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Post-Translational Modifications of DRP1 in Alzheimer's Disease

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ABSTRACT

Mitochondrial dysfunction is increasingly recognized as a central feature in the pathophysiology of Alzheimer's disease (AD). Among the mitochondrial alterations implicated in AD, aberrant mitochondrial fission, principally mediated by dynamin-related protein 1 (DRP1), has emerged as a critical pathological mechanism. This review delineates the role of post-translational modifications (PTMs) in regulating DRP1 function and highlights emerging evidence on its pathological interactions and therapeutic targeting in AD. PTMs dynamically modulate DRP1 activity, stability, and subcellular localization in response to AD-related cellular stressors, including amyloid-β (Aβ) accumulation, oxidative stress, and calcium dysregulation. Hyperphosphorylation of DRP1 has been shown to enhance its translocation to mitochondria, promoting excessive fragmentation. In addition, alternative PTMs, including O-GlcNAcylation, S-nitrosylation, and ISGylation, influence DRP1 function, either enhancing or suppressing its pathological activity. Proteolytic cleavage of DRP1 by calpain further disrupts its integrity, contributing to mitochondrial dysfunction and synaptic degeneration. In addition to being regulated by PTMs, DRP1 is abnormally activated through direct interactions with Aβ and phosphorylated tau (pTau), contributing to excessive fission and impaired mitophagy. Together, these findings underscore DRP1 as a pivotal regulatory node whose modulation, through both PTMs and pathological interactions with Aβ and pTau, disrupts mitochondrial dynamics in AD. Therapeutic strategies aimed at targeting DRP1 activity offer promising avenues to restore mitochondrial homeostasis and mitigate neurodegeneration.

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the leading cause of dementia worldwide [1]. While its precise etiology remains largely unknown, histopathological hallmarks of AD include extracellular amyloid-β (Aβ) plaques and intracellular neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau (pTau) protein. These pathological hallmarks are widely believed to contribute to synaptic dysfunction and the ensuing neurodegenerative symptoms of AD [1]. The strongest risk factor for AD is advancing age, and with an aging global population, it poses an escalating threat to global public health [1,2]. Currently available treatment options are predominantly symptomatic and fail to halt or reverse disease progression. Furthermore, the repeated failure of clinical trials aimed at reducing Aβ production or enhancing its clearance has cast doubt on the amyloid-centric model of AD pathogenesis [3,4]. This has prompted increased interest in alternative mechanisms, among which mitochondrial dysfunction has emerged as a compelling candidate implicated in both the initiation and progression of AD [5,6].

Mounting evidence suggests that disturbances in mitochondrial dynamics, particularly imbalances in mitochondrial fission, fusion, and mitophagy, play a critical role in AD pathophysiology [5]. These processes are essential for maintaining mitochondrial homeostasis, energy metabolism, and neuronal integrity. Disruptions in these mechanisms are closely linked to early neuronal dysfunction, characterized by impaired ATP production, elevated oxidative stress, and defective mitochondrial quality control [5,7]. These mitochondrial impairments may not only precede but also may exacerbate AD pathology [5,8]. Thus, targeting mitochondrial processes and their associated regulatory proteins has emerged as a potential avenue for the development of disease-modifying therapies.

Dynamin-related protein 1 (DRP1), a GTPase, is a key regulator of mitochondrial fission [9,10]. In neurons, hyperactivation of DRP1 leads to excessive mitochondrial fragmentation, loss of membrane potential, reduced ATP synthesis, and ultimately, synaptic dysfunction and apoptosis [9]. The activity and subcellular localization of DRP1 are tightly regulated by post-translational modifications (PTMs), which are often induced by AD-related cellular stressors, including oxidative damage, Aβ accumulation, and tau pathology [9]. In particular, DRP1 has been found to interact pathologically with Aβ and pTau, contributing not only to mitochondrial fragmentation, but also to defective mitophagy [11,12]. Moreover, partial suppression of DRP1 expression or pharmacological inhibition using Mitochondrial Division Inhibitor 1 (Mdivi1) has demonstrated neuroprotective effects in preclinical AD models, including improvements in mitochondrial function, synaptic integrity, and reductions in Aβ burden [13]. This review highlights DRP1 as a key modulator of mitochondrial dysfunction in AD, with a particular focus on the regulatory role of its PTMs. Recent advances elucidating the mechanistic impact of these PTMs on DRP1

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function are discussed, with a focus on their potential contributions to mitochondrial pathology and neurodegeneration in AD.

