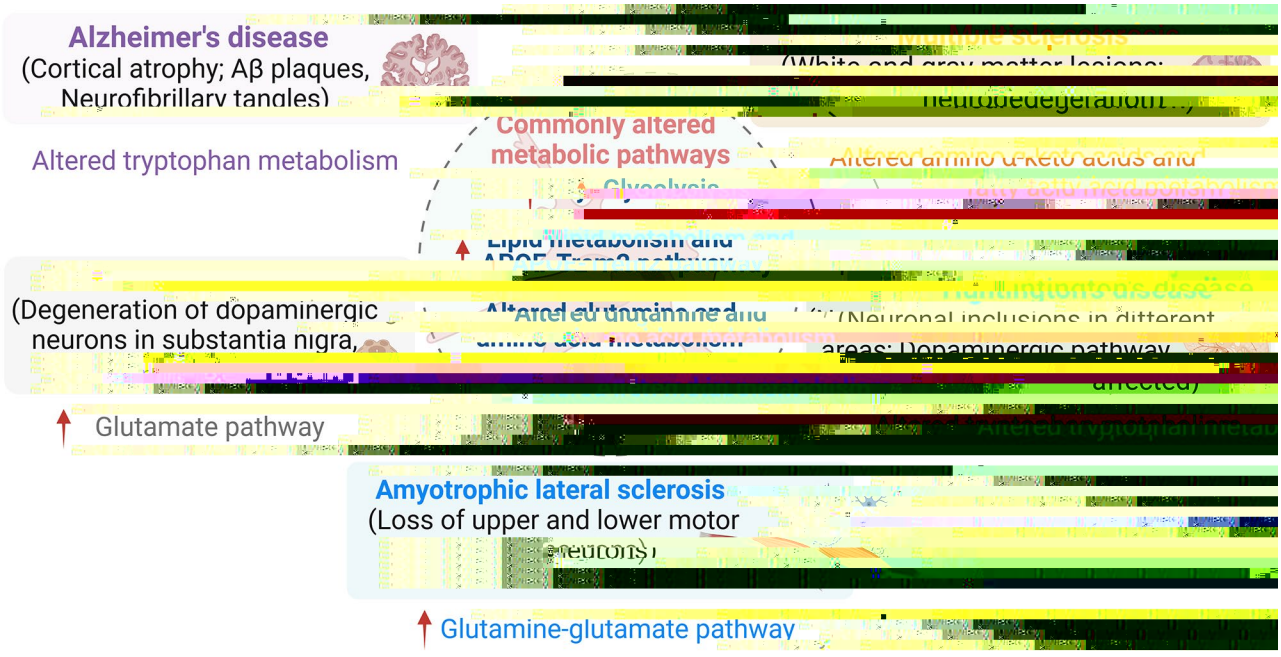

Fig. 1 Key pathological features of neurodegenerative diseases highlight key metabolic events in microglia. This gure illustrates the core metabolic changes in microglia that are common across several neurodegenerative diseases. The gure also highlights disease-speci c pathway changes within microglia in each of the listed CNS disorders

e ects of Aβ plaques by limiting their outward expansion and contact with nearby Fig. 1.

healthy neurons [21–23]. On the other hand, sustained microglia activation, which results in increased in ammasome activation and the secretion of in ammatory cytokines, has detrimental e ects on the surrounding brain tissue, leading to irreversible neurodegeneration [24–26].

It is generally believed that microglia utilize glycolysis and oxidative phosphorylation (OXPHOS) to meet the required energy demands for their functions under homeostatic conditions (Fig. 2A) [27, 28]. Glycolysis begins with the uptake of extracellular glucose by glucose transporters (GLUTs). In a homeostatic state, microglia predominantly express GLUT1 and GLUT5 (a fructose transporter) as the primary transmembrane sugar transporters [29, 30]. However, decreased transportation of glucose into the brain coupled with reduced oxidation rates contributes to a state referred to as 'hypometabolism', which is associated with AD pathology [31]. Under in ammatory conditions, GLUT1 expression is

