

REVIEW



## The multifaceted regulation of mitophagy by endogenous metabolites

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### ABSTRACT

Owing to the dominant functions of mitochondria in multiple cellular metabolisms and distinct types of regulated cell death, maintaining a functional mitochondrial network is fundamental for the cellular homeostasis and body fitness in response to physiological adaptations and stressed conditions. The process of mitophagy, in which the dysfunctional or superfluous mitochondria are selectively engulfed by autophagosome and subsequently degraded in lysosome, has been well formulated as one of the major mechanisms for mitochondrial quality control. To date, the PINK1-PRKN-dependent and receptors (including proteins and lipids)-dependent pathways have been characterized to determine the mitophagy in mammalian cells. The mitophagy is highly responsive to the dynamics of endogenous metabolites, including iron-, calcium-, glycolysis-TCA-, NAD<sup>+</sup>-, amino acids-, fatty acids-, and cAMP-associated metabolites. Herein, we summarize the recent advances toward the molecular details of mitophagy regulation in mammalian cells. We also highlight the key regulations of mammalian mitophagy by endogenous metabolites, shed new light on the bidirectional interplay between mitophagy and cellular metabolisms, with attempting to provide a perspective insight into the nutritional intervention of metabolic disorders with mitophagy deficit.

**Abbreviations:** acetyl-CoA: acetyl-coenzyme A; ACO1: aconitase 1; ADCYs: adenylate cyclases; AMPK: AMP-activated protein kinase; ATM: ATM serine/threonine kinase; BCL2L1: BCL2 like 1; BCL2L13: BCL2 like 13; BNIP3: BCL2 interacting protein 3; BNIP3L: BCL2 interacting protein 3 like; Ca<sup>2+</sup>: calcium ion; CALCOCO2: calcium binding and coiled-coil domain 2; CANX: calnexin; CO: carbon monoxide; CYCS: cytochrome c, somatic; DFP: deferiprone; DNM1L: dynamin 1 like; ER: endoplasmic reticulum; FKBP8: FKBP prolyl isomerase 8; FOXO3: forkhead box O3; FTMT: ferritin mitochondrial; FUNDC1: FUN14 domain containing 1; GABA:  $\gamma$ -aminobutyric acid; GSH: glutathione; HIF1A: hypoxia inducible factor 1 subunit alpha; IMMT: inner membrane mitochondrial protein; IRP1: iron regulatory protein 1; ISC: iron-sulfur cluster; ITPR2: inositol 1,4,5-trisphosphate type 2 receptor; KMO: kynurenine 3-monooxygenase; LIR: LC3 interacting region; MAM: mitochondria-associated membrane; MAP1LC3: microtubule associated protein 1 light chain 3; MFNs: mitofusins; mitophagy: mitochondrial autophagy; mPTP: mitochondrial permeability transition pore; MTOR: mechanistic target of rapamycin kinase; NAD<sup>+</sup>: nicotinamide adenine dinucleotide; NAM: nicotinamide; NMN: nicotinamide mononucleotide; NO: nitric oxide; NPA: Niemann-Pick type A; NR: nicotinamide riboside; NR4A1: nuclear receptor subfamily 4 group A member 1; NRF1: nuclear respiratory factor 1; OPA1: OPA1 mitochondrial dynamin like GTPase; OPTN: optineurin; PARL: presenilin associated rhomboid like; PARPs: poly(ADP-ribose) polymerases; PC: phosphatidylcholine; PHB2: prohibitin 2; PINK1: PTEN induced kinase 1; PPARG: peroxisome proliferator activated receptor gamma; PPARGC1A: PPARG coactivator 1 alpha; PRKA: protein kinase AMP-activated; PRKDC: protein kinase, DNA-activated, catalytic subunit; PRKN: parkin RBR E3 ubiquitin protein ligase; RHOT: ras homolog family member T; ROS: reactive oxygen species; SIRT6: sirtuin 6; STK11: serine/threonine kinase 11; TCA: tricarboxylic acid; TP53: tumor protein p53; ULK1: unc-51 like autophagy activating kinase 1; VDAC1: voltage dependent anion channel 1

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### Introduction

Mitochondria are critical organelles determining a myriad of cellular metabolisms, including but not limited to the ATP production *via* electron transport coupled with oxidative phosphorylation, tricarboxylic acid (TCA) cycle, fatty acid  $\beta$ -oxidation, amino acid synthesis, calcium homeostasis and iron metabolism (bio-synthesis of heme and iron-sulfur cluster). Besides, from last two decades, it has been well

understood that mitochondria serve as the signaling hubs to orchestrate intra-cellular and extra-cellular signals and communicate to other cellular compartments to fulfill the diverse functions under homeostatic and stressed conditions [1,2]. Moreover, mitochondria produce overwhelming majority of reactive oxygen species (ROS) as the inevitable by-product during the electron transport, while themselves are particularly vulnerable to the ROS mediated oxidative damage [3].

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Mitochondria also dominate programmed cell death mainly by tuning the release of pro-apoptotic molecules, especially CYCS (cytochrome c, somatic) and DIABLO (diablo IAP-binding mitochondrial protein) [4,5]. The mitochondria associated BCL2 family, categorized into three sub-families including the anti-apoptotic proteins, the BH3-only pro-apoptotic proteins, and the pore-forming apoptotic proteins, coordinates the mitochondrial membrane permeabilization and the release of these apoptogenic factors [6]. The compromised mitochondria would also drive other forms of regulated cell death, including necroptosis, ferroptosis and pyroptosis [7]. Moreover, the accumulation of dysfunctional mitochondria has been widely documented to associate with the pathogenesis of multiple human diseases, especially the neurodegenerative diseases, autoimmune disorders and cancers [8]. Therefore, maintenance of a functional mitochondria pool is fundamental for the cellular homeostasis and body fitness.

Mitochondrial quality control is precisely achieved by distinct mechanisms. Mitochondrially resident proteases and chaperons determine the integrity of mitochondrial proteome by hydrolyzing and unfolding-refolding the misfolded proteins, respectively [9,10]. Mitochondrial unfolded protein response (UPR<sup>mt</sup>), referring to the sufficient accumulation of misfolded mitochondrial proteins driving a retrograde signaling to activate the transcriptional response and facilitate the expression of mitochondrial chaperones and proteases, could reduce the mitochondrial unfolded proteins and promote recovery of mitochondrial proteome [11]. Mitochondria are highly dynamic organelles, with constant fusion and fission, which is conferred by the fusion proteins MFNs (mitofusins), OPA1 (OPA1 mitochondrial dynamin like GTPase) and fission protein DNMI1L (dynamin 1 like), as well as its mitochondrially localized receptors. Mitochondrial fusion neutralizes the damaged mitochondrial components, while mitochondrial fission could effectively segregate the damaged mitochondria from the whole mitochondrial architectural network for the subsequent degradation [12]. Furthermore, mitochondria-derived vesicles (MDVs), generated through the selective incorporation of mitochondrial outer membrane, inner membrane, or matrix content, subsequently deliver specific mitochondrial contents to late endosome or multi-vesicular bodies for degradation, are recognized as a novel avenue for mitochondrial quality control at sub-organelle level [13,14]. Increasing evidence has emerged that mitophagy, a selective recognition and degradation of mitochondria by autophagic machinery, is regarded as one of the major mechanisms for mitochondrial quality control [15,16].

