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Review

Aging-Related Metaflammation and Mitochondrial Dysfunction in Neurodegenerative Diseases

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ABSTRACT: Neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) are increasingly recognized as manifestations of aging-associated systemic dysfunction, rather than isolated brain disorders. Central to this dysfunction is the interplay among metaflammation, mitochondrial breakdown, and chronic neuroinflammation. Metaflammation, driven by peripheral metabolic stress, may prime the brain's immune environment through cytokine signaling and blood–brain barrier compromise. This metabolic-inflammatory crosstalk is thought to impair mitochondrial integrity in neurons and glial cells, promoting oxidative stress and the release of pro-inflammatory mitochondrial components. These mitochondrial signals, in turn, may activate microglial and astrocytic innate immune responses, creating a potentially self-reinforcing cycle of neuroinflammation and energy failure that may contribute to neuronal loss. This review outlines a proposed framework linking metaflammation to neurodegeneration, emphasizing shared mechanisms across AD, PD, and ALS. We further examine preclinical and clinical advances in therapeutic strategies that target this axis including anti-inflammatory agents, caloric restriction, mitophagy enhancers, mitochondrial antioxidants, and senescence-targeted therapies. Together, these interventions reflect a shift from symptom management to systemic metabolic and immune modulation, offering a unified framework for understanding and potentially influencing age-related neurodegeneration.

Keywords: aging, metaflammation, mitochondrial dysfunction, neurodegenerative diseases, therapeutic strategies

Introduction

Aging is the predominant risk factor for neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) [1]. These diseases, despite their clinical differences, appear to share overlapping pathological features, involving systemic metabolic inflammation (metaflammation), mitochondrial dysfunction, and neuroinflammation. Metaflammation refers to chronic, low-grade inflammation driven by metabolic stress and is thought to be a key disruptor of cellular and immune homeostasis during aging [2]. Importantly, peripheral metabolic disturbances such as obesity, insulin resistance, and metabolic syndrome initiate and amplify systemic cytokines, which then affect the brain by weakening the blood–brain barrier (BBB) and activating glial cells. Within the central nervous system, mitochondrial dysfunction not only results from but also contributes to neuroinflammation. Damaged mitochondria release reactive oxygen species (ROS) and mitochondrial DNA (mtDNA), which activate innate immune pathways including the cGAS–STING axis and NLRP3 inflammasome in microglia and astrocytes [3]. These events have been proposed to participate in a feed-forward loop of inflammation and cellular injury that progressively impairs neuronal energy metabolism. As a result, metabolically vulnerable brain regions such as the hippocampus and substantia nigra may become especially prone to degeneration.

In this review, we synthesize current evidence linking metaflammation, mitochondrial dysfunction, and neuroinflammation into a working framework for understanding age-related neurodegenerative diseases.

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Our central contribution lies in prioritizing metaflammation as a systems-level upstream driver that may influence glial mitochondrial function and innate immune signaling. Unlike prior reviews that treat inflammation, mitochondria, or the gut–brain axis separately, we present an integrated framework in which chronic metaflammation is hypothesized to contribute to mitochondrial–immune dysfunction across microglia, astrocytes, and neurons. While mechanistic studies support this model in animal and cellular contexts, evidence in humans remains limited and variable across diseases, particularly in ALS. This integrated approach offers a potentially useful perspective on modifying the course of neurodegenerative diseases. To avoid confusion stemming from overlapping terminology, we include a Definition Box that distinguishes metaflammation, inflammaging, and related terms. Here, we specifically define metaflammation as a metabolically triggered form of systemic inflammation distinct from general immune aging and emphasize its putative role in initiating mitochondrial and glial dysfunction across neurodegenerative conditions.

Box 1. Definitions of Inflammation-Related Terminology

- **Inflammaging:** Chronic, low-grade, and sterile inflammation that accumulates with age, primarily due to immunosenescence and innate immune activation.
- **Metaflammation:** A metabolically triggered form of inflammation driven by overnutrition, insulin resistance, mitochondrial stress, and nutrient-sensing disruption. Distinct from inflammaging in origin and mechanism. This term describes the chronic inflammatory signals arising from dysfunctional metabolic organs such as adipose tissue, liver, and gut.
- **Systemic low-grade inflammation:** A broader term encompassing both inflammaging and metaflammation, characterized by persistently elevated circulating inflammatory mediators (e.g., IL-6, TNF-α, CRP), without overt infection.

1. Aging-related Meta-inflammation: Upstream Driver of Neurodegeneration

1.1 Immunological Basis and Sensing Architecture of Metaflammation

Chronic, low-grade, and sterile inflammation that ubiquitously accompanies aging has been conceptualized as inflammaging, whereas the subset predominantly driven by nutritional excess and metabolic dysregulation is defined as metaflammation [2]. Notably, these two processes overlap substantially at the levels of immune sensors, effector molecules, and tissue-level inflammatory circuits. From an immunological sensing perspective, inflammaging does not arise from a single causal trigger but rather represents the cumulative convergence of multiple long-term inputs within innate immune networks, including pathogen-associated molecular patterns (PAMPs) derived from microbial sources, damage-associated molecular patterns (DAMPs) released during cellular injury and tissue degeneration, and so-called "quasi-self" signals associated with nutritional overload and gut microbiota–derived cues [2, 4, 5]. Despite their distinct origins, these inputs converge on a limited set of highly conserved immune sensing systems, most prominently membrane-bound Toll-like receptors (TLRs), cytosolic NOD-like receptors such as NLRP3 (a core sensor of the inflammasome), the cytosolic DNA receptor cGAS, and the aryl hydrocarbon receptor (AhR). Activation of these systems is thought to initiate or reshape inflammatory transcriptional programs and downstream effector responses [2, 6, 7]. Mechanistically, these sensing systems activate interconnected inflammatory outputs, including TLR–NF-κB/IRF signaling, NLRP3 inflammasome-dependent IL-1β/IL-18 maturation, cGAS–STING-mediated type I interferon programs, and AhR–IL-22 regulation [7-10]. This multi-pathway convergence is hypothesized to maintain the immune–metabolic network in a persistent state of metastable, heightened vigilance. This state may represent a fundamental immunological backdrop of aging-associated metaflammation (Fig. 1).

1.2 Mechanisms of Metaflammation Maintenance and Amplification

Clinically, obesity, type 2 diabetes mellitus (T2DM), and metabolic syndrome (MetS) represent the most characteristic and readily quantifiable manifestations of aging-associated metaflammation, with their histopathological origins typically residing in metabolic organs, particularly visceral adipose tissue [11]. Chronic energy surplus drives adipocyte hypertrophy accompanied by local hypoxia, endoplasmic reticulum stress, and increased cell death, which in turn induces upregulation of chemokines such as MCP-1/CCL2 and promotes monocyte recruitment [12-14]. Infiltrating macrophages subsequently undergo preferential M1-like pro-inflammatory polarization within the adipose tissue microenvironment, becoming a dominant source of cytokines such as TNF-α and IL-6. These mediators further exacerbate adipocyte insulin resistance and dysregulated lipolysis, thereby establishing a potentially self-reinforcing loop between inflammation and metabolic dysfunction [12]. As inflammatory mediators and adipose-derived signals continuously spill into the

circulation, localized metaflammation increasingly manifests as a systemic, measurable low-grade inflammatory milieu, reflected by persistently elevated pro-inflammatory cytokines and high-sensitivity C-reactive protein (hs-CRP), and tightly coupled to impaired insulin signaling across multiple tissues [15, 16] (Fig. 1).

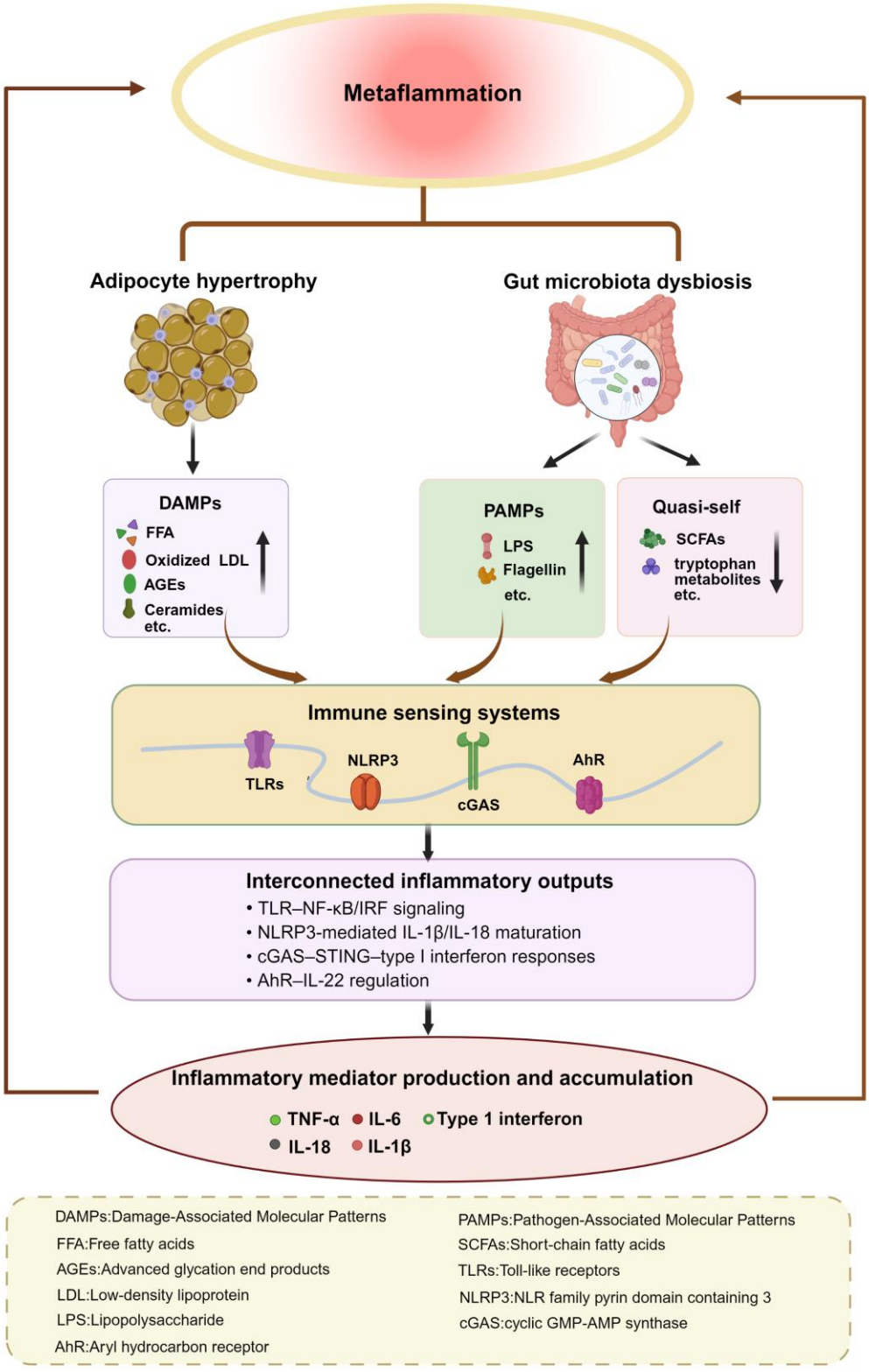

Figure 1. Self-perpetuating loop of metaflammation. Aging-associated metaflammation is primarily driven by metabolic stress originating from visceral adipocyte hypertrophy and gut microbiota dysbiosis. Adipose expansion promotes excessive generation of DAMPs (e.g., FFA, oxLDL, AGEs, and ceramides), whereas gut microbiota dysbiosis promotes excessive generation of PAMPs (e.g., LPS and flagellin). In addition, microbiota dysbiosis also disrupts quasi-self signals, characterized by reduced levels of beneficial microbial metabolites (e.g., SCFAs and tryptophan-derived metabolites). Collectively, DAMPs, PAMPs, and disrupted quasi-self signals converge on innate immune sensing systems, including TLRs, NLRP3, cGAS–STING, and AhR. Activation of these sensing pathways generates interconnected inflammatory outputs, including TLR–NF-κB/IRF signaling, NLRP3-dependent IL-1β/IL-18 maturation, cGAS–STING-mediated type I interferon responses, and AhR–IL-22 regulation. The sustained production and accumulation of these inflammatory mediators, such as TNF-α, IL-1β, IL-6, IL-18, further exacerbate metaflammation, ultimately forming a self-perpetuating cycle that maintains and amplifies metaflammation.