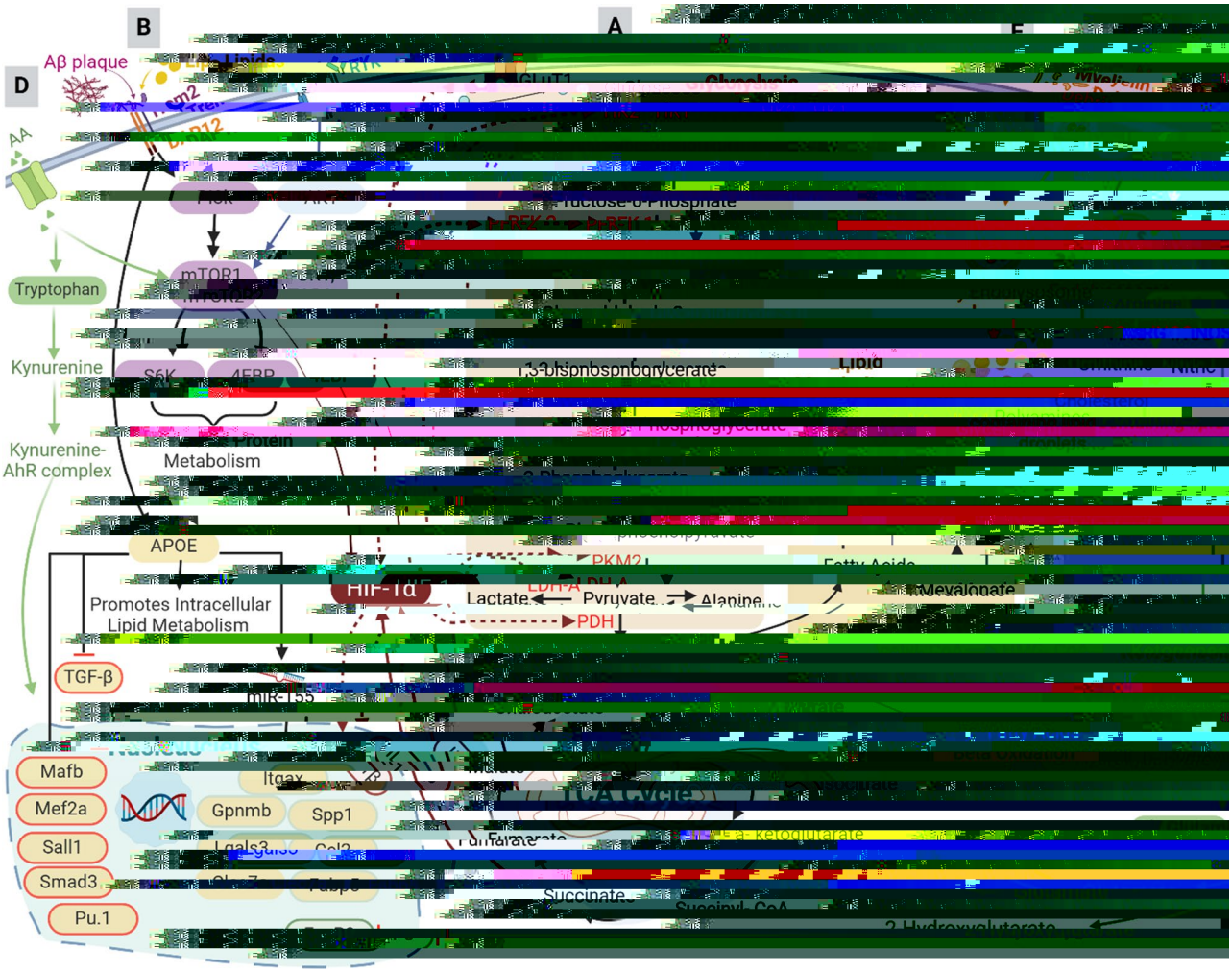

Fig. 2 A comprehensive summary of metabolic pathways and intermediates regulating microglia immunological function. (**A**) During glycolysis, glucose is converted to pyruvate, which either enters the TCA cycle via acetyl-CoA or is converted to lactate under low-oxygen conditions (anaerobic glycolysis) or in normoxic conditions (aerobic glycolysis; Warburg phenomenon). This metabolic switch promotes the expression of anti-in□ammatory markers such as IL-10, TGFβ, CD206, and VEGFα. In□ammatory conditions disrupt the TCA cycle at stages involving IDH and SDH, resulting in citrate and succinate accumulation. Citrate enhances the production of prostaglandins, NO, and itaconate, whereas succinate stabilizes HIF-1α, increasing the expression of multiple glycolytic enzymes. Microglia in proin□ammatory states favor fatty acid synthesis from acetyl Co-A, which leads to the secretion of additional proin□ammatory cytokines. Conversely, anti-in□ammatory microglia prefer β-oxidation of fatty acids, which converge into acetyl-CoA and upregulate the production of unsaturated fatty acids. (**B**) The receptor TREM2 on microglia enhances mTOR signaling, increasing microglial metabolic capacity, and promoting the transition to a mature disease-associated microglial pro□le. Amino acid sensing via mTORC1 triggers lysosomal activation, promoting proin□ammatory responses. (**C**) Glutamine metabolism yields glutamate and α-ketoglutarate, supporting proin□ammatory processes through the TCA cycle. Arginine metabolism results in the production of NO and cytokines, while its conversion to ornithine can modulate in□ammation. (**D**) Tryptophan breakdown to kynurenine activates anti-in□ammatory gene transcription through AhR binding

upregulated to boost glucose uptake and facilitate glycolysis in microglia [32, 33]. Biswas et al. reported a reduction.

In GLUT1 and GLUT3 expression, as well as a decrease in brain glucose concentration, in an experimental rat model of AD, which was generated by the administration of streptozotocin, an alkylating glucosamine nitrosourea compound commonly used in rodent models to induce AD [34]. ese changes were accompanied by a decrease in CD11b immunoreactivity, a biomarker expressed on the surface of myeloid cells, including microglia in the brain. Early studies in the 1990s revealed a diminished concentration of GLUT1 and GLUT3 in the brains of AD patients, which was correlated with decreased brain glucose uptake and subsequent cognitive impairment [35, 36]. However, in vivo imaging of neuroin ammation via small-animal positron emission tomography (PET) revealed a positive correlation between glucose metabolism and the concomitant neuroin ammation as measured by the translocator protein (TSPO), an 18 kDa biomarker expressed in the mitochondrial membrane of activated microglia, in a transgenic AD mouse model [37]. A large proteomic study on AD, involving over 2,000 AD brain samples and 400 cerebrospinal uid (CSF) samples from individuals with AD, revealed elevated levels of glucose metabolism-related proteins [38]. ese proteins, which include astrocyte/microglial carbohydrate metabolism enzymes such as pyruvate kinase M2 (PKM2), lactate dehydrogenase (LDH)-B, and glyceraldehyde 3-phosphate dehydrogenase, were found to be highly interconnected within speci c protein networks known as M4 modules [38]. In addition, the M4 module contained microglial markers that increased in response to Aβ deposition and decreased in response to lipopolysaccharide (LPS) stimulation, implying that the microglial activity re ected by the M4 module is likely inclined towards an anti-in ammatory, disease-related phenotype. While hypometabolism is recognized as a biomarker of AD, the increased expression of metabolic proteins and elevated glucose consumption in microglia has the propensity to mask the hypometabolic phenotypes of AD brains [39].