MITOCHONDRIA

Mitochondria are double-membraned, highly dynamic organelles that are the primary source of neuronal ATP [5]. They play essential roles in synaptic transmission, calcium homeostasis, reactive oxygen species (ROS) production, and intrinsic apoptotic regulation [5,14]. In AD, mitochondrial dysfunction has been observed as an early pathological event, leading to impaired energy metabolism, elevated oxidative stress, and defective mitophagy [5,7,15]. These mitochondrial abnormalities contribute not only to neuronal degeneration but also to the exacerbation of hallmark AD pathologies, including Aβ accumulation and pTau [16].

Structurally, mitochondria are composed of an outer mitochondrial membrane (OMM), inner mitochondrial membrane (IMM), intermembrane space (IMS), and matrix. Despite possessing their own genome, the majority of mitochondrial proteins are encoded by nuclear DNA and imported posttranslationally [17]. Mitochondria continuously undergo dynamic remodeling through the processes of fusion and fission – mechanisms that are critical for responding to cellular stress, maintaining bioenergetic balance, and preserving mitochondrial quality via biogenesis and mitophagy [14]. Mitochondrial fusion is primarily mediated by mitofusins (MFN1 and MFN2) in the OMM and optic atrophy 1 (OPA1) in the IMM, allowing the mixing of mitochondrial contents and functional complementation under stress [11]. In contrast, mitochondrial fission, predominantly regulated by DRP1, facilitates organelle division, intracellular transport, and the selective elimination of damaged mitochondria through mitophagy [9,10,17]. While physiological fission is essential for mitochondrial homeostasis, excessive or dysregulated fission leads to pathological outcomes, including mitochondrial fragmentation, loss of membrane potential, decreased ATP production, and increased apoptotic vulnerability. Such aberrant fission dynamics have been consistently implicated in the early stages of AD and are thought to play a contributory role in disease progression [5,9].

DRP1 STRUCTURE AND REGULATION

DRP1, also known as dynamin-like protein 1 (DLP1), is a large GTPase critical for mediating mitochondrial fission [10]. Structurally, DRP1 comprises several conserved domains: a GTPase domain responsible for binding and hydrolyzing GTP; a middle domain that mediates oligomerization; a variable domain that may contribute to interactions with adaptors, and a GTPase effector domain (GED), which regulates GTPase activity through self-assembly (Figure 1). These structural elements enable DRP1 to detect membrane curvature, assemble into spiral-like oligomers around mitochondrial tubules, and drive membrane constriction and scission through GTP hydrolysis [9,10].

In resting cells, DRP1 is primarily localized in the cytosol. Upon activation, it is recruited to the OMM by a set of adaptor proteins, including FIS1, MFF, MID49, and MID51. These adaptors facilitate the anchoring of DRP1 to mitochondria, where it oligomerizes into ring-like structures that encircle the mitochondrial surface [9,10,18]. GTP hydrolysis then induces conformational changes in the DRP1 oligomers, leading to membrane constriction and fission.

DRP1 exists in several isoforms generated through alternative splicing, which exhibit tissue-specific expression patterns and potentially distinct regulatory features. These isoforms help fine-tune mitochondrial fission in response to cellular context and energetic demands, particularly in neurons and other metabolically active tissues [9,10,18]. DRP1 activity is tightly regulated by various PTMs, which modulate its localization, oligomerization, and fission activity (Figure 1) [9]. Dysregulation of DRP1, whether through aberrant recruitment, proteolytic cleavage, or impaired GTPase activity, disrupts mitochondrial dynamics and contributes to neurodegeneration [9].

ABNORMAL INTERACTIONS OF DRP1 WITH Aβ AND PTAU

DRP1 has been shown to directly interact with AD-related pathological proteins, including Aβ and pTau [19,20]. These abnormal protein–protein interactions contribute significantly to mitochondrial fragmentation and neuronal dysfunction. A study from Manczak et al. (2011) found that both monomeric and oligomeric forms of Aβ physically interact with DRP1 in postmortem brain tissue from AD patients and in transgenic AD mouse models [19]. Co-immunoprecipitation and immunofluorescence analyses revealed progressive colocalization of DRP1 with intracellular Aβ, particularly oligomeric forms, as the disease progressed. This interaction was associated with increased expression of DRP1, FIS1 and decreased expression of MFN1, MFN2, and OPA1, thus promoting excessive mitochondrial fragmentation. Aβ-accumulating neurons showed a reduction in branching, disrupted mitochondrial distribution, and signs of degeneration. These findings suggest that the direct binding of Aβ to DRP1 promotes its activation or mislocalization, contributing to early mitochondrial dysfunction and synaptic loss in AD. Moreover, DRP1 also appears to interact abnormally with pTau in both AD brains and tau transgenic mice [20]. DRP1 co-immunoprecipitates with pTau, particularly the PHF-1-reactive form, and exacerbates disease progression. The DRP1–pTau complex is associated with decreased mitochondrial size, reduced mitochondrial density, and reduced ATP levels. Inhibition or knockdown of DRP1 in these models partially reversed these mitochondrial defects, suggesting that pTau may directly recruit or trap DRP1 on mitochondria, enhancing pathological fission independent of its canonical regulatory pathways. These interactions reveal a critical mechanism by which hallmark AD proteins disrupt mitochondrial homeostasis via direct molecular interactions with DRP1. Targeting these aberrant interactions, alongside the modulation of DRP1 activity itself, may represent a promising therapeutic approach for preserving mitochondrial integrity in AD.