Mechanistically, the persistent and outward-spilling nature of the aforementioned tissue inflammatory circuits hinges on the continual generation and accumulation of metabolic stress into danger signals that can be sensed by the innate immune system, including free fatty acids, ceramides, oxidized LDL, and advanced glycation end products (AGEs) [17]. Such signals can chronically activate inflammatory transcriptional pathways, such as NF-κB and JNK, by engaging receptors including TLR4 and RAGE, thereby providing a persistent priming context for inflammasome activation [17, 18]. Within this framework, the NLRP3 inflammasome serves as a crucial amplifier, catalyzing the caspase-1-dependent maturation and release of IL-1β and IL-18, further exacerbating metabolic tissue inflammation and undermining the integrity of insulin signaling [18, 19]. While many of these mechanisms are supported by animal and cellular models, their generalizability to human physiology remains under investigation. This combination of transcriptional priming and effector amplification is hypothesized to sustain a chronic feedback loop, in which metabolic stress is continually translated into inflammatory signaling. Such a loop may extend beyond peripheral tissues to affect central organs. DAMP-induced systemic inflammation is increasingly viewed as a possible contributor to BBB dysfunction, whereby metabolic and immune signals may propagate along the vascular–barrier axis and influence the brain's microvascular endothelium. This process is proposed to represent one route by which metaflammation contributes to chronic neuroinflammation in the aging brain (Fig. 1 and 2).

Beyond endogenous DAMPs generated by metabolic organs, gut microbiota dysbiosis constitutes another major and persistent input pathway, serving as a critical source of PAMPs, such as lipopolysaccharide (LPS), lipoproteins, and flagellin, as well as quasi-self metabolic signals, including short-chain fatty acids (SCFAs), bile acid derivatives, and tryptophan metabolites [2, 20] (Fig. 1). During aging, elderly individuals typically exhibit diminished microbial diversity, depletion of SCFA-producing bacteria (such as butyrate producers), and an increased abundance of LPS-rich Gram-negative bacteria and various pathobionts [20-22]. Such microbial imbalance predisposes to compromised gut barrier function, decreased protective metabolite supply, and increased intestinal leakiness of LPS, which together may amplify localized dysregulation into systemic low-grade inflammation [20, 23]. While the proposition that gut-derived signals are sufficient to drive systemic inflammation has been supported by causal evidence in animal models, its direct validation in humans remains limited.

Notably, in the context of aging and metabolic syndrome, the contribution of the gut microbiota to metaflammation extends beyond the persistent, low-dose stimulation of innate immune receptors such as TLRs by translocated gut-derived PAMPs (e.g., LPS) [2]. It also encompasses the prolonged modulation of immune thresholds and metabolic homeostasis by quasi-self metabolic signals [24]. In healthy individuals, SCFAs such as acetate and butyrate enhance Treg function and inhibit NF-κB activation via receptors like FFAR2/GPR43 and through epigenetic regulation, thereby counteracting systemic low-grade inflammation [24-26]. However, in obesity and T2DM, the depletion of SCFA-producing bacteria along with the expansion of pro-inflammatory microbiota impairs this anti-inflammatory buffering axis [27, 28]. Simultaneously, microbiota-driven bile acid reprogramming modulates hepatic lipid metabolism and energy expenditure through FXR and TGR5 signaling, suggesting a role in integrating inflammatory and energetic homeostasis as another key component in sustaining metaflammation [29]. Additionally, microbiota-derived tryptophan metabolites can regulate metaflammation and insulin resistance via the AhR receptor [30]. Together, these findings support the concept of a gut–metabolism–immunity feedback loop, in which elderly individuals may experience chronic exposed to low-level stimuli of PAMPs, metabolic DAMPs, and quasi-self signals, even in the absence of overt infection. However, while this framework is compelling, it has been primarily substantiated in experimental systems, and further research is needed to confirm its relevance in human aging (Fig. 1).

1.3 Clinical Evidence Linking Metaflammation to Neurodegenerative Disease Risk

From a theoretical standpoint, age-related metaflammation is thought to possess many of the biological prerequisites to disrupt cerebral homeostasis via systemic inflammation and metabolic toxicity. A substantial body of population-based and prospective cohort studies offers epidemiological evidence supporting this hypothesis: classic metaflammatory phenotypes such as obesity, T2DM, and MetS consistently exhibit elevated risk patterns for dementia and specific neurodegenerative diseases [31-34]. It is important to note that this association does not imply a simple linear relationship where increased body weight translates directly into heightened risk. On the contrary, emerging evidence suggests that body composition and metabolic burden are more accurate determinants of risk than total body weight itself [31]. Indices reflecting fat accumulation are consistently correlated with increased dementia risk, whereas indicators of muscle mass tend to demonstrate a protective association. This pattern underscores that risk is more likely attributable to metabolic imbalance and low-grade inflammation associated with adipose tissue expansion, rather than body weight as a crude surrogate.

In specific disease profiles, T2DM and related metabolic abnormalities are implicated across AD, PD, and to a more limited extent ALS. For instance, genetic and epidemiological studies support an association between insulin resistance/metabolic burden and increased risk of late-onset AD or AD related dementias, with metabolically driven stress from environmental and lifestyle factors potentially serving as a more critical pathway [33-36]. Regarding PD, large-scale cohort studies and meta-analyses consistently indicate a positive correlation between diabetes/MetS and PD risk, exhibiting a dose–response trend in relation to disease progression, comorbidity burden, and increased number of MetS components, alongside possible synergistic amplification based on genetic susceptibility [37-39]. By contrast, in ALS, clinical evidence for metabolic contributions remains more heterogeneous and less consistent. While the relationship between single metabolic markers and risk may be nonlinear [40], some high-quality cohorts have reported associations between persistent, aggregated MetS states and ALS onset, pointing to a potential but unconfirmed interaction between metaflammation and ALS susceptibility [41]. However, these findings remain preliminary and require further validation across diverse populations and study designs.

Overall, metaflammation arising in the context of aging, shaped by nutritional burden, metabolic syndrome, and gut microbiota dysbiosis, represents a persistent systemic inflammatory and metabolic state rather than a focal response limited to metabolic organs. From an epidemiological perspective, this state shows a strong and consistent association with increased risks of various neurodegenerative diseases, such as AD, PD, and with more tentative links to ALS that merit further mechanistic investigation. However, population-level data alone cannot elucidate how systemic metaflammation evolves at the molecular and cellular levels into neuronal energy imbalance and localized neuroinflammation, nor how gut microbiota disruption serves as a critical bridge in this cascade. The following sections will focus on the central nexus of mitochondrial dysfunction and neuroinflammation within the brain, exploring how these processes are initiated and amplified in the setting of metaflammation, and proposing key pathways by which metaflammation contributes to neurodegenerative pathologies.

2. Mitochondrial Dysfunction and Neuro-inflammation: Core Hub Connecting Metaflammation to Neurodegenerative Pathology

2.1 Transmission of Peripheral Metaflammation to CNS Mitochondria

Age-related metaflammation does not exert its effects directly on the central nervous system. Instead, its impact is thought to converges upon and acts on key relay points such as the BBB or the blood–spinal cord barrier, where peripheral inflammatory signals may influence central processes [42, 43]. At this interface, metaflammatory cues are hypothesized to promote vascular inflammation and impair barrier dysfunction. This reduction in BBB integrity may lower the threshold for peripheral inflammatory signals to access the brain parenchyma and is proposed to contribute to the disruption of mitochondrial homeostasis within neurons and glial cells [43-45]. Current evidence suggests that this influence is not mediated by a single mechanism, but rather by multiple, overlapping pathways. These include mitochondrial oxidative damage induced by metabolic stress and the activation of inflammatory cascades through receptor-ligand interactions on epithelial cells. Together, these mechanisms may compromise the structure and function of BBB, creating a permissive environment for neuroimmune activation (Fig. 2).

2.1.1 Mechanisms of Blood–Brain Barrier Disruption

Metabolic stress-induced BBB structural damage appears to primarily involve cerebral microvascular endothelial cells and their tight junction complexes. In aged obese mice and high-fat diet models, metabolic stress has been

shown to reduce tight junction proteins such as claudin-5 and occludin, increase plasma protein or albumin leakage, and promote hippocampal neuroinflammation [44, 46]. At the mechanistic level, hyperglycemia and AGEs can induce mitochondrial dysfunction and excessive mitochondrial ROS (mtROS) production in cerebral microvascular endothelial cells [47, 48]. Elevated mtROS may then promote phosphorylation, redistribution, and degradation of tight junction proteins, resulting in reduced transendothelial electrical resistance and increased BBB permeability [45]. These findings suggest that endothelial mitochondrial dysfunction and mtROS overproduction may represent an important mechanism by which peripheral metabolic stress compromises BBB integrity and primes the barrier for subsequent inflammatory amplification (Fig. 2).

In addition to metabolic stress-induced endothelial mitochondrial injury, peripheral metaflammation may disrupt BBB integrity through receptor-mediated endothelial activation at the luminal surface (Fig. 2). Specifically, circulating cytokines, metabolic DAMPs, and microbe-associated molecules, including TNF-α, IL-1β, IL-6, LPS, and AGEs, can interact with receptors or sensing systems on brain microvascular endothelial cells, such as TNFR, IL-6R, RAGE, TLRs, and caspase-11 [49-54]. These interactions are associated with activation of inflammatory signaling pathways, including NF-κB, JNK, and AKT, leading to adhesion molecule upregulation, tight junction downregulation, reduced transendothelial electrical resistance, and increased permeability [49, 52-56]. Notably, in some models, molecular events related to inflammatory cell death, such as the involvement of GSDMD, have been observed to occur in parallel with barrier disruption, suggesting that these processes may act as amplifying mechanisms of increased permeability [53]. However, the precise causal hierarchy of these pathways remains to be fully elucidated and may depend on the specific metabolic and inflammatory context. In addition, although some reports indicate that certain cytokines can cross the BBB via saturable transport mechanisms, available evidence suggests that, in most chronic metaflammatory conditions, the endothelial luminal receptor-mediated inflammatory activation likely plays a more critical role [57]. This process can lower the threshold of barrier function prior to any structural damage and, following structural disruption, can further amplify the dissociation of tight junctions and increase permeability. Additionally, it facilitates the adhesion and transmigration of circulating monocytes across the endothelium and may promote the dissemination of inflammatory signals into the brain parenchyma.

2.1.2 Actions of Metaflammation-Associated Factors on CNS Mitochondria

When the BBB threshold is diminished, resulting in greater exposure of brain parenchyma, circulating inflammatory mediators and molecules associated with metabolic injury are more likely to interact with neurons and glial cells, potentially perturbing mitochondrial homeostasis (Fig. 2). Tangpong et al. were the first to demonstrate in primary neuron–glia co-culture systems that TNF-α treatment significantly induces iNOS expression, leading to increased NO production, MnSOD nitration, and mitochondrial dysfunction [58]. Moreover, another study confirmed that, in cortical neurons, TNF-α-induced iNOS expression is dependent on NF-κB activation [59]. These findings support the idea that inflammatory mediators can initiate a mitochondrial toxicity pathway within central nervous system cells, specifically mediated by the TNF-α–NF-κB–iNOS–NO axis. Furthermore, work by Brown et al. systematically showed that excessive NO and its derivative peroxynitrite can interact with multiple mitochondrial respiratory chain complexes (particularly complex I and cytochrome c oxidase), thereby inhibiting the electron transport chain and ATP production, inducing mitochondrial membrane depolarization [60]. Taken together, these findings suggest a mechanistic link between peripheral inflammatory factors and central mitochondrial respiratory dysfunction via NO.

On the other hand, AGE–RAGE signaling has been established as another critical pathway through which metabolic DAMPs may affect central mitochondrial function. Early work by Wautier et al. in vascular endothelial cells demonstrated that AGE–RAGE engagement activates NADPH oxidase, driving ROS generation and altering gene expression, thereby laying the conceptual foundation for AGEs as metabolic DAMPs that induce oxidative stress via RAGE [61]. Subsequent studies in hippocampal neurons showed that AGEs increase ROS and induce mitochondrial dysfunction (membrane depolarization, ATP depletion, and cytochrome c release), and that these effects are abolished by RAGE blockade [62]. Further evidence suggests that the damage-associated molecule HMGB1, also acting as a RAGE ligand, may impair mitochondrial quality control by arresting late-stage mitophagic flux, thereby compromising the clearance of damaged mitochondria and leading to sustained mtROS accumulation [63]. However, many of these findings are based on cell and animal models, and the extent to which they apply to human aging and neurodegeneration remains to be fully validated.