Pioneering studies reported the focal cytoplasmic degradation of mitochondria from 1950s to 1970s. Specifically, Hruban and colleagues observed that mitochondria are broken down within the cytoplasmic inclusions in 1963 [17]. In 1979, Greene and colleagues observed a selective degeneration of mitochondria associates with electron-lucent mitochondrial inclusions in proximal renal tubular epithelium induced by hyperbaric oxygen exposure [18]. These early studies based on electron microscopy groundbreakingly proposed the concepts of autophagosome maturation and selective autophagy. The early history of mitophagy research was comprehensively

summarized [19]. In 2002, the phenomenon was reemerged. A complete removal of mitochondria was observed in cultured primary sympathetic neurons during apoptosis induction in the presence of CASPs (caspases) inhibitors [20]. In 2005, the term “mitophagy” was first proposed to describe the selective mitochondrial autophagy by John Lemasters [21]. Since then, increasing studies focused on this booming field and several regulatory pathways including the PINK1 (PTEN induced kinase 1)-PRKN/PARKIN (parkin RBR E3 ubiquitin protein ligase)-dependent mitophagy and the receptors (including protein and lipid mitophagy receptors)-mediated mitophagy have been deciphered. Furthermore, defects in mitophagy have been evidenced to result in the accumulation of damaged mitochondria, which is implicated in several disease pathogenesis [22]. Herein, we critically summarize the major regulatory circuits of mitophagy in mammalian cells, with a focus on dissecting the mitophagy regulation by endogenous metabolites, in an attempt to provide a perspective insight into the nutritional intervention of metabolic disorders with mitophagy deficit.

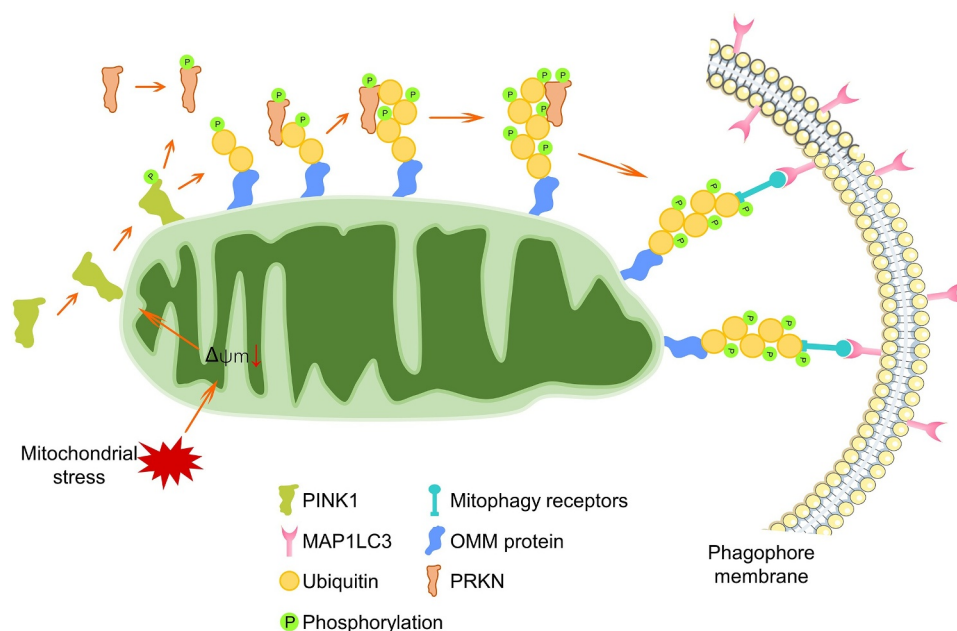
## Major mitophagy pathways

Macroautophagy/autophagy refers to a cellular catabolic process, sequentially manifested by the formation of sequestering compartments, phagophores, that engulf the to-be-degraded cellular components, including proteins, protein aggregates, lipid, organelles, invading pathogens and even nuclear lamina. The phagophores then mature into double-membraned vesicles (autophagosomes) that fuse with an endosome and/or lysosome, resulting in subsequent degradation of the engulfed components by the lysosomal hydrolases [23]. Mitophagy is a specialized form of autophagy to selectively recognize and remove the damaged or superfluous mitochondria, sharing fundamental features and core proteins with general autophagy. The specificity of the phagophore engulfing mitochondria is achieved by distinct mechanisms. To date, both the PINK1-PRKN-dependent mitophagy and receptor-mediated mitophagy have been elucidated in mammalian cells.

### PINK1-PRKN axis-dependent mitophagy

Early studies using loss-of-function mutants of *Drosophila* suggested that both the mutations in *Pink1* (encoding a homolog of the serine-threonine kinase PINK1) and *park* (encoding a homolog of the E3 ubiquitin ligase PRKN), two major genes associated with Parkinson disease, result in disturbed mitochondrial morphology and declined mitochondrial functionalities, accompanied with locomotor deficits, muscle degeneration, male sterility and neuronal loss [24,25]. The transgenic expression of *park* markedly ameliorates mitochondrial functionalities and restores the neuronal fitness at the genetic background with *Pink1* loss of function, but not *vice versa*, suggesting that PRKN functions downstream of PINK1 to determine the mitochondrial integrity [24,26].

