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Invited Mini Review

Emerging perspectives on mitochondrial dysfunction and inflammation in Alzheimer's disease

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Despite enduring diverse insults, mitochondria maintain normal functions through mitochondrial quality control. However, the failure of mitochondrial quality control resulting from excess damage and mechanical defects causes mitochondrial dysfunction, leading to various human diseases. Recent studies have reported that mitochondrial defects are found in Alzheimer's disease (AD) and worsen AD symptoms. In AD pathogenesis, mitochondrial dysfunction-driven generation of reactive oxygen species (ROS) and their contribution to neuronal damage has been widely studied. In contrast, studies on mitochondrial dysfunction-associated inflammatory responses have been relatively scarce. Moreover, ROS produced upon failure of mitochondrial quality control may be linked to the inflammatory response and influence the progression of AD. Thus, this review will focus on inflammatory pathways that are associated with and initiated through defective mitochondria and will summarize recent progress on the role of mitochondria-mediated inflammation in AD. We will also discuss how reducing mitochondrial dysfunction-mediated inflammation could affect AD. [BMB Reports 2020; 53(1): 35-46]

INTRODUCTION

Mitochondria play a wide range of roles in apoptosis, calcium homeostasis, cell proliferation, production of metabolic substrates, and inflammation, in addition to their primary responsibility of energy production in cells (1). Mitochondria operate various defense mechanisms from the protein level to the organelle level through mitochondrial quality control (MQC) to maintain normal functions (2). Notably, the failure of MQC results in mitochondrial dysfunction, which has been frequently associated with many diseases (3). Interestingly, damaged mitochondria are also found in the brains of patients with AD, and mitochondrial dysfunction is known to accelerate AD symptoms. In recent years, accumulating evidence has highlighted the essential role of inflammation in AD. Here, we provide an overview of the features of inflammation and mitochondrial dysfunction, and the mechanisms underlying the mitochondria-mediated inflammatory response in AD pathogenesis (Fig. 1). Furthermore, we explore possible ways of adjusting MQC and inflammation to ameliorate AD symptoms and pathogenesis (Table 1).

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ROLE OF INFLAMMATION AND MITOCHONDRIA IN AD

Inflammation as a central mechanism of AD

Recent findings strengthen the implication of inflammation on the pathogenesis of AD. Genetic studies have consistently identified a list of genes that can act as risk factors for AD, regardless of amyloid-beta (Aβ) signal transduction. Triggering receptor expressed on myeloid cells 2 (TREM2) is expressed on microglial membranes, recognizes lipoproteins and phospholipids, and is involved in phagocytosis of microglial cells. Lack of TREM2 suppresses tau disease, gliosis, and neuroinflammation, because it helps the microglia respond to damage caused by tau disease (4). Besides, Apolipoprotein E (ApoE) is secreted by microglia and astrocytes and has three alleles, ε2, ε3, and ε4. In the central nervous system, ApoE binds to ApoE receptors present on nerve cells to regulate the development of the central nervous system and recovery of nerve defects. Among them, the ApoE4 allele is a genetic risk factor for sporadic AD (5), and as the ε4 gene increases, the age of onset of AD decreases. It is known that an impaired function of ApoE4 adversely affects Aβ removal and Aβ-induced inflammatory response (6, 7). As mentioned above, inflammatory process-linked proteins, such as TREM2 and ApoE, may act independently of Aβ signaling. In a bioinformatics study conducted by Zhang *et al*., the immune- and microglia-specific pathway, including TYROBP which is restricted to cells involved in the innate immunity, was also identified as a critical regulator of AD pathogenesis (8).

Since the 1980s, researchers have found components of the immune response, such as immunoglobulins and complement