As a prototypical component of PAMPs, LPS has been shown to induce mitochondrial dysfunction in both

neurons and glial cells. For instance, a previous study demonstrated that treatment of primary neurons with LPS resulted in significant mitochondrial damage, characterized by reduced oxidative phosphorylation, loss of mitochondrial membrane potential (ΔΨm), and ATP depletion, ultimately leading to cell death [64]. Mechanistically, this phenotype was associated with Drp1–Fis1 activation and was rescued by P110, a selective Drp1 inhibitor. Similarly, LPS exposure in microglia caused excessive mitochondrial fragmentation, a metabolic shift toward glycolysis, and increased ROS generation, which together promoted microglial activation [65]. Notably, the application of the mitochondrial division inhibitor Mdivi-1 reversed these changes. Moreover, LPS-induced mitochondrial fragmentation in neurons and neuroinflammation could be reversed by overexpressing mitochondrial fusion protein 2 (Mfn2) [66]. Neuronal Mfn2 appears to modulate the release of IL-1β and attenuate neuroinflammation by specifically influencing microglial activation, rather than astrocytic activation.

2.2 CNS Mitochondrial Dysfunction as an Immunometabolic Hub Driving Neuroinflammation and Neurodegeneration

In the central nervous system, neuroinflammation is no longer viewed simply as elevated cytokine levels, but rather as a state of chronic immune activation driven by transcriptional and metabolic reprogramming of microglia and astrocytes [67, 68]. Mitochondria are increasingly recognized as a central hub in this process. Respiratory chain dysfunction, loss of membrane potential, and impaired mitochondrial quality control are proposed to promote energy stress and mitochondrial ROS (mtROS）accumulation, which may lead to the release of mitochondrial DAMPs (mtDAMPs), thereby potentially converting metabolic stress into innate immune signals [69]. Experimental studies suggest that mtDAMP-induced inflammation is amplified mainly through two complementary pathways, namely the cGAS–STING–dependent inflammatory transcriptional program and the NLRP3 inflammasome. Taken together, these pathways are proposed to sustain glial activation and exacerbate neurodegenerative pathology [3]. Notably, although neurons are not classical immune effector cells and primarily act as passive recipients of inflammatory insults, neuronal mitochondrial damage can release mtDAMPs and disrupt energy and Ca^{2+} homeostasis, potentially rendering glial cells more prone to persistent activation and stabilizing inflammatory amplification loops (Fig. 2). However, the relative contribution of these mitochondrial immune pathways to human disease remains to be fully elucidated. Additional studies, particularly in human-derived systems, will be required to delineate their precise roles and disease-specific relevance in CNS aging and pathology.

2.2.1 Microglia: Mitochondrial DAMP–Driven cGAS–STING/NLRP3 Signaling

Microglia are the resident innate immune cells of the central nervous system, often referred to as the brain's macrophages, and play a central role in pathogen clearance and inflammatory immune responses [67]. In addition, microglia function as a key hub and amplifier of neuroinflammation, with mitochondrial damage increasingly suggested as a critical contributing factor [69]. Under mitochondrial stress, oligomerization on the outer mitochondrial membrane (OMM) gives rise to large pores (such as BAX/BAK or VDAC associated membrane pores), which are thought to increase OMM permeability [70, 71]. Oxidatively damaged mtDNA is thereby released into the cytoplasm or extracellular space, where it may be detected by cGAS [72]. This recognition catalyzes the production of cGAMP and subsequently activates the STING–IRF3/ NF-κB axis, initiating type I interferon and a broad spectrum of inflammatory gene expression [3]. Notably, activation of the cGAMP–STING pathway is proposed to perpetuate microglial activation and promotes the secretion of pro-inflammatory cytokines, thereby exacerbating neuro-inflammation [3, 73-75]. Additionally, mitochondrial stress in microglia can trigger NLRP3 inflammasome activation via mtROS burst, which may promote microglial polarization toward the M1 phenotype and thereby inducing neuroinflammation (Fig. 2) [76].

Furthermore, the relevance of this mechanism to neurodegenerative diseases has begun to emerge. Excessive accumulation of Aβ and impaired clearance are hallmark features of AD, and microglia play a central role in Aβ removal. Recent evidence suggested that excessive microglial uptake of Aβ may trigger cytosolic leakage of mtDNA, potentially activating the cGAS–STING pathway and initiating neuroinflammatory programs [77]. In addition, pathological tau has been shown to induce, at least in part, cytosolic mtDNA leakage in microglia and activate cGAS-dependent type I interferon responses, thereby reshaping transcriptional networks linked to synaptic homeostasis and cognitive resilience [78]. Notably, genetic risk factors for AD further amplify this cascade: in tauopathy models, risk allele–associated stress couples with BAX-mediated mitochondrial membrane permeabilization to promote mtDNA release and enhance cGAS–STING/IFN signaling in parallel with senescence-like microglial phenotypes, which may contribute to neurodegeneration [79]. Similarly, in PD, Liu et al. reported that 3-n-butylphthalide alleviates rotenone-

induced neuroinflammation and behavioral deficits by suppressing mtDNA-mediated cGAS–STING activation in BV2 microglia [80]. In the context of ALS, mechanistic studies remain relatively nascent but offer emerging insights. In SOD1-mutant ALS models, mutant SOD1 induced mitochondrial membrane depolarization in microglia, leading to cytosolic accumulation of mtDNA and sustained activation of the cGAS–STING pathway and its downstream type I interferon program [81]. A recent study supports this hypothesis. This study demonstrated that microglia in misfolded SOD1–driven ALS models exhibit markedly elevated expression of MGnD- and IRM-associated gene programs, while mtDNA further activates the cGAS–STING pathway [81]. Although these findings provide preliminary causal links between mtDNA leakage and microglial phenotypic shifts in ALS, further *in vivo* validation across diverse ALS models is warranted. Notably, the depletion of mtDNA reduced IFN-β expression, an effect that is markedly attenuated in the absence of cGAS or STING (Fig. 2).

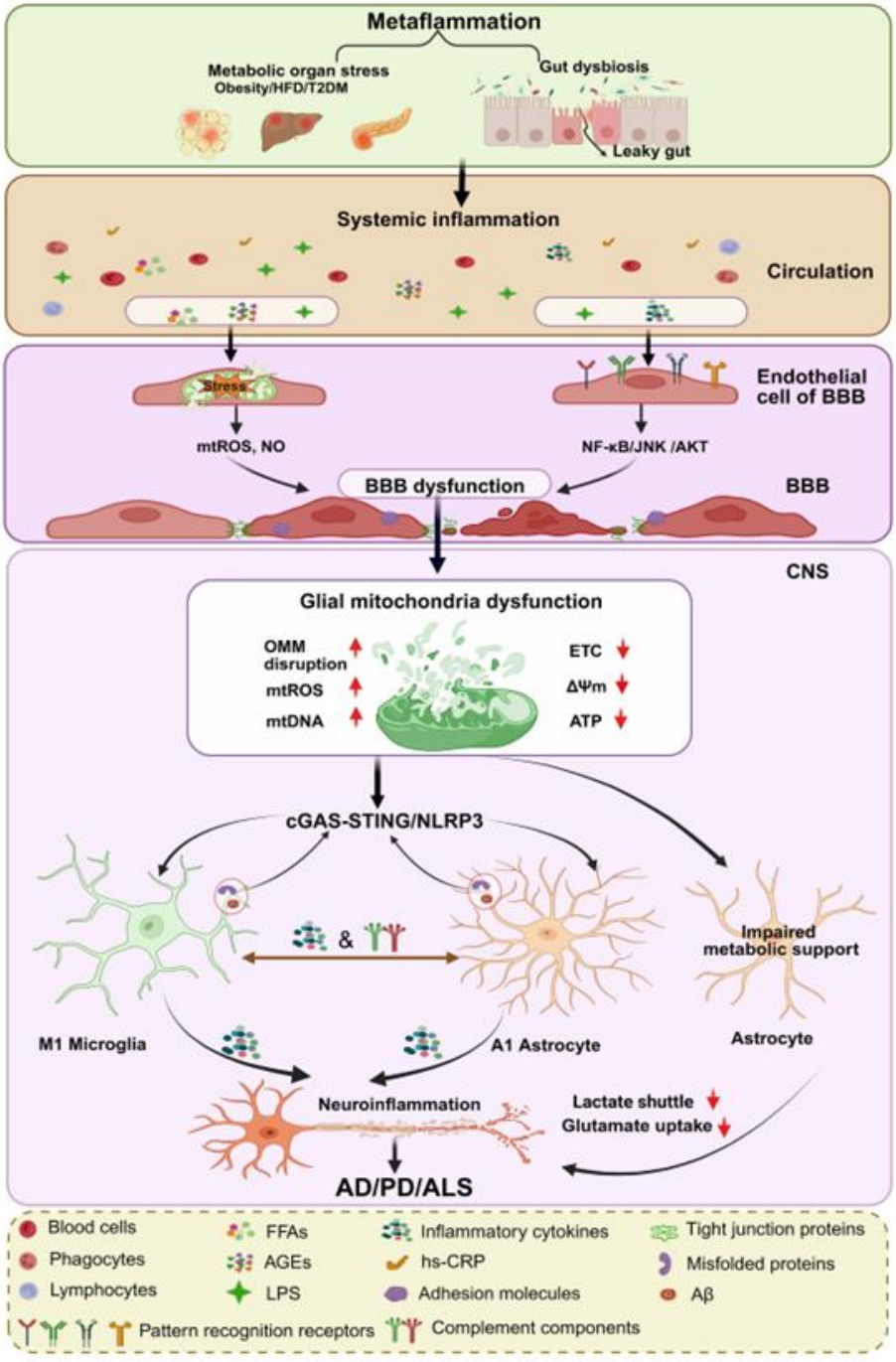

Figure 2. Metaflammation drives neuroinflammation through central mitochondrial dysfunction. (1) Metaflammation arises primarily from metabolic organ dysfunction and gut microbiota dysbiosis, which together induce systemic inflammation and elevate circulating DAMPs (e.g., AGEs and FFA), gut-derived PAMPs (e.g., LPS), inflammatory cytokines, and hs-CRP. **(2)** Furthermore, these factors can disrupt BBB integrity through multiple mechanisms. Generally, LPS, AGEs and FFA induce mitochondrial stress in brain endothelial cells, leading to excessive mtROS production and promoting the degradation of tight junction proteins, thereby increasing BBB permeability. In parallel, LPS, AGEs and inflammatory cytokines (TNF-α, IL-1β, and IL-6) can activate NF-κB/JNK signaling via endothelial receptors such as TNFR, TLRs, and RAGE, further compromising BBB function. **(3)** BBB disruption allows inflammatory mediators, DAMPs, and PAMPs to enter the CNS and impair glial mitochondrial function, resulting in ETC dysfunction, mtROS accumulation, loss of mitochondrial membrane potential (ΔΨm) or ATP, increased outer mitochondrial membrane (OMM) permeability, and mtDNA release. **(4)** Subsequently, in microglia and astrocytes, the leaked mtDNA further activates cGAS–STING signaling, inducing the formation of M1 microglia and A1 astrocytes and promoting inflammatory cytokine release, which in turn drives neuroinflammation. In addition, excessive mtROS can activate the NLRP3 inflammasome, thereby further regulating glial inflammatory responses and aggravating neuronal damage. Furthermore, misfolded proteins such as Aβ, SOD1, and α-synuclein can also act as upstream signals to activate the mtDNA–cGAS–STING or mtROS–NLRP3 pathways in microglia or astrocyte, thereby exacerbating neurotoxicity. Notably, as important metabolic support cells for neurons, mitochondrial dysfunction in astrocytes impairs their ability to supply lactate and clear glutamate, which further induces neuroinflammation. Additionally, activated microglia and astrocytes interact through inflammatory cytokines and complement components, forming a feed-forward loop that promotes neuroinflammation. Ultimately, the chronic accumulation of neuroinflammation induced by these factors further drives the onset and progression of neurodegenerative diseases such as AD, PD, and ALS.