The initial understanding of the PINK1-PRKN axis-dependent mitophagy was originated by Dr. Richard Youle and colleagues. In 2008, they reported that PRKN is recruited to the outer membrane of depolarized mitochondria, where it



**Figure 1.** The regulatory circuit of PINK1-PRKN-mediated mitophagy. PINK1 is imported into healthy mitochondria and cleaved by mitochondrial protease, leading to a quick degradation. During mitochondrial depolarization, PINK1 is stabilized and translocated onto the outer mitochondrial membrane, where it recruits and phosphorylates PRKN, phosphorylates the ubiquitin molecules, leading to the enzymatic activation of PRKN. PRKN ubiquitinates numerous mitochondrial outer membrane proteins. These signals lead to autophagy receptors OPTN and CALCOCO2 translocating onto mitochondria for the selective recognition of mitochondria by the phagophore membrane.

facilitates the autophagic degradation of these damaged mitochondria [27]. This groundbreaking study boosted up the mitophagy research. Since then, the regulatory circuit of the PINK1-PRKN axis-dependent mitophagy has been well understood (Figure 1). Under basal condition, PINK1 is imported into the mitochondria, where it is cleaved by the mitochondrial rhomboid protease PARL (presenilin associated rhomboid like) [28,29]. The processed product is released into the cytosol and constitutively degraded by the E3 ubiquitin ligases UBR1, UBR2 and UBR4 [30]. During mitochondrial depolarization, PINK1 escapes from PARL proteolytic cleavage and trans-localizes onto the mitochondrial outer membrane [31,32]. On the outer membrane, PINK1 forms a dimer and associates with the TOMM (translocase of outer mitochondrial membrane) complex to reduce the mitochondrial import of newly synthesized proteins [31,33]. The TOMM complex guides the correct positioning of dimeric PINK1 and facilitates its kinase activity through supporting its auto-phosphorylation, which is required for the PRKN recruitment and mitophagy execution [32]. Besides, TOMM7 [34,35], IMMT/Mitofilin/MIC60 (inner membrane mitochondrial protein) [36] and mitochondrial protease OMA1 [34] are involved in regulating PINK1 stabilization on the outer membrane [37]. On one hand, PINK1 phosphorylates the preexisting ubiquitin at Ser65 on the mitochondrial surface [38,39]. On the other hand, the phosphorylated ubiquitin could be captured by PRKN, inspiring PRKN phosphorylation at Ser65 in the ubiquitin-like domain by PINK1 [40–42]. Phosphorylation at Ser65 and binding to the phosphorylated ubiquitin facilitate the conformational change of the ubiquitin-like domain and relieve of auto-inhibition [43–45], leading to PRKN activation to ubiquitinate mitochondrial proteins on the outer membrane, which

serves as a “eat-me” signaling for ultimate mitophagy [46,47]. Furthermore, phosphorylated MFN2 [48] and VDAC1 (voltage dependent anion channel 1) [49] are also important for PRKN translocation. PINK1 and the phosphorylated ubiquitin also drive the mitochondrial recruitment of autophagy receptor proteins including CALCOCO2/NDP52 (calcium binding and coiled-coil domain 2) and OPTN (optineurin), which facilitate mitochondria engulfed by autophagosome through direct interaction with MAP1LC3 (microtubule associated protein 1 light chain 3) [50,51].

According to the mechanistic studies based on *Drosophila*, mammalian cells, mice and epidemiological analysis of Parkinson disease, genetic variations of *PINK1* and *PRKN* are strongly associated with the pathogenesis of Parkinson disease, in which the mitochondrial dysfunction is primarily formulated [52]. However, it is still not certain whether this is due to their functions in mitophagy or others, as basal mammalian mitophagy could occur independently of PINK1 or PRKN in a variety of tissues including brain [53,54]. Moreover, PINK1 and PRKN have been reported to engage in a wide range of mitochondrial behaviors. PINK1 could regulate mitochondrial mobility by phosphorylating and promoting the proteasomal degradation of RHOT/MIRO (ras homolog family member T) in a PRKN-dependent manner [55,56]. PRKN sustains PPARGC1A (PPARG coactivator 1 alpha) expression and supports mitochondrial biogenesis by ubiquitinating and promoting the proteasomal degradation of ZNF746/PARIS (zinc finger protein 746), a transcriptional repressor of PPARGC1A [57,58]. Knockdown of PINK1 reduces the enzymatic activities of several respiratory chain complexes [59,60]. Additionally, both *Pink1* and *Prkn* genetically interact with multiple mitochondrial dynamics associated genes, including *Dnm1l*, *Mfn* and *Opa1* [61–63]. Recently, Han et al. reported that PINK1 could

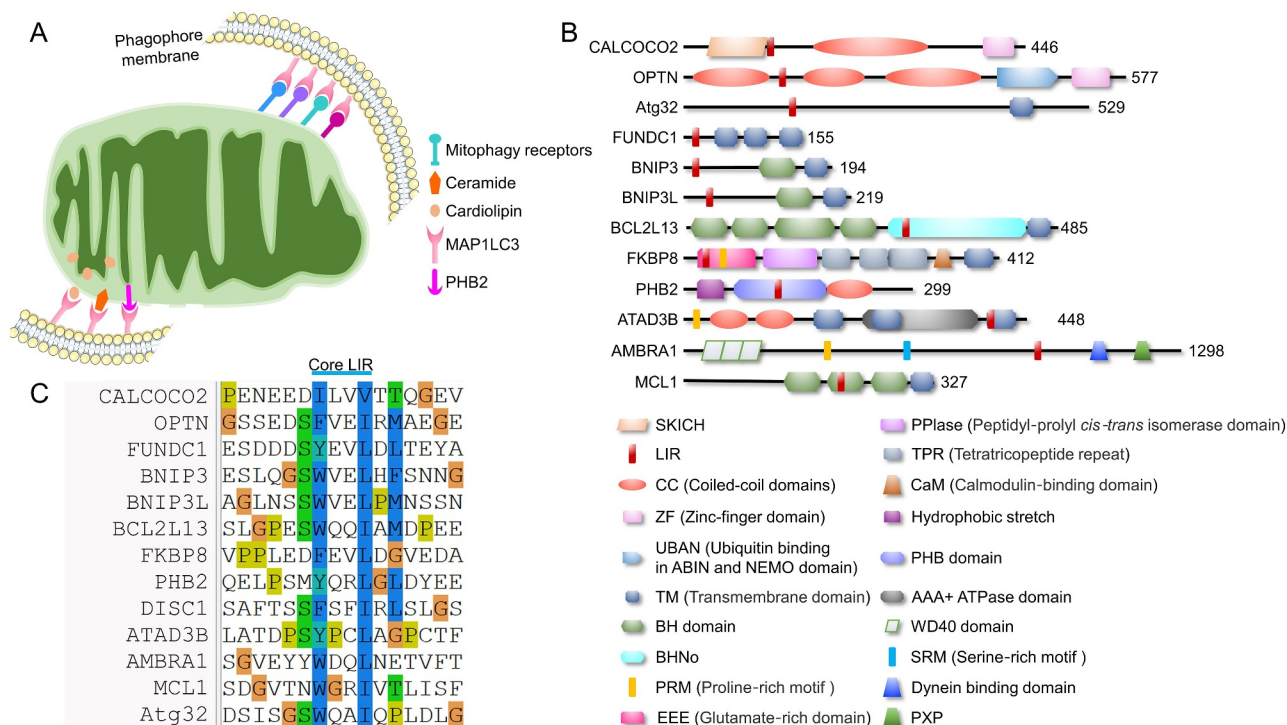
phosphorylate DNMI1 at S616 to regulate mitochondrial fission [64]. Other studies elaborated that PINK1 and PRKN could modulate mitochondrial PRKA/PKA (protein kinase AMP-activated) signaling [65,66], mitochondrial calcium homeostasis [67,68] and mitochondrial chaperone [69]. Therefore, further studies are needed to dissect the exact physio-pathological functions of the PINK1-PRKN-mediated mitophagy in Parkinson disease.