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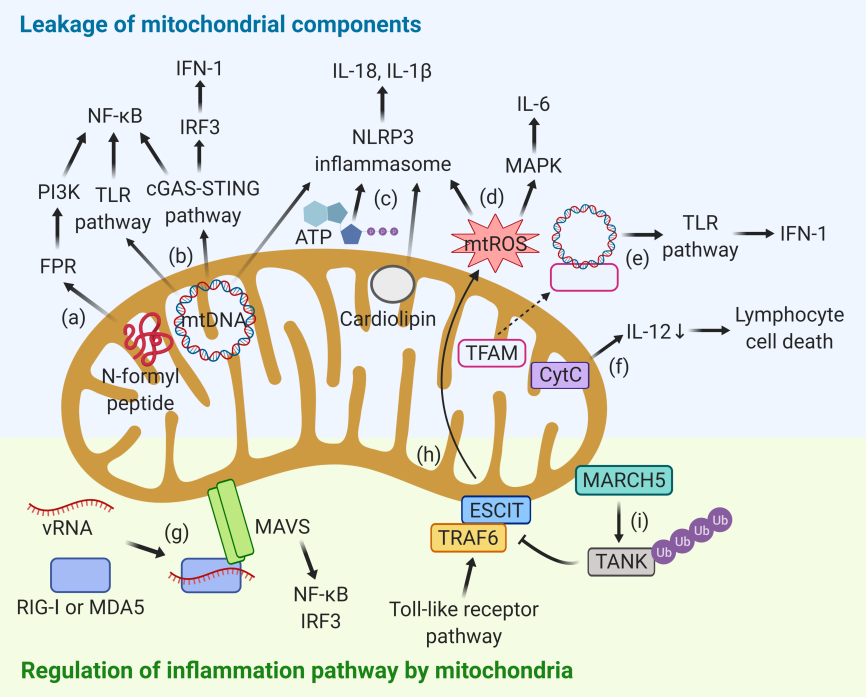

Fig. 1. Mitochondria as a regulator of inflammation. (Upper) Leakage of mitochondrial components. (a) Leaked N-formyl peptide binds to formyl peptide receptor (FPR) to activate NF-κB. (b) Leakage of mtDNA to the cytosol activates Toll-Like-Receptor (TLR), cyclic GMP-AMP synthase-simulator of interferon genes (cGAS-STING) pathways, and NLRP3 inflammasome. (c) ATP and cardiolipin activate NLRP3 inflammasome. (d) Mitochondrial ROS (mtROS) activates NLRP3 inflammasome and mitogen-activated protein kinase (MAPK) signaling. (e) Binding of mtDNA to cytosolic TFAM activates the TLR pathway. (f) Cytosolic cytochrome C (Cyt C) reduces IL-12 and increases lymphocyte cell death. (Lower) Regulation of inflammation pathway by mitochondrial factors. (g) MAVS recruits RIG-I or MDA5 to viral RNA to activate NF-κB and IRF3. (h) ESCIT generates mtROS by binding to TRAF6. (i) MARCH5 ubiquitinates TANK to enhance TRAF6 signaling.

Table 1. Strategies to modify the stress in the mitochondria-inflammation pathway

Targeting of mitoinflammation pathways		Strategies	Beneficial or detrimental*	References
Targeting mtDAMP and mtPAMP	mtROS	Mitochondria-targeted antioxidant	Mito Q, MitoVitE, Tiron	(112-116)
	mtDNA	Mitochondrial genomic editing	mtCRISPR/Cas9, mtTALEN	(42, 123-125)
	TFAM	TFAM ectopic expression	TFAM transgenic mouse	(126-129)
Targeting inflammasome	NLRP3 inflammasome	Pharmacological inhibition of NLRP3	MCC950, JC-124, Fenamate NSAIDs	(131-133)
Regulating mitochondrial quality control	Mitophagy	Pharmacological enhancement of mitophagy	Nicotinamide mononucleotide (NMN), Urolithin A (UA), Actinonin (AC), Mitochonic acid 5 (MA-5)	(136, 137)
	Mitochondrial dynamics	Mitochondrial fission	Mdivi-1, Heptapeptide P110	(140-142)
		Mitochondrial fusion	*$Mfn2^{-/-}$ mouse	(139)
	cGAS-STING pathway	Inhibition of cGAS-STING pathway	*$Prkn^{-/-}$ mouse, *$Pink1^{-/-}$ mouse	(145)

proteins near Aβ and elevated levels of cytokines and chemokines, in AD brains (9, 10). It has also been shown that anti-inflammatory drugs activate microglia and lower Aβ42 *in vivo* in mouse models (11, 12). Several human clinical trials have revealed that anti-inflammatory drugs reduce the risk of AD (13, 14). Thus, many researchers now agree that an association between neuroinflammation and AD pathogenesis exists and that AD pathogenesis and inflammation are the cause and effect of each other, regardless of what is triggered first. In the case of acute inflammation, microglia eliminate Aβ and prevent the ensuing detrimental consequences. Contrastingly, cytokines, chemokines, and ROS are over-produced by immune cells and exacerbate neurotoxicity in chronic inflammation. Whereas the former is beneficial in relieving neuropathology, the latter aggravates neurotoxicity. Next, we investigate the roles of inflammation with the opposing side to the pathogenesis of AD.