Abnormal DRP1 Interactions and Defective Mitophagy in AD

In addition to promoting excessive mitochondrial fragmentation, abnormal interactions between DRP1 and Aβ and pTau also disrupt mitophagy [11,12]. Mitophagy is the selective autophagic clearance of damaged mitochondria and is essential for maintaining mitochondrial quality and neuronal health. In AD, mitophagy is disrupted, contributing to the accumulation of dysfunctional mitochondria and heightened cellular stress [11,12]. Studies have shown that Aβ and pTau not only enhance DRP1 recruitment to mitochondria but also promote its pathological activation, leading to excessive fission and fragmentation [11,12]. These changes impair mitophagy by producing dysfunctional mitochondria in excess and overwhelming the cellular clearance machinery.

Under healthy conditions, DRP1 facilitates mitochondrial fission as a preparatory step for mitophagy and thus enables the segregation of damaged mitochondrial fragments. However, in AD, pathological activation and direct binding of DRP1 by Aβ and pTau appear to

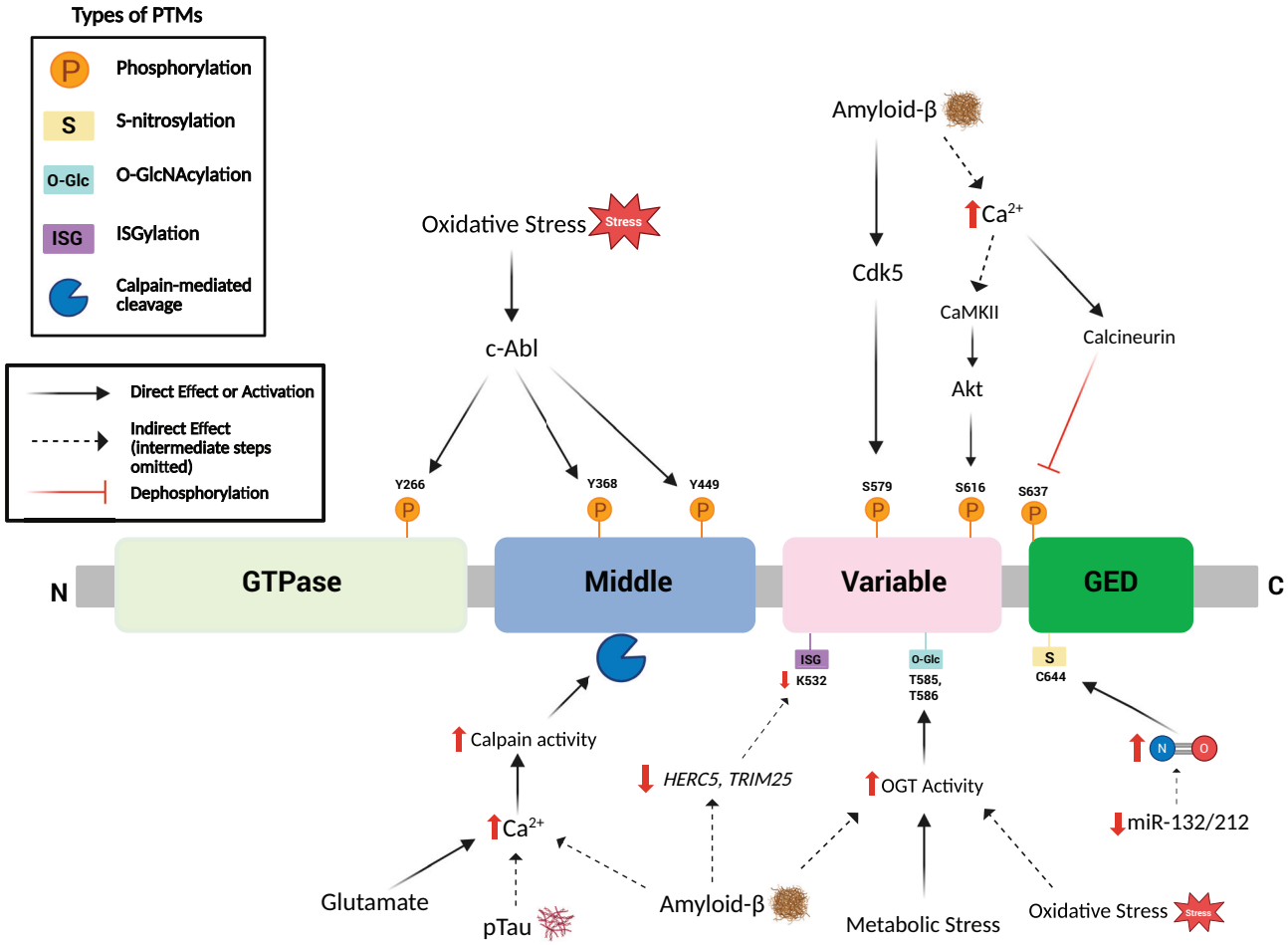

Figure 1. Schematic diagram of DRP1 domain structure and distribution of PTMs and their respective upstream regulators.
DRP1 is composed of four main domains: a GTPase domain, a middle domain, a variable domain, and a GTPase effector domain (GED). Identified PTMs include phosphorylation (orange circles), O-GlcNAcylation (green rectangles), Snitrosylation (yellow rectangles), ISGylation (purple rectangle), and calpain-mediated proteolytic cleavage (blue pacman). Specific PTM sites are mapped to their corresponding residues: Y266, Y368, and Y449 (tyrosine phosphorylation by c-Abl in response to oxidative stress); S579 (phosphorylation by Cdk5 following Aβ exposure); S616 (phosphorylation via Akt activation downstream of Aβ and Ca^{2+} signaling); S637 (dephosphorylation by calcineurin); T585/T586 (OGlcNAcylation promoted by OGT under metabolic stress, oxidative stress, and Aβ exposure); K532 (ISGylation which stabilizes active DRP1 and is reduced with loss of HERC5/TRIM25); and C644 (S-nitrosylation in response to nitric oxide (NO), regulated by downregulation of miR132/212 and oxidative stress). Calpain-mediated cleavage of DRP1 within the middle domain is induced by calcium influx resulting from Aβ, glutamate excitotoxicity, and pTau. Solid arrows indicate direct regulatory interactions, dashed arrows denote indirect steps, and red inhibition bars indicate dephosphorylation events.

dysregulate this process. Excessive mitochondrial fission leads to the accumulation of fragmented mitochondria, many of which escape degradation due to impaired mitophagy signaling [11,12]. This imbalance between mitochondrial division and clearance results in the buildup of depolarized, ROS-producing mitochondria, which further impair neuronal function. Moreover, DRP1 hyperactivation has been linked to decreased expression of key mitophagy regulators, including PINK1 and Parkin, and reduced mitochondrial clearance through autophagolysosomes [11]. These disruptions not only hinder mitochondrial turnover but also feed back into the cycle of oxidative stress and synaptic degeneration.