### Receptor-mediated mitophagy

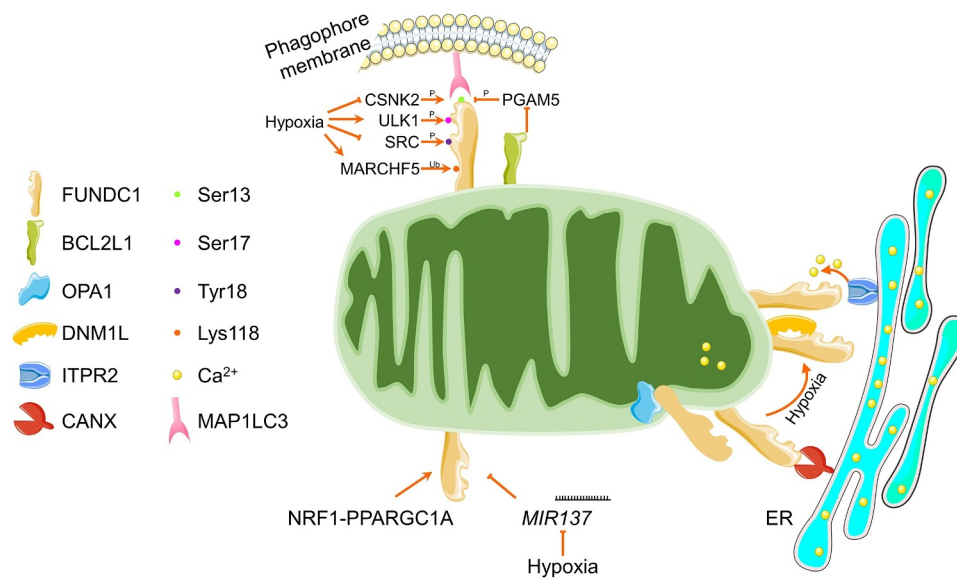
The specific sequestration of the certain cargo for selective autophagy is mainly achieved by autophagy receptors. The autophagy receptors always target the to-be-degraded cargo (damaged organelles, protein aggregates or invading pathogens) and tether them to the phagophore membrane by interacting with MAP1LC3 members (including MAP1LC3A, MAP1LC3B, MAP1LC3B2 and MAP1LC3C) or the homologs (GABARAP, GABARAPL1 and GABARAPL2) *via* an LC3-interacting region (LIR) motif [70]. The canonical LIR is composed of a (W/F/Y)XX(L/I/V) core motif that interacts with two hydrophobic pockets of the LIR docking site in MAP1LC3 and the homologs anchored in the phagophore membrane (Figure 2) [71]. In yeast, Atg32 was identified as a selective mitophagy receptor by two independent groups [72,73]. In mammalian cells, more than 10 mitophagy receptors have been identified for the specific sequestration of mitochondria for mitophagy program. Emerging evidence shows that these different receptors sense distinct stress signals to coordinate the mitochondrial quality control.

### FUNDC1-mediated mitophagy

FUNDC1 (FUN14 domain containing 1) is a mitochondrial outer membrane protein, with its N terminus exposed to the cytosol and C terminus inserted into the mitochondrial outer membrane. In the N terminus, FUNDC1 possesses a canonical LIR motif (Y<sub>18</sub>XXL<sub>21</sub>) (Figure 2). Dependent on this LIR, FUNDC1 could directly interact with MAP1LC3 and homologs, and thus drive mitophagy. Mutants in the LIR disrupt the FUNDC1-MAP1LC3 interaction and significantly prevent hypoxia-induced mitophagy [74]. The mitophagy-driving activity of FUNDC1 is determined by several dynamic phosphorylation and dephosphorylation. Specifically, SRC (SRC proto-oncogene, non-receptor tyrosine kinase) kinase and CSNK2 (casein kinase 2) phosphorylate FUNDC1 at Tyr18 (exactly in the LIR motif) and Ser13, respectively, which restrain the FUNDC1-MAP1LC3 interaction. Dephosphorylation of FUNDC1 at Ser13 by the mitochondrial phosphatase PGAM5 strengthens the FUNDC1-MAP1LC3 interaction and facilitates the FUNDC1-dependent mitophagy [74–76]. BCL2L1 (BCL2 like 1), an anti-apoptotic member in BCL2 family, directly binds to PGAM5 phosphatase, limits the phosphatase activity, and thus maintains the FUNDC1 phosphorylation at Ser13 to antagonize the FUNDC1-dependent mitophagy [77,78]. Besides, ULK1 (unc-51 like autophagy activating kinase 1), an upstream kinase for autophagy initiation, phosphorylates FUNDC1 at Ser17, which expedites the FUNDC1-MAP1LC3 interaction and is required for the FUNDC1-dependent mitophagy [79]. It is still elusive but of great interests that why FUNDC1 needs these distinct phosphorylated regulations,



**Figure 2.** Major receptors mediated mitophagy. (A) Mitophagy receptors are mainly localized on mitochondrial outer membrane. The mitochondrial inner membrane resident cardiolipin could transfer to the outer membrane and bind to MAP1LC3 directly, while the rupture of outer membrane leads to the exposure of PHB2, leading to the PHB2-MAP1LC3 interaction to promote the PINK1-PRKN-mediated mitophagy. (B) Domain architectures of major protein mitophagy receptors. (C) Protein mitophagy receptors harbor LIR regions and directly bind to MAP1LC3 and homologs to initiate mitophagy.