NLRP3, as a highly conserved innate immune receptor, has also been implicated in the process by which mitochondrial dysfunction in microglia may contribute to neurodegeneration. For example, previous studies have shown that in a PD animal model, excessive mtROS production in microglia induced by pesticides was associated with activation of NLRP3 inflammasome signaling, promoting the release of IL-1β and thereby exacerbating the degeneration of dopaminergic neurons [76]. Moreover, microglial uptake of misfolded α-synuclein can likewise promote ROS production, ultimately activating NLRP3 and enhancing PD-associated neuroinflammation [82]. Similarly, other studies showed that Aβ activates the NLRP3/caspase-1 axis in microglia as a key mechanism in AD pathogenesis, and this process is ROS-dependent, supporting the hypothesis that inhibiting NLRP3 inflammasome activity may be a novel therapeutic strategy for the disease [83, 84]. In ALS models, evidence is more limited. Deora et al. found that in ALS animal models, NLRP3 is the key inflammasome complex driving microglial secretion of IL-1β in response to pathogenic SOD1 protein, with ROS serving as the critical trigger for SOD1-mediated NLRP3 activation [85]. However, these findings are predominantly based on familial ALS models involving SOD1 mutations and may not generalize to sporadic or non-SOD1 forms of the disease.

Taken together, microglial mitochondrial dysfunction is proposed as a crucial upstream event that may activate the NLRP3 inflammasome, thereby promoting neuroinflammation and neurodegeneration (Fig. 2). Nevertheless, the strength and generalizability of these pathways across neurodegenerative conditions vary. While well-supported in AD and PD, ALS-related evidence remains preliminary and should be interpreted with appropriate caution.

2.2.2 Astrocytes: A1 Neurotoxicity Driven by Mitochondrial Dysfunction

It is important to emphasize that innate immune activation of microglia is not the endpoint; rather, the cytokines, complement factors, and metabolic stress they release can further influence the metabolic and mitochondrial states of astrocytes [86]. This transition may drive inflammation from an immune cell event into a metabolic-toxic reorganization at the neural network level. Astrocytes, the most abundant type of glial cell in the central nervous system, provide essential metabolic and functional support to neurons through diverse mechanisms including supplying energy substrates, maintaining ionic homeostasis, and participating in neurotransmitter metabolism [87]. These supportive functions are largely dependent on the highly active mitochondrial metabolism of astrocytes [88]. Consequently, when mitochondrial dysfunction occurs within astrocytes, their capacity to provide metabolic and homeostatic support to neurons may be compromised, potentially heightening neuronal susceptibility to stress and toxic insults, and thereby contributing to the onset and progression of neurodegenerative pathologies (Fig. 2). However, the specific causal hierarchy between astrocytic mitochondrial failure and neurodegeneration likely differs across disease contexts and remains under active investigation.

Mitochondria-Dependent Failure of Lactate or Glutamate Metabolic Support Induces Neuronal Injury

Lactate is widely recognized as a key energy substrate supplied by astrocytes to neurons and is essential for sustaining neuronal function, giving rise to the concept of the astrocyte–neuron lactate shuttle [89]. Central to this

model is that, in response to increased neuronal energy demand, astrocytes metabolize glucose to lactate via glycolysis and deliver it to neurons through monocarboxylate transporters. Seminal work by Suzuki et al. demonstrated that selective inhibition of hippocampal astrocytic glycogenolysis reduces lactate production and impairs hippocampal memory in rats, whereas exogenous lactate supplementation rescues neuronal dysfunction, underscoring a critical dependence of neurons on astrocyte-derived lactate for synaptic function [90]. In addition, Christian et al. showed that impaired mitochondrial transcription in astrocytes exacerbates stress-induced neuronal death, highlighting the essential role of astrocytic mitochondrial function in neuronal viability under stress [91]. While these findings are supportive, they remain largely associative or based on selective interventions, and the extent to which early astrocytic mitochondrial dysfunction causally disrupts lactate-based metabolic coupling in human neurodegenerative disease remains to be firmly established. It should be noted, however, that direct causal evidence simultaneously tracking astrocytic mitochondrial dysfunction, lactate output, and neuronal degeneration within a single model remains lacking, and this hypothesis awaits validation by future studies employing lineage-specific labeling and metabolic flux tracing. Glutamate is the principal excitatory neurotransmitter in the CNS, and its safe regulation critically depends on metabolic support provided by astrocytes [87]. While neurons are responsible for releasing glutamate, astrocytes play a vital role in glutamate uptake, metabolism, and the subsequent supply of glutamine, thereby maintaining synaptic excitatory homeostasis, preventing excitotoxicity, and furnishing neurons with metabolic substrates [89]. Notably, the processes of glutamate uptake and metabolism in astrocytes are highly reliant on mitochondrial integrity and function (Fig. 2).

Initially, glutamate uptake by astrocytes is mediated by Na^+-dependent excitatory amino acid transporters (EAATs) [92]. Due to the concentration gradient between the intra- and extracellular environments, this requires active transport against the gradient, which relies continuously on Na^+/K^+-ATPase activity [93]. It is estimated that the uptake of a single glutamate molecule consumes more than one molecule of ATP, rendering this process one of the most energy-intensive transport mechanisms within the CNS [94]. Furthermore, glutamate internalized by astrocytes can be metabolized through glutamate dehydrogenase and aminotransferases to α-ketoglutarate, entering the tricarboxylic acid (TCA) cycle [89]. The resulting ATP production is typically sufficient to offset the energy costs associated with glutamate uptake, establishing a self-sustaining glutamate self-funding metabolic loop [89, 94]. Additionally, a proportion of the absorbed glutamate is converted in the cytoplasm via glutamine synthetase to glutamine, which is then shuttled back to neurons as a precursor for the resynthesis of glutamate or γ-aminobutyric acid [95]. The glutamate–glutamine cycle is similarly dependent on adequate ATP supply and mitochondrial-derived NADPH. Thus, mitochondrial dysfunction within astrocytes emerges as a plausible risk factor for glutamate dysregulation, which may trigger neurotoxicity and contribute to the pathogenesis of neurodegenerative diseases. Supporting this hypothesis, Volobouéva et al. demonstrated that treatment with the mitochondrial inhibitor fluorocitrate (FC) led to a precipitous decrease in ATP levels and mitochondrial membrane potential, accompanied by a marked reduction in astrocytic glutamate uptake [96]. Moreover, when astrocyte-neuron co-cultures were exposed to glutamate in the presence of FC, there was an enhancement of glutamate-induced neuronal death. Nevertheless, these findings are largely derived from pharmacological studies in rodent or *in vitro* systems. Therefore, additional *in vivo* studies, particularly those using human-derived models or patient tissues, are needed to clarify the relative contribution and translational relevance of this mechanism across disease contexts.

Moreover, impaired glutamate uptake has been consistently observed in several neurodegenerative disorders, including AD, ALS, Huntington's disease (HD), and PD. For example, a recent study showed that astrocytic glutamate clearance is markedly impaired in AD [97]. Interestingly, this deficit could not be fully explained by changes in glutamate transporter-1 expression but instead appeared to be more closely associated with aberrant glutamate localization. In addition, glutamate excitotoxicity is considered a pathogenic factor in HD and is thought to underline the motor and cognitive deficits seen in HD patients. Notably, in *Drosophila* HD models, EAAT2 activators such as GT951, GTS467, and GTS551 have been shown to ameliorate motor dysfunction, memory impairment, and reduce mortality [98]. In the case of ALS, evidence for glutamate dysregulation is supported primarily by studies examining spinal cord pathology and transporter expression. A seminal study by Howland et al. confirmed that focal loss of EAAT2 in the spinal cord anterior horn precedes motor neuron and axon degeneration [99]. As the disease progresses, the loss of EAAT2 exceeds 90%, implicating diminished glutamate uptake in the process of ALS-associated cell death. While this strongly supports the role of astrocytic dysfunction in ALS pathogenesis, it should be noted that the majority of data derives from familial ALS models, particularly those involving SOD1 mutations. Thus, broader applicability to sporadic ALS

remains to be fully established. Currently, glutamate excitotoxicity is also a prominent hypothesis regarding the etiology of PD. There is evidence that striatal GLT-1 is decreased in PD rat models; and the targeted knockout of GLT-1 in wild-type rat astrocytes induces PD-like behaviors, whereas GLT-1 agonists can reverse these effects. This suggests that GLT-1-mediated glutamate excitotoxicity may serve as a key regulator in PD [100] (Fig. 2). However, as with ALS, additional studies are needed to confirm these mechanistic pathways in human PD tissues and across diverse disease models.

Mitochondrial DAMPs Drive Astrocytic Neurotoxicity via cGAS–STING/NLRP3 Signaling

Astrocytic mitochondrial dysfunction is not merely a matter of impaired support function, but rather has been proposed to drive astrocytes toward a neurotoxic and pro-inflammatory phenotype via metabolic reprogramming and activation of inflammatory pathways, thereby potentially contributing to the amplification of neuroinflammation. Liddelow et al. first proposed that astrocytes shift from a resting to a reactive state in response to brain injury and neuroinflammation and broadly classified reactive astrocytes into A1-like and A2-like states [86]. In brief, A1 astrocytes possess neurotoxic properties and promote neuroinflammation, whereas A2 astrocytes exert neuroprotective effects. However, although the A1/A2 classification has served as a useful conceptual framework, it is increasingly recognized that reactive astrocytes exist on a phenotypic continuum influenced by disease context, regional identity, and signaling milieu. Thus, the A1/A2 terminology should be interpreted as a heuristic rather than a definitive classification scheme. Notably, analyses of human samples have revealed a significant abundance of A1 astrocytes in a range of neurodegenerative diseases, including AD, PD, ALS, and HD [86]. This observation raises the possibility of a link between astrocytic mitochondrial impairment and neurotoxic phenotypic shifts. Indeed, since the classification of A1 and A2 subtypes, no direct evidence had demonstrated that intrinsic mitochondrial dysfunction in astrocytes could induce the neurotoxic A1 phenotype, until recent work by Liang's team filled this critical gap [101]. Their study showed that astrocytic mitochondrial dysfunction was sufficient to induce transcriptional and functional hallmarks of neurotoxic astrocytes, ultimately leading to neuronal death *in vitro*.

It is important to note that direct *in vivo* evidence demonstrating that endogenous mitochondrial defects in astrocytes are sufficient to drive the A1 neurotoxic phenotype and cause neurodegeneration remains limited. Nevertheless, recent studies of CNS diseases have suggested the plausibility of this mechanism. For instance, knockout of the kir6.2 gene in a PD mouse model inhibited LPS-induced A1-like astrocyte activation, dopaminergic neuron loss, and behavioral deficits, indicating that Kir6.2 deficiency may counteract the neurotoxic effects of astrocytes in PD by improving mitochondrial function [102]. Additionally, in a transient middle cerebral artery occlusion model, investigators discovered that EXO-Hep (Hep-loaded macrophage-derived exosomes) ameliorated neuronal damage by inhibiting Drp1/Fis1-mediated mitochondrial fission in A1-type astrocytes and promoting the transfer of healthy astrocytic mitochondria to neurons [103]. Although these findings support a functional link between mitochondrial homeostasis and astrocyte phenotype, further studies are needed to clarify whether mitochondrial disruption alone is a primary driver of A1 conversion *in vivo* across disease contexts.

As previously noted, the mtDNA-cGAS–STING axis represents a canonical pathway driving microglial M1 polarization, and recent findings suggest that this mechanism is similarly applicable to the activation of A1 astrocytes (Fig. 2). A recent study demonstrated that mitochondrial mtDNA release from astrocytes in a model of neuromyelitis optica activates the cGAS–STING pathway, initiating an A1-like reactive transcriptional program [104]. Notably, inhibition of cGAS or STING in this model attenuated the A1-like astrocytic signature and reduced its neurotoxic effects, highlighting a potential mechanistic role for mtDNA in astrocytic immune activation [105]. As discussed above, the NLRP3 inflammasome has been implicated in shaping astrocyte phenotypes across multiple disease contexts, including depression and PD [106-108]. Its activation is often driven by mtROS, which has been linked to astrocyte-mediated pro-inflammatory responses. Experimental inhibition of NLRP3 or its upstream regulators like UCP2 has been shown to reduce astrocytic inflammation and neuronal damage in these models, pointing to an astrocytic mtROS–NLRP3 axis as a potential contributor to neurodegenerative pathology.