Of further interest is the emergence of studies indicating that alterations in glucose metabolism may regulate phenotype-related changes in microglia. Under normoxia (normal oxygen levels), pyruvate dehydrogenase transforms pyruvate into acetyl-CoA, which subsequently enters the tricarboxylic acid (TCA) cycle, generating reduced avin adenine dinucleotide (FADH2) and nicotinamide adenine dinucleotide (NADH) as electron donors for electron transport chain (Fig. 2A). Alternatively, pyruvate can be preferentially converted to lactate through a process catalyzed by LDH-A. While traditionally associated with anaerobic conditions, recent evidence from immune activation demonstrates that this pathway occurs even under normoxic conditions. is process, known as aerobic glycolysis, is similar to what is observed in tumor cells and is often referred to as the Warburg e ect [18, 40]. Aerobic glycolysis supports the quick production of adenosine triphosphate (ATP) and also facilitates the generation of cytokines and reactive oxygen species (ROS) in activated microglia through several ancillary pathways [41]. Maintenance of an equilibrium between OXPHOS and glycolysis is vital for orchestrating the shift between in ammatory and homeostatic functions in immune cells [42–44]. Baik et al. reported that in vitro exposure to Aβ plaques directly induced microglial activation by shifting OXPHOS to aerobic glycolysis, which led to a surge in proin ammatory cytokine production and an increase in the phagocytic phenotype of microglia, which depended on the mTOR-HIF-1α (hypoxia-inducible factor 1-alpha) pathway (Fig. 2A and B) [45].

During AD progression, the metabolism of microglia shifts from OXPHOS to aerobic glycolysis [45]. is alteration leads to the accumulation of intracellular lactate, which is then transported to the extracellular space by virtue of monocarboxylate transporters (MCTs). While neurons utilize lactate as a source of fuel in the wake of decreased glucose availability, excessive lactate leads to neuronal damage by altering the acidity of the AD brain microenvironment [46]. Further, lactate stimulates the microglial release of proin ammatory cytokines, interleukin (IL)-6, tumor necrosis factor (TNF)-α, and IL-1β [47]. e glycolysis-driven lactate is transported to the cell nucleus, where it leads to histone 'lactylation' [48]. Indeed, histone lactylation is notably increased in the brain tissues of both AD patients and mouse models of AD [48]. In particular, histone lactylation at H4 lysine 14 (H4K12la) has been identi ed as the most prevalent di erentially altered epigenetic marker in this context [49]. In addition, H4K12la, which is speci cally upregulated in Aβ-associated microglia, enhances the activity of glycolytic genes (*Pkm* and *Ldha*). is establishes a positive feedback loop involving glycolysis, H4K12la, and PKM2, exacerbating glucose metabolism, which induces microglial dysfunction in AD pathogenesis. Intriguingly, interrupting this cycle resulted in a reduced Aβ burden, inhibited microglial activation, and improved memory and spatial learning in mice [46]. ese ndings suggest that targeting the glycolysis/H4K12 lactylation/PKM2 axis in microglia has potential as a therapeutic strategy for the treatment of AD.

Studies involving the triggering receptor expressed on myeloid cells-2 (TREM2) have provided additional evidence supporting the role of metabolic pathways in enhancing microglial immune responses. TREM2, an immunoglobulin-like orphan receptor of the TREM

family, is essential for microglial phagocytic and apoptotic responses [50]. TREM2 augments mTOR signaling, enhances microglial metabolic capacity, and facilitates the transition of microglia to a disease-associated microglia pro le, which ultimately supports the microglial response to Aβ-plaques [51, 52]. e transmembrane region of TREM2 is associated with the adaptor proteins DNAX-activation protein 12 (DAP12) and DAP10 (Fig. 2B). Consequently, TREM2 activates mTOR through DAP12 and/or DAP10, given that both signaling adaptors have the capacity to recruit upstream mTOR activators [53]. Kleinberger et al. created a mouse model of neurodegenerative disorders by introducing disease-associated Trem2p.T66M mutation (T66M) in mice, which mirrored frontotemporal dementia associated with AD [54]. PET imaging revealed that the brains of T66M mutants exhibited greater glucose utilization than those of the wild-type brains. Additionally, there was an age-dependent decrease in proin ammatory activation of microglia in these mice, as shown by Iba1 immunohistochemistry and longitudinal PET imaging of the TSPO ligand. A study by Ulland et al. demonstrated that the microglia in the TREM2-de cient mouse model of AD and AD patients who harbor TREM2 risk variants experienced aberrant autophagy, which is associated with impaired mTOR signaling [55]. Autophagy, an intracellular degradation pathway that is partly controlled by mTOR-dependent signaling, is vital for maintaining energy equilibrium and clearance of misfolded proteins and damaged organelles [56, 57]. Furthermore, compared to wild-type bone marrow-derived macrophages (BMDMs), $Trem2^{-/-}$ BMDMs presented a reduction in the levels of glycolytic metabolites such as glucose 6-phosphate and fructose 1,6-bisphosphate, as well as TCA cycle intermediates, including citrate and succinate. $Trem2^{-/-}$ BMDMs presented a decreased extracellular acidi cation rate, suggesting diminished glycolytic ux [55]. However, it is still unclear whether TREM2 promotes neuroprotection through its functional roles in microglia.

Enhanced lipid metabolism also provides the energy needed for microglia activation, and disruptions in this process are strongly associated with lipid metabolism disorders, such as hypercholesterolemia, hypertriglyceridemia, diabetes, and even AD [58–60]. Apolipoprotein E (ApoE), the primary cholesterol transporter in the brain, is widely recognized as a signi cant genetic risk factor for the onset of late-stage AD [61]. ApoE, together with TREM2, is implicated in AD pathogenesis, particularly in the context of microglia activation (Fig. 2B) [13]. erefore, understanding the interactions between these two pathways may provide insights into the underlying mechanisms of AD pathogenesis and design potential therapeutic strategies. In the 5XFAD mouse model of AD, a novel disease-associated microglia was identi ed [51]. ese microglia subsets had a unique transcriptional pro le involving lipid and metabolism-related genes, including *Trem2*, a lipoprotein lipase, and *ApoE*. is subset of microglia preferentially utilized lipids as an energy source to meet their heightened metabolic demands when activated. Similarly, in both AD and APP-PS1 mouse models, the TREM2-driven ApoE pathway triggered a shift in microglial phenotypes from a homeostatic state to a neurodegenerative one, suggesting that activation of the TREM2-ApoE pathway impairs the ability of microglia to maintain homeostasis in the brain [13].

