Review

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An exquisite symphony: protein post-translational modifications govern mitochondrial fate

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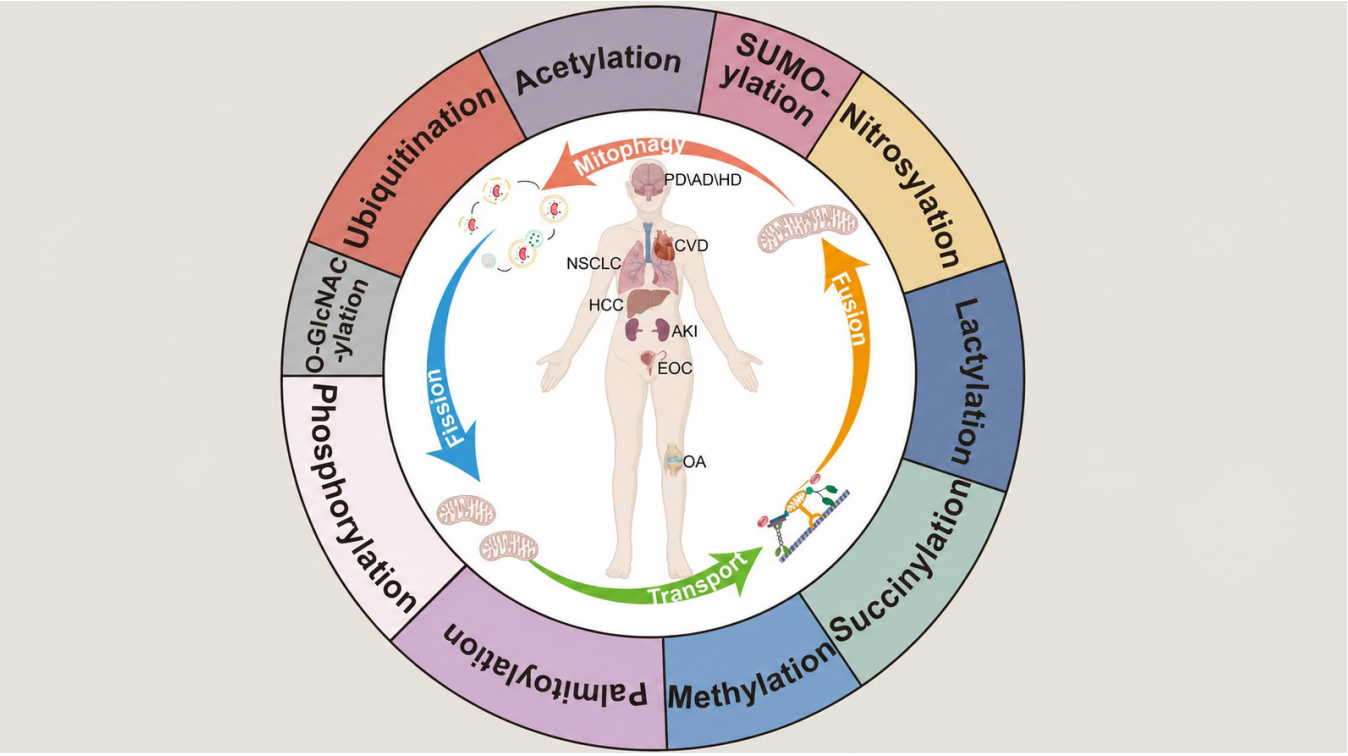
Graphical abstract



Key Points

- Ten post-translational modifications converge on core mitochondrial dynamics proteins.
- Post-translational modifications target functional domains with site-specific, context-dependent outcomes.
- Dysregulated post-translational modification site serve as dual-value candidates for biomarkers and therapeutic targets.
- Post-translational modification crosstalk and emerging tools open new frontiers for dissecting mitochondrial fate.

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An exquisite symphony: protein post-translational modifications govern mitochondrial fate

Haolin Ding[1,#], Taoxia E[1,#], Jingcai He[1,#], Yi Wu[2,#], Xinlin Zheng[1], Liting Duan[3], Xingguo Liu[1,2,4], Linpeng Li[1]

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ABSTRACT

Mitochondria are central hubs of metabolic activities in eukaryotic cells and play pivotal roles in various physiological and pathological processes. To accommodate fluctuating metabolic demands and respond to intracellular and extracellular stress, mitochondria undergo highly coordinated fission, fusion, mitophagy, and transport events mediated by dynamics-related proteins. Disrupting this delicate balance impairs mitochondrial bioenergetics and quality control, driving the onset and progression of numerous diseases, including neurodegeneration, heart failure, and cancer. Protein post-translational modifications (PTMs) constitute a critical regulatory layer, conferring remarkable functional diversity upon mitochondrial dynamics proteins beyond their genetic regulation. While extensive studies have characterized canonical PTMs such as phosphorylation and ubiquitination, the intricate roles of a broader spectrum of modifications - particularly those considered "atypical" - in fine-tuning mitochondrial behavior remain underexplored. In this review, we systematically summarize ten key PTMs, including lactylation, succinylation, SUMOylation, and S-nitrosylation, acting on core regulators such as dynamin-related protein 1(DRP1), optic atrophy 1 (OPA1), Parkin, and mitochondrial Rho GTPase 1 (MIRO1). We emphasize how these modifications integrate metabolic cues with mitochondrial dynamics and highlight their potential as diagnostic biomarkers and therapeutic targets. Furthermore, we discuss the sophisticated crosstalk between different PTM types and review emerging protein modification omics and genetic code expansion (GCE) tools designed to dissect the spatiotemporal dynamics of these modifications. By synthesizing current knowledge on these regulatory mechanisms, we aim to provide a comprehensive resource for understanding mitochondrial plasticity in health and disease.

Keywords: Mitochondrial, mitochondrial dynamics, mitochondrial dynamics protein, post-translational modification, physiology, pathology

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INTRODUCTION

Mitochondria are essential organelles in eukaryotic cells. Beyond supplying adenosine triphosphate (ATP) to sustain cell survival and proliferation, they support cell-specific demands through diverse metabolic pathways, thereby participating in various physiological and pathological processes. Although research on mitochondria spans over 150 years, it mirrors the evolution of scientific technology. As early as 1857, Swiss embryologist and histologist Rudolph Albert Von Kölliker used an optical microscope to observe a granular compartment with a membrane structure in the cytoplasm in muscle cells, and Retzius called them "Sarcosomes"[1-4]. In 1897, German biologist Carl Benda found abundant granules in muscle cells with either linear or granular morphology, introducing the term "mitochondrion" (derived from the Greek words 'mitos' and 'chondros', meaning thread and grain) [5]. By 1914, advances in microscopy allowed Lewis and colleagues to demonstrate that mitochondrial morphology was not static. They documented that mitochondria in cells could undergo morphological changes by fission or fusion, giving rise to the concept of mitochondrial dynamics[6,7]. Later in 1931, the dynamic changes of mitochondrial fission and fusion were confirmed during liver development[7-10], solidifying the notion of mitochondria as inherently dynamic organelles [Figure 1].

Because of the seminal discovery of mitochondria and its potential functions, numerous studies on this organelle were subsequently conducted. For example, the β-oxidation, tricarboxylic acid cycle, and oxidative phosphorylation (OXPHOS) occurring inside mitochondria were elucidated in the 1940s and 1950s, indicating the metabolic function of mitochondria[11,12]. The ultrastructural characteristics of mitochondria as double-membraned organelles with inner cristae were discovered by high-resolution electron microscopy in 1953, confirming their identity as a distinct organelle[13,14]. The genetic material, including DNA/RNA and their polymerases in mitochondria, was found in the 1960s, demonstrating that mitochondria are semi-autonomous organelles[15-17]. The four major complexes of the respiratory chain and the proposal of the chemiosmotic theory were established in the 1960s and 1970s, deepening the understanding of bioenergetics[18,19]. Mitochondrial Rho GTPase (Miro), a member of the Rho GTPase family, and Milton/Trafficking kinesin-binding protein (TRAK) proteins were identified as the core adapter complex linking kinesin/dynein to mitochondria, elucidating the mechanism of mitochondrial transport between the 1970s and 2000s[20-28]. The mitochondrial cytochrome C-mediated apoptosis pathway was uncovered in 1996[29], indicating the important role of mitochondria in apoptosis[30-34]. Mitochondrial fission/fusion proteins including dynamin-related protein 1(DRP1)[35], mitochondrial fission protein 1 (FIS1), mitochondrial dynamics proteins of 49 and 51 KDa (MID49/51), mitochondrial fission factor (MFF), optic atrophy 1 (OPA1), mitofusins (MFN1/2), and their regulatory mechanisms on mitochondrial dynamics were identified in 1990s and 2000s, demonstrating the regulatory role of mitochondrial dynamics in cellular processes[36-40]. Further, the role of phosphatase and tensin homolog (PTEN)-induced putative kinase 1 (PINK1) and E3 ubiquitin-protein ligase parkin (Parkin) mediated mitophagy as well as the transmembrane receptor proteins B-cell lymphoma 2 (BCL2)/adenovirus E1B 19 kDa protein-interacting protein 3 (BNIP3) and FUN14 domain-containing protein 1 (FUNDC1) mediated Parkin-independent mitophagy pathways were uncovered in 2005-2010, highlighting the selective degradation of mitochondria in various diseases[41-49]. Currently, research on mitochondria mainly focuses on mitochondrial signaling, mitochondrial quality control, and mitochondrial dynamics in regulating physiological and pathological processes[50-54]. For example, our team demonstrated that superoxide signaling of mitochondrial superoxide bursts during early reprogramming leads to reduced DNA methylation on the Nanog promoter, thereby enhancing Nanog expression and facilitating the reprogramming of somatic cells into induced pluripotent stem cells (iPSCs)[55-57]. Mitochondrial quality control and mitochondrial dynamics were also important for the generation of iPSCs and maintenance of pluripotency in embryonic stem cells (ESCs)[58-60]. Moreover, mitochondrial signaling, quality control, and dynamics have been implicated in many physiological and pathological processes, including early embryonic development, neural activation, aging, cancer development, and immune regulation[61-67]. Among these processes, the regulation of mitochondrial dynamics - encompassing mitochondrial fission/fusion, transport, and mitophagy - plays a central role, linking these mitochondrial processes to cell fate decisions.

Protein post-translational modifications (PTMs) refer to the covalent attachment of functional groups - such as phosphate, ubiquitin, and methyl groups - to proteins, regulating protein activity or stability[68-72]. The activity and function of mitochondrial dynamics-related proteins can also be regulated by different PTMs. Accumulating evidence links specific PTMs on these proteins to disease. For example, phosphorylation, ubiquitination, and acetylation of DRP1 dynamically regulate mitochondrial fission and fusion, impacting neuronal function, metabolic reprogramming, and disease progression[58,73-75]. However, the therapeutic relevance of PTM-mediated regulation of mitochondrial dynamics has been largely overlooked. To better understand the role of PTMs on mitochondrial dynamics-related proteins, we summarize in detail the effects of ten key PTMs on mitochondrial dynamics-related proteins across various physiological and pathological processes in detail. Furthermore, based on the roles and mechanisms of PTMs on mitochondrial dynamics-related proteins, we propose that they can serve as predictive markers for clinical disease prognosis and treatment. Moreover, we discuss the cross-talk of PTMs and highlight novel tools for studying their regulatory functions in mitochondrial dynamics.