Neuroprotective inflammation in the pathogenesis of AD: Many studies have demonstrated that overexpression of inflammatory mediators in the AD mouse model plays a

beneficial role in pathogenesis. Whereas aged amyloid precursor protein (APP) transgenic (TG) mice display increased production of astroglial TGF-β1 and reduction in the number of parenchymal amyloid plaques, mice expressing hAPP and TGF-β1 show Aβ accumulation in cerebral blood vessels (15). In the study conducted by Wyss-Coray *et al*., researchers observed that hAPP/TGF-β1 mice have markedly higher levels of C3, a component of the complement system, than do hAPP mice, and inhibition of C3 activation causes an increase in Aβ deposition and the number of degenerating neurons (16). Furthermore, pathogenic Aβ is eliminated by immune-related clearance mechanisms. For example, low-density lipoprotein receptor-related protein 1 (LRP-1) mediates the uptake of Aβ in astrocytes and neurons (17, 18). ATP-binding cassette subfamily A member 7 (ABCA7) also participates in phagocytic clearance of Aβ in the brain (19). These results suggest that immune activation and the subsequent microglial activation help relieve AD pathology.

Detrimental effect of inflammation on AD: Based on various AD mouse models, it is known that higher levels of cytokines trigger inflammation and thereby exacerbate AD pathology. The APP TG mouse model with exogenous expression of interleukin (IL)-10 in the brain displays elevated Aβ accumulation and memory deficit (20). The most common mechanism whereby Aβ is produced because of inflammation is inflammation-mediated regulation of APP, β-secretase 1 (BACE1), and γ-secretase expression. Activation of immune-related transcriptional factor NK-κB was reported to cause APP upregulation in neurons (21). Interferon (IFN)-γ also induces BACE1 expression through the JAK2-ERK1/2 signaling pathway in astrocytes (22). In addition, inflammation is thought to play a role in tau pathology in AD. Lipopolysaccharide (LPS) administration induces inflammation and aggravates tau pathology in the 3xTg AD mouse model (23). These results offer compelling evidence for the harmful effects of inflammation on AD pathogenesis.

Mitochondrial cascade in AD

Mitochondria are considered to play a critical role in the pathology of AD. Neurons need to produce large amounts of neurotransmitters and establish membrane excitability. Since mitochondria are responsible for ATP production, iron homeostasis, and Ca^{2+} signaling, neuronal viability relies highly on mitochondrial function. For example, mitochondria in the presynaptic nerve terminal primarily regulate presynaptic calcium at central glutamatergic terminals (24). Axon regeneration is also facilitated by increasing mitochondrial motility and recovering the energy deficit in mature neurons (25). Thus, mitochondrial defects are commonly observed in neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), and AD. In ALS and PD, mitochondrial dysfunction and impaired mitochondrial fusion cause neuronal loss (26); mitochondria also play a pivotal role in the loss of hippocampal and cortical neurons in AD.

Electron microscopic studies have revealed that AD brains display abnormal mitochondrial structure in the hippocampus, acoustic cortex, frontal cortex, and cerebellum (27). A recent report identified a mitochondrial fission-arrest phenotype and elongated interconnected mitochondria in the hippocampus and entorhinal cortex of patients with AD (28). In addition to the structural abnormality, AD brains also exhibit mitochondrial malfunction, such as changes in glucose metabolism and oxygen consumption. The activity of the pyruvate dehydrogenase complex (PDHC) and 2-ketoglutarate dehydrogenase complex is reduced in the affected regions of AD brains (29, 30). The activity of complex I, complex II-III, and cytochrome oxidase is reduced in the cortex of AD brains (31). Increased oxidative damage to mitochondrial DNA is found in AD (32). Despite these studies on the corruption of mitochondrial function in AD brains, it is still debatable whether mitochondrial disruption is the main cause of AD or occurs as a consequence of pathological conditions in AD. This section describes the correlation between abnormal mitochondria and AD pathogenesis, focusing on the evidence from two conflicting hypotheses.

Mitochondrial dysfunction as an outcome of AD pathogenesis: The majority of researchers contend that Aβ-induced ROS generation and impaired calcium homeostasis lead to mitochondrial lesions, which are known as the secondary mitochondrial cascade. Overexpression of mutant APP in HT22 mouse hippocampal cell line results in defective mitochondrial dynamics and changes mitochondrial structure and function in neurons (33). APP can accumulate in mitochondrial import channels of AD brains and cause mitochondrial dysfunction (34). It has also been reported that Aβ directly disrupts mitochondrial function and inhibits key enzymatic activities. Lustbader *et al*. reported that alcohol dehydrogenase (ABAD) interacts with Aβ and mediates Aβ-induced apoptosis and free-radical generation in neurons (35). AD brains express higher levels of voltage-dependent anion-selective channel 1 (VDAC1), which interacts with Aβ and phosphorylated tau to block mitochondrial pores, precipitating mitochondrial dysfunction (36).