Moreover, in AD, increasing evidence supports a close relationship between NLRP3 activation and Aβ pathology. Previous studies have shown that $A\beta_{1-42}$ induces the upregulation of NLRP3, caspase 1, and its downstream effector IL-1β in astrocytes, suggesting that the Aβ–NLRP3 axis may be a crucial mechanism in the pathogenesis of AD [109]. In addition, Aβ has been confirmed to provoke mitochondrial dysfunction and the generation of ROS in astrocytes, along with increased expression of pro-inflammatory mediators such as IL-6 and TNF-α [110, 111]. These findings collectively support a model in which Aβ may function as an upstream regulator that activates the mtROS–NLRP3 pathway in

astrocytes, thereby contributing to neurodegeneration. In ALS, preclinical and postmortem studies have similarly pointed to a potential role for astrocytic mitochondrial dysfunction and NLRP3 activation in disease progression. Mitochondrial dysfunction in astrocytes, including increased superoxide production and decreased mitochondrial membrane potential, facilitates motor neuron degeneration in ALS models [112]. Notably, astrocytes express the NLRP3 inflammasome accompanied by elevated levels of IL-1β or IL-18 in both SOD1 mouse models of ALS and in human sporadic ALS patients [113]. However, it is important to note that the strength and consistency of evidence for this pathway in ALS remain less robust than in AD or PD and are primarily derived from select models. Taken together, astrocytic mitochondrial dysfunction and inflammasome activation may represent a mechanistic bridge linking glial pathology across various neurodegenerative diseases. However, the generalizability and causal relevance of these pathways differ by disease and model system. This insight provides a foundation for integrating disease mechanisms and identifying novel therapeutic targets (Fig. 2).

2.2.3 Microglia–Astrocyte Coupling in Neuroinflammation

Within the mitochondrial dysfunction–neuro-inflammation–neurodegeneration axis, microglia and astrocytes do not function as merely parallel or independent inflammatory effectors. Instead, they are interconnected through a highly organized bidirectional communication network that forms a self-sustaining inflammatory amplification loop. Generally, microglia are widely regarded as the first responders to injury and pathological signals within the central nervous system [114]. Consequently, they are persistently activated via multiple innate immune pathways, including TLRs, cGAS–STING, and NLRP3. This activation has been implicated in a gradual shift from a homeostatic phenotype to an M1-like pro-inflammatory state, as well as disease-associated phenotypes such as DAM/MGnD [105, 115-117]. As part of this process, microglia secrete cytokines and complement molecules, including IL-1α, TNF-α, and C1q, which have been shown to induce neurotoxic A1 astrocytes in both *in vitro* and *in vivo* settings [86]. This suggests a mechanistic link through which microglial activation may reshape astrocyte phenotypes and promote neurotoxic glial reprogramming, although the strength and temporal sequence of this interaction likely vary across disease models (Fig. 2).

Astrocytes, in contrast, appear less responsive to direct pathogen sensing, as most TLRs are expressed at low levels except for TLR3 [118]. Their innate immune activation often depends on microglia-derived mediators. For example, during LPS-induced neuroinflammation, astrocytic responses are largely contingent on microglial TLR4 activation and the release of cytokines or danger signals that engage astrocytic receptors [119]. This highlights the pivotal role of microglia-astrocyte crosstalk in coordinating glial reactivity under inflammatory stress. Conversely, astrocytes can modulate microglial function. For instance, under inflammatory conditions, TGFβ produced by IL-10-redirected astrocytes can attenuate microglial activation, suggesting bidirectional regulatory potential [120]. Other modes of glial crosstalk include Extracellular vesicles signaling. Astrocyte-derived ATP induces neighboring microglia to form membrane-bound vesicles containing IL-1β, and the subsequent shedding of these vesicles facilitates IL-1β release [121]. Once astrocytes transition into an A1/A1-like reactive state, they do not simply act as passive end-effectors, but actively reinforce a chronic neuroinflammatory microenvironment by releasing C3 and proinflammatory cytokines such as IL-1β and TNF-α [122]. This reciprocal loop is particularly evident in the C3-C3a axis, where astrocyte-derived C3 interacts with microglial C3aR to impair phagocytosis of Aβ. Loss of C3aR enhances microglial clearance capacity in AD models, reinforcing the functional impact of this coupling [123]. Importantly, the nature and consequences of microglia–astrocyte coupling are not uniform across neurodegenerative diseases. In ALS, for instance, astrocytes appear to influence microglial polarization dynamically, inducing an M2 microglial phenotype in early disease stages and promoting the M1 phenotype later in disease progression via NF-κB signaling [124]. In PD models, microglia may exert protective effects by preventing the conversion of astrocytes to the neurotoxic A1 phenotype, highlighting context-dependent heterogeneity [125]. Moreover, recent findings also showed that microglia-derived exosomes are critical mediators of astrocyte polarization toward neurotoxic phenotypes, a process closely associated with the transfer of pro-inflammatory factors and toxic α-synuclein oligomers within these vesicles [126] (Fig. 2).

3. The Gut Microbiota–Mitochondria–Neuro-inflammation Axis in Neurodegenerative Diseases

3.1 Clinical Evidence of Gut Microbiota Dysbiosis in Neurodegenerative Diseases

The gut microbiome of AD patients has consistently shown pattern of dysbiosis across multiple clinical studies. Early clinical cohorts reported a marked reduction in fecal microbial α-diversity in AD patients, with decreased *Firmicutes* and *Bifidobacterium* and increased *Bacteroidetes*, indicative of a global restructuring of the

gut microbiota [127]. In addition, a further study identified an upregulation of pro-inflammatory *Escherichia*/*Shigella* and a reduction in anti-inflammatory *Eubacterium rectale* in individuals with mild cognitive impairment and early-stage AD [128]. Notably, these pro-inflammatory bacteria positively correlated with peripheral levels of IL-1β, NLRP3, and CXCL2, raising the possibility of a metabolically and immunologically coupled axis linking gut dysbiosis, peripheral inflammation, and cerebral amyloid pathology. From a metabolic perspective, multiple studies and meta-analyses report decreased abundance of SCFA-producing bacteria (such as *Clostridiales, Ruminococcaceae,* and *Butyricicoccus*) in AD patients. Fecal SCFA levels, particularly butyrate, appear to decline progressively from aMCI to AD, suggesting potential relevance to disease progression [129-132]. Systemically, AD has also been associated with an asymmetric reconstruction of circulating SCFAs, with decreased plasma butyrate and increased acetate and valerate [133]. This may reflect both impaired gut SCFA production and altered peripheral SCFA handling, although causality remains unclear. In parallel, the tryptophan-indole axis and bile acid metabolism are increasingly recognized as altered in AD. Longitudinal studies of elderly cohorts revealed that lower microbiota-derived 5-hydroxyindoleacetic acid is a significant predictor of subsequent AD risk, pointing to possible biomarker value [134]. Postmortem brain metabolomic analyses have identified elevated levels of gut-derived secondary bile acids, including taurodeoxycholic acid and deoxycholic acid, supporting the hypothesis that microbial lipid stress may contribute to cerebral pathology in the AD [135].

Dysbiosis of the gut microbiota in PD in humans shares some overlapping features with AD and is similarly characterized by a combination of reduced SCFA-producing bacteria and increased pro-inflammatory taxa. A reduction in SCFA-producing bacteria, such as *Prevotella*, in PD patients, is correlated with elevated levels of peripheral inflammatory markers [136]. Even during the prodromal phase of PD, such as REM sleep behavior disorder, a decrease in butyrate-producing genera and an enrichment of pro-inflammatory *Collinsella* were observed, suggesting that gut microbiota imbalance precedes the onset of motor symptoms [137]. Metabolomic studies support this association**,** showing significantly reduced levels of fecal SCFAs, including acetate, propionate, and butyrate, in PD patients. These reductions exceed those observed in normal aging and parallel the depletion of *Prevotellaceae* and *Faecalibacterium* [138]. In addition, significant alterations in bile acids such as 3β-hydroxy-5-cholenoic acid and glycoursodeoxycholic acid in PD patients raise the possibility that the bile acid axis may play a role in PD pathogenesis [139].

Similar to the patterns observed in AD and PD, patients with ALS also exhibit gut microbiota dysbiosis. These include reduced microbial diversity, a decreased *Firmicutes/Bacteroidetes* ratio, elevated fecal calprotectin, and increased serum LPS levels**,** suggesting the coexistence of gut dysbiosis and intestinal barrier inflammation [140]. Moreover, there is a marked decline in SCFA-producing genera such as *Ruminococcus*, as well as a reduction in total concentration of fecal SCFAs, both of which are implicated in maintaining gut and immune homeostasis. Emerging large-cohort studies in ALS patients further support the presence of gut dysbiosis, reporting not only the reduction in the *Firmicutes*/*Bacteroidetes* ratio, but also downregulation of microbial metabolic pathways involved in amino acid, nucleotide, and carbohydrate metabolism [141]. These findings have led to the hypothesis that microbial dysregulation–induced metabolic disturbances may contribute to ALS pathophysiology in certain subpopulations. Additionally, a 2024 systematic review of 18 human ALS studies reported marked gut microbiota remodeling, with reduced butyrate producers and enriched pro-inflammatory taxa [142]. Notably, several studies employing integrated microbiome–metabolome analyses have linked disrupted SCFA, bile acid, and lipid metabolism to lower ALS functional scores and cognitive impairment, suggesting potential clinical relevance. However, it is important to emphasize that most available evidence in ALS remains correlative, and the degree of inter-individual heterogeneity across ALS cohorts is substantial. While these findings highlight a possible contributory role for gut microbiota dysregulation in ALS progression, further mechanistic studies are needed to determine whether these alterations actively influence disease onset or reflect secondary responses to neurodegeneration.

3.2 Gut Microbiota Dysbiosis to CNS Mitochondrial Dysfunction: Pathways Underlying Neuro-inflammation Amplification and Neurodegeneration

Collectively, clinical studies in AD, PD, and ALS suggest a systemic remodeling of the gut microbiome at both compositional and functional levels, accompanied by perturbations in microbiota-derived metabolic axes, including LPS, SCFAs, tryptophan derivatives, and bile acids. However, most of these observations largely remain correlative rather than causally established. The central unresolved question is how gut dysbiosis may interact with systemic and neural physiology to promote chronic neuroinflammation and drive neurodegeneration. Mitochondria are increasingly viewed not only as central

regulators of cellular energy supply and redox status, but also as integrators of metabolic and inflammatory stress. Therefore, in neurodegenerative diseases, it has been proposed that gut-derived signals (e.g., LPS) may contribute to mitochondrial dysfunction in glial cells, which may in turn amplify innate immune activation and neuroinflammatory responses. This hypothesis provides a possible link between peripheral dysbiosis and the pathological progression associated with Aβ/tau, α-synuclein, or motor neuron degeneration (Fig. 2).

Recent studies have provided evidence supporting a potential role for the microbiota and microbiota-derived metabolites in modulating microglial mitochondrial function. A seminal study demonstrated that aging-related gut microbiota alterations impair microglial mitochondrial function by increasing oxidative stress and metabolic stressors, such as N^6-carboxymethyllysine, in aged mice. [143]. Foundational studies also demonstrate that microbial metabolites like SCFAs are essential for maintaining microglial mitochondrial homeostasis [144]. During health and early life stages, microbiota and their SCFAs support metabolic adaptation and homeostasis of microglial mitochondria. However, under conditions of aging or compromised barrier function, a shift toward inflammatory and metabolic stress may occur, which has been proposed to lower the activation threshold of microglial mitochondria and promote inflammatory priming. This framework is primarily based on preclinical models, and its relevance to human brain aging remains to be confirmed. Similar to microglia, astrocytes may also possess an energy metabolism and mitochondrial response program that is highly sensitive to gut-derived metabolites. Co-stimulation with LPS and IFN-γ directly impaired mitochondrial integrity in astrocytes, as evidenced by a decrease in ΔΨm and excessive generation of ROS, while also accelerating the release of TNF-α and IL-1β [145]. Also, it has been shown that LPS-treated rats receiving healthy donor fecal microbiota transplantation were protected against astrocytic mitochondrial dysfunction by promoting the production of SCFAs and enhancing the release of anti-inflammatory cytokines [146]. *In vitro* studies also suggest that the tryptophan-derived metabolite indoxyl sulfate reduces ΔΨm and increases ROS in astrocytes, suggesting that gut-derived metabolic stress can disrupt mitochondrial homeostasis [147]. Supplementation with SCFAs has been reported to attenuate mitochondrial dysfunction and downregulate inflammatory genes in astrocytes from mouse models of autoimmune encephalomyelitis. This protective effect appears to be mediated in part through tryptophan-derived activation of the AhR signaling pathway [148]. Nonetheless, these findings have primarily been demonstrated in animal and *in vitro* models, and their applicability to chronic neurodegenerative disease settings in humans remains to be established.