PTMS ON MITOCHONDRIAL DYNAMICS-RELATED PROTEINS

Mitochondrial dynamics refers to the process by which mitochondria maintain their morphology, mass, and functional balance through mitochondrial fission/fusion, transport, and mitophagy[51]. Mitochondrial dynamics are necessary for mitochondrial self-renewal and functional stability, serving as a key self-repair mechanism that governs cell energy metabolism, calcium homeostasis, reactive oxygen species (ROS) regulation and cell fate determination[50]. Mitochondrial dynamics related-proteins include fission proteins (DRP1, MID49, MID51, MFF and FIS1)[35,76-78], fusion proteins (OPA1, MFN1 and MFN2), transport proteins (TRAK1, TRAK2, MIRO1 and MIRO2)[20-23], and mitophagy proteins (PINK1 and Parkin)[41-44] [Table 1]. To date, PTMs have been identified in almost all of these mitochondrial dynamics-related proteins. Moreover, PTMs on these proteins exhibit specificity for specific functional domains [Figure 2]. For instance, PTMs on DRP1 predominantly occur in the variable domain (VD) - a region critical for membrane lipid binding, which suggests PTMs may regulate DRP1-membrane interactions[79]. PTMs on FIS1 primarily localize to its N-terminal arm, a domain negatively correlated with DRP1 binding, indicating potential modulation of FIS1-DRP1 complex formation[80]. PTMs on MFF, particularly phosphorylation, are predominantly clustered within its central intrinsically disordered region (IDR), implying a role in modulating MFF-DRP1 interactions[76,81]. PTMs on OPA1 localize to its BSE (bundle signal-

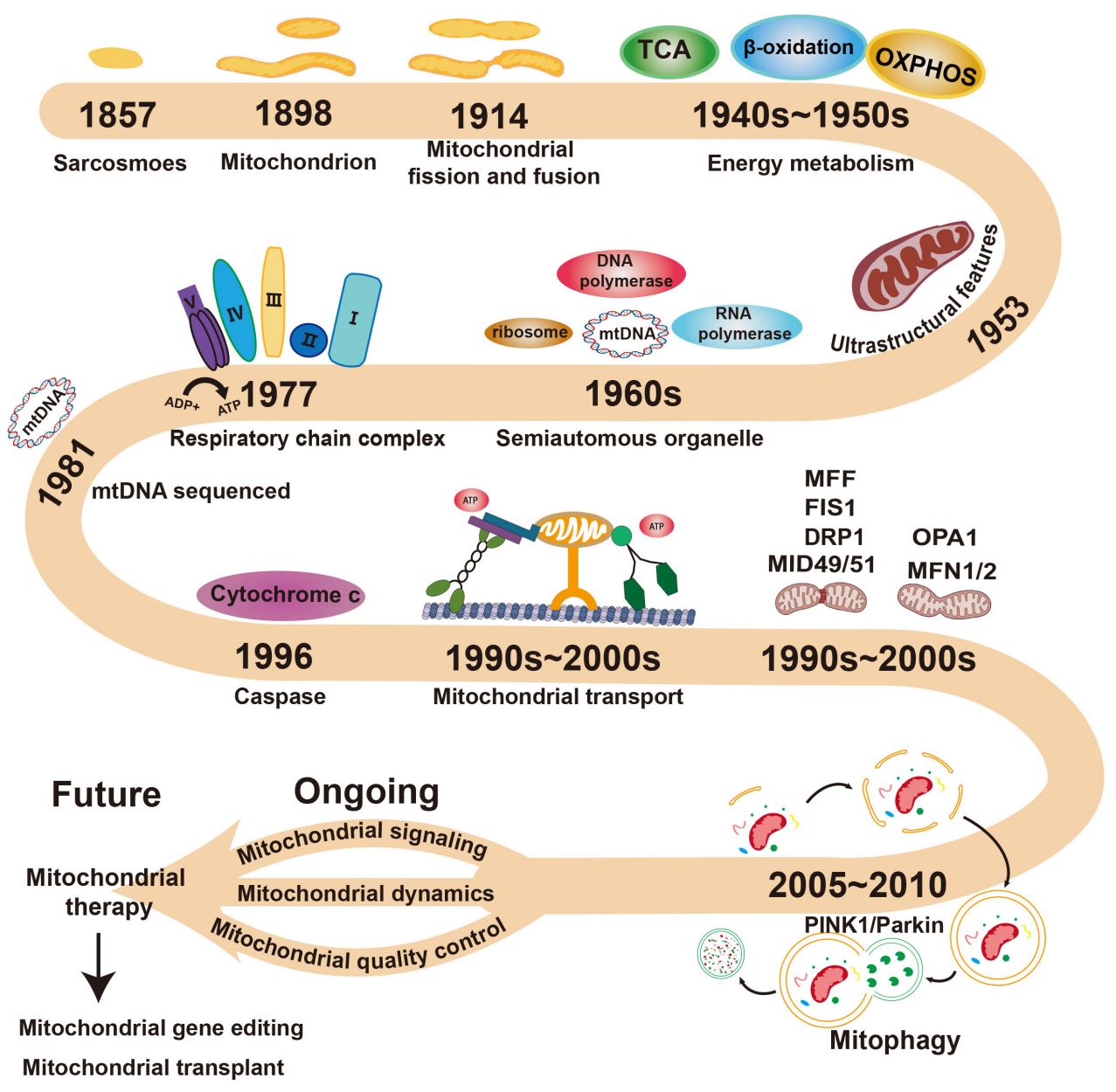

Figure 1. The research history of mitochondria.
Here, we outline key milestones in mitochondrial research history: the initial discovery and naming of sarcosomes; the observation of morphology and coining of the term "mitochondria"; the proposal of mitochondrial dynamics; elucidation of energy metabolism and the respiratory chain; characterization of mitochondrial ultrastructure, DNA, and semi-autonomy; identification of the cytochrome c apoptosis pathway, transport, and mitophagy; and the discovery of dynamics-related proteins, culminating in the analysis of fission/fusion mechanisms and novel mitochondrial functions. The data source for Figure 1 is generated based on references[1,5,6,8,11,13-23,29,35]. The figure was redrawn and designed by the authors based on existing reference images. OXPHOS: Oxidative phosphorylation; MFF: mitochondrial fission factor; FIS1: mitochondrial fission 1 protein; DRP1: dynamin-related protein 1; MID49/51: mitochondrial dynamics proteins of 49 and 51 KDa; MFN1/2: mitofusins 1/2; OPA1: optic atrophy 1; TCA: tricarboxylic acid cycle.

ing element) domain, which is spatially adjacent to the GTPase domain, suggesting that these PTMs may regulate the function of OPA1[82,83]. PTMs on MFN1/2 were concentrated in the GTPase domain, essential for GTP hydrolysis and conformational changes, implying that PTMs may regulate the efficiency of MFN1/2 conformational transitions[84,85]. Phosphorylation of Parkin primarily

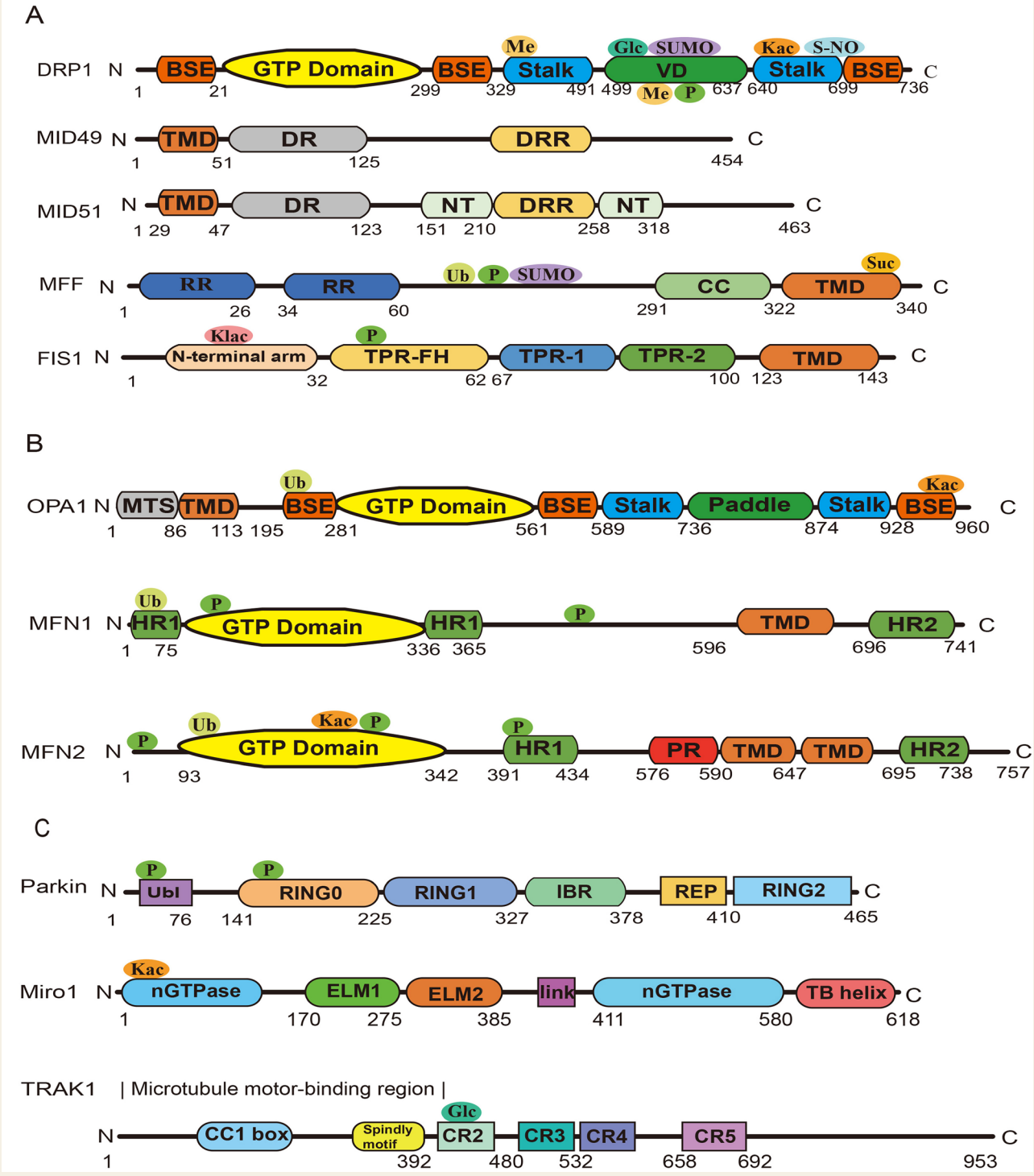

Figure 2. PTMs on mitochondrial dynamics-related proteins.
We mapped all the PTMs on mitochondrial dynamics-related proteins, and annotated their structural locations. The data source for Figure 2 is generated based on references[76,79-87,159]. The figure was redrawn and designed by the authors based on existing reference images. (A) The PTMs on mitochondrial fisson proteins, and annotated their structural locations; (B) The PTMs on mitochondrial fussion proteins, and annotated their structural locations; (C) The PTMs on mitochondrial mitophagy and transoprt proteins, and annotated their structural locations. Ub: Ubiquitination; SUMO: small ubiquitin-like modifier; Kac: lysine acetylation; P: Phosphorylation; Met: Methylation; Glc: GlcNAc; Suc: Succinylation; Klac: lysine lactylation; PTMs: post-translational modifications; DRP1: dynamin-related protein 1; MID49/51: mitochondrial dynamics proteins of 49 and 51 KDa; MFF: mitochondrial fission factor; FIS1: mitochondrial fission 1 protein; OPA1: optic atrophy 1; MFN1: mitofusins 1; Miro1: mitochondrial Rho GTPase 1; TRAK1: trafficking kinesin-binding protein 1.