**Figure 3.** Regulatory circuit of FUNDC1-mediated mitophagy. FUNDC1 is phosphorylated by CSNK2, ULK1 and SRC kinases at Ser13, Ser17 and Tyr18, respectively. The Ser13 is dephosphorylated by mitochondrial phosphatase PGAM5, which is finely tuned by BCL2L1. The phosphorylation at Ser17 while dephosphorylation at Ser13 and Tyr18 under mitochondrial stresses (especially hypoxia) enhances the FUNDC1-MAP1LC3 interaction and stimulates mitophagy induction. The mitochondrial E3 ligase MARCHF5 could ubiquitinate FUNDC1 at Lys118 for its proteasomal degradation and thus desensitize hypoxia induced mitophagy. FUNDC1 is also tuned by transcriptional factor NRF1-PPARGC1A and *MIR137* at transcriptional and post-transcriptional level, respectively. FUNDC1 is enriched in MAM structure by interacting with ER resident CANX and ITPR2, where it promotes the release of ER  $\text{Ca}^{2+}$  to mitochondria and cytosol. Under mitochondrial stresses, FUNDC1 disassociates with OPA1 and CANX, while associates with DNM1L at MAMs to facilitate mitochondrial fission and mitophagy.

and why phosphorylation at different (but adjacent) sites by the corresponding kinases or phosphatases leads to completely opposite MAP1LC3-binding capacity. Furthermore, it is also unclear which phosphatases are involved in the dephosphorylation of FUNDC1 at Tyr18 and Ser17. Additionally, the mitochondrially resident E3 ligase MARCHF5 (membrane associated ring-CH-type finger 5) could directly interact with FUNDC1 and catalyze its ubiquitination at Lys119 for the subsequent proteasomal degradation, thus desensitize hypoxia-induced mitophagy (Figure 3) [80]. FUNDC1 is evolutionally conserved. Recently, it has been reported that the FUNDC1 ortholog, FNDC-1 and *Fundc1*, similarly serve as mitophagy receptor and mediate mitophagy in *C. elegans* and *D. rerio*, respectively [81–83].

FUNDC1-mediated mitophagy is also finely tuned at transcriptional and post-transcriptional levels (Figure 3). Specifically, our recent study reported that NRF1 (nuclear respiratory factor 1) and PPARGC1A, the key transcriptional factor and co-factor involved in mitochondrial biogenesis, transcriptionally up-regulate the FUNDC1 expression and expedite mitophagy [84], which highlights the coordination of mitochondrial integrity by coupling mitophagy and mitochondrial biogenesis via PPARGC1A-NRF1-FUNDC1 axis [85]. *MIR137* (microRNA 137), a hypoxia down-regulated microRNA, could target 3' UTR of *FUNDC1* mRNA and significantly reduce the FUNDC1 protein level, leading to impaired mitophagy without affecting general autophagy [86].

Chen and colleagues reported that FUNDC1 could interact with the mitochondrial dynamics proteins OPA1 and DNM1L, thus coordinate both mitochondrial fusion and fission. Mitochondrial stress drives the disassembly of the FUNDC1-OPA1 complex while strengthens the DNM1L recruitment onto mitochondria by enhancing the FUNDC1-

DNM1L interaction. The dephosphorylation at Ser13 is important for this switch from FUNDC1-OPA1 interaction to FUNDC1-DNM1L interaction, thus triggers the mitochondrial network disruption and mitophagy initiation [87]. Mitochondria always connect with endoplasmic reticulum (ER) by the so-called mitochondria-associated membrane (MAM) structure. MAM is important for rapid exchange of biological molecules between mitochondria and ER to fulfill the diverse signaling transduction [88]. Moreover, MAM provides a unique location for DNM1L recruitment and mitochondrial fission [89,90]. It has been reported that MAM involves in the autophagosome and specific mitophagosome formation [91,92]. Two independent studies reported that FUNDC1 is enriched in MAM structure, and binds to the MAM components CANX (calnexin) and ITPR2 (inositol 1,4,5-trisphosphate receptor type 2) [93,94], which is functionally important for mitochondrial fragmentation and mitophagy initiation (Figure 3).

By using *fundc1* knockout mice, increasing evidence is emerging that the FUNDC1-dependent mitophagy is essential for mitochondrial quality control, while defect in this pathway leads to diverse disease pathogenesis. On one hand, FUNDC1-mediated mitophagy in brown fat tissue is essential for adaptive thermogenesis by coordinating mitophagy and mitochondrial biogenesis [84]. FUNDC1-mediated mitophagy in white adipose tissue is important for restraining high-fat diet induced obesity and insulin resistance. Deficiency in this mitophagy by specific deletion of *Fundc1* in adipose tissue exacerbates the accumulation of dysfunctional mitochondria in adipocytes, leading to aggravated oxidative stress, apparent macrophages infiltration and abominable metabolic disorder [95]. Muscle-specific deletion of *Fundc1* also impairs the mitochondrial function, however antagonizes the high-fat

diet-induced obesity and insulin resistance [96]. It is still unknown why FUNDC1 in adipose tissue and skeletal muscle possesses completely opposite impact on metabolic homeostasis in mice, although in both tissues FUNDC1-mediated mitophagy is important for the removal of damaged mitochondria. On the other hand, it has been revealed that the FUNDC1-mediated mitophagy is indispensable for tissue protection from injury and toxic insults (especially the ischemia-reperfusion injury) in brain [97], heart [93,98–100], liver [101], kidney [102], and intestine [103]. Furthermore, FUNDC1 is regarded as a tumor suppressor and defect in this mitophagy accelerates the tumorigenesis of hepatocellular carcinoma by hyperactivating inflammasome and excessively secreting pro-inflammatory cytokines [104].

### **BNIP3- and BNIP3L-mediated mitophagy**

Both BNIP3 (BCL2 interacting protein 3) and BNIP3L/NIX (BCL2 interacting protein 3 like) were originally identified as BH3-only pro-apoptotic proteins integrated in the mitochondrial outer membrane *via* C-terminal transmembrane domain, although their BH3 domains are poorly conserved [105]. BNIP3 harbors a canonical LIR motif essential for the interaction with MAP1LC3 and mitophagy induction (Figure 2) [106–108]. The phosphorylation of BNIP3 at Ser17 and Ser24 flanking the LIR motif enhances the BNIP3-MAP1LC3 interaction and facilitates mitophagy [109]. However, the detailed regulatory mechanism is still vague.

BNIP3L is essential for the maturation of red blood cells. *Bnip3l* ablation results in the retardation of erythroid cells differentiation, leading to anemia and splenomegaly in mice [110]. The following studies revealed that mitochondria are retained during the maturation of reticulocytes in *bnip3l* null mice [111,112]. Structurally, BNIP3L contains a LIR motif in the N terminus toward cytoplasm. Through this LIR, BNIP3L could directly interact with GABARAP and MAP1LC3 to initiate mitophagy (Figure 2) [113,114]. Similarly, BNIP3L-mediated mitophagy can be regulated by dynamic phosphorylated modifications. PRKA kinase phosphorylates BNIP3L at Ser212 leading to the translocation of BNIP3L from mitochondria and sarcoplasmic reticulum to cytosol, subsequently impairing mitophagy program [115]. The phosphorylation of Ser34 and Ser35 adjacent to the LIR motif strongly enhances the interaction between BNIP3L and MAP1LC3 homologs, thus facilitates the phagophore sequestration of mitochondria [116]. Ser81 was reported as another phosphorylatable residue. Phosphorylation at this site reinforces the binding affinity to MAP1LC3 family members [117]. Additionally, BNIP3L dimerization robustly strengthens the MAP1LC3-BNIP3L interaction and subsequently boosts the mitophagy induction [118].