Gut microbiota and their metabolites have been shown to influence mitochondrial function not only in glial cells but also in neurons, particularly within energy-demanding synaptic regions of the brain such as the hippocampus and cortex. Synaptic mitochondria in neurons are highly sensitive to metabolic and inflammatory stress [149]. For example, the microbial metabolite butyrate has been reported to improve neuronal mitochondrial function and reduce neuroinflammation, including in high-glucose conditions, in part mitophagy enhancement through PRKN/Parkin pathways [150, 151]. In contrast, certain microbiota-derived secondary bile acids like DCA and LCA may harm mitochondria, although direct experimental evidence of these effects in neurons remains limited and mostly indirect [152, 153]. Other metabolites such as gut-derived serotonin have been proposed to support neuronal mitochondrial function via the SIRT1–PGC-1α pathway, potentially promoting energy homeostasis [154]. Germ-free animal models have further demonstrated that the absence of gut microbiota disrupts mitochondrial energy metabolism in the hippocampus, impairing oxidative phosphorylation and the TCA cycle [155]. Conversely, interventions like fecal microbiota transplantation (FMT) or SCFA supplementation improve mitochondrial activity, boost ATP production, and reduce neuronal injury and cognitive deficits, especially under hypoperfusion conditions [156]. However, these outcomes are derived primarily from rodent models and may not fully translate to the complexity of human neurodegenerative pathology. Critically, these effects are not confined to individual cell types. Microglia, astrocytes, and neurons interact dynamically to amplify neuroinflammatory responses during neurodegeneration. A key study using α-synuclein overexpressing mice revealed that the presence of gut microbiota aggravates striatal mitochondrial dysfunction and motor symptoms in PD models, while microbiota depletion or enhanced ROS clearance alleviates them [157]. Together, these findings support the broader hypothesis of a gut–mitochondria–neuroinflammation axis, in which gut microbial metabolites may modulate brain energy metabolism and may contribute to neurodegenerative disease progression through mitochondrial and glial pathways.

However, in AD, direct evidence that gut microbiota promotes disease progression through modulation of brain mitochondrial function remains limited. While accumulating studies indicate that intervention such as antibiotic treatment or FMT can alter cerebral amyloid-β deposition and shift glial activation profiles in APP/PS1 mice [158], these findings should be interpreted with caution. Proteomic studies in GF mice have identified

acetylation signatures consistent with OXPHOS and TCA cycle disruption [155], and SCFA administration has been shown to improve hippocampal mitochondrial function and cognition [156]. Together, these findings suggest a plausible metabolic framework in which gut dysbiosis may impair mitochondrial energy networks and thereby accelerates AD-related neurodegeneration. However, causality remains to be conclusively demonstrated in human studies.

Compared to AD and PD, research in the field of ALS is still lacking in direct *in vivo* investigations that assess whether manipulation of the gut microbiota can alter mitochondrial function within the central nervous system. The current evidence base is largely comprised of inferred associations or cellular-level observations rather than comprehensive *in vivo* validation. On one hand, transcriptomic analysis of the spinal cord indicated remodeling of gene pathways associated with mitochondrial function and oxidative stress, suggesting that a microbiota–mitochondrial metabolic axis might influence ALS progression. On the other hand, in motor neuron-like cell models harboring SOD1 mutations, the gut-derived butyrate has been shown to improve mitochondrial network architecture and enhance respiratory capacity, suggesting that microbial metabolites have the potential to directly regulate mitochondrial bioenergetics in ALS-associated neurons [159]. However, this evidence remains primarily based on transcriptomic analyses or *in vitro* models and does not yet confirm that gut microbiota-derived metabolites can directly rectify mitochondrial dysfunction in the spinal cords of ALS patients *in vivo*.

Table 1. Comparative summary of key mechanisms and evidence maturity across AD, PD, and ALS.

Mechanism or Pathway	Alzheimer's Disease (AD)	Parkinson's Disease (PD)	Amyotrophic Lateral Sclerosis (ALS)
Aβ/Tau Aggregation	Central pathology	Absent	Absent
α-Synuclein Pathology	Absent	Core feature	Indirect or absent
Metaflammation Evidence	Strong (obesity, T2DM, microbiota links)	Moderate (metabolic syndrome, microbiota)	Tentative (mainly correlative)
BBB Dysfunction	Supported in animal & human data	Supported in animal models	Emerging evidence (model-dependent)
Mitochondrial Dysfunction	Strong (neuronal, glial)	Strong (especially dopaminergic neurons)	Moderate (spinal neurons, limited glial data)
Microglial NLRP3 Activation	Strongly validated	Increasing support	Preliminary evidence (mainly SOD1 models)
Astrocyte Reactivity (A1/A2)	Strong (A1 phenotype in postmortem brains)	Present (especially under α-syn stress)	Limited (context- and subtype-dependent)
cGAS–STING Activation	Validated in microglia, astrocytes	Emerging evidence	Tentative; needs broader validation
Gut Microbiota Dysbiosis	Strong evidence (human & animal)	Strong (e.g., Prevotella depletion)	Moderate (high heterogeneity across cohorts)
Clinical Intervention Trials	Multiple early-phase studies	Several small-scale studies	Few; largely preclinical

In summary, although a working model can be constructed from existing epidemiological, animal, and *in vitro* data, this gut–mitochondria–neuroinflammation framework remains a hypothesis requiring further validation. Dysbiosis of the gut microbiota perturbs SCFAs, bile acids, tryptophan metabolites, and barrier homeostasis, shaping a peripheral-to-central inflammatory environment. Within this context, brain mitochondria serve as signal amplifiers of these gut-derived metabolic stressors. The release of mtROS, mtDNA, and impaired mitophagy ultimately determines the glial inflammatory threshold and neuronal energy vulnerability. This gut microbiota–mitochondria–neuroinflammation axis provides a plausible unifying concept for the metabolic and immune alterations shared across AD, PD, and ALS, and may offer a promising therapeutic entry point, particularly in early disease stages. Future research will be necessary to test this framework across diverse models and human populations, ideally using longitudinal designs and mechanistic interventions (Table 1).

4. Targeting the Metaflammation–Mitochondria–Neuroinflammation Axis in Neurodegenerative Diseases

4.1 Anti-Inflammatory and Inflammasome-Targeted Therapies

Chronic neuroinflammation is a common downstream feature of neurodegeneration, and mid-life inflammaging creates a permissive environment for CNS pathology. Therefore, anti-inflammatory interventions ranging from conventional Non-Steroidal Anti-Inflammatory Drugs

(NSAIDs) to specific NLRP3 inflammasome inhibitors have been explored as potential aging-targeted therapies [160, 161]. Clinical evidence for NSAID use has been inconclusive and context-dependent. While early epidemiological observations initially suggested that long-term NSAIDs use correlates with lower AD incidence, randomized trials in patients with established dementia have generally failed to demonstrate therapeutic benefit [162]. These discrepancies likely reflect issues of timing and target engagement. NSAIDs may confer neuroprotection when used during mid-life (before extensive pathology), but not reverse dementia once it's clinically manifest. Indeed, a large meta-analysis found no overall AD prevention with NSAIDs in late life, yet hinted that certain agents (e.g. diclofenac) might slow cognitive decline [163, 164]. Similar uncertainty exists in PD, epidemiological data are also conflicting–one analysis found only ibuprofen modestly reduced PD risk [165], while another reported that non-aspirin NSAIDs as a class were associated with lower PD incidence [166]. In ALS, emerging observational studies intriguingly suggest that use of non-aspirin NSAIDs or even acetaminophen has been associated with reduced ALS risk [167, 168], although these findings remain correlational and causality has not been established. Mechanistically, NSAIDs inhibit cyclooxygenase (COX)-mediated prostaglandin production, thereby blunting one axis of the inflammatory response [169]. In experimental PD mouse models, systemic administration of NSAID (aspirin) reduced microglial activation and suppressed the propagation of α-synuclein, suggesting that systemic anti-inflammatories may influence central pathology in early disease stages [170-172].

In contrast, preclinical research has focused on the NLRP3 inflammasome, a key innate immune sensor that links metabolic stress to glial cytokine release [8]. Activation of NLRP3 promotes maturation of IL-1β and IL-18, amplifying inflammatory cascades. NLRP3 is highly implicated in age-related metaflammation and microglial activation in AD, PD, and ALS. In APP/PS1 mouse models, the small-molecule inhibitor MCC950 promoted non-phlogistic clearance of Aβ and rescued memory deficits [173]. Similarly, MCC950 and related inflammasome blockers enhanced the clearance of misfolded α-synuclein and prevented the loss of dopaminergic neurons in rodent PD models [174]. These findings suggest that targeting inflammasome signaling may attenuate glial-driven neuroinflammation in a non-immunosuppressive manner. However, most data remain preclinical, and translation into human trials is limited. Overall, anti-inflammatory therapies offer a promising strategy to dampen the metaflammation–neuroinflammation axis. However, their success in clinical translation will likely depend on early intervention and precise stratification of patient populations. Preventive use in mid-life or prodromal phases may hold greater promise than treatment during late-stage neurodegeneration, when neuronal loss and gliosis are likely irreversible. As highlighted in Table 3, these strategies remain at a mixed stage of translational maturity, and further trials with robust biomarkers and early-stage cohorts will be required.

4.2 Mitochondria-Targeted Therapies

Mitochondrial dysfunction is a pivotal mediator between systemic aging and neurodegeneration, as energetic failure and excess ROS production from mitochondria can activate inflammatory pathways [45, 47]. Accordingly, therapies that specifically target mitochondrial health are being pursued to break this vicious cycle. Preclinical studies have focused extensively on enhancing mitophagy and mitochondrial quality control. Small molecules like urolithin A, which stimulates mitophagy, have been shown to improve mitochondrial respiratory capacity and memory performance in aged animal models, with potential relevance for AD and PD [175, 176]. Similarly, boosting cellular NAD^+ levels (with precursors such as nicotinamide riboside) can likewise activate sirtuin pathways that promote mitophagy and mitochondrial biogenesis, with secondary anti-inflammatory effects [177, 178]. For instance, raising NAD^+ was reported to protect dopaminergic neurons in toxin-based PD models by enhancing PINK1/Parkin-mediated mitochondrial quality control and decreasing microglial activation markers [179, 180]. However, these effects remain confined to preclinical systems.

In parallel, mitochondrial-targeted antioxidants aim to suppress oxidative stress at their source. Prototypical compounds include MitoQ (a ubiquinone derivative) and peptide SS-31 (elamipretide). In AD mouse models, long-term MitoQ supplementation prevented spatial memory loss and synaptic damage, while markedly reducing Aβ accumulation, astroglial activation, and lipid peroxidation in the brain [181]. These mice maintained cognitive function on par with non-transgenic controls, indicating that scavenging mitochondrial ROS can halt the toxic inflammation-oxidative stress spiral in AD. By contrast, a 12-month placebo-controlled trial of MitoQ in early-stage PD found no significant slowing of clinical progression, raising the possibility that monotherapy with an antioxidant may be insufficient to modify disease course in humans or that mitochondrial damage is already advanced by the time of clinical diagnosis [182].

Therapies that restore mitochondrial bioenergetics are also under investigation. The SS-31 peptide, for example, binds cardiolipin on the inner mitochondrial membrane, stabilizing electron transport and reducing

leakage of electrons that form ROS [183, 184]. In animal models of AD and PD, SS-31 has been reported to improve neuronal ATP production and synaptic plasticity while dampening glial production of IL-6 and TNF-α [185]. Treatment of aged AD-model mice with SS-31 led to lower brain IL-1β levels and rescued performance on learning tasks, correlating with preserved mitochondrial respiratory enzyme activity. Another mitochondrial strategy involves stimulating biogenesis via upregulating PGC-1α. The compounds like bezafibrate and certain polyphenols can activate this pathway, thereby increasing mitochondrial mass and antioxidant capacity [186-188]. In transgenic ALS models, PGC-1α activation extended survival and reduced muscle denervation, and it attenuated markers of microglial activation in the spinal cord, illustrating a possible crosstalk between improved muscle/neuronal mitochondrial function and reduced neuroinflammation [189]. While more experimental in nature, mitochondrial transplantation and gene therapies (e.g., delivering nuclear genes that enhance mitochondrial dynamics) are being explored, but these remain in early experimental stage [190, 191].