In addition, there are reports showing that mitochondrial fusion and fission factors are affected by Aβ. Aβ induces oxidative stress that triggers mitochondrial fragmentation through decreased mitofusin-2 (Mfn2) expression by activating cyclin-dependent kinase 5 (Cdk5)-mediated peroxidase 2 (Prx2) phosphorylation (37). Aβ also mediates dynamin-related protein 1 (Drp1) phosphorylation via AKT activation, promoting excessive mitochondrial fission and leading to neuronal apoptosis (38). Collectively, the results suggest that the accumulation of mitochondrial APP and Aβ contributes to the defective energy metabolism and mitochondrial abnormalities seen in AD.

Mitochondrial defects as a causative factor of AD: In stark contrast to the above, several studies have also implied that

mitochondrial failure drives disease progression, which is known as the primary mitochondrial hypothesis. Mitochondrial loss leads to changes in ROS generation, altered calcium homeostasis, failure of mitochondrial homeostasis, and cell death. Neuron-specific deficiency of cytochrome C oxidase (COX) leads to a decrease in amyloid plaques, Aβ42 levels, β-secretase activity, and oxidative damage in the mouse model expressing mutant APP and PS1 (39). Other groups also claimed that high levels of mitochondrial DNA (mtDNA) deletion could cause COX deficiency (40). In the same context, an ultrasensitive next-generation sequencing analysis revealed an increase in mtDNA mutation frequency in AD brains (41, 42). Furthermore, injection of the mitochondrial complex I inhibitor rotenone into rats triggers tauopathy in the striatum (43). Whereas molecular mechanisms that corroborate the secondary mitochondrial hypothesis have been identified, there is only phenomenological evidence for the primary mitochondrial hypothesis that mitochondrial impairments dictate AD pathology. Nonetheless, based on the above observations, mitochondrial failure possibly facilitates AD pathogenesis.

RELATIONSHIP BETWEEN MITOCHONDRIA AND INFLAMMATION

Mitochondrial quality control

Because mitochondria in eukaryotic cells are the major organelles that provide ATP through the electron-transport chain (ETC) and ETC inevitably generates ROS, mitochondrial DNA, proteins, and lipids are damaged first, causing mitochondrial dysfunction (44). As mentioned earlier, however, MQC preserves the normal function of mitochondria. At the molecular level, mitochondria have a specific DNA polymerase subunit gamma (PolG) for mtDNA repair (45) and chaperones, such as Hsp60/70, to repair misfolded proteins (46). Mitochondrial AAA protease in the mitochondrial intermembrane space, Chip in the mitochondrial inner membrane, and LON protease in the mitochondrial matrix decompose damaged and misfolded proteins (47). Damaged proteins in the mitochondrial envelope are also ubiquitinated by the E3 ubiquitin-protein ligase MARCH5 and degraded by proteasomes (48). Antioxidants can directly quench ROS to prevent ROS-mediated damages from occurring (45). At the organelle level, mitochondrial biogenesis responds to a variety of stress conditions, such as calorie restriction, exercise, NO, CO, and ROS. This process creates new mitochondria (49) and promotes mitochondrial fusion through MFN and optic atrophy 1 (OPA1) to compensate for the deficient components. Damaged mitochondria are separated by the fission process including Drp1 or by the budding from the mitochondrial membrane. Damaged mitochondria are wrapped in autophagosomes and then eventually degraded within lysosomes (2).

Mitochondria in inflammation

Inflammation involves pathogen-associated molecular patterns (PAMPs) presented by pathogens or external ligands and damage-associated molecular patterns (DAMPs), which are endogenous molecules released into the extracellular space because of tissue damage. PAMPs and DAMPs are recognized by pattern recognition receptors (PRRs), which generate innate immunity-related substances through intracellular signaling pathways. Mitochondria have many similarities to bacteria, so the escape of mitochondrial content into the cytosol or the extracellular space serves as a PAMP or DAMP, invoking PRR signaling (50). Hence, mitochondria act as regulators of inflammatory signaling.

Inflammation triggered by the leakage of mitochondrial components

Mitochondrial DNA: Mitochondria originated from α-proteobacteria through endosymbiosis in ancient eukaryotes (51) and have circular DNA and CpG motifs similar to those of bacteria (52). Circular DNA with unmethylated CpG motifs interacts with Toll-like receptor 9 (TLR9) and activates NF-κB (53). In addition, oxidized mtDNA binds to the leucine-rich repeat pyrin domain containing 3 (NLRP3) to activate the NLRP3 inflammasome and increase interleukin-1 beta (IL-1β) during cell death (54). The cyclic GMP-AMP synthase (cGAS) stimulator of interferon genes (STING) pathway also recognizes mtDNA in the cytosol and produces IFN-1 through the interferon regulatory factor 3 (IRF3) and NF-κB (55).