In AD, in addition to disruptions in lipid metabolism, alterations in amino acid metabolism play crucial roles in disease progression. Amino acids play vital roles in the biosynthesis of proteins, thereby in uencing a range of metabolic pathways essential for cellular functions. Amino acids also support immune cell energy acquisition, biomass production, and metabolic reprogramming during activation [62]. Glutamine, which serves as an important energy source for microglia, is absorbed through the amine transporters, SLC1A5 and SLC38A1 [63]. Inside mitochondria, glutamine is converted to glutamate and ammonia by the activity of glutaminase (Fig. 2C). Glutamate is further metabolized to α-ketoglutarate by glutamate dehydrogenase 1, which then enters the TCA cycle to produce ATP. Glutamate and α-ketoglutarate eventually generate succinate via the gamma-aminobutyric acid (GABA)-shunt pathway, triggering the production of proin ammatory IL-1β by modulating HIF-1α and promoting a shift to the proin ammatory phenotype [64–66]. Glutaminase is, thus, upregulated in activated microglia under pathological conditions [67–69]. In vitro studies highlight that microglia express glutamine synthetase, which facilitates the conversion of glutamate to glutamine upon stimulation with in ammatory triggers such as LPS [70]. Furthermore, elevated levels of glutaminase in AD transgenic mouse brain tissues compared with those in littermate controls are correlated with increased levels of proin ammatory markers [67]. Tryptophan metabolism within microglia also plays a signi cant role in AD pathology (Fig. 2D). Tryptophan metabolites such as 5-hydroxyindole-acetic acid (5-HIAA) and kynurenic acid enhanced neprilysin expression, a key enzyme involved in the clearance of Aβ peptides in the brain [71]. Tryptophan is metabolized mainly via the kynurenine pathway, with indoleamine 2,3-dioxygenase serving as the rate-limiting enzyme [72]. is enzyme is notably upregulated in AD brains, which facilitates the conversion of tryptophan into quinolinic acid [73]. e kynurenine pathway begins with the oxidative cleavage of the indole ring of l-tryptophan by either indoleamine 2,3-dioxygenase or tryptophan 2,3-dioxygenase, leading to the formation of N-formylkynurenine [72]. is is

followed by a series of metabolic reactions that ultimately generate NAD+and 3-hydroxykynurenine, which further generate highly reactive free radicals. 3-hydroxykynurenine is metabolized into neurotoxic compounds, including hydroxyanthranilic and quinolinic acids. Quinolinic acid stimulates glutamate release in microglia, triggering substantial production of ROS, lipid peroxidation, and tau protein hyperphosphorylation [71, 74, 75]. Methionine and Arginine metabolism are also of interest to the eld [76–80]. Recent ndings have shown that repeated high-dose administration of methionine enhanced microglial proin ammatory activation [76–78]. Further, Arginine contributed to pro- and anti-in ammatory responses through enzymes such as inducible nitric oxide synthase, arginase-1, arginine decarboxylase, and arginine-glycine amidino transferase in microglia [79, 80]. In a mouse model of AD, hippocampal neuronal death was associated with an increase in immunosuppressive CD11c+microglia and extracellular arginase, leading to arginine breakdown and decreased brain arginine levels [81]. Pharmacological blocking of arginase and ornithine decarboxylase shielded the mice from AD-like pathology and notably lowered CD11c expression [81]. Additionally, Aβ speci cally triggered disease-associated microglial signatures to enhance the phagocytic response, whereas a de ciency in myeloid arginase 1 selectively induced a homeostatic, nonphagocytic microglia signature [82].

Microglia also express diverse iron-related proteins, including the transferrin receptor, divalent metal transporter-1, ferritin, and ferroportin, which play integral roles in the absorption and metabolic processes associated with iron [83–85]. Compared with neurons and astrocytes, microglia exhibit superior e ciency in the accumulation and storage of iron in vitro [84]. Iron-laden microglia have been identi ed in the hippocampus [86] and in the frontal cortex of individuals with AD and are typically concentrated in the vicinity of Aβ plaques [87].

e retention of iron within microglia is associated with elevated glycolytic activity and enhanced TNFα expression [88]. Indeed, exposure of microglia to IFNγ and Aβ peptides in vitro increased glycolysis and associated glycolytic enzymes and enhanced iron retention while concurrently diminishing phagocytic and chemotactic functions [89]. ese ndings indicate that in ammation driven by iron-associated microglia, particularly in conjunction with Aβ, may play a pivotal role in the process of neurodegeneration during AD pathology.

Multiple sclerosis (MS)

MS is an immune-mediated neurodegenerative disease characterized by the demyelination of axons within the CNS (Fig. 1). According to the Multiple Sclerosis International Federation report, more than 2.9 million patients su er from MS worldwide [90]. While the etiology of MS remains incompletely understood, the immunopathophysiology of MS involves intricate interactions among various peripheral immune cells and CNS-resident cells. In the early stages of pathology, the integrity of the blood-brain barrier (BBB) is compromised, as evidenced by gadolinium-enhancing MRI re ecting active lesions within the brains of MS patients [91, 92]. e breached BBB allows the in ltration of peripheral monocytes, B cells, and autoreactive CD4+T cells, particularly T helper ( )1, 17, and CD8+T cells, into the CNS parenchyma [93–97]. ese in ltrating cells initiate an attack on myelin within the CNS, leading to the degeneration of oligodendrocytes [98, 99], a process that involves the loss of myelin and the release of myelin debris [100]. Microglia and macrophages are essential for the phagocytic removal of inhibitory myelin debris (Fig. 2E); however, prolonged activity of microglia leads to the destruction of neuronal myelin, which eventually compromises axonal and synaptic activity [101–104].