PROTECTIVE EFFECTS OF REDUCED DRP1 EXPRESSION IN AD MODELS

Reducing DRP1 expression itself may confer protection against AD-related mitochondrial damage. Studies using heterozygous DRP1 knockout mice crossed with APP or Tau transgenic mice showed that reduced DRP1 expression mitigates hallmarks of AD-associated mitochondrial pathology [21,22]. Mice with partial DRP1 deficiency exhibited decreased protein levels of mitochondrial fission markers (DRP1 and FIS1) alongside increased protein levels of fusion markers such as MFN1, MFN2, and OPA1, resulting in more balanced mitochondrial morphology. Enhanced mitochondrial biogenesis, including upregulation of *Pgc1α, Nrf1, Nrf2*, and *Tfam*, as well as improved mitochondrial function characterized by increased ATP production and reduced oxidative stress markers were also observed. Reducing DRP1 levels also attenuates the synaptic deficits typically seen in APP transgenic mouse models. Levels of synaptic proteins, including synaptophysin, PSD95, and GAP43, are higher in mice carrying both the APP transgene and a partial DRP1 deficiency compared to APP-only mice, indicating a restoration of synaptic integrity [22]. These mice also showed a significant reduction in soluble Aβ levels, suggesting that DRP1 modulation may influence upstream amyloidogenic processes.

POST-TRANSLATIONAL MODIFICATIONS OF DRP1 IN ALZHEIMER'S DISEASE

Phosphorylation of DRP1

PTMs of DRP1, particularly phosphorylation, play a critical role in modulating its mitochondrial localization and fission activity. In AD, phosphorylation-driven dysregulation of DRP1 has been repeatedly implicated in mitochondrial fragmentation and neuronal dysfunction [10,23-26]. Various kinases activated by pathological stimuli, such as Aβ, oxidative stress, and calcium dysregulation, have been shown to enhance DRP1-mediated fission, contributing to neurodegeneration [10,23]. One such phosphorylation event occurs at serine 579 (S579), driven by cyclin-dependent kinase 5 (Cdk5) in response to Aβ42 exposure [27]. This modification promotes excessive mitochondrial fragmentation and has been implicated in synaptic and neuronal damage. In a key study by Xu et al. (2021), expression of a phospho-defective DRP1 mutant (S579A) in primary cortical neurons blocked S579 phosphorylation and significantly attenuated Aβ-induced neurotoxicity [27]. Neurons expressing DRP1-S579A preserved dendritic structure and synaptic integrity, which reduced expression of apoptotic markers. These findings support a mechanistic role for S579 phosphorylation in linking Aβ stress to DRP1 overactivation and mitochondrial dysfunction, although in vivo validation is needed.