N-formyl peptides: Mitochondria synthesize bacteria-like peptides using 22 tRNAs and 2 mitochondrial ribosomes, and like those of prokaryotes, mitochondrial proteins are characterized by the presence of formyl-methionine (formyl-Met) at the N-terminal (56). The mitochondrial formyl-Met acts as a chemoattractant for neutrophils when exposed outside of the cells (57) and formyl-peptides bind to the formyl peptide receptors (FPRs) to activate the FPR signaling pathway in neutrophils (58). In experiments with formyl methionine-leucine-phenylalanine (fMLP), fMLP induces IL-1β production through a rapid increase in PI3K- NF-κB activity (59).

Cardiolipin: Cardiolipin is a phospholipid that constitutes about 20% of the mitochondrial inner membrane. This phospholipid is common in bacteria but is found only in the mitochondrial inner membrane in eukaryotic cells. Cardiolipin regulates mitochondrial dynamics, apoptotic signaling, mitophagy, and ROS generation by noncovalent interactions (60). Exposure of cardiolipin on the mitochondrial outer membrane activates NLRP3 inflammasome by directly binding to NLRP3, resulting in the production of IL-1β (61). Externalized cardiolipin also induces mitophagy by binding to light-chain 3 (LC3), a receptor for autophagy (62).

ATP: Under normal conditions, extracellular ATP is rapidly degraded by the nucleotidases CD39 and CD73 (63). However, an acute increase in extracellular ATP induces IL-18 by binding to P2X7 receptor and activating NLRP3 inflammasome

in macrophages (64). In the acute lung-injury model, LPS-mediated inflammation leads to a temporary accumulation of ATP in the airways of mice. Treatment with apyrase to degrade extracellular ATP reduces LPS-mediated inflammation (65).

Cytochrome C: Cytochrome C (Cyt C) is a protein that transports electrons from complex III to complex IV of ETC in the mitochondrial inner membrane. The release of Cyt C into the cytosol induces apoptosis by binding to Apaf-1, but the role of extracellular Cyt C is not clear. Some reports have shown that Cyt C may affect inflammation (66). Cyt C injected into $CD8^+$ dendritic cells reduces IL-12 production (67). Extracellular Cyt C promotes lymphocyte death and leucine-rich alpha-2-glycoprotein-1 (LRG1) binds to Cyt C and reduces its toxicity (68). Additionally, it has been shown that extracellular Cyt C increases NF-κB activity and cytokine production in mouse spleen cells (69).

Mitochondrial ROS: In general, ROS induces functional errors by oxidizing proteins, lipids, and DNA. Mitochondria produce energy through ETC, which also generates mitochondrial ROS (mtROS) during electron transfer at the complex I and III in the mitochondrial inner membrane (70). The mtROS is released into the cytoplasm when high concentrations of Ca^{2+} and cyclophilin D convert the ATP synthase into a non-specific pore or when ROS opens mitochondrial permeability transition pores (71) and drives proinflammatory cytokine production. Inhibition of mtROS reduces IL-6 levels produced by LPS treatment (72), whereas mtROS increases IL-1β by activating NLRP3 inflammasomes and induces IL-6 production through inflammasome-independent transcriptional regulation (73).

Mitochondrial transcription factor A: The primary role of mitochondrial transcription factor A (TFAM) is to regulate nucleoids, a condensed form of mitochondrial DNA. TFAM deficiency induces mtDNA mutations and mtDNA escapes into the cytosol, where it induces Type I IFN production through the cGAS-STING pathway (74). Additionally, extracellular TFAM is inactive, but has structural homology with HMGB1, which binds to DNA and induces inflammation (75). Similarly, binding of TFAM to mtDNA activates Type 1 IFN in plasmacytoid dendritic cells through the RAGE-TLR9 signaling pathway (76).

Regulators of inflammatory signaling pathway in mitochondria

Mitochondrial antiviral signaling protein: Retinoic acid-inducible gene 1 receptor (RIG1)-like receptors RIG-I and MDA5 recognize different types of viral RNA (vRNA) in the cytosol and bind to mitochondrial antiviral signaling protein (MAVS) on the mitochondrial outer membrane or peroxisome by interacting via caspase activation and recruitment domains (CARDs) (77). MAVS present on the mitochondrial outer membrane activates NF-κB and IRF3 (78) or recruits NLRP3 inflammasomes to mitochondria for IL-1β production (79). In addition, MAVS is activated by mitochondrial dynamics; mitochondrial elongation induces MAVS activation, but its fission decreases MAVS expression (80). MFN2, which is required for mitochondrial fusion, directly binds to MAVS and inhibits its activity (81). Mitochondrial dynamics affect MAVS, probably because of the need for self-oligomerization for activation (82).