Abnormalities in glucose metabolism, such as elevated blood glucose, increased pyruvate levels, as well as increased activity of cerebral metabolic enzymes, including enolase, pyruvate kinase, and LDH, have been implicated in the pathophysiology of MS (Fig. 2A) [105–111]. Currently, information on the cellular distribution of GLUTs in the brains of people with MS is limited. Nijland et al. examined brain tissue from non-neurological human controls and individuals with MS presenting chronic active lesions [112]. ese lesions exhibited an inactive center surrounded by a periphery of hypertrophic microglia and macrophages, which are hallmarks of chronic active lesions [112]. e study revealed prominent expression of GLUT3 in the active rim of the lesions, notably in astrocytes. While this study found no such changes within microglia, additional sugar transporters within these cells and across the MS lesions are warranted. Immune cells that undergo excessive glycolysis witness enhanced LDHA activity. is enzyme, which converts pyruvate to lactate, helps maintain glycolytic ux as it replenishes the necessary NAD+to sustain glycolysis [113]. In this context, our previous research highlighted that CNS-in ltrating macrophages in MS brains and the brains of experimental autoimmune encephalomyelitis (EAE), a mouse model of MS, expressed high levels of LDHA and MCT-4, which enables the export of excessive lactate from macrophages [114]. e study further revealed that inhibitors of MCT-4 or knockdown of LDHA dampened macrophage activation, leading to reduced EAE severity [114]. Whether microglia exhibit similar phenotypes while contributing to MS progression remains to be identi ed. Nevertheless, microglia exhibit metabolic exibility, i.e., they have the potential to utilize alternative carbon sources for energy pathways, allowing them to adapt to diverse CNS conditions. Microglia

utilize glucose as a preferred metabolite to ful ll their energy demands in a healthy CNS [115]. However, they can quickly adapt to changes in the CNS microenvironment by switching to alternative pathways. In this context, a study by Bernier et al. found that, under aglycemic (no glucose) conditions in cerebellar slice cultures, microglia shifted to glutaminolysis [116]. In this process, microglia switched to using the amino acid glutamine, which was then converted into α-ketoglutarate to feed into the TCA cycle for its homeostatic functions (Fig. 2

accumulation has been observed in MS histologically and via MRI, and studies have demonstrated that elevated levels of iron in the brain induced oxidative stress, potentially leading to neurodegeneration [139]. Another single-nucleus RNA sequencing study conducted on the postmortem MS brain cortices revealed a coupling of HIF-1α and the iron-induced responses in at least one subset of microglia [140]. ese ndings imply that alterations in iron metabolism result in oxidative stress, which triggers in ammatory pathways in microglial cells. Such observations align with other neurodegenerative disorders, such as AD [141]. On the other hand, microglia in the normal-appearing white matter (NAWM) of MS brains exhibit enrichment in genes related to lysosomal pathway, lipid catabolism, and foam cell di erentiation, indicating early lipid processing [137]. Moreover, PET imaging of TSPO was enhanced in the NAWM of SPMS patients [142]. Despite these observations, our understanding of microglial metabolism in the context of MS remains limited. is is partly because most analyses conducted on postmortem MS brains fail to account for the complexity and diversity of distinct cellular phenotypes.

Parkinson's disease (PD)

As the second most prevalent neurodegenerative disorder, PD a ects approximately 1% of the population aged over 60 years [143]. A genetic mutation is present in 5–10% of patients, while the etiology of the disease is unknown in the majority of cases [144]. PD is characterized by the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and the aberrant accumulation of misfolded α-synuclein (α-SYN) protein, all of which lead to movement abnormalities (Fig. 1) [145]. Microglia play a crucial role in PD pathophysiology, where they are activated by α-SYN oligomers and proin ammatory signals released from degenerating neurons [146]. Microglia actively participate in the uptake and clearance of α-SYN oligomers, which are secreted from neurons [147–151]. Notably, phagocytosis of neurons by microglia is evidenced by the accumulation of neuromelanin within microglia, a synaptic engulfment mechanism analogous to the Aβ-positive synapse engulfment observed in AD [152, 153]. However, phenotypic changes over time likely interfere with the ability of microglia to maintain homeostasis and neuronal support. Consequently, the presence of hypertrophic and 'activated' microglia is strongly associated with irreversible neurodegenerative processes in PD [154].

e intricate interplay between microglial activation and altered glucose metabolism in PD remains a subject of investigation. Activated microglia release proin ammatory cytokines and generate excessive ROS, thereby creating a neuroin ammatory milieu that has the potential to directly impact neighboring neurons by targeting neuronal metabolism [155]. Concomitantly, PET studies revealed decreased brain glucose metabolism in the initial stages of PD [156], which correlated with increased microglial activation in the cortex and basal ganglia of PD patients [157–159]. Further investigations revealed substantial upregulation of *Slc2A1* transcript levels (GLUT1 gene) and enhanced glycolysis as manifested by increased lactate production in primary microglia cultures exposed to α-SYN [160, 161]. Interestingly, recombinant α-SYN also enhanced glucose uptake both in the adipose tissues and skeletal muscles of mice as well as in cultured mouse preadipocytes through the PI3K/Akt pathway [162]. Acute stimulation of microglia by prefabricated α-SYN bers in a PD mouse model resulted in a metabolic shift from OXPHOS to aerobic glycolysis through the AKT–mTOR–HIF-1α pathway in these cells (Fig. 2A) [163]. While α-SYN enhances aerobic glycolysis through pyruvate kinase M2 and suppresses mitochondrial biogenesis and OXPHOS [160], silencing of α-SYN signi cantly downregulates HIF-1α in microglia [164]. Notably, the mTOR/HIF-1α and ROS/HIF-1α pathways play important roles in the induction of aerobic glycolysis, which likely occurs during the Cdc-like kinase 1 (CLK1) de ciency. *Clk1*, also known as *Coq7*, encodes a mitochondrial hydroxylase essential for the biosynthesis of ubiquinone (UQ or coenzyme Q), which is crucial for the electron transport system within the mitochondrial respiratory chain and contributes to antioxidant activity [165]. e activation of these signaling pathways due to CLK1 de ciency reduced dopaminergic neurons in a mouse model of PD [166]. is investigation provided additional validation that HIF-1α assists with metabolic reprogramming to promote subsequent in ammatory responses by microglia. Increased glycolysis coincides with enhanced production of ROS in proin ammatory microglia [167]. ROS production, in turn, activates the NF-κB pathway, which serves as an in ammatory cascade capable of escalating neuroin ammation, ultimately contributing to PD pathogenesis [168–170].