Despite promising mechanistic evidence in animal models, clinical translation of mitochondria-targeted therapies remains limited. No mitochondrial agent has yet demonstrated clear disease-modifying efficacy in large-scale trials across neurodegenerative diseases. To facilitate progress, future studies will need to better characterize heterogeneity in mitochondrial pathology across patients and identify robust oxidative stress or mitochondrial dysfunction biomarkers to guide intervention. Combining mitochondrial-targeted therapies with anti-inflammatory or metabolic interventions may also improve efficacy. As noted in Table 3, most of these therapies are currently in preclinical or early clinical stages. Nonetheless, with improved mechanistic understanding, it is conceivable that a mitochondria-targeted drug could be used prophylactically in high-risk individuals to maintain a youthful systemic inflammatory profile and neuroglial homeostasis.

4.3 Caloric Restriction and Fasting-Mimicking Diets

Caloric restriction (CR) is a well-established lifespan-extending intervention that counters many aging processes, including metaflammation and mitochondrial dysfunction. Preclinical models of neurodegeneration have provided substantial support for its neuroprotective effects. In models of AD and PD, CR and its variants (intermittent fasting, fasting-mimicking diets (FMD)) have consistently shown neuroprotective effects through multi-faceted mechanisms [192-195]. A recent study in 3xTg-AD mice demonstrated that when calories are consumed is as important as how much. A prolonged daily fasting interval was required for the full benefits of a 30% CR diet on AD pathology [196]. Mice allowed to binge and fast (mimicking human time-restricted feeding) showed improved insulin sensitivity, reduced tau phosphorylation and neuroinflammatory gene expression, and better memory performance, whereas simply reducing calories without fasting yielded lesser benefits. These findings align with other work indicating that periodic fasting may trigger cellular stress responses (autophagy, ketogenesis) that may contribute to mitochondrial and immune homeostasis. Indeed, intermittent fasting in a PD mouse model enhanced autophagic clearance of α-synuclein, limited its aggregation, and preserved dopaminergic neurons [195]. The fasting regimen also produced a marked shift in glial activation. Fasted PD mice had significantly fewer reactive astrocytes and a microglial phenotype skewed toward anti-inflammatory, neurotrophic profiles. Pro-inflammatory cytokines like TNF-α and IL-1β were suppressed, while genes associated with microglial repair functions were upregulated [193], indicating that fasting can influence the neuroimmune environment. Notably, these neuroinflammatory changes were not only secondary to reduced protein pathology – transcriptomic analysis showed IF directly modulated inflammation-related pathways, and the elevation of the ketone metabolite β-hydroxybutyrate (BHB) during fasting contributed to protective effects [197, 198]. Increased BHB, either through fasting or exogenous administration, has been shown to improve neuronal bioenergetics and mitigate microglial activation, suggesting a link between peripheral metabolic switches and central glial function. However, these mechanistic insights remain largely based on preclinical models and require further clinical validation to assess their therapeutic relevance in humans. CR and fasting regimens also support mitophagy and antioxidant defenses systemically [199]. By promoting the clearance of damaged mitochondria, these diets may reduce mitochondria DAMP release and subsequent inflammatory activation. Cyclic FMDs have further demonstrated compelling efficacy in AD animal models, where monthly FMD cycles were associated with reductions in Aβ plaques and tau aggregation, and glial activation, including decreased microglia and astrocytic reactivity [193]. Oxidative stress markers (like superoxide production) were also decreased in the brains of FMD-treated AD mice. Functionally, these mice exhibited preservation of cognitive abilities similarly to healthy controls, suggesting potential disease-modifying effects. Impressively, FMD regimens not only curbed pathological hallmarks but also reversed learning and memory deficits across two different AD mouse models. Early clinical data also offer promising signs. A small pilot trial in patients with mild cognitive impairment or

early AD found that monthly 5-day FMD periods were safe and feasible, with ongoing assessments suggesting potential improvements in inflammation and cognition. However, these human findings remain exploratory, and larger randomized controlled trials will be required to validate therapeutic impact. In ALS, the relevance of CR and FMD is more complex due to the presence of hypermetabolism and progressive weight loss, which are associated with worse outcomes [200]. In this context, CR may be counterproductive, and instead, caloric supplementation—particularly with high-fat or ketogenic formulations—has been associated with prolonged survival in some rapidly progressing ALS patients [201-203]. This distinction underscores the disease-specific nuances of applying nutrient-sensing interventions in neurodegeneration. Nevertheless, the broader principle holds that modulating nutrient-sensing pathways represent a modifiable interface between metabolism, inflammation, and mitochondrial function. Whether through fasting, FMD, or mimetics like ketone esters, resveratrol, and metformin, targeting these pathways may help recalibrate the metaflammation–mitochondria–neuroinflammation axis. By inducing autophagy, enhancing mitochondrial efficiency, and lowering pro-inflammatory signaling, such interventions could foster a systemic environment less permissive to neurodegenerative progression—though disease stage, metabolic state, and individual variability must be carefully considered in translational efforts.

4.4 Senolytics and Senomorphics (Targeting Cellular Senescence)

Cellular senescence, defined as a permanent arrest accompanied by a pro-inflammatory secretory phenotype (SASP), accumulates with aging and has been implicated as a potential upstream driver of metaflammation [204]. Senescent cells, whether in adipose tissue, blood vessels, or even the brain, secrete cytokines (IL-6, IL-1β, TNFα), proteases, and growth factors that collectively constitute the SASP and may contribute to chronic immune activation. In experimental models, interventions that selectively eliminate senescent cells (senolytics) or suppress their SASP output without killing them (senomorphics) have shown promising outcomes [205, 206]. By clearing the reservoirs of SASP factors, senolytics aim to reduce systemic and CNS inflammation and improve tissue regenerative capacity. In a tauopathy mouse model, Bussian et al. (2018) demonstrated that senescent microglia and astrocytes accumulate around amyloid plaques and tau tangles [207]. A transgenic strategy to eliminate $p16^{Ink4a}$-positive senescent cells resulted in reduced tau pathology, preserved neurons, and enhanced cognitive performance. Although these findings are preclinical, these results support the notion that senescence contributes to neurodegeneration. Pharmacological senolytics mirror these benefits. Treatment of progeroid AD mice with a combination of Dasatinib (a senolytic kinase inhibitor) and Quercetin (a flavonoid) cleared senescent glia and significantly reduced NFT tau burden, attenuating neuroinflammation and neuronal loss [207, 208]. Likewise, the natural senolytic fisetin and the Dasatinib and Quercetin cocktail (D+Q) have shown efficacy in amyloid models by reducing microglial activation and improving memory performance [209, 210]. One study noted that D+Q treatment in aged wild-type mice alleviated normal age-related cognitive decline, accompanied by decreased plasma IL-6 levels and enhanced hippocampal synaptic plasticity [210]. While mechanistically compelling, these results have yet to be validated in large-scale clinical trials, and their relevance to human neurodegeneration remains under investigation. These findings nonetheless support the working hypothesis that senescent cell accumulation contributes to brain aging and inflammation, and that its targeted modulation may represent a viable therapeutic strategy.

The SASP from senescent cells provides a plausible mechanism linking senescence to the metaflammation–mitochondria–neuroinflammation axis [206]. Neurons undergoing senescence (or a senescence-like state under chronic stress) may secrete pro-inflammatory HMGB1 and other DAMPs, directly engaging innate immune receptors on glia [211]. Senolytic therapies aim to remove the source of such signals, potentially attenuating chronic glial activation. Though direct senolytic trials in PD models are still underway, one can hypothesize that clearing senescent glia would reduce the self-amplifying cycle of protein aggregation and inflammatory cytokine release. In ALS, senescence has been noted in proliferative cell pools like astrocytes and $NG2^{+}$ glial progenitors in the spinal cord. Their SASP (including IL-6 and metalloproteinases) might contribute to motor neuron death and extracellular matrix remodeling in ALS [212]. Targeting these cells with senomorphics such as JAK/STAT inhibitors, or senolytics may offer neuroprotective potential, but further mechanistic clarification is required to define their role ALS models and stages.

Senolytic approaches are now moving toward clinical application in age-related diseases. Early-phase trials of D+Q in idiopathic pulmonary fibrosis and diabetic kidney disease showed reduced senescence markers and systemic inflammation, as well as functional improvements in patients [213, 214]. In the neurodegenerative diseases, researchers have initiated studies (e.g., with fisetin or D+Q) in individuals with mild cognitive impairment, to assess safety and whether clearing senescent cells can

modulate CSF inflammatory factors or cognition. Senomorphics like the selective JAK1/2 inhibitor ruxolitinib have also attracted interest for their ability to suppress SASP without eliminating cells, which may be theoretically useful when senescent cell removal poses risks in the brain [215]. Despite crossing the blood–brain barrier and ensuring cell specificity remain challenges, senescence-targeting therapies offer a unique upstream strategy. Rather than inhibiting one inflammatory cytokine or one toxic protein, these approaches aim to disrupt a broader age-associated mechanism that gives rise to the inflammatory milieu and impaired cellular repair in multiple tissues. Ultimately, they can reduce metaflammation (lowering systemic IL-6, CRP levels), improve mitochondrial function (since SASP factors like IL-1β can impair mitochondrial biogenesis in neighboring cells), and attenuate neuroinflammation (by removing chronically pro-inflammatory glia) [207, 216, 217]. As aging is the greatest risk factor for AD, PD, and ALS, adjuvant senolytic therapy could conceivably ease the burden of all three, especially if used early. Future work will need to balance efficacy with potential off-target effects and determine optimal timing (e.g., midlife prevention vs. late-life slowing of degeneration).

4.5 Microbiome and Probiotic Strategies

Aging-associated shifts in the gut microbiome contribute to chronic metaflammation, suggesting microbiota-directed interventions as a promising therapy. Probiotics and related approaches (prebiotics, postbiotics, and FMT) aim to restore a healthy microbial ecosystem, thereby reducing systemic inflammatory signaling and improving brain metabolism. Preclinical studies have provided foundational insight into these mechanisms. In rodent models, dietary interventions such as fasting-mimicking diet or supplementing SCFAs not only rebalances the gut microbiome but also reduces neuroinflammation and enhances brain energetics [193, 218]. In an aging/hypoperfusion rat model, microbiota normalization via either healthy-donor FMT or SCFA feeding reversed hippocampal microglial activation, alleviated neuronal injury, and improved cognitive deficits, concomitant with elevated ATP production and restored mitochondrial enzyme activities in the brain [156].

Table 2. Summary of Therapeutic Strategies and Research Focus in Neurodegeneration.

Intervention Strategy	Mechanistic Focus	Representative Preclinical and Clinical Research Evidence
Anti-inflammatory Therapy	● Inhibition of COX pathway ● Suppression of NLRP3 inflammasome ● Attenuation of microglial activation and systemic cytokines	● NSAIDs associated with reduced AD/PD risk in observational studies ● MCC950 ameliorates Aβ and α-synuclein pathology in mice ● Reduced IL-1β and neuroinflammation in PD and ALS models
Mitochondria-targeted Therapy	● Improved mitochondrial respiration, ROS scavenging, mitophagy stimulation ● Reduction of mtDAMPs	● MitoQ and SS-31 restore synaptic plasticity and reduce inflammation in AD models ● NAD+ precursors promote PINK1/Parkin-mediated mitophagy in PD ● Mitochondrial antioxidants under clinical trial in ALS
Caloric Restriction (CR) / Fasting	● Enhancement of autophagy, ketogenesis, mitophagy ● Downregulation of SASP ● Downregulation of innate immune activation	● FMD reverses cognitive decline and reduces glial activation in AD models ● Intermittent fasting limits α-synuclein aggregation in PD ● β-hydroxybutyrate restores mitochondrial and microglial homeostasis
Senolytics/Senomorphics	● Clearance or silencing of senescent cells ● Reduction of SASP-mediated inflammation ● Rejuvenation of glial environment	● Dasatinib + quercetin reduces tau pathology and microglial activation in tauopathy models ● Fisetin reverses age-related cognitive deficits ● Clinical trials in MCI/AD under way
Microbiome and Probiotics	● Modulation of gut dysbiosis ● Restoration of SCFA production ● Suppression of peripheral and neuroinflammation via gut–brain–mitochondria axis	● Improved cognitive outcomes in AD models with Bifidobacterium breve A1 ● Reduction of TNF-α in PD clinical probiotic trials ● Enhanced nicotinamide availability and survival in ALS mouse models via *Akkermansia muciniphila*

These findings suggest how restoring gut microbial homeostasis can reduce systemic metaflammatory signals and support brain mitochondrial function. Similarly, in transgenic ALS models, administration of *A. muciniphila* improved motor performance and higher CNS nicotinamide levels, with transcriptomic evidence of mitochondrial and oxidative stress pathway remodeling in the spinal cord [219]. These findings suggest that microbiota-based strategies may influence glial mitochondrial function and neuroinflammation in disease-relevant contexts. However, the bulk of this evidence is still preclinical, and translational relevance to human neurodegenerative disease remains to be confirmed.