Evolutionarily conserved signaling intermediate in Toll pathway: Evolutionarily conserved signaling intermediate in Toll pathway (ECSIT) was identified as a TRAF-6 binding protein and is an E3 ligase involved in the TLR signaling pathway. ECSIT is a cytosolic protein, but interacts with the chaperone NDUFAF1 and traffics to the mitochondria to regulate complex I assembly (83). In the TLR signaling pathway, ECSIT binds to TRAF6 to recruit mitochondria to the phagosomal membrane and produce mtROS (84). An increase in constitutive mtROS production in ECSIT-deleted macrophages prevents further TLR-induced mtROS production, demonstrating the key role of ECSIT in mtROS production and mitophagy-dependent MQC (85).

Membrane-associated ring finger (C3HC4) 5: Membrane-associated ring finger (C3HC4) 5 (MARCH5), an E3 ligase present in the mitochondrial outer membrane, increases inflammation by poly-ubiquitinating and attenuating TANK, a TRAF-interacting protein. TANK inhibits TRAF6 in the TLR7 signaling pathway, revealing a role of mitochondria in modulating innate immunity and linking mitochondria to the TLR signaling pathway (86).

MITOCHONDRIAL-INFLAMMATION AXIS IN AD PATHOLOGY

Evidence for mitochondrial DAMPs and PAMPs in AD pathology

As discussed, mitochondrial DAMPs and PAMPs can activate inflammation. In the central nervous system (CNS), they initiate pro-inflammatory immune responses in glial cells, thereby leading to chronic neuroinflammation and accelerating the pathology of neurodegenerative diseases, including AD (87-89).

Mitochondrial DNA: It has been shown that mtDNA induces neuroinflammation *in vivo*. Injection of mitochondrial lysates or mtDNA into the hippocampal dentate gyri triggers pro-inflammatory signaling (90). Hippocampal injection of mitochondria or mtDNA leads to NF-κB phosphorylation, induction of TNFα mRNA, and a decrease in TREM2 expression, all of which are closely associated with AD pathology (91-93) and are involved in anti-inflammatory and phagocytic pathways (94, 95). Simultaneously, hippocampal injection of mtDNA increases astrocyte proliferation with elevated levels of cortical colony-stimulating factor 1 receptor (CSF1R) and GFAP proteins. Interestingly, mitochondrial lysates also upregulate endogenous APP and Aβ (90), strongly supporting the correlation between mtDNA and AD pathology. Moreover,

the relevance of mtDNA levels to AD pathology was reported (96). Circulating cell-free mtDNA is profoundly downregulated in the cerebrospinal fluid (CSF) of patients with sporadic AD as well as asymptomatic subjects at risk (96). Notably, preclinical subjects with pathogenic mutations in PSEN1 exhibit a reduction in the mtDNA concentration in CSF before other AD-related biomarkers in CSF can be detected, highlighting the use of mtDNA as a potential AD biomarker. A recent study using post-mortem brain tissues reported the regional differences in mtDNA levels in human brains; the mtDNA levels in the parietal cortex is lower in non-diabetic AD subjects, but not in diabetic AD patients than in non-cognitively impaired controls (97).

Cardiolipin: It has been described that aged brains, in addition to elevated ROS production, have lower levels of cardiolipin (98, 99). In contrast, the proportion of peroxidized cardiolipin is higher in the brains of aged rodents (100), which results in various mitochondrial defects, such as low respiratory chain efficiency and elevated ROS production (99-101). This excessive level of ROS may contribute to chronic inflammation. Activation of the NLRP3 inflammasome is attenuated by pharmacological inhibitors of ROS production (61). Therefore, age-related cardiolipin oxidation results in mitochondrial dysfunction and aberrant ROS production that subsequently provokes chronic inflammation.

Mitochondrial transcription factor A: TFAM is implicated in the inflammation of the CNS in neurodegenerative diseases (89). TFAM upregulates secretion of IL-6 and cytotoxins in primary microglia that were obtained from post-mortem human samples or THP-1 human monocytic cells, a model of human microglia (102). Administration of TFAM into the cisterna magna in the rodent model increases levels of pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-α, in the hippocampus and frontal cortex (103), which are the predominant regions affected by AD (89). These results underscore the ability of extracellular TFAM to induce pro-inflammatory responses in microglia. Furthermore, when combined with CpG-rich mtDNA, TFAM can activate RAGE to mediate a pro-inflammatory immune response and promote the production of TNF-α via the PI3K/AKT and ERK pathways (104). Accordingly, blocking RAGE with antagonistic antibodies inhibits the secretion of monocyte chemotactic protein-1 (MCP-1) in TFAM-stimulated THP-1 cells (103). Considering that RAGE binds to Aβ (105, 106) and that microglia express high levels of RAGE in patients with AD (107), the TFAM-RAGE pathway may potentially play a role in AD pathogenesis (87).