Table 1. Mitochondrial dynamics proteins and their function

Category	Protein	Localization	Core function & Notes
Mitochondrial fission	DRP1	Translocates from the cytoplasm to the OMM upon activation	Core mitochondrial fission executor[35]
	FIS1	OMM	Recruits DRP1 to mitochondria[78]
	MFF	OMM	Recruit DRP1 to fission sites[76]
	MID49/51	OMM	Recruit DRP1 to fission sites[163]
Mitochondrial fusion	MFN1	OMM	Mediate OMM fusion[84]
	MFN2	OMM	Cooperate with MFN1 for OMM fusion[85]
	OPA1	IMM	Mediate IMM fusion; regulate cristae morphology and respiratory complex assembly[164]
Mitochondrial transport	MIRO1/2	OMM	Links mitochondria to TRAK proteins[21]
	TRAK1/2	OMM/cytoplasm	Connect MIRO to kinesin (anterograde) and dynein (retrograde)[23]
Mitophagy Pathways Ubiquitin-Dependent (PINK1/Parkin)	PINK1	Stabilized-on-damaged OMM	Accumulate upon loss of membrane potential[155]
	Parkin (PRKN)	Translocate from cytoplasm to OMM upon activation	Ubiquitinates OMM proteins[44]

DRP1: Dynamin-related protein 1; FIS1: mitochondrial fission 1 protein; MFN1: mitofusins 1; MFF: mitochondrial fission factor; MID49/51: mitochondrial dynamics proteins of 49 and 51 KDa; OPA1: optic atrophy 1; OMM: outer mitochondrial membrane; IMM: inner mitochondrial membrane; PINK1: PTEN-induced putative kinase 1; PRKN: parkin RBR E3 ubiquitin protein ligase; MIRO1/2: mitochondrial Rho GTPase 1/2; TRAK1/2: trafficking kinesin-binding protein 1/2.

occurs at its N-terminal region, which constitutes the active site for its ubiquitin ligase activity[86]. This suggests that phosphorylation modulates Parkin's protein ubiquitination function. Acetylation of Miro1 takes place within its N-terminal GTPase domain, indicating that this modification regulates the protein's catalytic activity[87]. These findings demonstrate that PTMs in mitochondrial dynamics-related proteins preferentially target functional domains, underscoring their crucial roles in modulating protein function. This domain-specific PTM pattern warrants focused investigation. Below, we discuss the roles of ten key PTMs on mitochondrial dynamics-related proteins in detail [Table 2].

PTMS DRIVE MITOCHONDRIAL DYNAMICS

Protein phosphorylation

Protein phosphorylation constitutes an enzyme-catalyzed process in which the γ-phosphate of ATP is transferred to amino acid side chains of proteins. This reversible modification is mediated by protein kinases (PKs) for phosphorylation and reversed by protein phosphatases (PPases) for dephosphorylation. As a critical regulatory mechanism for protein activity and function, phosphorylation occurs predominantly on serine (Ser), threonine (Thr), and tyrosine (Tyr) residues[88].

Mitochondrial fusion proteins

During heart failure, beta II protein kinase C (βIIPKC) translocates to the mitochondrial outer membrane and phosphorylates MFN1 at Ser86 within its GTPase domain. Phosphorylation within this domain inhibits GTPase activity and exacerbates mitochondrial fragmentation, leading to cell cytotoxicity. Targeted disruption of the MFN1-βIIPKC interaction using selective antagonists attenuates mitochondrial fragmentation and improves cardiac function[89]. In neurons, extracellular signal-regulated protein kinases (ERK) phosphorylate MFN1 at Thr562, inducing mitochondrial fragmentation via MEK/ERK pathway activation and promoting neuronal apoptosis. In immortalized mouse embryonic fibroblast cells (MEFs) under endoplasmic reticulum (ER) stress, the cellular Abelson gene product(c-Abl) translocates to mitochondria and phosphorylates MFN2 at Tyr269, leading to mitochondrial fragmentation and accelerated neuronal death. c-Abl inhibition reduces fragmentation and delays Amyotrophic Lateral Sclerosis (ALS) progression, suggesting therapeutic potential[90]. In MEFs and human embryonic kidney 293 (HEK293) cells, MFN2 was phosphorylated at Thr111, Ser378 and Ser442 sites by PINK1, leading to mitochondrial fragmentation[91].

Mitochondrial fission proteins

In murine tissues, phosphorylation of DRP1 at Ser600 and Ser579 is mutually correlated and occurs simultaneously upon activation of cyclic adenosine monophosphate (cAMP)-dependent protein kinase A (PKA), leading to mitochondrial fission. Notably,

Table 2. PTMs of mitochondrial dynamics proteins and their sites

Proteins	PTMs	Sites	Regulatory	Effect on mitochondria
OPA1	Ubiquitination	Lys228	TRIM22	Inhibit mitochondrial fusion
OPA1	Acetylation	Lys926/Lys931	Pathological cardiac stress[165]	Inhibit mitochondrial fusion
MFN1	Phosphorylation	Ser86/Thr562	βIIPKC[89]/E$^{RK[16}$6]	Inhibit mitochondrial fusion
MFN1	Ubiquitination	Lys48	MARCH5[116]	Inhibit mitochondrial fusion
MFN2	Phosphorylation	Ser442/Tyr269	PINK1[91]/c-Abl[90]	Inhibit mitochondrial fusion
MFN2	Ubiquitination	Lys129	MARCH5[120]	Inhibit mitochondrial fusion
MFN2	Acetylation	Lys243	Lipid overload[132]	Mitochondrial dysfunction
DRP1	Phosphorylation	Ser616	PINK1[93]/CDK5[94]	Promote mitochondrial fission
DRP1	Phosphorylation	Ser637	TBK1[95]	Inhibit mitochondrial fission
DRP1	Acetylation	Lys642	Lipid overload[133]	Promote mitochondrial fission
DRP1	Methylation	Arg403/Arg634	CARM1[167]	Promote mitochondrial fission
DRP1	O-GlcNAcylation	Thr585/Thr586	Diabetic patients[139]	Promote mitochondrial fission
DRP1	S-palmitoylation	Cys	ZDHHC13[142]	Normal mitochondrial fission-fusion dynamics
DRP1	S-Nitrosylation	N/A	Amyloid-β[148]	Promote mitochondrial fission
DRP1	SUMOylation	Multiple sites	IRI[128]	Promote mitochondrial fission
DRP1	SUMOylation	N/A	SENP5L[129]	Inhibit mitochondrial fission
DRP1	Inhibition of SUMOylation	N/A	SENP5S[129]	Promote mitochondrial fission
FIS1	Phosphorylation	Tyr38/Thr34	Met[96]/DNA-PKcs[97]	Promote mitochondrial fission
FIS1	Lactylation	Lys20	Nalac[144]	Promote mitochondrial fission
MFF	Phosphorylation	Ser131	AKT[99]	Promote mitochondrial fission
MFF	Succinylation	Lys302	CPT1A[146]	Promote mitochondrial fission
MFF	Ubiquitination	N/A	PARKIN[121]	Promote mitophagy
MFF	SUMOylation	Lys151	SUMO1/SUMO2/3[168]	Promote mitochondrial fission
MID49	Ubiquitination	N/A	MARCH5[169]	Inhibit mitochondrial fission
PARKIN	phosphorylation	N/A	PINK[109]	Critical for its translocation to mitochondria
PINK1	phosphorylation	Ser228/Ser402	Autophosphorylation[103]	Promote mitophagy
MAP1LC3	Phosphorylation	Serine 12	PKA[106]	Inhibit PE binding
MIRO1/2	ubiquitination	N/A	PARKIN[125]	Degradation of hmiro1/2
MIRO1	deacetylation	lysine 105	HDAC6[134]	Inhibit mitochondrial transport
MID51	ubiquitination	N/A	N/A	Promote Mid51 degradation[126]
TRAK1	O-GlcNAcylation	N/A	N/A	Reduce mitochondrial motility[170]
FIS1	deSUMOylation	N/A	SENP1	Maintained mitochondrial integrity[130]

PTMs: Post-translational modifications; OPA1: optic atrophy 1; MFN1: mitofusins 1; DRP1: dynamin-related protein 1; FIS1: mitochondrial fission 1 protein; MFF: mitochondrial fission factor; MID49: mitochondrial dynamics proteins of 49 KDa; PINK1: PTEN-induced putative kinase 1; MAP1LC3: microtubule-associated protein 1 light chain 3; PARKIN: parkin RBR E3 ubiquitin protein ligase; MIRO1: mitochondrial Rho GTPase 1; TRAK1: trafficking kinesin protein 1; TRIM22: tripartite motif-containing protein 22; MARCH5: membrane-associated RING-CH; ERK: extracellular signal-regulated protein kinases; TBK1: Tank-binding kinase 1; CDK5: cyclin-dependent kinase 5; CARM1: coactivator-associated arginine methyltransferase 1; IRI: ischemia-reperfusion injury; AKT: protein kinase B; CPT1A: carnitine palmitoyltransferase 1A; SUMO1: small ubiquitin-related modifier 1; PKA: protein kinase A; SENP1: sentrin-specific protease 1; PE: phosphati-dylethanolamine; N/A: Not applicable.