Another critical phosphorylation site is serine 616 (S616), which is activated downstream of calcium-dependent signaling. Aβ treatment increases intracellular calcium, triggering activation of calcium/calmodulin-dependent protein kinase II (CaMKII) and subsequently protein kinase B (Akt) [28]. Akt-mediated phosphorylation of DRP1 at S616 promotes its translocation to the OMM, leading to excessive fission and neuronal apoptosis. Inhibition of Akt effectively blocked S616 phosphorylation, prevented mitochondrial recruitment of DRP1, and attenuated mitochondrial damage and cell death [28]. Further supporting this mechanism, a study using SH-SY5Y neuroblastoma cells and primary cortical neurons demonstrated that acetaldehyde, an ethanol-derived neurotoxin, mimicked Aβ-induced mitochondrial dysfunction by promoting S616 phosphorylation [29]. This effect was mediated by ROS and intracellular calcium signaling, which activated stress-responsive kinases such as JNK and p38 MAPK, as well as CaMKII. Pharmacological inhibition of these kinases suppressed S616 phosphorylation, restored mitochondrial morphology, and improved cell viability. While not an AD-specific model, these findings mirror key features of Aβ-induced toxicity, underscoring the convergence of oxidative and calcium stress on DRP1 regulation.

Phosphorylation of DRP1 at S616 also interacts with dephosphorylation at serine 637 (S637), a site generally associated with DRP1 inactivation [9,30]. In AD models, Aβ42 exposure leads to increased S616 phosphorylation coupled with reduced S637 phosphorylation, enhancing DRP1 recruitment to mitochondria and amplifying mitochondrial fragmentation [9]. This bidirectional modulation of phosphorylation has been demonstrated in SH-SY5Y cells and fibroblasts derived from AD patients [30]. Pharmacological inhibition of the DRP1-FIS1 interaction using the peptide inhibitor P110 reversed these phosphorylation patterns, normalized mitochondrial morphology, and reduced markers of oxidative stress, apoptosis, and ATP depletion [30]. These effects emphasize the functional interplay between S616 and S637 in determining DRP1 activity and suggest that calcineurin, a calcium-activated phosphatase, may mediate S637 dephosphorylation in response to Aβ-induced calcium influx.

Beyond serine residues, DRP1 is also regulated via tyrosine phosphorylation, particularly under oxidative stress conditions [31]. The non-receptor tyrosine kinase c-Abl, which is activated in several neurodegenerative conditions, phosphorylates DRP1 at Y266, Y368, and Y449 [31]. This modification enhances DRP1's GTPase activity without affecting its mitochondrial localization, thereby promoting fission and increasing neuronal susceptibility to apoptosis. Site-directed mutagenesis of these tyrosines to phenylalanine attenuated DRP1 hyperactivation, confirming the functional importance of c-Abl-mediated tyrosine phosphorylation in regulating DRP1-driven mitochondrial dynamics [31].

Together, these findings establish phosphorylation as a central mechanism in DRP1 dysregulation during AD pathogenesis. Multiple signaling pathways converge on DRP1 to enhance its activation and mitochondrial translocation, highlighting phosphorylation, particularly at serine and tyrosine residues, as a critical regulatory axis and a potential therapeutic target in AD.

O-GlcNAcylation of DRP1

O-GlcNAcylation is a nutrient- and stress-responsive PTM involving the addition of oxygen linked N-acetylglucosamine (O-GlcNAc) to serine or threonine residues [32]. This modification is catalyzed by the enzyme O-GlcNAc transferase (OGT) and plays a critical role in cellular signaling, particularly under conditions of metabolic or oxidative stress [32]. In the context of AD, Aβ exposure has been shown to increase O-GlcNAcylation of DRP1 at threonine (T) residues 585 and 586, as demonstrated in both primary neurons and AD mouse models [32]. This modification enhances DRP1's translocation to the OMM and promotes excessive mitochondrial fission. Importantly, substitution of T585 and T586 with alanine prevents this modification and restores normal mitochondrial morphology in the presence of Aβ, underscoring O-GlcNAcylation as a gain-of-function alteration that pathologically enhances DRP1 activity under amyloidogenic stress [32]. These findings align with the observation of Bhatti et al. (2023) who reported that O-GlcNAcylation of DRP1 is associated with dysregulated energy in AD [9]. Impaired glucose utilization, an early feature of AD, combined with elevated OGT activity may act synergistically to promote hyper-O-GlcNAcylation of DRP1, thereby driving mitochondrial fragmentation [9]. This evidence supports a mechanistic link between metabolic stress and aberrant mitochondrial dynamics via O-GlcNAc-mediated modification of fission machinery in AD.