Both BNIP3 and BNIP3L are transcriptionally dominated by the transcriptional factor HIF1A (hypoxia inducible factor 1 subunit alpha) [119–121]. The hypoxia-responsive element in the promoter region encoding by *Bnip3* confers it hypoxia-responsive [122]. Alternatively, FOXO3 (forkhead box O3) was reported to transcriptionally regulate the expression of BNIP3 and BNIP3L [123]. Circadian gene *ARNTL* (aryl hydrocarbon receptor nuclear translocator like) also regulates the transcription of BNIP3 *via* binding to the E-Box element

within its promoter region, which is important for mitophagy induction and sustains the cardiac function [124]. Additionally, BNIP3 is also transcriptionally regulated by TP53 (tumor protein p53), NFKB1 (nuclear factor kappa B subunit 1), and other tumor-relevant transcriptional factors in the corresponding circumstances [125]. Furthermore, the expression of BNIP3 could be epigenetically suppressed by hypermethylation of the promoter region [126,127]. These complicated regulations of BNIP3 and BNIP3L suggest a regulatory necessity of the BNIP3- and BNIP3L-mediated mitophagy in response to distinct physiological adaptations and stressed conditions.

Similar to FUNDC1, BNIP3- and BNIP3L-mediated mitophagy is important for maintaining the mitochondrial integrity and tissue-protective. Specifically, the HIF1A-BNIP3 and HIF1A-BNIP3L axes are critical to protect brain [117,128] and kidney [129,130] against ischemia-reperfusion injury. On the contrary, Jin and colleagues reported that the BNIP3-mediated mitophagy overtly depletes the mitochondria resulting in metabolic disorder and aggregating cardiac ischemia-reperfusion injury [131]. BNIP3 is proved as a tumor suppressor [125], and loss of BNIP3-mediated mitophagy promotes mammary tumor growth and increases lung metastasis by remodeling the cellular metabolism toward the aerobic glycolysis [132]. BNIP3 expression also restrains the pancreatic cancer [127] and colorectal cancer [126,133]. However, whether the mitophagy-driving activity of BNIP3 is involved in these tumor suppressions was not studied. On the contrary, BNIP3L-mediated mitophagy may function as a tumor promoter in pancreatic ductal adenocarcinoma through limiting the mitochondrial glucose flux and supporting the redox regulation. *Bnip3l* deletion markedly delays the progression of pancreatic cancer and improves survival in a murine model of pancreatic ductal adenocarcinoma [134]. Hence, it is of great interest to further dissect the exact roles of BNIP3- and BNIP3L-mediated mitophagy in tissue injury and tumorigenesis.

It should not be ignored that both BNIP3 and BNIP3L are originally identified as pro-apoptotic proteins. They interact with BCL2 and BCL2L1 *via* the transmembrane domain, release BH3-only proteins to interact with BAX or BAK1 and induce CYCS release, CASPs activation, and cell death. It has been assumed that the BNIP3- and BNIP3L-mediated mitophagy is cell-protective, while loss of this mitophagy would accelerate the cell death [121]. Moreover, BNIP3- and BNIP3L-mediated mitophagy and metabolic reprogramming regulate the cell fate determination during the differentiation of stem cells and de-differentiation of the induced pluripotent stem cells [135]. However, it is still unclear whether any endogenous metabolites could dominate the cellular fates decision toward protective mitophagy, apoptosis, differentiation or de-differentiation by manipulating BNIP3 and BNIP3L.

### **BCL2L13-mediated mitophagy**

BCL2L13/BCL-Rambo (BCL2 like 13) was originally identified as a pro-apoptotic protein anchored on mitochondrial outer membrane with its N terminus exposed to the cytosol and C terminus in the intermembrane space [136]. Previous studies

reported that BCL2L13 interacts with mitochondrial permeability transition pore (mPTP) components SLC25A4/ANT (solute carrier family 25 member 4) and VDAC, thus regulates the conformational transformation of mPTP for the release of CYCS [137,138]. In 2015, BCL2L13 was nominated as a mammalian Atg32 homolog as evidenced by its compensation of Atg32 to initiate mitophagy in yeast [139]. The residues 273–276 constitute a functional LIR to selectively interact with MAP1LC3C, GABARAP and GABARAPL1 to promote mitophagy in response to mitochondrial depolarization (Figure 2) [139,140]. Murakawa and colleagues recently reported that BCL2L13 recruits the ULK1 complex to drive mitophagy [141]. It has been well documented that BCL2L13 functions in multiple physiological processes including development and energy metabolism, while its dysregulation is associated with several pathological processes including tumorigenesis, bacterial infection, cardiovascular diseases and degenerative diseases [142]. However, whether BCL2L13-mediated mitophagy is engaged in these processes is still unclear.

#### **FKBP8-mediated mitophagy**

FKBP8 (FKBP prolyl isomerase 8), a unique member of the FK506-binding protein family, is predominantly localized in mitochondrial outer membrane. Early studies indicated that FKBP8 suppresses apoptosis by recruiting the anti-apoptotic proteins BCL2 and BCL2L1 to mitochondria [143]. In addition, FKBP8 serves as a multifunctional chaperone important in hypoxia signaling and MTOR (mechanistic target of rapamycin kinase) pathway [144]. FKBP8 was reported as a MAP1LC3-interacting protein. Dependent on its LIR motif in the N terminus, FKBP8 can directly bind to MAP1LC3A and profoundly induce PRKN-independent mitophagy (Figure 2) [145]. A following study revealed that FKBP8 is critical for the mitochondrial fragmentation and mitophagy induction in response to iron depletion and hypoxia [146]. Interestingly, FKBP8 itself escapes from the to-be-degraded mitochondria to ER during both the PRKN-mediated mitophagy and the FKBP8 ectopic-expression-induced mitophagy. This translocation is highly dependent on the basic amino acids in its C-terminal signal sequences [145,147]. Nevertheless, the detailed regulatory mechanisms and the physiological relevance of the FKBP8-mediated mitophagy are far from understood.