Ser579 phosphorylation serves as a downstream event of Ser600 phosphorylation following PKA activation. Even in the absence of external stimuli, Ser600 phosphorylation on DRP1 alone was sufficient to elevate phosphorylation levels of Ser579 on DRP1, protecting Ser579 from dephosphorylation. However, complete activation of DRP1-mediated mitochondrial fission activity requires simultaneous phosphorylation at both residues[92]. Impeding Ser579 phosphorylation on DRP1 redirects the outcome of Ser600 phosphorylation of DRP1 toward mitochondrial tubulation rather than fission. In Parkinson's disease (PD) pathogenesis, PINK1-dependent Ser616 phosphorylation of DRP1 facilitates mitophagy by recruiting Parkin to damaged mitochondria, serving as both a potential PD biomarker and therapeutic target. PINK1 knockout models exhibit significantly reduced Ser616 phosphorylation levels[93]. Chronic ethanol exposure in male C57BL/6 mice induces cyclin-dependent kinase 5 (CDK5)-mediated Ser616 phosphorylation on DRP1 in hippocampal neurons, promoting mitochondrial fragmentation, irreversible synaptic damage, and cognitive impairment. Pharmacological modulation of CDK5 activity may mitigate ethanol-induced neurotoxicity[94]. In chondrocytes, Tank-binding kinase 1 (TBK1) overexpression phosphorylates Ser637 on DRP1, inducing mitochondrial elongation, mitophagy, and apoptosis resistance, thereby ameliorating osteoarthritis progression. The TBK1/DRP1 axis represents a promising therapeutic target for osteoarthritis[95]. In hepatocellular carcinoma (HCC) cells, receptor tyrosine kinase Met directly phosphorylated FIS1 at Tyr38, which facilitates DRP1 recruitment to mitochondria, thereby promoting tumor growth and chemoresistance. Pharmacological inhibition of Met effectively suppresses these malignant phenotypes, suggesting this axis as a therapeutic target for metastatic HCC[96]. In renal tubular epithelial cells, DNA-dependent protein kinase catalytic subunit (DNA-PKcs) interacts with FIS1 and phosphorylates it at Thr34, enhancing FIS1-DRP1 binding and inducing pathological mitochondrial fragmentation, thereby contributing to acute kidney injury (AKI). DNA-PKcs inhibitors show protective potential against AKI progression[97]. In ovarian cancer cells (OCCs), knockdown of CRL4CUL4A/DDB1 (E3 ubiquitin ligase) significantly enhances AMP-activated protein kinase (AMPK) activity and induces Ser172/Ser146 phosphorylation of MFF, thereby recruiting DRP1 to mitochondria. Phosphorylation of MFF at Ser172/Ser146 leads to mitochondrial fragmentation and enhanced autophagy in cisplatin-resistant OCCs, indicating the therapeutic significance of CRL4CUL4A/DDB1 knockdown in ovarian cancer treatment[98]. In mice, fasting combined with sensory stimulation (visual/olfactory exposure to inaccessible food or light stimulation of proopiomelanocortin neurons) activates protein kinase B (AKT), which subsequently phosphorylates MFF at Ser131, rapidly inducing hepatic mitochondrial fragmentation. Inhibition of MFF phosphorylation abolishes AKT-driven mitochondrial fragmentation in the liver[99]. In human renal tubular epithelial cells (HK-2), regulator of calcineurin 1 (RCAN1) binds to c-Jun N-terminal kinase (JNK) to increase MFF phosphorylation, promoting DRP1 mitochondrial translocation. MFF phosphorylation induces mitochondrial fragmentation, resulting in mitochondrial dysfunction and apoptosis, and accelerates progression of AKI. RCAN1 deletion suppresses apoptosis and alleviates renal damage[100]. During mammalian cell mitosis (excluding interphase), protein kinase D (PKD) specifically phosphorylates MFF at Ser155, Ser172, and Ser275, driving mitochondrial fission to promote cell survival. PKD/MFF-dependent mitochondrial fission is essential for maintaining genomic integrity during cell division[101]. In human osteosarcoma cells (U2OS) and MEFs, AMPK phosphorylates MFF at Ser155/Ser172, recruiting DRP1 to induce fragmentation. AMPK-dependent MFF phosphorylation signals to the nucleus and initiates mitochondrial biogenesis to replace damaged mitochondria[102].

Beyond mitochondrial fission and fusion, protein phosphorylation also plays pivotal roles in mitophagy. For instance, phosphorylation of PINK1 is essential for recruiting Parkin during mitophagy[103,104]. Furthermore, phosphorylation of Parkin itself is critical for its translocation to mitochondria[105]. In autophagy, phosphorylation of microtubule-associated protein 1 light chain 3A (MAP1LC3A) at serine 12 (S12) inhibits its binding to phosphatidylethanolamine (PE), thereby suppressing autophagy[106]. Phosphorylation of MAP1LC3C at serine 93 (S93) facilitates the formation of a stable lipidated LC3C/GABARAP-L2 coat on early-stage autophagosomes and contributes to maintenance of unidirectional autophagosome-lysosome flux[107]. Concurrently, Parkin is recruited to mitochondria, promoting mitochondrial autophagy and apoptosis[91]. Paradoxically, PINK1-dependent Ser442 phosphorylation in macrophages facilitates Parkin-mediated ubiquitination of mitochondrial outer membrane (MOM) proteins, initiating mitophagy. PINK1 deficiency exacerbates mitochondrial damage during renal fibrosis[108,109]. In doxorubicin-stressed U2OS cells, JNK phosphorylates MFN2 at Ser27, promoting mitochondrial fragmentation and apoptosis[110].

In summary, protein phosphorylation regulates mitochondrial dynamics and quality control through three recurring principles: (i) reversibility via paired kinase/phosphatase modules, allowing rapid toggling; (ii) site-level encoding, whereby a single protein (e.g., DRP1 Ser616 *vs.* Ser637) can be switched between opposing functional outputs depending on which residue is modified; and (iii) context dependence, wherein the same phosphorylation site may exert pro-pathological or compensatory effects across cancer, neurodegeneration, and metabolic injury. These features collectively make phosphorylation both a mechanistic link and a pharmacologically accessible node in mitochondrial PTM networks.

Protein ubiquitination

Ubiquitination is a multi-component collaborative process requiring ATP, E1 ubiquitin-activating enzyme, E2 ubiquitin-conjugating enzyme, E3 ubiquitin ligase, and substrates. Initially, the E1 activating enzyme utilizes energy to hydrolyze ATP to activate ubiquitin (Ub), forming a thioester bond between the C-terminal glycine (Gly) of Ub and a cysteine residue in E1. The Ub-E1 complex transfers Ub to E2 via transesterification to generate the Ub-E2 complex. Subsequently, the Ub-E2 complex transfers Ub to substrates through two distinct pathways: (1) E3 directly recognizes the substrates and catalyzes the attachment of Ub's C-terminal Gly to a lysine (Lys) ε-amino group on the target protein; (2) Ub is first transferred to E3 via transesterification, after which E3 specifically recognizes the substrate and links Ub's C-terminal Gly to the Lys residue's amino group. Ubiquitin attaches to substrates in a specific manner, with E3 ubiquitin ligases determining the specificity of target protein recognition[111]. Additionally, ubiquitination modifications can occur at the N-terminus of proteins or on other amino acids (cysteine, serine, threonine)[112]. Most mitochondrial dynamics-related proteins undergo ubiquitination modifications, which play critical roles in regulating mitochondrial morphology and function. For instance, in high glucose-induced HK-2 cells and diabetic mouse models, Wilms tumor 1-associating protein (WTAP) upregulates the expression of tripartite motif-containing protein 22 (TRIM22), and promotes TRIM22-OPA1 interaction, inducing ubiquitination at the Lys228 site of OPA1. Ubiquitination decreases OPA1 stability and triggers mitochondrial fragmentation, dysfunction, apoptosis, and renal injury, thereby accelerating diabetic nephropathy (DN) progression. In HK-2 cells, M1 (Mitochondrial fusion promoter) can reverse mitochondrial dysfunction and apoptosis caused

by TRIM22 overexpression[113]. In the diabetic mouse model, M1 can alleviate kidney injury and improve pathological features, highlighting that targeting the TRIM22-OPA1 pathway may help improve the progression of DN[113]. In carbonyl cyanide m-chlorophenylhydrazone (CCCP)-treated cells, PINK1/Parkin ubiquitinates MFN1 and MFN2, and inhibition of PINK1/Parkin results in defective mitochondrial accumulation, contributing to PD[114]. Mitochondria-localized apolipoprotein A-I binding protein (AIBP) also modulates MFN1/MFN2 ubiquitination via its N-terminal domain through PINK1/Parkin, thereby inducing mitophagy. MFN1 and MFN2 can also be independently ubiquitinated[115]. In MEFs, membrane-associated RING-CH (MARCH5) could ubiquitinate MFN1 at Lys48 to promote mitochondrial fusion. Treatment with antimycin A (AMA) or CGP 37157 (an inhibitor of mitochondrial calcium efflux) further enhances MARCH5-mediated MFN1 ubiquitination, causing excessive mitochondrial fusion and eventual cell death, highlighting a potential therapeutic target[116]. In melanoma, Parkin directly binds and ubiquitinates MFN2. Inhibition of Parkin decreases MFN2 ubiquitination and suppresses melanoma growth/metastasis, offering a potential therapeutic avenue[117]. In post-subarachnoid hemorrhage (SAH) neuronal cells, downregulation of the deubiquitinating enzyme ubiquitin-specific protease 30 (USP30) enhances Parkin-mediated MFN2 ubiquitination, promoting mitophagy and mediating neuroprotective effects[118]. In HK-2 cells, sirtuin 3 [SIRT3, nicotinamide adenine dinucleotide (NAD^+)-dependent histone deacetylase]-mediated MFN2 ubiquitination mitigates mitochondrial damage, reduces fragmentation, and alleviates ischemia reperfusion-induced acute kidney injury (IR-AKI), providing insights for AKI treatment[119]. In neurons, MARCH5 binds and ubiquitinates MFN2 at Lys129, regulating ER-mitochondria tethering to determine mitochondrial fission sites. Then DRP1 is recruited to these sites, facilitating mitochondrial fission and maintaining neuronal functionality[120]. During mitochondrial depolarization in human colorectal human colorectal carcinoma (HCT) 116 cells, Parkin induced MFF ubiquitination at Lys251. CCCP treatment increases MFF ubiquitination, impairing p62 recruitment and clearance of damaged mitochondria[121]. Knockout of MARCH5 suppresses MID49 ubiquitination and proteasomal degradation, causing MID49 accumulation, exacerbated mitochondrial fragmentation, disrupted energy metabolism, and increased cell death[122]. Additionally, Parkin can undergo ubiquitination, which represents a key regulatory mechanism for controlling Parkin protein levels[123,124]. On the other hand, human PINK1 and Parkin coordinately regulate the ubiquitination and degradation of hMIRO1 and hMIRO2. The depletion of hMIRO promotes perinuclear clustering of mitochondria and facilitates mitophagy of damaged mitochondria[125]. In addition, staurosporine (STS) treatment induces the degradation of MIEF1(MID51) via the ubiquitin-proteasome system (UPS), promoting mitophagy[126].