ISGylation of DRP1

In contrast to O-GlcNAcylation, which promotes DRP1 activity and mitochondrial fragmentation, ISGylation exerts a protective role by stabilizing DRP1 and preventing its degradation [33]. ISGylation involves the covalent conjugation of ISG15, a ubiquitin-like protein, to lysine residues, specifically lysine 532 (K532) in DRP1. This modification competes directly with ubiquitylation at the same site, thereby inhibiting proteasomal degradation of DRP1. Importantly, ISGylation preferentially modifies phospho-DRP1 at S616, which is associated with its active, fission-competent state. Although ISGylation does not directly enhance DRP1 activity, it preserves DRP1 function by shielding it from ubiquitin-mediated turnover. Loss of ISGylation shifts the balance toward DRP1 ubiquitylation and subsequent degradation, resulting in reduced levels of functional DRP1. This deficit impairs mitochondrial fission, promotes mitochondrial hyperfusion, and facilitates cytosolic release of mitochondrial DNA (mtDNA), which is a proinflammatory signal that can exacerbate neuroinflammation [33]. Notably, in ISGylation-deficient contexts, DRP1 is targeted for

degradation by the E3 ligase TRIM25, rather than by canonical ligases such as Parkin or MITOL, which are ineffective in the absence of ISG15 modification. In AD, ISGylation of DRP1 is significantly decreased in both human postmortem brain tissue and AD mouse models [33]. This reduction correlates with lower expression of ISGylation components, including HERC5 and TRIM25, suggesting a broader disruption of the ISGylation machinery in AD brains. The resulting increase in DRP1 degradation compromises mitochondrial quality control and contributes to neurodegenerative pathology [33]. These findings position ISGylation as a critical PTM regulating DRP1 stability and mitochondrial homeostasis, with potential implications for disease progression and therapeutic targeting in AD.

S-nitrosylation of DRP1

S-nitrosylation is a redox-sensitive PTM in which nitric oxide (NO) covalently binds to cysteine residues [34]. In AD, DRP1 undergoes S-nitrosylation at cysteine 644 (C644) in response to elevated NO levels resulting from miR-132 and miR-212 downregulation. This redox-mediated modification enhances DRP1's mitochondrial fission activity, contributing to excessive mitochondrial fragmentation and subsequent synaptic damage. Unlike O-GlcNAcylation, which arises from metabolic stress, S-nitrosylation is triggered by redox imbalance, highlighting distinct yet converging mechanisms by which AD-related stressors pathologically activate DRP1 [34]. However, these findings are debated as others have found that S-nitrosylation does not increase DRP1 GTPase activity or oligomerization and is not elevated specifically in AD brains [35].

Calpain-Mediated DRP1 Cleavage

In addition to reversible PTMs, DRP1 is also subject to irreversible inactivation via proteolytic cleavage by calpain, a calcium-activated cysteine protease that is upregulated in AD [36]. Calpain cleaves DLP1 within its middle domain, producing non-functional N-terminal fragments of approximately 65 kDa and 50 kDa. This domain is essential for DRP1 oligomerization and GTP hydrolysis, and its disruption impairs DRP1's ability to mediate mitochondrial fission. The cleavage is induced by AD-related pathology, including glutamate-induced excitotoxicity, soluble Aβ oligomers, and pTau, all of which elevate intracellular calcium and activate calpain. The accumulation of cleaved DRP1 fragments corresponds with a depletion of full-length, functional DLP1 and leads to aberrant mitochondrial morphology, impaired distribution, and fragmentation [36]. These cleavage products were detected in the neurons of CRND8 APP transgenic mice as well as in postmortem human AD brains, where they correlate with increased levels of calpain activity markers such as spectrin breakdown products [36]. Pharmacological inhibition of calpain using calpeptin, a selective calpain inhibitor, effectively prevented DLP1 cleavage in both in vitro and in vivo models, confirming the specificity and pathological relevance of this mechanism.

Unlike reversible PTMs that fine-tune DLP1 activity, calpain-mediated proteolysis represents a terminal, irreversible event that eliminates DRP1 activity. This loss contributes to progressive mitochondrial dysfunction, synaptic failure, and neurodegeneration in advanced stages of AD [36]. A comprehensive summary of PTMs affecting DRP1 is provided in Table 1.