Cytochrome C: Given that Cyt C is critical for the regulation of apoptosis, it has been implicated in the excessive cell death observed during the progression of AD. Reports showed that CSF Cyt C levels are increased in patients with MCI (87, 108). Whereas the release of Cyt C from mitochondria is considered to be a mediator of cell death in AD (109), Cyt C released into the extracellular space may be able to provoke PAMP responses (87). Mouse splenocytes exposed to Cyt C show pro-inflammatory activity, including the release of inflammatory mediators such as chemokine ligand 5 (CCL5)/RANTES, CCL3/MIP-1α, and MCP-1 (69). As circulating Cyt C is increased in many chronic inflammatory diseases, such as liver injury, SIRS, and myocardial infarction (110), extracellular Cyt C could also activate microglia-like cells to exacerbate inflammatory damage, probably by interacting with TLR4 on microglia (111).

STRATEGIES FOR TARGETING MITOINFLAMMATION PATHWAYS

Targeting mtDAMP and mtPAMP

Mitochondrial ROS: Oxidative stress mediates mitochondrial damages during aging, particularly by damaging mtDNA and peroxidizing cardiolipin, and generates excessive ROS in turn as a byproduct. In this regard, the mitochondria-targeted antioxidants (MTAs) that specifically curtail oxidative stress within mitochondria have greater advantages than do untargeted cellular antioxidants (112). MTAs can cross the mitochondrial phospholipid bilayer and sequester ROS where it is generated. MTAs, such as MitoQ and MitoVitE, are more efficient in alleviating the damage caused by excessive ROS levels and blocking apoptosis than are untargeted antioxidants (113). Particularly, MitoQ is protective in the aged rodent model of neurodegenerative diseases, such as PD (114, 115), and suppresses the NLRP3 inflammasome-mediated production of inflammatory cytokines in THP-1 cells (116). In addition, the release of metals can further exacerbate the oxidative damage mediated by high ROS levels (112). Tiron, one of the MTAs, can confer marked protection against mtROS, because it targets not just ROS but also free intracellular metals that are released as a consequence of oxidative stress (112). Since iron accumulation and mtROS synergistically contribute to neurodegenerative pathology in AD and PD (117, 118), and chronic inflammation in microglia is characterized by an increase in intracellular iron levels (119), Tiron may mitigate chronic inflammation by reducing iron-mediated ROS stress in neurodegenerative disorders.

Mitochondrial DNA: mtDNA is relatively unstable and vulnerable to oxidative insults because they lack histones and have a limited enzymatic repair system. As a result, mtDNA mutations accumulate during aging (120, 121) and are a significant risk factor for AD (41, 122). Mutated mtDNA can be revised via genome-editing technologies, such as clustered regularly interspaced short palindromic repeats/associated protein 9 (CRISPR/Cas9) and transcription activator-like effector nucleases (TALENs) (42, 123). This strategy to revise the mutated mtDNA involves expressing a gRNA targeting the pathogenic mtDNA and mitoCas9 that is localized to the mitochondrial matrix and specifically cleaves the mtDNA. In addition, mitoTALENs were used to eliminate pathogenic mtDNA and thus recover respiratory capacity and improve

oxidative phosphorylation (124).

Mitochondrial transcription factor A: Overexpression of mitochondrial TFAM exerted beneficial effects in model systems for aging-related hearing loss (125), memory loss (126), and AD (127, 128). In TFAM TG mice, age-related symptoms, such as mitochondrial deficits in the brain, motor learning memory, working memory, and hippocampal long-term potentiation (LTP), are alleviated (126). Remarkably, IL-1β was significantly reduced in aged TFAM TG mice, indicating compensatory suppression of the TFAM-mediated aberrant inflammatory response. TFAM overexpression also exhibits a protective effect in the 3xTg AD mouse model (PS1M146V, APPswe, and MAPT P301L triple TG), reducing cognitive dysfunction, mtDNA oxidative stress, and Aβ accumulation (128).