Studies have also investigated the role of amino acid metabolism in microglia during PD pathology. Activated microglia have the potential to release substantial amounts of glutamate, leading to excitoneurotoxicity and subsequent neuronal damage in neurodegenerative disorders, including PD (Fig. 2C) [171]. Furthermore, stimulation of microglia by α-SYN led to a reduction in the level of intracellular glutamate while increasing extracellular concentrations. is modulation is believed to impact the glutamate-glutamine cycle, a crucial cycle for bioenergetic homeostasis and, therefore, neurotransmission within the neurons [172, 173]. Moreover, in *Park7* gene knockout mice, which lack the protein deglycase DJ-1 and exhibit PD pathology, microglia undergo signi cant alterations in their central amino acid metabolism [174].

is leads to a reduction in glutamine in ux and serine biosynthesis, which ultimately enhances the susceptibility of dopaminergic neurons to early cell death.

Histological examination of brain specimens revealed that microglia signi cantly accumulated intracellular lipids in the substantia nigra of PD patients [175], which likely fosters in ammatory processes [176, 177]. Despite these intriguing observations, the role of microglial lipid metabolism in mediating PD pathogenesis remains poorly de ned.

Huntington's disease (HD)

HD is a fatal autosomal-dominant genetic disease of the brain in which a single defective gene on chromosome 4 results in an expanded stretch of polyglutamine close to the amino terminus of the HD protein, huntingtin [178]. Consequently, pathological changes in multiple brain regions lead to a progressive disease course which is associated with a broad range of cognitive and movement disorders (Fig. 1). Recent literature suggests that microglia upregulate the production of proin ammatory cytokines, which strongly contributes to the chronic in ammation associated with HD [179, 180].

In HD brains, microglia engage in diverse signaling pathways- the kynurenine pathway, cannabinoid receptor pathway, and NF-κB signaling [181–184]. Mutant huntingtin stimulates NF-κB signaling, which contributes to the sustained activation of microglia as they secrete proin ammatory cytokines such as TNF-α [181]. is leads to chronic in ammation manifested by oxidative stress, mitochondrial dysfunction, and neuronal death, all of which drive neurodegeneration in HD [185–188].

erefore, modulation of in ammatory response should mitigate neurotoxicity associated with mutant huntingtin [189]. In this regard, treatment of primary mouse microglia with deoxy-D-glucose, an inhibitor of glycolysis, resulted in a reduction in TNFα and IL-6 production, which was attributed to NF-κB inhibition [190]. Further, the kynurenine pathway is responsible for more than 95% of tryptophan metabolism in mammals (Fig. 2D) [191]. e activation of microglia and the subsequent neuroin ammatory response in HD patients resulted in increased levels of downstream kynurenine pathway metabolites. Mutant huntingtin fragments also activate the kynurenine pathway in microglia, which is ameliorated by treatment with histone deacetylase inhibitors in a mouse model of HD [192]. Moreover, L-kynurenine, a substrate of the kynurenine pathway, exerted a dose-dependent inhibitory e ect on the LPS response within microglia [72].

Treatment with pyruvate has neuroprotective e ects on striatal neurons through blocking the expression of inducible nitric oxide synthase and nitrotyrosine in activated microglia [193, 194]. Further, there was a signi cant increase in iron levels in the basal ganglia in symptomatic and asymptomatic HD patients [195, 196]. Using the human brain samples and the R6/2 transgenic mouse model of HD, Simmons et al. reported that disturbances in iron metabolism in HD are linked primarily to microglia and occur early enough to contribute to the progression of HD [197]. Further, dysregulation of lipid metabolism, particularly brain cholesterol metabolism, is another important feature of HD brains [198]. Despite this information, research on the speci c role of lipid and iron metabolism in microglia related to HD is limited. Gaining insight into these cellular mechanisms within microglia is essential for developing therapies that could slow HD progression and improve patient outcomes.

Amyotrophic lateral sclerosis (ALS)

ALS, commonly referred to as Lou Gehrig's disease or motor-neuron disease, is a progressive neurodegenerative disorder that a ects motor neurons in both the brain and the spinal cord (Fig. 1). While the majority of ALS cases are sporadic, approximately 10% of ALS cases exhibit a familial pattern, implicating a genetic component in the disease's etiology [199]. Mutations in genes such as superoxide dismutase 1 (SOD1) lead to the misfolding of proteins, resulting in the formation of toxic aggregates within neurons [200]. ese protein aggregates interfere with cellular processes and cause susceptibility of motor neurons in ALS. Microglia play dual roles in ALS pathology, as they exhibit neuroprotective functions by assisting in the clearance of cellular debris and promoting tissue repair while also contributing to a proin ammatory state that causes neuronal damage as a result of persistent activation [201, 202].