In conclusion, protein ubiquitination regulates mitochondrial dynamics through two features: (i) cascade layering - the E1-E2-E3 architecture delegates substrate choice to the E3 tier, making ubiquitination mechanistically more modular than phosphorylation (kinase/phosphatase pair) and amenable to lineage-specific E3 recruitment; and (ii) bidirectional E3/deubiquitinase (DUB) circuitry, wherein ligases (TRIM22, Parkin, MARCH5) and DUBs (e.g., USP30) impose opposing fluxes on shared substrates, so that the net ubiquitin signal is a balance rather than a binary on/off.

Protein SUMOylation

SUMOylation is a post-translational modification process involving three enzymes: E1 activating enzyme, E2 conjugating enzyme, and E3 ligase. Initially, small ubiquitin-like modifier (SUMO) forms a thioester bond with the E1 activating enzyme (e.g., Aos1/Uba2) and is subsequently transferred to the E2 conjugating enzyme (e.g., Ubc9). With the assistance of E3 ligase, SUMO is conjugated to lysine residues of substrate proteins. This process is dynamically reversible, as SUMO can be removed by SUMO-specific proteases [e.g., sentrin-specific proteases (SENPs)], thereby modulating the SUMOylation status of substrates[127]. For instance, in MEF and 293T cells, treatment with CCCP induces AMPK-mediated phosphorylation of MFF at Ser155 and Ser172, then enhances SUMO1- and SUMO2/3-dependent SUMOylation of MFF at Lys151, accelerating mitochondrial fragmentation and cell apoptosis. AMPK inhibition blocks CCCP-induced MFF SUMOylation and suppresses excessive mitochondrial fission. Thus, targeting SUMOylation represents a viable therapeutic avenue for mitochondrial-related diseases. In hepatocytes from mice with liver ischemia-reperfusion injury (IRI), SUMOylation of DRP1 is markedly increased at multiple sites (K532, K535, K558, K568, K594, K597, K606, K608) within its GTPase domain. SUMOylation on DRP1 promotes mitochondrial fission and impairs energy metabolism, exacerbating hepatocyte apoptosis and liver injury. Augmenter of liver regeneration (ALR) protects against IRI by suppressing DRP1 SUMOylation[128]. In mouse ESCs and mature neurons, the long isoform of SUMO-specific protease 5 (Senp5L) promotes DRP1 deSUMOylation to enhance mitochondrial fusion, while the short isoform (Senp5S) inhibits DRP1 deSUMOylation to drive mitochondrial fission. Balanced expression of Senp5L and Senp5S is essential for neuronal polarization and migration, which is critical for normal cortical development. Mechanistically, Senp5S competitively binds DRP1, blocking Senp5L-mediated deSUMOylation and maintaining DRP1 in a SUMOylated state[129]. Additionally, short-term hypoxia-induced SENP1 translocation to endothelial mitochondria regulates FIS1 deSUMOylation, preserving mitochondrial integrity and ER-mitochondria calcium communication across mitochondrial-associated membranes, subsequently maintaining pulmonary endothelial function and vascular homeostasis[130].

In summary, protein SUMOylation regulates mitochondrial dynamics through two PTM-intrinsic principles: (i) E2 singularity and modification parity - UBC9 serves as the near-unique E2, and SUMO installs predominantly as monomers/short chains, biasing SUMO toward interaction remodeling rather than degradative signaling; (ii) stress-gated reversibility, wherein SENPs and stimulus-coupled E3 recruitment render SUMOylation a rapid, oxidation- and energy-sensitive switch that interfaces closely with phosphorylation and ubiquitination at shared substrates (e.g., DRP1, MFN1/2).

Protein acetylation

Protein acetylation is primarily categorized into two types: N-terminal acetylation of proteins and lysine acetylation. Lysine acetylation occurs when lysine acetyltransferases (KATs) transfer an acetyl group from acetyl-CoA to the ε-amino side chain of lysine residues. This dynamic and highly specific process plays broad and critical roles in both physiological and pathological processes[131]. Under pathological cardiac stress (e.g., chronic angiotensin II infusion or aortic constriction) and diabetic conditions, acetylation modifications at Lys926 and Lys931 of OPA1 reduce its GTPase activity and impair mitochondrial fusion capacity, inducing mitochondrial fragmentation. These alterations ultimately lead to cardiomyocyte dysfunction and disease progression. SIRT3 could directly bind and deacetylate OPA1. SIRT3-mediated deacetylation enhances OPA1 GTPase activity and mitochondrial fusion capacity, protecting cardiomyocytes against stress-induced damage (e.g., doxorubicin-induced cell death) and mitigating myocardial injury. In cardiomyocytes, lipid overload induces acetylation of MFN2 at Lys243, promoting its degradation via

the ubiquitin-proteasome pathway. This degradation disrupts mitochondrial-lipid droplet membrane contacts (MLC), hindering fatty acid (FA) transfer from lipid droplets to mitochondria for oxidation. Consequently, intracellular lipid accumulation exacerbates mitochondrial dysfunction and cardiac injury[132]. Additionally, excessive lipid supply reduces NAD^+ levels and enhances DRP1 acetylation at Lys642. Acetylation of DRP1 increases its GTPase activity and promotes its binding to mitochondrial voltage-dependent anion channel 1 (VDAC1), triggering excessive mitochondrial fission and cardiomyocyte death[133]. On the other hand, histone deacetylase 6 (HDAC6)-mediated deacetylation at lysine 105 of MIRO1 decreases mitochondrial transport[134].

Overall, protein acetylation regulates mitochondrial dynamics and transport through two PTM-intrinsic principles: (i) charge-based remodeling - ε-acetylation neutralizes lysine positivity, thereby rewiring substrate charge, protein-protein interaction, and stability; and (ii) metabolic linking, wherein KATs or deacetylases activities, particularly NAD^+-dependent sirtuins, couple mitochondrial acetylation output to cellular acetyl-CoA, positioning acetylation as a direct metabolic sensor within PTM networks.

Protein methylation

Protein methylation refers to the transfer of methyl groups from methyl donors to protein residues catalyzed by methyltransferases. The primary methyl donor is S-adenosylmethionine (SAM), and common acceptors include the ε-amino group of lysine and the guanidino group of arginine. Methylation can also occur on the imidazole group of histidine, the amide groups of glutamine/asparagine, the sulfhydryl group (-SH) of cysteine, the carboxyl group of cysteine, and the side-chain carboxyl groups of glutamic/aspartic acid[135]. Among mitochondrial dynamics-related proteins, methylation has been specifically identified on arginine residues of DRP1. In MEFs, coactivator-associated arginine methyltransferase 1 (CARM1) methylates DRP1 at Arg403 and Arg634. The methylation promotes its interaction with MFF, its self-assembly and recruitment to mitochondria, triggering mitochondrial fission. Excessive fission reduces oxygen consumption and increases reactive oxygen species (ROS) levels. Elevated ROS further stimulates CARM1 translocation from the nucleus to the cytoplasm, amplifies DRP1 methylation and mitochondrial fission, establishing a self-reinforcing feedback loop that ultimately drives cellular senescence[136].

All in all, protein methylation regulates mitochondrial dynamics through two features: (i) dedicated enzyme dependence - installed by methyltransferases [e.g., protein arginine methyltransferases (PRMTs)] and reversed by demethylases, without the multi-enzyme cascades typical of ubiquitination or SUMOylation; and (ii) narrow substrate targeting, wherein DRP1 Arg methylation is the only confirmed example on fission/fusion/mitophagy machinery and couples fission defects to cellular senescence in aging-related pathologies.

Protein O-GlcNAcylation

Protein glycosylation is an enzymatic process where glycosyltransferases catalyze the attachment of carbohydrate chains to reactive groups on amino acid side chains of proteins via glycosidic bonds. The diversity in carbohydrate composition and linkage patterns contributes to the high structural heterogeneity of glycoproteins. Based on the type of glycosidic bond formed between the carbohydrate chain and the protein, glycosylation is categorized into N-linked glycosylation and O-linked glycosylation[137]. N-linked glycosylation (the most common type) involves the covalent attachment of carbohydrate chains to the free amino group of asparagine (N) residues via an N-glycosidic bond. O-linked glycosylation occurs when carbohydrate chains are attached to the hydroxyl group (-OH) of serine/threonine (S/T) residues via an O-glycosidic bond[137]. Among mitochondrial dynamics-related proteins, O-linked glycosylation has been identified as the predominant modification[138]. In diabetic patients, DRP1 undergoes O-GlcNAcylation at Thr585 and Thr586 residues. O-GlcNAcylation on DRP1 promotes its translocation from the cytoplasm to mitochondria, and accelerates mitochondrial fragmentation, impairing electron transport chain (ETC) activity and OXPHOS. These alterations collectively drive diabetic pathophysiology[139]. In mitochondrial movement, glycosylation of TRAK1 impairs mitochondrial transport, causing motility arrest within cells[140].

In summary, protein O-GlcNAcylation regulates mitochondrial dynamics through two features: (i) nutrient-coupled modification - installed by O-GlcNAc transferase (OGT) and removed by O-GlcNAcase (OGA), with flux dictated by the hexosamine biosynthetic pathway, so that glucose excess directly scales modification output; and (ii) phosphorylation competition, wherein O-GlcNAc and phosphate vie for overlapping Ser/Thr sites (e.g., DRP1 Thr585/586), making glycosylation a context-dependent toggle rather than a standalone switch.

Protein S-palmitoylation

Protein S-palmitoylation refers to a PTM in which a palmitoyl group (C16:0) covalently attaches to the sulfhydryl group of cysteine residues at the C-terminus of proteins via a thioester linkage, a process mediated by palmitoyl acyltransferases (PATs). The modification sites are typically localized on one or more cysteine residues near the C-terminal region[141]. In mice, ZDHHC13 (zinc finger DHHC-type palmitoyltransferase 13) catalyzes the S-palmitoylation of DRP1 at specific cysteine residues. This modification enhances the lipophilicity of DRP1, thereby modulating its subcellular distribution and functional activity. Importantly, S-palmitoylation augments both the enzymatic activity of DRP1 and its binding capacity to mitochondrial membranes, which is essential for maintaining the equilibrium between mitochondrial fission and fusion. ZDHHC13 deficiency leads to reduced S-palmitoylation of DRP1, resulting in mitochondrial dynamic dysregulation characterized by aberrant mitochondrial clustering, impaired OXPHOS, and subsequent cerebral energy metabolism deficits. These pathological changes manifest as neurotransmitter imbalances and behavioral abnormalities related to motor function and anxiety. Pharmacological inhibition of DRP1 S-palmitoylation using 2-bromopalmitate (2-BP) disrupts its mitochondrial targeting and exacerbates mitochondrial dynamic imbalance[142]. Conversely, restoration or enhancement of DRP1 palmitoylation may ameliorate these pathological phenotypes, suggesting that DRP1 palmitoylation represents a potential therapeutic target against neurodegenerative disorders[142].