MITOCHONDRIAL FISSION INHIBITION IN AD: ROLE OF MITOCHONDRIAL DIVISION INHIBITOR 1

While targeting PTMs of DRP1 presents one therapeutic avenue in AD, direct pharmacological suppression of excessive mitochondrial fission has gained attention as an alternative approach. Mitochondrial Division Inhibitor 1 (Mdivi1), a selective, cell-permeable mitochondrial fission inhibitor, has been investigated for its ability to counteract mitochondrial and synaptic deficits induced by Aβ. A recent study found Mdivi1 to counteract several pathological features of Aβ42 toxicity in N2a neuroblastoma cells [13]. Treatment with Mdivi-1 not only suppressed the upregulation of fission genes (*Drp1 and Fis1*) but also enhanced the expression of mitochondrial fusion (*Mfn1, Mfn2, Opa1*) and biogenesis genes (*Pgc1α, Nrf1, Tfam*). Functional assays further demonstrated that Mdivi1 attenuated oxidative stress, improved mitochondrial ATP production and cytochrome

Table 1. DRP1 Post-Translational Modifications in AD: Findings from Selected Literature.

Reference	Study Focus	DRP1 PTM(s)	Functional Outcome	Relevance to AD
[27]	Blocking S579	Phosphorylation at S579	Blocking S579 prevents fission, synapse loss, and apoptosis	Cdk5-mediated S579 phosphorylation is neurotoxic in AD
[28]	Aβ-induced DRP1 activation via Akt	Phosphorylation at S616	Mitochondrial fission, ROS ↑, ATP ↓, autophagy↓, apoptosis ↑	Aβ drives DRP1 activation via S616 →mitochondrial damage
[29]	Acetaldehyde induced DRP1 activation	Phosphorylation at S616	Fission, mitochondrial dysfunction, neuronal death	Highlights alcohol metabolite's role in neurotoxicity via DRP1 S616
[31]	Role of c-Abl in oxidative stress	Phosphorylation at Y266, Y368, Y449	↑ DRP1 activity → fission ↑, apoptosis ↑	Introduces tyrosine phosphorylation as a novel mechanism of DRP1 activation in stress
[32]	How Aβ enhances DRP1 activity via O-GlcNAcylation	O-GlcNAcylation (T585, T586)	↑ Mitochondrial fission and dysfunction	Links Aβ to mitochondrial dysfunction via DRP1 modification
[33]	Discovery of ISGylation as akey DRP1 regulator	ISGylation(K532), Ubiquitylation, Phosphorylation	DRP1stabilization and functional fission vs. degradation	ISGylation loss in AD leads to mitochondrial fusion, decreased DRP1 stability
[34]	Role of miR132/212 in regulating NO/SNO signaling	S-nitrosylation (C644)	SNO-DRP1promotes mitochondrial fragmentation and cell death	Reduced miR132/212 in AD enhances SNODRP1 and tau pathology
[36]	Proteolytic regulation of DRP1 by calpain	Calpain-mediated cleavage	Loss of fulllength DRP1, impaired fission	Calpain activity and DRP1 fragments are elevated in AD brains

Note: Only original research articles with a direct focus on PTMs of DRP1 were included. Review articles and studies lacking direct analysis of DRP1 PTMs were excluded.

oxidase activity, and preserved overall cell viability in the presence of Aβ. Interestingly, the protective effects of Mdivi1 were more pronounced when administered prior to Aβ exposure, suggesting that it may be particularly effective in preventing, rather than reversing, mitochondrial damage. However, in both pre- and post-treatment conditions Mdivi1 appeared to reduce intracellular Aβ42 levels, potentially indicating a mechanism where improved mitochondrial dynamics can attenuate Aβ pathology itself.

DISCUSSION

This review highlights the central role of PTMs of DRP1 in mediating mitochondrial dysfunction and neurodegeneration in AD. Among these, phosphorylation is the most well-characterized PTM, with numerous studies demonstrating how AD-associated stressors, including Aβ, oxidative stress, and calcium dysregulation, trigger kinase pathways that modify DRP1 function (Table 1). Specifically, the combined effects of hyperphosphorylation at S616 and dephosphorylation at S637 promote DRP1 recruitment to the OMM, thereby enhancing mitochondrial fission and precipitating neuronal injury [9,28,30].