Targeting the inflammasome

Byproducts of mitochondrial dysfunction, such as mtROS and mtPAMP, can regulate the pro-inflammatory response by activating the inflammasome (123). Using *Nlrp3* knockout and *Caspase-1* knockout mice, the NLRP3/caspase-1 axis was shown to play an important role in the pathogenesis of AD (129). In agreement, inhibitors of the NLRP3 inflammasome ameliorate AD pathology in animal models of AD (130-132). MCC950, which inhibits inflammasome and microglial activation in the APP/PS1 mouse model of AD (131), might inhibit NLRP3-induced oligomerization of ASC, a key adaptor protein that is required for the activation of the inflammasome (133). In addition, several clinically approved fenamate NSAIDs inhibit the NLRP3 inflammasome via the blockade of the volume-regulated anion channels (VRAC), a Cl channel, and consequently ameliorate cognitive impairment in animal models of AD (130).

Regulating mitochondrial quality control

Mitophagy: Tight regulation of MQC by facilitating mitophagy and subsequent inhibition of chronic inflammation were suggested as a potential therapeutic strategy for AD (134). A recent study by Fang *et al*. showed that enhancing mitophagy prevents AD pathology, including cognitive impairment, tau hyper-phosphorylation, Aβ accumulation, and neuroinflammation (135), highlighting the importance of MQC in AD intervention. Furthermore, mitochonic acid 5 (MA-5) was shown to regulate mitophagy via BCL2/adenovirus E1B 19-kDa protein-interacting protein 3 (BNIP3), reducing mitochondrial apoptosis in BV-2 cells (136). Mitophagy may inhibit inflammation by down-regulating ROS-producing mitochondria, since blocking mitophagy results in the increase of ROS, followed by NLRP3 activation (137).

Mitochondrial dynamics: Several studies reported that an imbalance of mitochondrial dynamics induces chronic inflammatory stress and thus aggravates the pathogenesis of neurodegenerative disorders. Disruption of mitochondrial fusion by *Mfn2* knockout in the hippocampus results in excessive mitochondrial fragmentation and inflammatory response, which are the characteristic features of AD pathology (138). In contrast, negative regulation of mitochondrial fission by genetic or pharmacological methods significantly alleviates inflammation. Inhibiting mitochondrial fission by Mdivi-1, a chemical inhibitor of Drp1 or *Drp1* knockdown, reduces pro-inflammatory signaling in the LPS-stimulated BV-2 cells (139) and a kainic acid-injected rodent model (140). Recently, Joshi *et al*. demonstrated that neurotoxicity can be directly attributed to the release of neurotoxic proteins from microglia displaying Drp1 and Fis1-mediated mitochondrial fragmentation, followed by the activation of naive astrocytes to the A1 state (141). This neurotoxicity could be reversed by the treatment with a heptapeptide (P110) that blocks the Drp1-Fis1 interaction. Interestingly, AD patients show a distinct pattern of mitochondrial dynamics (142). AD mitochondria exhibit significant fragmentation in a Drp1-dependent manner, whereas MCI mitochondria have increased mitochondrial Mfn2 levels, likely promoting mitochondrial fusion. These changes in mitochondrial dynamics may contribute to the induction of pro-inflammatory signaling in microglial cells. Taken together, subtle regulation of mitochondrial dynamics during disease progression may be a possible therapeutic strategy to relieve inflammatory stress and thus alleviate AD pathology.

cGAS-STING pathway

Binding of oxidized mtDNA to cGAS results in the translocation of STING to the Golgi apparatus, leading to phosphorylation of the transcription factor IRF3 and activation of NF-κB signaling (143). The cGAS-STING pathway has also been found to be involved in autophagy in innate immune cells (55). Activation of the cGAS-STING pathway promotes mitophagy through cGAS/beclin-1 interaction, which in turn negatively regulates cGAS activity and increases cytosolic DNA degradation (144). A recent study has elucidated that aberrant mitophagy in *Prkn* or *Pink1* knockout mice leads to a strong inflammatory phenotype, which is mitigated by genetic inactivation of STING (145). Thus, the cGAS–STING pathway may be a potent therapeutic target to counter mitoinflammation.

CONCLUSION

Mitochondrial functions and inflammatory signals are closely linked to AD symptoms and pathogenesis. In this review, we described mitochondrial components as being causative factors of inflammation, but simultaneously are suitable therapeutic targets in regulating the neuroinflammation (Fig. 1, Table 1). Indeed, inhibiting mitochondrial inflammation or maintaining functional mitochondria through MQC reverts many symptoms observed in the AD model. Thus, mitochondrial inflammation is a valuable diagnostic target and requires further study as an emerging therapeutic target for treating AD.

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CONFLICTS OF INTEREST

The authors have no conflicting interests.

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