In conclusion, protein S-palmitoylation regulates mitochondrial dynamics through two features: (i) thioester-based membrane anchoring - PATs (e.g., ZDHHC13) install C16:0 onto substrate cysteines, with reversal by APTs/PPT1 (palmitoyl-protein thioesterase 1); the resulting hydrophobic shift promotes DRP1 translocation to the outer mitochondrial membrane, making palmitoylation a direct switch for fission machinery recruitment; and (ii) substrate narrowness with cell-type nuance, wherein DRP1 is the only confirmed mitochondrial dynamics protein bearing this modification, and ZDHHC13-DRP1 coupling shows neuronal-subtype-specific variation, suggesting brain-region-resolved therapeutic windows.

Protein lactylation

Protein lactylation is a novel PTM characterized by the covalent

Table 3. PTM modifying enzymes of mitochondrial dynamics proteins

PTMs	Proteins	Writer	Eraser
Phosphorylation	MFN1	ERK1/2[166]	PGAM5[171]
		PKA[172]	
	MFN2	c-Abl[90]	Unknown
		PINK1[91]	
	DRP1	CDK5[173]	Calcineurin[174]
		ERK1/2[175]	PP2A[176]
	FIS1	Met[96]	Unknown
		DNA-PKcs[97]	
	MFF	AKT[177]	Unknown
		AMPK[178]	
Ubiquitination	OPA1	TRIM22[113]	Unknown
	MFN1	MARCH5[179]	USP30[180]
		RBCK1[181]	
	MFN2	MARCH5[179]	Unknown
		RFFL[182]	
	DRP1	TRIM25[183]	Unknown
	FIS1	MARCH5[184]	Unknown
		RNF5[185]	
	MFF	Parkin[121]	Unknown
	MID49	MARCH5[186]	Unknown
SUMOylation	DRP1	MAPL[187]	SENP5[129]
	FIS1	Unknown	SENP3[188]
	MFF	Unknown	SENP3/5[168]
Acetylation	OPA1	Unknown	SIRT3[165]
	MFN2	Unknown	SIRT1[189]
	DRP1	GCN5L1[190]	SIRT1[191]
		Unknown	SIRT3[192]
	Miro1	Unknown	HDAC6[134]
Methylation	DRP1	CARM1[139]	Unknown
O-GlcNAcylation	DRP1	Unknown	Unknown
Palmitoylation	DRP1	ZDHHC13[142]	Unknown
Lactylation	FIS1	Unknown	SIRT3[144]
Succinylation	MFF	CPT1A[146]	Unknown
S-Nitrosylation	DRP1	PDI[193]	GSNOR[194]

ERK1/2: Extracellular signal-regulated kinase 1/2; PGAM5: phosphoglycerate mutase family member 5; PKA: protein kinase A; c-Abl: cellular Abelson tyrosine kinase; PINK1: PTEN-induced putative kinase 1; CDK5: cyclin-dependent kinase 5; PP2A: protein phosphatase 2A; DNA-PKcs: DNA-dependent protein kinase catalytic subunit; AKT: protein kinase B; AMPK: AMP-activated protein kinase; TRIM22: tripartite motif-containing protein 22; MARCH5: membrane-associated RING-CH; USP30: ubiquitin-specific protease 30; RBCK1: RANBP2-type and C3HC4-type zinc finger containing 1; RFFL: RING finger and FYVE-like domain-containing E3 ubiquitin protein ligase; SENP5: SUMO-specific protease 5; SENP3: SUMO-specific protease 3; MAPL: mitochondria-anchored protein ligase; SIRT3: sirtuin 3; HDAC6: histone deacetylase 6; CARM1: coactivator-associated arginine methyltransferase 1; ZDHHC13: zinc finger DHHC-type palmitoyltransferase 13; CPT1A: carnitine palmitoyltransferase 1A; PDI: protein disulfide isomerase; GSNOR: S-nitrosoglutathione reductase.

attachment of a lactyl group to the ε-amino side chain of lysine residues. This modification occurs on both histone and non-histone proteins, playing critical regulatory roles in diverse cellular processes[143]. In renal tubular epithelial cells, downregulation of SIRT3 leads to hyperacetylation and inactivation of the pyruvate dehydrogenase E1 component subunit alpha (PDHA1), leading to excessive lactate production. Subsequently, lactate induces lactylation at Lys20 of FIS1 and promotes pathological mitochondrial hyperfission. This cascade results in ATP depletion, excessive mitochondrial reactive oxygen species (mtROS) generation, and mitochondrial apoptosis[144]. Pharmacological activation of PDHA1 using dichloroacetate (DCA) or SIRT3 overexpression reduces lactate levels and FIS1 lactylation, thereby ameliorating AKI[144].

In a word, protein Lactylation regulates mitochondrial dynamics through two features: (i) lactate-direct supply - the lactyl donor derives from cytosolic glycolysis-derived lactate rather than CoA activation, so that glycolytic flux and hypoxia directly scale modification output without passing through acetyl-CoA pools; and (ii) substrate sparsity with discovery bias, wherein FIS1 is the only confirmed mitochondrial dynamics protein bearing this modification, leaving fusion, mitophagy, and other fission components uncharted and warranting systematic screening.

Protein succinylation

Protein succinylation involves covalent attachment of succinyl groups from succinyl-CoA to lysine residues under the catalysis of succinyltransferases[145]. In OCCs, carnitine palmitoyltransferase 1A (CPT1A) facilitates succinylation at Lys302 on MFF and promotes mitochondrial fission. This process supports the elevated metabolic demands of tumor cells, thereby promoting ovarian carcinogenesis. The succinylation of MFF represents a novel therapeutic target for ovarian cancer[146].

Notably, protein succinylation regulates mitochondrial dynamics through two features: (i) dicarboxylic charge expansion - the succinyl group introduces two negative charges per modified lysine, producing a stronger electrostatic perturbation than acetylation or lactylation and thereby reshaping substrate interaction more markedly; and (ii) TCA-gated substrate sparsity, wherein MFF is the only confirmed mitochondrial dynamics protein bearing this modification, with succinyl-CoA flux coupled to SDH activity and TCA intermediates, suggesting other fission/fusion components may be gated by metabolic-state-dependent succinylation yet to be mapped.

Protein S-nitrosylation

Protein S-nitrosylation is a critical post-translational modification entailing the covalent attachment of nitric oxide (NO) to the sulfhydryl group (-SH) of cysteine residues, forming S-nitrosothiols (-SNO). This modification represents a signaling paradigm analogous to phosphorylation and plays a pivotal role in diverse physiological and pathological processes[147]. In Alzheimer's disease (AD) patients, β-amyloid (Aβ) oligomers induce S-nitrosylation of DRP1 through a NO-dependent pathway. S-nitrosylation promotes DRP1 dimerization and enhances its GTPase activity, leading to accelerated mitochondrial fission, synaptic damage, and neuronal apoptosis. This finding identifies DRP1 as a critical mediator of Aβ oligomer-induced mitochondrial fragmentation and neurotoxicity. Site-directed mutagenesis of the target cysteine to block DRP1 S-nitrosylation effectively mitigates these effects, positioning DRP1 as a promising pharmacological target for counteracting neurodegenerative progression in AD and related disorders[148]. Conversely, S-nitrosylation of Parkin inhibits mitophagy by inhibiting its E3 ubiquitin ligase activity, thereby promoting the progression of PD[149].

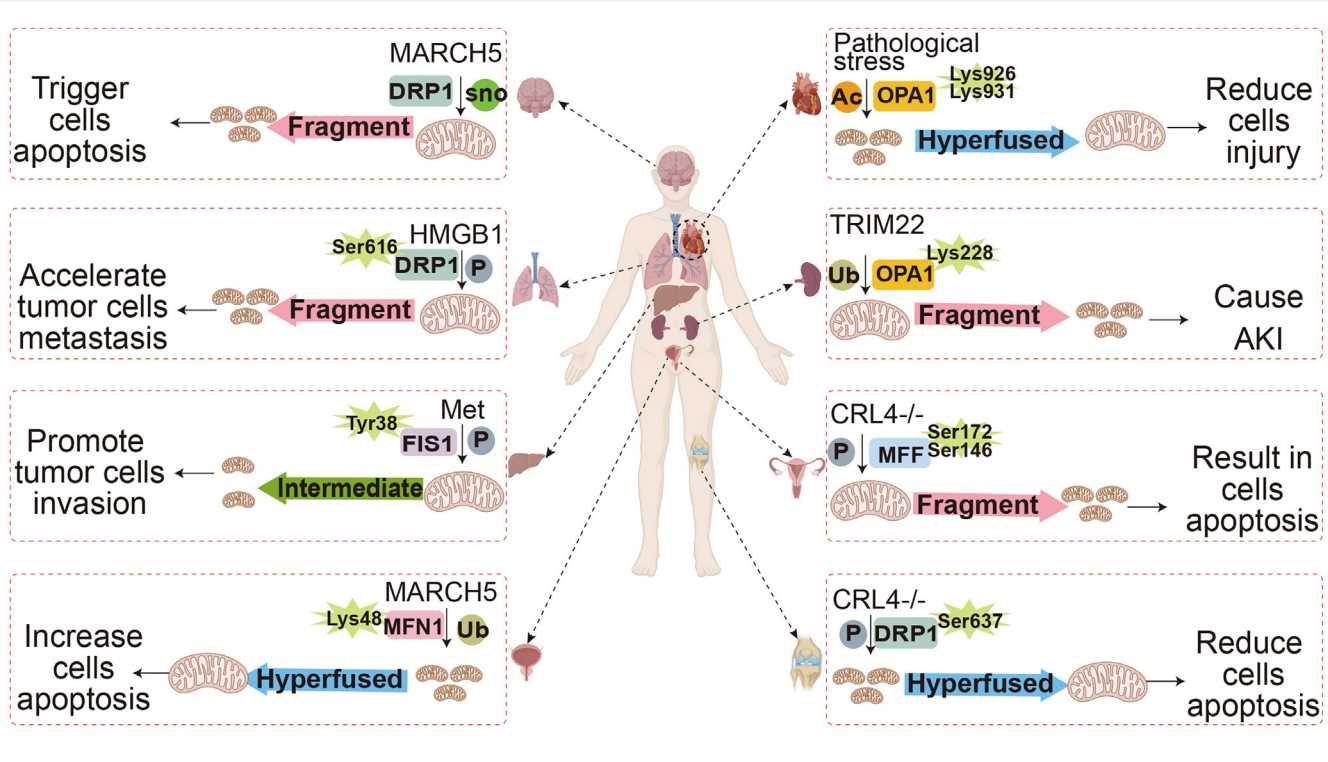

Figure 3. PTMs on mitochondrial dynamics-related proteins regulate many physiological and pathological processes. Mitochondrial dynamics-related proteins undergo diverse PTMs across tissues, eliciting distinct mitochondrial phenotypes that orchestrate or disrupt physiological and pathological processes. The data source for Figure 3 is generated based on references[96,98,116,148,160-162]. The human organs shown in Figure 3 are created with BioRender.com. P: Phosphorylation; Ub: ubiquitination; Ac: acetylation; sno: nitrosylation; AKI: acute kidney injury; PTMs: post-translational modifications; DRP1: dynamin-related protein 1; FIS1: mitochondrial fission 1 protein; MFN1: mitofusins 1; MFF: mitochondrial fission factor; OPA1: optic atrophy 1.