#### **PHB2-mediated mitophagy**

PHB2 (prohibitin 2) is a multifunctional protein possessing multiple localizations. Notably, PHB2 in mitochondrial inner membrane functions as a chaperone to stabilize the mitochondrial respiratory complexes and support the mitochondrial bioenergetics. In the nucleus, PHB2 was reported to modulate several transcriptional factors involved in the cell cycle regulation. PHB2 also localizes on the plasma membrane to modulate the cell signaling [148]. In 2017, Wei and colleagues reported that PHB2 harbors a functional LIR motif and could interact with MAP1LC3, which is functionally important for the PRKN-mediated mitophagy in mammalian cells and *C. elegans* when the mitochondrial outer membrane is ruptured (Figure 2). Thus, PHB2 is the first protein mitophagy receptor identified in the

mitochondrial inner membrane. This enlightening study revealed a novel mitophagy paradigm, in which mitochondrial inner membrane performs a key role in cargo recognition for mitophagy [149]. However, a recent study challenged this hypothesis and put forward an alternative proposal. Yan et al. found that the LIR motif is dispensable for PHB2-mediated mitophagy. PHB2 destabilizes and negatively regulates the enzymatic activity of PARL, the mitochondrial protease resident in the inner membrane essential for PINK1 hydrolysis. In this regard, PHB2 enhances PINK1 recruiting onto mitochondrial outer membrane and facilitates the PINK1-PRKN-mediated mitophagy [150]. Therefore, further investigations are needed to explore the detailed regulatory circuit and physiological significance of PHB2-mediated mitophagy.

#### **Mitochondrial lipid as mitophagy receptors**

Besides to these mitochondrial proteins functioning as mitophagy receptors, mitochondrial lipid molecules, especially cardiolipin and ceramide, similarly serve as mitophagy receptors to mediate the specific sequestration of damaged mitochondria by autophagosome (Figure 2). Cardiolipin is a unique phospholipid exclusively located in the mitochondrial inner membrane, where it supports proper cristae folding, respiratory chain and ATP synthesis [151]. Upon pro-mitophagy stresses, cardiolipin externalizes to the mitochondrial surface, where it binds to MAP1LC3 for the subsequent phagophore recognition of mitochondria. Mechanistically, Arg10 and Arg11 residues in MAP1LC3 constitute the cardiolipin-binding pocket responsible for the MAP1LC3-cardiolipin interaction [152,153]. NME4 (NME/NM23 nucleoside diphosphate kinase 4), a hexameric protein resident in the mitochondrial intermembrane space, enables the cardiolipin externalization and is important for mitophagy initiation [154]. A recent study reported that pro-IL1A (interleukin 1 alpha) is translocating onto mitochondria, where it directly interacts with cardiolipin through a similar motif found in MAP1LC3 for interaction with cardiolipin. This pro-IL1A-cardiolipin interaction competitively disrupts the MAP1LC3-cardiolipin interaction, leading to mitophagy defect, damaged mitochondria accumulation, and NLRP3 inflammasome hyper-activation. This study confirms the mitophagy-driving activity of cardiolipin [155]. In addition, ceramide, a group of bioactive sphingolipids present in the bio-membrane, was also reported as a novel mitophagy receptor. Supplementation of a ceramide analog, or enhancing the generation of endogenous C<sub>18</sub>-ceramide by ectopic expression of CERS1 (ceramide synthase 1), triggers lethal mitophagy in cancer cells. The C<sub>18</sub>-ceramide can localize on mitochondria, where it binds to MAP1LC3 and mediates the phagophore engulfing mitochondria for mitophagy [156,157]. These findings collectively define novel mitophagy pathways mediated by the phospholipid components of mitochondrial membrane.

#### **Other mitophagy receptors**

Various studies characterized some other mitochondrial proteins as selective receptors for mitophagy in response to diverse stresses, including DISC1 (DISC1 scaffold protein)

[158], MCL1 [159], AMBRA1 (autophagy and beclin 1 regulator 1) [160] and ATAD3B (ATPase family AAA domain containing 3B) [161]. The canonical xenophagy receptors CALCOCO2 and OPTN are also engaged in the PINK1-PRKN-mediated mitophagy as discussed above (Figure 2).

It has been widely documented that different mitophagy pathways sense different mitochondrial stresses to initiate mitophagy for mitochondrial quality and quantity control in distinct circumstances [15]. Recent studies have revealed the cross-talk between different mitophagy pathways for the coordination of mitophagy. The complicated but precise regulations ensure a proper mitophagy activity to maintain the cellular homeostasis.

### Endogenous metabolites determine mitophagy

As the fundamental compartments for cellular metabolisms, mitochondria are highly sensitive to the intracellular metabolic programs and extracellular nutrients availabilities. Mitochondrial behaviors including morphological dynamics, mitochondrial metabolism and mitochondrial retrograde signaling are finely tuned by the physiological and pathological programs. Additionally, mitophagy, the major mechanism for mitochondrial quality and quantity control, is tightly manipulated by certain endogenous metabolites. It has been well characterized that the mitochondrial inevitable by-product ROS could facilitate mitophagy *via* distinct mechanisms, which has been comprehensively summarized in a recent review article [162]. Specifically, Dagda and colleagues reported that the loss of PINK1 increases the mitochondrial superoxide production and elicits oxidative stress, which are critically important for the coordination of mitophagy and mitochondrial dynamics [163]. Other studies suggested that the generation of mitochondrial ROS also initiates the PINK1-PRKN-dependent mitophagy, and this mitophagy could be abolished by expression of the mitochondrial antioxidant proteins [164]. The decline in ATP production due to certain mitochondrial stresses could drive mitophagy through activation of AMP-activated protein kinase (AMPK) signaling pathway [165]. Furthermore, other cellular metabolites associated with iron-, calcium-, glycolysis-TCA-, nicotinamide adenine dinucleotide (NAD)<sup>+</sup>-, amino acids-, fatty acids-, and cAMP-metabolism, also modulate mitophagy in corresponding circumstances.

### Iron metabolites and mitophagy

Mitochondria provide the center compartment for cellular iron metabolism. The cytosolic iron is imported into mitochondrial matrix *via* the iron transporters SLC25A37/MFRN1 in erythroid cells and SLC25A28/MFRN2 in non-erythroid cells [166]. Mitochondrial iron could be safely sequestered by FTMT (ferritin mitochondrial), or directly utilized for synthesis of heme and iron-sulfur cluster (ISC), two major iron-containing molecules required for a number of enzymes [167]. Iron deprivation has been well documented to trigger mitophagy in different models. By utilizing a chemical screen, iron chelator deferiprone (DFP) was nominated as a potent mitophagy inducer in U2OS osteosarcoma and SH-SY5Y neuroblastoma cells. The exposure of DFP declines the