Beyond phosphorylation, other PTMs to DRP1 have emerged as critical modulators in AD pathogenesis (Table 1). O-GlcNAcylation links metabolic dysfunction, particularly impaired glucose utilization, to aberrant mitochondrial fission by enhancing DRP1 activity under amyloidogenic conditions [37]. Similarly, S-nitrosylation, driven by redox imbalance, amplifies DRP1 activity through NO-mediated cysteine modification, however, findings are conflicting as another study found no rise in DRP1 activity or assembly and no AD-specific increase [34,35]. In contrast, ISGylation acts as a protective PTM that stabilizes DRP1 by preventing its ubiquitylation and proteasomal degradation [33]. The observed reduction of ISGylation in AD suggests a loss of this regulatory safeguard, contributing to impaired mitochondrial turnover and quality control. Moreover, calpain-mediated cleavage represents an irreversible and terminal modification of DRP1. This proteolytic inactivation, induced by calcium overload and excitotoxicity, leads to aberrant mitochondrial distribution and progressive synaptic dysfunction. Unlike reversible PTMs that modulate DRP1 activity dynamically, calpain-mediated cleavage likely represents a late-stage pathological mechanism in AD, contributing to irreversible mitochondrial damage and neuronal loss. In addition to PTMs, DRP1 directly interacts with AD-associated proteins, including Aβ and pTau [19,20]. These interactions disrupt mitochondrial morphology, mitochondrial bioenergetics, and interfere with mitophagy signaling [11,12]. Excessive DRP1 activation leads to fragmented mitochondria that accumulate due to impaired clearance by PINK1/Parkin-dependent pathways [11]. This failure of mitochondrial quality control further exacerbates oxidative stress and synaptic degeneration. Notably, reduced DRP1 expression has been shown to restore mitochondrial dynamics and improve synaptic outcomes in APP transgenic mouse models [21,22]. These protective effects extend to reducing soluble Aβ levels, suggesting upstream regulatory effects of DRP1 modulation on amyloid metabolism. Pharmacological inhibition of DRP1 using Mdivi1 also shows therapeutic promise. Mdivi1 not only reverses mitochondrial fragmentation but also improves ATP production, and reduces ROS generation and Aβ levels [13].

Together, these findings highlight DRP1 as a dynamic and stress-sensitive signaling hub, whose function is modulated through multiple PTMs in response to diverse pathological cues. The convergence of upstream signals, including Aβ accumulation, oxidative stress, and calcium dysregulation on DRP1 suggests its integrative role in mitochondrial stress response and neurodegeneration. From a therapeutic perspective, DRP1 represents a promising target for disease modification. Interventions aimed at suppressing pathogenic modification (e.g., S616 phosphorylation or O-GlcNAcylation) or enhancing protective ones (e.g., ISGylation) hold potential for restoring mitochondrial homeostasis in AD.

However, several limitations should be noted. Much of the current evidence stems from in vitro experiments or transgenic mouse models, with limited validation in human AD postmortem brain tissue. The mechanistic roles of ISGylation, in particular, have not yet been directly linked to neurodegeneration or cognitive decline in vivo. Further research should prioritize integrative studies in physiologically relevant models, including human-derived neurons and advanced organoid systems, to fully elucidate the translational relevance of DRP1 PTMs in AD.

CONCLUSION

PTMs of DRP1 represent a critical regulatory axis linking mitochondrial dysfunction to the molecular pathology of AD. This review highlights how various PTMs, including phosphorylation, O-GlcNAcylation, ISGylation, S-nitrosylation, and proteolytic cleavage, modulate DRP1's activity, stability, and subcellular localization in response to AD-associated stressors such as Aβ, oxidative damage, and calcium dysregulation. These modifications can act synergistically or antagonistically, leading to either hyperactivation of mitochondrial fission or destabilization of DRP1, both of which contribute to energy failure, synaptic loss, and neuronal degeneration. While phosphorylation and O-GlcNAcylation generally enhance DRP1's pathological fission activity, ISGylation functions as a stabilizing mechanism that maintains mitochondrial quality control. Conversely, S-nitrosylation and calpain-mediated cleavage represent pathological modifications induced by redox imbalance and calcium stress, respectively. In addition to PTM-mediated mechanisms, DRP1 also contributes to disease progression through its aberrant interactions with Aβ and pTau, which impair mitophagy and exacerbate mitochondrial fragmentation. Notably, experimental models show that partial DRP1 reduction or pharmacological inhibition with Mdivi1 can rescue mitochondrial and synaptic defects, improve bioenergetics, and reduce Aβ accumulation. Together, these findings highlight the multifactorial role of DRP1 in AD pathogenesis and support its targeting as a promising therapeutic approach to restore mitochondrial homeostasis and attenuate neurodegeneration in AD. However, further in vivo validation and translational research are essential to confirm the efficacy of these targets and to explore their clinical application for disease intervention.

AUTHOR CONTRIBUTIONS

JL and SL contributed expert input. SL finalized the manuscript, and SL, SH, and JL participated in the drafting and literature review. All authors approved the final manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

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