Table 4. Drugs targeting mitochondrial dynamics proteins PTMs

Name	Target/Mechanism	Development stage	Disease
Mdivi-1	Suppressing the GTPase activity of DRP1, a key regulator of mitochondrial fission, leads to reduced S616 phosphorylation in embryonic tissues[195,196]	Preclinical	Myocardial I/R injury, heart failure, pulmonary hypertension
P110	Blocks DRP1-adaptor protein FIS1 binding; Treatment effectively reduced DRP1 phosphorylation in a mouse model of subarachnoid hemorrhage[197,198]	Preclinical	ALS/motor neuron disease
MTX115325	USP30 (deubiquitinase, removes ubiquitin from OMM)[199]	Phase I	Parkinson's disease

Preclinical: Research phase before human trials; Phase I: first human trial; DRP1: dynamin-related protein 1; FIS1: mitochondrial fission 1 protein; USP30: ubiquitin-specific protease 30; OMM: outer mitochondrial membrane; ALS: Amyotrophic Lateral Sclerosis.

In summary, protein S-nitrosylation regulates mitochondrial dynamics through two features: (i) redox-gated thiol modification - installed by NO· donors and reversed by GSH/Trx systems rather than a dedicated multi-enzyme cascade, making SNO output sensitive to cellular redox and nitrosative tone; and (ii) paired node coverage, wherein established substrates DRP1 (fission) and Parkin (mitophagy) span two arms of dynamics quality control, though whether fission/fusion components beyond DRP1 are broadly S-nitrosylated remains open.

PTMS ON MITOCHONDRIAL DYNAMICS-RELATED PROTEIN AS TARGETS FOR DISEASE PREDICTION AND TREATMENT

In conclusion, the functional homeostasis of the four core mitochondrial processes - fusion, fission, transport, and mitophagy - is governed by site-specific PTMs of key proteins. Dysregulation of PTMs at specific sites constitutes a key driver in the pathogenesis

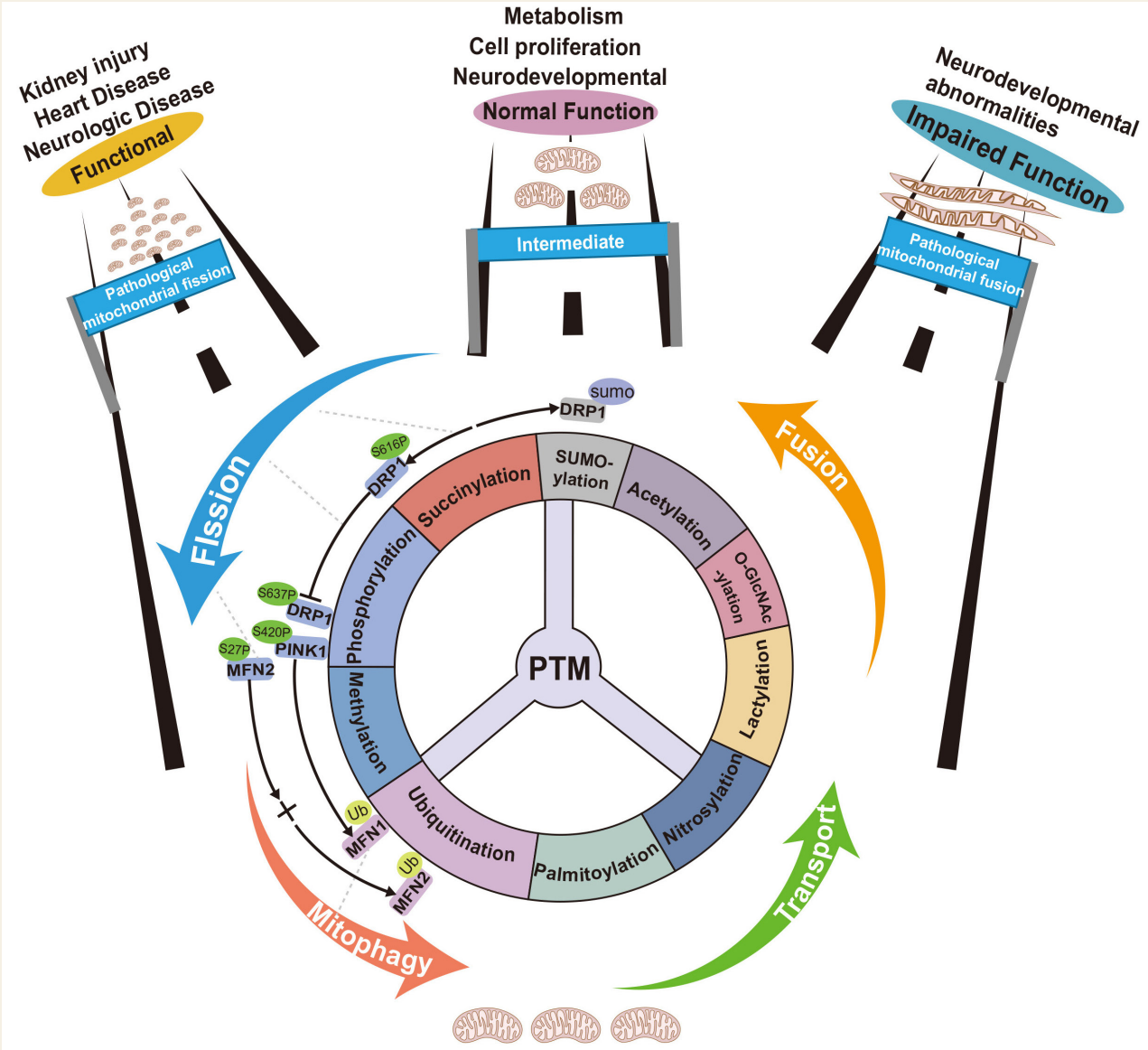

Figure 4. PTMs are the drivers of mitochondrial dynamics balance.
The steering wheel comprising PTMs - including ubiquitination, SUMO, acetylation, phosphorylation, methylation, GlcNAc, palmitoylation, succinylation, lactylation, and S-nitrosylation -coordinates mitochondrial dynamics. PTMs occurring on dynamics-related proteins jointly regulate fission, fusion, transport, and mitophagy, maintaining homeostasis. Disruption of this PTM balance shifts mitochondrial morphology toward excessive fission or fusion, culminating in mitochondrial dysfunction and disease. Graphic reference:⊥: Competitive modification; →: Progressive modification; ←→: Collaborative modification; →+→: 'Induced modification. The data source for Figure 4 is generated based on references[142,146,148,154-156]. The figure was redrawn and designed by the authors based on existing reference images. DRP1: Dynamin-related protein 1; MFN1: mitofusins; Ub: ubiquitination.

of various diseases [Figure 3]. Therefore, we propose that PTMs on mitochondrial dynamics-related proteins represent dual-value candidates for both molecular biomarkers for disease diagnosis and promising therapeutic targets. As previously discussed, dysregulated PTMs on mitochondrial dynamics-related proteins have already emerged as disease indicators across multiple pathologies. In neurological disorders, elevated S-nitrosylated DRP1 (SNO-DRP1) levels in the brains of AD and Huntington's disease (HD) patients drive excessive fission and neuronal damage. Furthermore, PINK1-mediated phosphorylation of DRP1 at Ser616 has been linked to PD pathogenesis. Beyond neuroscience, clinical evidence shows that: the level of DRP1 SUMOylation in liver tissue correlates with poor prognosis in patients undergoing liver transplantation; increased phosphorylation of FIS1 at Thr34 in urinary sediment is detected and associated with renal dysfunction in patients with septic AKI; and FIS1 phosphorylation is significantly elevated in HCC tumor tissues compared to adjacent non-tumor tissues. These findings from patient-derived samples

Glossary

Mitochondrial dynamics

A process governing mitochondrial morphology, distribution, and function via antagonistic fusion (MFN1/2, OPA1) and fission (DRP1) cycles. Fusion facilitates content complementation and bioenergetic efficiency; fission enables organellar inheritance and segregation of damaged components for mitophagy. Their equilibrium dictates bioenergetics and apoptosis susceptibility.

Mitophagy

A selective autophagy eliminating dysfunctional mitochondria. Loss of $\Delta\Psi m$ stabilizes PINK1 on the outer membrane, which phosphorylates ubiquitin (Ser65) and Parkin. Activated Parkin ubiquitinates outer membrane proteins, recruiting autophagy receptors (p62, OPTN, NDP52) that bridge LC3-phagophores for lysosomal delivery and degradation.

Genetic code expansion (GCE)

A synthetic biology method enabling site-specific, co-translational incorporation of noncanonical amino acids (ncAAs) via an engineered orthogonal aaRS/tRNA pair. The orthogonal tRNA decodes a repurposed codon (typically amber UAG), while the engineered aaRS selectively charges it with the desired ncAA.

Mitochondrial fission

A conserved GTP-hydrolytic process cleaving a mitochondrial tubule into daughter organelles. Cytosolic DRP1 translocate to the outer membrane, assembling into ring-like helices at constriction sites. GTP hydrolysis drives a conformational twist that mechanistically scissions both outer and inner membranes simultaneously.

Mitochondrial transport

Cytoskeleton-based trafficking of mitochondria to sites requiring ATP or Ca^{2+} buffering. Microtubule motors drive bidirectional transport: kinesin-1 (KIF5B) mediates anterograde (peripheral) movement; cytoplasmic dynein mediates retrograde (perinuclear) movement. Adaptors Miro/Milton couple mitochondria to motors in a Ca^{2+}-sensitive manner.

Non−canonical amino acids (ncAAs)

Synthetic amino acid analogs beyond the 20 genetically encoded proteinogenic amino acids. They possess novel side-chain functionalities absent in canonical amino acids, including bioorthogonal handles, photocrosslinkers, spectroscopic probes, and PTM mimics (phosphorylated, acetylated, or ubiquitinated variants).

Mitochondrial fusion

A multistep membrane-remodeling process integrating adjacent mitochondria into a continuous network. Outer membrane tethering and fusion are mediated by MFN1/2 via GTP-dependent conformational changes. Inner membrane fusion is subsequently executed by OPA1, a dynamin-like GTPase essential for cristae integrity.