Metabolic dysfunction is increasingly recognized as a contributing factor to ALS progression. High metabolic levels at rest, abnormalities in energy metabolism, and mitochondrial dysfunction have been observed in both neurons and glial cells in ALS patients [203–205]. Aerobic glycolysis, which is believed to occur through the activation of GLUTs, pyruvate dehydrogenase kinase 1, PKM2, LDH-A, and MCT-1 and inactivation of the pyruvate dehydrogenase complex, is associated with ALS pathology (Fig. 2A) [206]. Notably, disruption of metabolic support for neurons, including impaired glucose uptake and utilization, likely results from altered microglial phenotypes in individuals with ALS [204].

is contributes to the energy imbalance as observed in the a ected neurons [204, 205]. In the context of ALS, TREM2-induced ApoE signaling plays a critical role (Fig. 2B), as targeting the TREM2-ApoE pathway restored the homeostatic signatures of disease-associated microglia and prevented neuronal loss in ALS mouse models [13]. Furthermore, mitochondria harvested from crude spinal cord homogenates in individuals with ALS

re ected a dysfunction in electron transport chain complexes I+III, II+III, and IV [207]. Moreover, a reduction in the activity of mitochondrial enzymes, citrate synthase, and cytochrome c oxidase was observed in the motor neurons of individuals a ected by ALS [208]. Proin ammatory signals from microglia likely a ect mitochondrial dynamics, leading to impaired energy production and increased oxidative stress [209]. is, in turn, contributes to the overall metabolic imbalance observed in ALS. On the other hand, Olesoxime, a novel neuroprotective compound believed to stabilize mitochondrial functions, was shown to decrease the activation of microglia and delay muscle denervation and motor neuron death in an ALS mouse model [210]. Studies have also focused on the role of amino acid metabolism in ALS. Niida-Kawaguchi et al. discovered that microglia increase glutamate release in the ALS spinal cord [211], which results from the buildup of intracellular iron. is accumulation activates aconitase 1, a TCA cycle enzyme, along with the TNF-alpha converting enzyme (Fig. 2C). is process also promotes upregulation of glutaminase C, which is stimulated by extracellular TNFα. In addition, group I metabotropic glutamate receptors (mGluRs) on microglia have immunoprotective functions. Suppressing mGluR1 or mGluR5 in ALS animal models has been shown to delay the onset of the disease, extend survival, protect neurons, and decrease microglial activation [212–214]. ese results emphasize the intricate relationship between metabolic disturbances and neuroin ammation in ALS, pointing to the importance of exploring metabolic treatments for managing the disease. Ongoing research into the metabolic pathways in ALS could lead to new therapeutic approaches that help protect neurons and improve patient survival.

Table 1 provides a broad overview of how di erent metabolic pathways, including glycolysis, lipid metabolism, and iron metabolism, a ect neurodegenerative diseases in distinct ways.

Conclusion

Metabolic reprogramming signi cantly in uences microglial functions and emerges as a common theme across di erent neurodegenerative disorders. One of the key points of discussion in this review is the central position that glycolytic pathways assume in promoting the proin ammatory phenotype of activated microglia.

e involvement of glucose metabolism in microglia is intricately linked to the complex mechanisms underlying neuroin ammation. Studies have shown that inhibiting glycolysis in microglia suppresses their proin ammatory response and reduces neuroin ammation [27, 226].

erefore, targeting glucose metabolism in microglia represents a promising therapeutic approach for the treatment of debilitating CNS disorders. One such potential therapeutic target is the enzyme hexokinase 1, which catalyzes the rst rate-limiting step of glycolysis by phosphorylating glucose to produce glucose-6-phosphate. e inhibition of hexokinase 1 has been shown to promote debris clearance by microglia while it reduced neuroin ammation in animal models [215, 218]. Another promising target is the enzyme pyruvate dehydrogenase kinase, which regulates the activity of the pyruvate dehydrogenase complex and thus controls the entry of pyruvate into the TCA cycle. Inhibition of pyruvate dehydrogenase kinase is a focal point in cancer research, but its impact on promoting anti-in ammatory phenotypes within microglia in degenerative disorders remains understudied [227]. In addition to discussing the relevance of glycolysis, the role of fatty acid metabolism in microglia has also been highlighted in this review. Fatty acid oxidation is essential for the anti-in ammatory phenotype of microglia, and enhancing this metabolic pathway may o er therapeutic bene ts for neuroin ammatory diseases. For example, the peroxisome proliferator-activated receptor is a crucial transcription factor that facilitates the transfer of fatty acids into the mitochondria for oxidation and might play a neuroprotective role by inhibiting microglia activation [228–230].

While numerous pathways have been discussed in this review, ascribing metabolic pathways to distinct microglia populations presents signi cant challenges. Microglia represent a heterogeneous population of cells with distinct metabolic pro les depending on their location, microenvironment, and activation states [137, 231]. Additionally, metabolic pathways are tightly linked to diverse functions of microglia, including immune responses, phagocytosis, and synaptic pruning. For example, interruption in glycolysis reduces TNFα and IL-6 production through the inhibition of NF-kB pathway within primary microglia [190, 232]. Further, glia-derived IL-33 enhanced mitochondrial activity and phagocytosis in microglia via the AKT-dependent pathway, facilitating synapse engulfment during neurodevelopment, while disruption of the IL-33-AKT signaling axis impaired metabolic adaptation and phagocytic functions, hindering neurodevelopment [233]. erefore, targeting metabolic pathways may impact di erent subsets of microglia in various ways, complicating therapeutic strategies. More importantly, modulating metabolic pathways in microglia may have o -target e ects, potentially leading to systemic dysfunction or disrupting physiological processes outside the CNS. On the other hand, microglia adapt their metabolic pro le in response to changes in the microenvironment or disease conditions [234]. erefore, targeting a single metabolic pathway might induce compensatory changes in other subsets, potentially negating the e ect of therapies. Moreover, approaches to address metabolic alterations in microglia