Translating these insights to clinical contexts, several early-phase trials have begun to evaluate therapeutic modulation of the microbiome in humans. In AD, small clinical trials have demonstrated that multi-strain probiotic supplementation can improve cognitive performance while lowering peripheral inflammation [220]. A 12-week probiotic trial in AD patients led to a ~28% improvement in mini-mental state examination cognitive scores (versus decline in controls), alongside lower CRP and oxidative damage markers, raising the hypothesis that microbial metabolite shifts may influence brain function via systemic inflammation. In PD, a recent randomized trial found that a single-donor FMT reported modest improvement in motor scores over 12 months, suggesting that gut-directed interventions might influence disease progression in early stages [221].

Table 3. Translational Maturity and Evidence Grading for Therapeutic Strategies Targeting the Metaflammation–Mitochondria–Neuroinflammation Axis.

Strategy	Disease Context (AD/PD/ALS)	Evidence Type	Translational Readiness	Reference
NSAIDs	AD, PD, ALS	Epidemiology, Preclinical	Moderate (timing-dependent)	[162-165, 167]
NLRP3 Inhibitors	AD, PD, ALS	Preclinical	Low-to-Moderate	[173, 174]
Urolithin A	AD, PD	Preclinical	Low	[175, 176]
NAD+ Precursors (e.g., NR)	PD	Preclinical	Low	[179, 180]
MitoQ	AD, PD	Preclinical, RCT	Low (mixed clinical results)	[181, 182]
SS-31	AD, PD, ALS (preclinical)	Preclinical	Moderate (ongoing trials)	[185]
Caloric Restriction/Fasting	AD, PD	Preclinical, Pilot RCT	Moderate	[193-196]
High-calorie Diets	ALS	Observational	Low-to-Moderate	[200, 201]
Senolytics (D+Q, Fisetin)	AD, ALS	Preclinical	Moderate (early trials)	[207, 210]
Senomorphics (JAK inhibitors)	ALS, AD	Preclinical	Low	[215]
Probiotics	AD, PD, ALS	Pilot RCT, Preclinical	Moderate	[219-221]
FMT	PD	RCT	Moderate	[221]

Note: "Translational Readiness" ratings are qualitative estimates based on strength of evidence, presence of human trials, and proximity to clinical application. RCT: Randomized Controlled Trial; NR: Nicotinamide Riboside; D+Q: Dasatinib + Quercetin.

For ALS, clinical data remain sparse. While microbial dysbiosis has been observed, interventional studies are limited, and causal effects on mitochondrial or neuroinflammatory markers in patients have yet to be established. Nevertheless, animal models and early findings raise the possibility that microbial metabolites could influence energy metabolism and inflammatory tone in ALS, though substantial further investigation is required. Taken together, microbiota-targeted strategies offer a conceptually attractive but still evolving avenue for influencing the metaflammation–mitochondria–neuroinflammation axis. By reducing gut-derived endotoxins, increasing anti-inflammatory metabolites such as butyrate, and decreasing gut permeability, can attenuate chronic metaflammation and influence the brain's innate immune cells. However, more well-controlled clinical trials are needed to determine the reproducibility and durability of these effects across patient populations.

To guide interpretation of therapeutic evidence, Table 2 and 3 summarize the relative evidence strength and translational maturity of key intervention classes discussed in this review. These grading frameworks help distinguish between mechanistic promise and current clinical applicability, offering clearer guidance for future research and clinical translation.

In summary, modern aging-targeted interventions are converging on the principle that improving the systemic

and cellular environment may help mitigate neurodegenerative processes. Each strategy, through distinct mechanisms, aims to attenuate metaflammation, protects mitochondrial function, and tempers glial overactivation, thereby addressing core pathophysiological nodes in AD, PD, ALS and related disorders. However, many of these strategies remain in preclinical or early clinical stages, and their therapeutic value will depend on further validation, particularly in humans. The challenge ahead lies in integrating these approaches, possibly in combination, and translating them to clinical use at the right stage of disease. Given the complex interplay of metabolism, immunity, and neurodegeneration, a multi-pronged therapeutic framework targeting the metaflammation–mitochondria–neuroinflammation axis offers a conceptually promising direction. With continued mechanistic research and carefully designed clinical trials, such strategies may eventually contribute to delaying or modifying disease progression in our aging population.

Box 2. Translational Biomarkers of the Metaflammation–Mitochondria–Neuroinflammation Axis

To support future clinical translation, several candidate biomarkers may operationalize this mechanistic axis

- **Metaflammation:**
  - High-sensitivity C-reactive protein (hs-CRP)
  - Circulating cytokines (e.g., IL-6, TNF-α)
  - Metabolic indices (e.g., fasting insulin, lipid profile, AGEs, free fatty acids, Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), Hemoglobin A1c)
  - Gut-derived inflammatory/metabolic markers (e.g., circulating LPS or LPS-binding protein, SCFA, bile acid profiles, tryptophan metabolites)
- **Mitochondrial Dysfunction:**
  - Cell-free mitochondrial DNA (cf-mtDNA)
  - Mitochondrial DNA copy number (mtDNAcn) in blood cells
  - ATP production or oxygen consumption rate
  - 8-OHdG
  - PINK1/Parkin-related markers
- **Neuroinflammation:**
  - CSF or plasma cytokines (e.g., IL-1β, IL-6)
  - Glial activation (TSPO-PET imaging, soluble TREM2, YKL-40)
  - GFAP, neurofilament light chain
  - ICAM-1/VCAM-1
  - Integrating these signals into composite panels may help track disease progression and therapeutic response across the proposed axis.

Discussion & Conclusion

Aging is the most prominent risk factor for neurodegenerative diseases [1]. Among its molecular mediators, metaflammation and mitochondrial dysfunction are increasingly recognized as contributing to a pathological axis that links systemic aging to chronic neuroinflammation and neuronal degeneration. This review has outlined how the metaflammation–mitochondria–neuroinflammation axis may underlie the progression of AD, PD, ALS, and other age-related neurodegenerative conditions.

Emerging interventions targeting the metaflammation–mitochondria–neuroinflammation axis act across distinct but interconnected pathological nodes. Some strategies aim to attenuate metaflammation by reducing peripheral cytokine load and systemic inflammation, as seen with the use of NSAIDs, NLRP3 inflammasome inhibitors, caloric restriction, and fasting-mimicking diets (Section 4). Others focus on restoring mitochondrial homeostasis; mitochondria-targeted antioxidants such as MitoQ and SS-31, along with mitophagy enhancers like urolithin A and NAD^+ precursors, have been shown in preclinical studies to improve neuronal energy metabolism, limit mitochondrial ROS leakage, and suppress proinflammatory signaling through pathways like cGAS–STING and the inflammasome (Section 4.2). Additionally, targeting cellular senescence using senolytics (e.g., dasatinib and quercetin) or senomorphics (e.g., JAK inhibitors) may help eliminate or reprogram senescent cells, thereby reducing SASP-driven inflammation and potentially restoring tissue balance, particularly in glial compartments (Section 4.4). Finally, modulation of the gut–brain axis through probiotics, short-chain fatty acid supplementation, and fecal microbiota transplantation offers a tentative means to reestablish microbial diversity and metabolite signaling, which may in turn provide systemic anti-inflammatory and neuroprotective benefits that reverberate along the gut–brain–mitochondria axis (Section 4.5). Collectively, these interventions underscore the conceptual relevance of the metaflammation–

mitochondria–neuroinflammation axis and support its potential as a multi-nodal therapeutic target. However, most strategies remain at the preclinical or early clinical stage, and further research is needed to determine their translational applicability. Rather than acting solely on downstream neuronal symptoms, these approaches aim to remodel the systemic and cellular environment that contributes to neurodegenerative progression, offering a framework for future therapeutic exploration. While this review highlights shared mechanisms across AD, PD, and ALS, it is important to clarify that the strength and quality of supporting evidence vary considerably. In AD and PD, many key mechanisms—such as microglial cGAS–STING activation, NLRP3 inflammasome signaling, and gut microbiota dysbiosis—have been validated in both animal and human studies. In contrast, ALS-related evidence remains comparatively limited and is often derived from rodent models or correlative transcriptomic data. Although mitochondrial dysfunction and astrocytic reactivity are well-documented in ALS, direct *in vivo* confirmation of cGAS–STING activation, metaflammation-related risk factors, and gut–brain–mitochondria interactions is still emerging.

Despite these compelling mechanistic insights and promising translational findings, several limitations temper the strength of current conclusions. First, many studies are preclinical and rely heavily on animal models, with limited direct causal validation of the proposed axis in human aging and neurodegeneration. Second, clinical trials of interventions such as probiotics or CR are often small-scale, with short durations and variable endpoints. Third, the robustness and maturity of evidence differ substantially across diseases. In AD and PD, gut microbiota dysbiosis, astrocytic phenotypic switching, and cGAS–STING pathway activation have been characterized in multiple *in vivo* models and supported by emerging clinical findings. By contrast, ALS-related evidence remains notably less developed. While mitochondrial dysfunction, microglial reactivity, and metabolic disturbances have been observed in ALS models, the direct demonstration of metaflammation, cGAS–STING activation, or gut–mitochondria–glia interactions in ALS patients is limited. Most findings are derived from SOD1-based rodent models or transcriptomic correlates, and mechanistic consistency across ALS subtypes (e.g., sporadic vs. familial) remains unclear. Thus, while ALS is included in the discussion of shared mechanisms, this inclusion should be interpreted as hypothesis-generating rather than confirmatory. Extrapolating shared mechanisms to ALS and other conditions should therefore be approached with appropriate caution. To advance in this field, integrated research strategies are needed. Longitudinal studies and multi-omics analyses in human cohorts will be critical to clarify the temporal and causal hierarchy linking metabolic stress, mitochondrial dysfunction, and neuroinflammation. In addition, future studies should determine whether rational combinations of dietary, microbiome-based, and pharmacological interventions can more effectively target multiple nodes of this axis than single interventions alone. Preventive clinical trials targeting middle-aged individuals at high risk may also offer crucial insights into the early modulatory potential of such interventions before irreversible neurodegenerative processes take hold. Moreover, the development of multitarget, personalized therapeutic regimens will be essential to account for both the commonalities and heterogeneity observed across different neurodegenerative diseases.

It is also important to clarify that although metaflammation overlaps with inflammaging and systemic sterile inflammation, it should not be used as an umbrella term for all chronic age-related inflammatory processes. In this review, we define metaflammation as chronic low-grade inflammation driven primarily by metabolic stressors, including nutrient excess, visceral adiposity, insulin resistance, metabolic syndrome, and gut microbiota dysbiosis. By contrast, inflammatory events driven primarily by protein aggregates, local glial activation, mitochondrial DAMP release, or CNS-intrinsic injury responses are better understood as downstream or interacting processes rather than metaflammation per se. Thus, the proposed framework does not imply that all neuroinflammatory mechanisms in aging-related neurodegeneration are metabolically derived. Rather, it highlights how metabolically driven systemic inflammation may converge with mitochondrial dysfunction and CNS-intrinsic inflammatory pathways to amplify disease progression. Future studies should further refine this boundary by identifying metabolic-state-dependent biomarkers, distinguishing peripheral metabolic inflammatory signatures from CNS-intrinsic inflammatory responses, and determining when these processes causally interact during disease progression.

In conclusion, the metaflammation–mitochondria–neuroinflammation axis offers a valuable systems-level perspective on how peripheral metabolic stressors may intersect with glial and mitochondrial dysfunction to shape age-related neurodegenerative trajectories. However, the clinical application of this model requires careful calibration of its components to the disease-specific context. For ALS in particular, further mechanistic and translational studies are essential before these pathways can be considered as established therapeutic targets. Continued mechanistic and translational validation across experimental models and human studies will be essential to determine whether

interventions targeting this axis can meaningfully alter neurodegenerative risk or progression in clinical settings.

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Author Contributions

W. Gao, H.Y. Lee, and K.J. Min designed the manuscript. W. Gao and H.Y. Lee wrote the paper. W. Gao drew the figures inserted into the manuscript. All authors critically reviewed the manuscript.

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