PTM crosstalk

Mechanistic interplay between distinct PTMs, comprising four functional patterns: collaborative - synergistic PTMs on same target; progressive - upstream PTM regulates downstream PTM on another protein; induced - one PTM triggers another on same protein; competitive - one PTM antagonizes another at adjacent sites.

TEXT BOX

Box 1. Translational hurdles of PTM-based biomarkers and proposed strategies

Despite their promise, PTM-based biomarkers face substantial obstacles before clinical adoption.

Key hurdles:
Evidence gap: Current supporting evidence derives predominantly from preclinical models, with limited clinical validation.

Technological barrier: Detecting specific PTMs in clinical samples is technically challenging due to substantial biological variability and a lack of large-scale validation data.

To bridge this gap, we propose the following strategies:
(i) Developing highly sensitive detection technologies (e.g., single-molecule detection or microfluidic enrichment) coupled with site-specific antibodies to overcome the difficulty of detecting low-abundance PTMs, thereby enhancing analytical reliability and reproducibility[200];

(ii) Integrating multi-omics PTM analysis with stable internal references and standardized protocols to establish reference intervals based on large-scale cohorts, addressing current issues of high biological variability;

(iii) Employing multi-omics technologies to systematically screen novel functional PTM sites and clinically validate their associations with disease onset, progression, or prognosis, thereby expanding the therapeutic scope[201].

highlight the considerable potential of mitochondrial dynamics PTMs as disease biomarkers, a notion strongly supported by extensive evidence from animal and cellular models. Consequently, therapeutically targeting specific PTM sites on mitochondrial dynamics proteins to restore the homeostatic balance represents a precision medicine strategy for treating diseases.

This novel therapeutic paradigm is defined by three key advantages: high target specificity, reversibility of regulation, and synergy between diagnosis and treatment. First, the extreme site specificity of PTMs allows drugs targeting a particular modified site to avoid disrupting the overall function of the protein, thereby minimizing off-target effects. Second, most PTMs, such as phosphorylation, acetylation, and ubiquitination, are reversible processes. Modulating the activity of the corresponding modifying enzymes via small molecules or gene editing enables dynamic regulation of mitochondrial function, making it suitable for long-term intervention in chronic diseases. However, the writers, erasers, and readers governing these PTMs on mitochondrial dynamics-related proteins remain poorly characterized and warrant further investigation [Table 3]. Third, aberrant levels of specific PTM sites can serve as biomarkers for early disease diagnosis while simultaneously guiding the selection of personalized treatment regimens.

In summary, targeting mitochondrial dynamics protein PTMs holds broad application prospects. Several therapeutics targeting mitochondrial dynamics-related protein PTMs are currently in clinical development or under investigation [Table 4].

CONCLUDING REMARKS

In summary, mitochondrial dynamics are driven by a variety of PTMs. PTMs on fission/fusion, transport, and mitophagy proteins act as triggers that orchestrate mitochondrial dynamics with exquisite spatiotemporal precision - effectively conducting a mitochondrial fate symphony [Figure 4]. Under normal physiological conditions, mitochondria maintain a dynamic equilibrium, balancing fission and fusion to sustain normal function. Disruption of this equilibrium triggers pathological fission or fusion, culminating in mitochondrial dysfunction. Interestingly, emerging evidence extends this regulatory role beyond cellular homeostasis, revealing a vital function for mitochondrial dynamics in sleep pressure control in Drosophila[150]. While this review has focused on ten prevalent PTMs governing mitochondrial dynamics, it is important to recognize that the regulatory landscape extends beyond these modifications. Emerging evidence suggests that other 'atypical' PTMs - such as tyrosine ubiquitination[151] and non-enzymatic modifications like carbonyl adducts[152,153] - add further layers of complexity. Although the functional impact of many of these other 'atypical' PTM modifications on core dynamics proteins remains largely uncharacterized, future investigations into these less-explored pathways may uncover novel mechanisms linking metabolic flux to mitochondrial architecture, particularly in the context of aging and metabolic disorders.

To date, new PTMs on mitochondrial dynamics-related proteins continue to be discovered, reshaping our understanding of mitochondrial biology and disease mechanisms. However, a fundamental question persists: Why have proteins evolved to utilize such a diverse array of PTMs to execute their functions? For example, mitochondrial fission protein DRP1 harbors at least six PTMs. How do these modifications cross-talk on a single protein? Current evidence suggests that multiple PTMs enable a protein to mount differential responses to varying environmental and stress conditions. This multiplicity necessitates precise spatiotemporal regulation, underscoring the protein's critical role in biological processes. Moreover, our previous perspective on the PTM crosstalk patterns, including "collaborative modification", "progressive modification", "induced modification", and "competitive modification", which govern pluripotent stem cell fate, offers a conceptual lens through which to dissect the mechanisms of mitochondrial dynamics in disease development[154]. This PTM crosstalk pattern is also readily apparent in the post-translational modifications of mitochondrial dynamics-related proteins. For instance, in human liver transplant patient tissues, elevated DRP1-S616 phosphorylation, paralleled by reduced DRP1-S637 phosphorylation, was identified as a key factor driving hepatic IRI, exemplifying a "competitive modification" pattern. Notably, concurrent upregulation of DRP1 SUMO1 modification in the same pathological context synergizes to enhance DRP1-mediated fission, illustrating the "collaborative modification" mode in mitochondrial dynamics. During mitophagy, PINK1 autophosphorylation and subsequent ubiquitin phosphorylation constitute the core of the PINK1/Parkin mitochondrial clearance pathway, exemplifying a "progressive modification" pattern[155]. In human papillary thyroid carcinoma (PTC) cell lines, leucine rich repeat kinase 2 (LRRK2) overexpression activates the LRRK2-mitogen-activated protein kinase kinase 4 (MKK4)/JNK signaling cascade, triggering phosphorylation of MFN2 at Ser27. This phosphorylation event subsequently induces ubiquitination-mediated degradation of MFN2, following the same "progressive modification" pattern[156] [Figure 4].

OUTSTANDING QUESTIONS

Deciphering the operational logic of the regulatory nexus composed of mitochondrial dynamics proteins represents a new frontier for investigating mitochondrial dynamics. Several questions remain worthy of consideration: (i)What evolutionary advantage drives the diversity of PTMs on proteins like DRP1 - representing redundancy, or a specific combinatorial code for spatial precision? (ii) How do distinct PTM pairs on a single protein (e.g., DRP1 phosphorylation-S616 *vs.* acetylation-K642) engage in crosstalk to decode specific fission or fusion outputs? (iii) How do fluctuations in mitochondrial metabolites (acetyl-CoA, NAD^+) directly alter modification stoichiometry to tip the fusion-fission balance? (iv) Beyond substrate binding, how are PTM-regulating enzymes (writers/erasers) themselves modulated by mitochondrial signals to maintain network homeostasis? (v) What paradigms will enable real-time, multiplexed visualization of PTM dynamics on single proteins within intact mitochondria in living cells? (vi) Can we develop tools targeting specific modification sites (e.g., DRP1 S-nitrosylation) directly, bypassing broad upstream enzyme modulation? Emerging technologies will be instrumental in addressing these questions. For instance, protein modification omics provides a powerful method to study specific modifications under defined cellular states[157]. Prime editing - an accurate and efficient gene editing technology based on CRISPR/Cas system - enables precise site-directed mutagenesis[158]. Furthermore, genetic code expansion (GCE) allows the incorporation of non-canonical amino acids (ncAAs) directly into proteins *in vivo*[158]. Strategic integration of these tools may efficiently resolve these questions, potentially unlocking new therapeutic avenues for mitochondrial diseases.

DECLARATIONS

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Authors' contributions

Conceptualization, writing - original draft, visualization: Ding, H.; E, T.; He, J.; Wu, Y.; Zheng, X.

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Conflicts of interest
All authors declared that there are no conflicts of interest.

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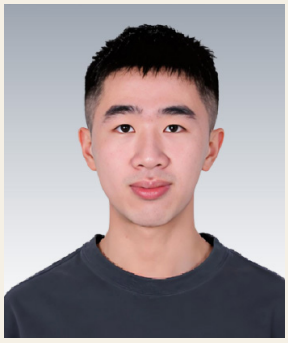
Linpeng Li is a Professor at the GMU-GIBH Joint School of Life Sciences, Guangzhou Medical University. His research focuses on metabolic regulation of cell fate, and he has published more than 20 peer-reviewed papers and filed one patent application. He has has been invited to speak at numerous deliver talks at major international and national conferences on metabolism, including a plenary talk at the 17th Annual Meeting of the Asian Society for Mitochondrial Research and Medicine & 3rd Annual Meeting of the Mitochondria Biology Branch of the Biophysical Society of China (2025). Prof. Li serves as Standing Council Member & Deputy Secretary-General of the Mitochondria Biology Branch of the Biophysical Society of China, as well as Chair of its Youth Working Committee, and was awarded the Huawei Zhongyi Outstanding Young Scientist Fund by the same branch.

Xingguo Liu is a Principal Investigator at the Guangzhou Institutes of Biomedicine and Health, Chinese Academy of Sciences (GIBH, CAS). He is a recipient of the National Science Fund for Distinguished Young Scholars and enjoys the Government Special Allowance of the State Council. He serves as a member of the Editorial Board of *Science Bulletin*, Vice President of the Asian Society for Mitochondrial Research and Medicine, President of the Mitochondrial Biology Branch of the Biophysical Society of China, and a Standing Council Member of the Biophysical Society of China. Prof. Liu has published over 90 papers with more than 8,000 citations, including more than 70 papers on which he was the first or corresponding author. His landmark discovery—"the first identification of the 14th protein encoded by mitochondrial genes"—was highlighted in the Chinese Academy of Sciences' 2024 Annual Work Report.

Liting Duan, Ph.D., is an Associate Professor at The Chinese University of Hong Kong (CUHK). Her research focuses on the intersection of optogenetics, mechanobiology, and organelle dynamics. Her lab pioneered the development of light-gated, mitochondria-specific mechanostimulators to precisely exert tensile forces on mitochondrial membranes in live cells. Using these tools, her work has uncovered key principles of force-induced mitochondrial remodelling: identifying "tail-autotomy fission" as a distinct mechanism for segregating outer membrane components into mitophagy-targeted mitochondrial-derived vesicles (MDVs), and demonstrating how stretching triggers inner-membrane-dependent "membrane pearling" to template DRP1-mediated fission and reorganize mtDNA nucleoids. Her research establishes the physical and molecular frameworks connecting mechanosensing to mitochondrial quality control and dynamics.



Haolin Ding worked in Dr. Li's laboratory, where his research focused on mitochondrial dynamics and protein post-translational modifications. He has been involved in three research projects and has contributed to several related publications. His research interests center on mitochondrial biology and the molecular mechanisms underlying disease progression..