	Key findings	Diseases	Select reference(s)
Glycolysis	Upregulation of *Glut1* mRNA levels and enhanced glucose uptake following exposure to α- SYN	PD	Qiao et al. [160]
	Decreased GLUT1 and GLUT3 expression, and microglial activity	AD	Biswas et al. [34]
	Decreased brain glucose metabolism in PET studies, downregulation of G6P and 6-PGD levels, and increased microglial activation	PD	Dunn et al. [156]
	Knockout of hexokinase 2 in microglia reduces glycolytic activity, inhibits their repopulation, and diminishes their ability to migrate in response to damage	AD	Hu et al. [215]
	Increased levels of LDH-B, pyruvate kinase, and glyceraldehyde 3-phosphate dehydrogenase in astrocytes and microglia	AD	Johnson et al. [38]
	A positive feedback loop involving glycolysis, H4K12 lactylation, and PKM2 in microglia contributes to the pathogenesis of AD	AD	Pan et al. [49]
	Aβ and α-SYN induce metabolic reprogramming of microglia from OXPHOS to aerobic glycolysis	AD and PD	Lu et al. [163]. Baik et al. [45]
	Neuroprotective effects of pyruvate on striatal neurons encompass the suppression of microglial activation	HD	Ryu et al. [193]
TREM2	Enhances mTOR signaling, facilitates the transition of microglia to a fully mature disease-associated microglia profile	AD	Ulland et al. [55] Keren-Shaul et al.[51]

Table 1 (continued)

	Key □ndings	Diseases	Select reference(s)
Iron	Iron-containing microglia in the frontal cortex (near Aβ plaques) and the hippocampus of AD patients	AD	Zeineh et al. [86] Van Duijn et al. [87]
	Enrichment of iron within activated microglia at the rim of chronic active white matter demyelinating lesions	MS	Zrzavy et al. [224] Mehta et al. [138]
	Iron retention within microglia elevates glycolytic activity and enhances TNFα expression.	AD	Holland et al. [88]
	IFNγ and Aβ peptides increase glycolytic enzymes, enhance iron retention, and reduce phagocytosis by microglia	in vitro	McIntosh et al. [89]
	Coupling of HIF-1α and iron-induced response in a subset of microglia	MS	Proto et al. [140]
	Disturbances in iron metabolism are primarily linked to microglia	HD	Simmons et al. [197]
Amino Acids	Upregulation of glutaminase enzymatic activity in microglia	AD, MS, and ALS	Gao et al. [67] Shijie et al. [225] Niida et al. [211]
	Stimulation of microglia by α-SYN leads to increased extracellular glutamate	PD	Reynolds et al. [173]
	A mutant huntingtin fragment can activate the kynurenine pathway in microglia	HD	Giorgini et al. [192]
	Repeated administration of methionine enhances microglial activation	AD	Alachkar et al. [76]
	Knocking out IL4I1 (the amino acid oxidase) in myeloid cells leads to failure in resolving in□ammation associated with microglia, resulting in ine□cient remyelination	MS	Hu et al. [135]
	Altered levels of aromatic amino acid metabolites in CSF samples of MS patients resulted in an imbalance in the production of immunomodulatory cytokines, particularly a□ecting a subset of monocytes with a gene signature resembling homeostatic microglia.	MS	Fitzgerald et al. [136]
	Hippocampal neuronal death is associated with immunosuppressive CD11c + microglia and extracellular arginase	AD	Kan et al. [81]

should involve compounds that are both low in molecular weight and lipophilic to ensure they can e ectively cross the BBB [235]. Neurodegenerative diseases like MS, AD, PD, HD, and ALS involve intricate pathophysiological mechanisms with multiple contributing factors. As a result, strategies aimed at targeting microglial metabolism may need to be customized to speci c disease stages and contexts, adding to the complexity of therapeutic development.

In summary, therapeutic modulation of metabolic processes in microglia represents a promising approach for developing novel treatments for neurodegenerative diseases. By understanding and manipulating microglial metabolic regulation, we can potentially harness their neuroprotective abilities, o ering new hope for patients with severe neurological conditions. Nevertheless, additional research is required to thoroughly understand the intricate metabolic regulation of microglial functions and to determine the most e ective strategies for targeting these processes.

Abbreviations

5-HIAA	5-hydroxyindole-acetic acid
7βHC	7β-hydroxycholesterol
7KC	Keto-cholesterol
Aβ	Amyloid-β
AD	Alzheimer's disease
ALS	Amyotrophic lateral sclerosis
ApoE	Apolipoprotein E
ATP	Adenosine triphosphate
BMDMs	Bone marrow-derived macrophages
CD	Cluster of Di□erentiation
CLK1	Cdc-like kinase 1
CNS	Central nervous system
CSF	Cerebrospinal □uid
DAP12	DNAX-activation protein 12
EAE	Experimental autoimmune encephalomyelitis
FADH2	Flavin adenine dinucleotide
G6P	Glucose-6-phosphate
GABA	Gamma-aminobutyric acid
GDP	Guanosine diphosphate
GLUT	Glucose transporter
H4K12la	Histone lactylation at H4 lysine 14
HD	Huntington's disease
HDAC3	Histone deacetylase 3
HIF-1α	Hypoxia-inducible factor 1-alpha
IL	Interleukin
LDH	Lactate dehydrogenase
LPC	Lysophosphatidylcholine
LPS	Lipopolysaccharide
mGluRs	Metabotropic glutamate receptors
MCT	Monocarboxylate transporter
mRNA	Messenger ribonucleic acid
MS	Multiple sclerosis
mTOR	Mechanistic target of rapamycin
NAD+	Nicotinamide adenine dinucleotide
NADH	Nicotinamide adenine dinucleotide (reduced form)
NAWM	Normal-appearing white matter
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NLRP3	NLR family pyrin domain containing 3
NO	Nitric oxide
OXPHOS	Oxidative phosphorylation
PD	Parkinson's disease
PET	Positron emission tomography

PI3Ks	Phosphoinositide 3-kinases
PKM2	Pyruvate kinase M2
PUFAs	Polyunsaturated fatty acids
ROS	Reactive oxygen species
SDH	Succinate dehydrogenase
SNpc	Substantia nigra pars compacta
SOD1	Superoxide dismutase 1
SYN	Synuclein
TCA	Tricarboxylic acid
Th	T helper
TNF	Tumor necrosis factor
TNFα	Tumor necrosis factor-alpha
TREM	Triggering receptor expressed on myeloid cells
α-SYN	α-synuclein

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Declarations

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