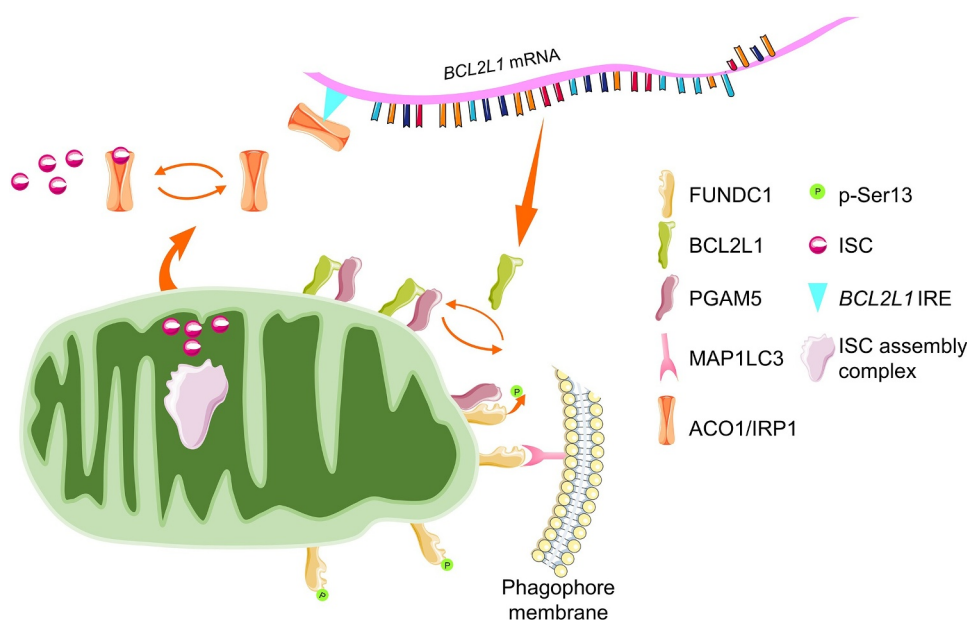
mitochondrial respiration and drives mitophagy induction independent on PINK1 and PRKN, leading to the metabolic reprogramming toward glycolysis [168]. DFP also elevates the expression of FTMT *via* HIF1A-SP1 (Sp1 transcription factor) axis and results in the translocation of FTMT precursor on the mitochondrial outer membrane, where FTMT precursor specifically interacts with NCOA4 (nuclear receptor coactivator 4, an autophagic receptor for ferritinophagy selectively degrading ferritin for iron turnover [169]) and initiates mitophagy [170]. Additionally, iron depletion was also reported to trigger mitophagy in pathogenic yeast *Candida glabrata* dependent on Atg32 homolog [171], and in *C. elegans* dependent on *pdr-1*/PRKN and *dct-1*/BNIP3 [172]. Specifically, pyoverdine, an iron-cheatable siderophore derived from bacterium *Pseudomonas aeruginosa*, disrupts the mitochondrial iron homeostasis and triggers mitophagy in the host *C. elegans* [173]. Taken together, these studies enlighten a crosstalk between mitophagy and iron homeostasis.

Recently, our group revealed a fundamental role of mitochondrial ISC assembly in determining mitophagy (Figure 4). RNAi screen identified that the silence of mitochondrial genes involved in ISC assembly triggers mitophagy in a FUNDC1-dependent manner. Mechanistically, ISC supports the aconitase activity of ACO1 (aconitase 1), while defective ISC biosynthesis switches ACO1 to ISC-free IRP1 (iron regulatory protein 1) apoprotein, which is then binding to the newly identified iron regulatory element (IRE) in the 5'UTR of *BCL2L1* mRNA. IRP1 apoprotein binding leads to the translational repression of *BCL2L1*, triggering FUNDC1 dephosphorylation and mitophagy initiation by releasing the PGAM5 phosphatase [174]. This study enlightens a novel regulatory circuit comprising ACO1/IRP1-BCL2L1-PGAM5-FUNDC1 axis in determining mitophagy in response to iron stress and sheds new light on the mitophagy-restraining activity of ISC by supporting *BCL2L1* translation. Similarly, a previous study revealed that the silence of FXN (frataxin), one of the most significant mitochondrial proteins involved in ISC bio-synthesis, also drives mitophagy program both in mammalian cells and *C. elegans* [172].

Hemin facilitates mitophagy in a BNIP3L-dependent manner in human chronic myeloid leukemia cell line K562 [175]. Knockdown of ALAS2 (5'-aminolevulinic acid synthase 2), the rate-limiting enzyme catalyzing heme synthesis, downregulates the expression of BNIP3L [176]. HMOX1 (heme oxygenase 1) is the stress-responsive enzyme catalyzing the degradation of heme and yielding biliverdin, carbon monoxide (CO) and ferrous iron. It was reported that HMOX1 is mitochondria-protective by maintaining the expression of PINK1 and PRKN [177,178]. CO is an endogenous gaseous molecule conferring protection against cellular stress at distinct aspects [179]. CO inhalation increases the expression of PINK1 and PRKN, leading to both mitophagy and mitochondrial biogenesis to maintain the mitochondrial homeostasis in cultured hepatocytes *in vitro* and in liver tissue *in vivo* [180]. However, the physiological role of endogenous CO in mitophagy is still unclear.

Collectively, the emerging evidence has revealed the tight communication between iron metabolism and mitophagy. As dozens of mitochondrial proteins possess heme or ISC





**Figure 4.** ISC antagonizes FUNDC1-mediated mitophagy. ISC is mainly synthesized in mitochondria by the ISC assembly complex. The newly assembled ISC is transported into the cytosol to support the aconitase activity of ACO1/IRP1 for the TCA cycle. During iron deficiency or genetic susceptibility, defective ISC assembly enables ACO1/IRP1 unbound. The free ACO1/IRP1 targets to the IRE region of *BCL2L1* mRNA, leading to the translational suppression and protein downregulation. The mitochondrial phosphatase PGAM5 is liberated to dephosphorylate FUNDC1 and facilitates mitophagy.

(or both) as the essential co-factors, it is not unexpected that iron deprivation and defective ISC assembly could disrupt the mitochondrial architecture, compromise mitochondrial functionalities and drive mitophagy. Furthermore, disrupted iron homeostasis (both iron deposition and iron deficiency) and abnormal iron metabolism have been widely reported to strongly associate with diverse disease pathogenesis, during which mitochondrial dysfunction is primarily formulated [181]. Therefore, it is of great clinical importance to explore the exact relevance of mitophagy and iron metabolism in the pathogenesis of these human diseases.

### **Ca<sup>2+</sup> and mitophagy**

Calcium ion (Ca<sup>2+</sup>) is one of the most versatile signal molecules. Mitochondria serve as important regulators of cellular Ca<sup>2+</sup>. The appropriate mitochondrial Ca<sup>2+</sup> facilitates mitochondrial bioenergetics by sustaining the TCA activity through supporting several fundamental enzymes, including pyruvate dehydrogenase, isocitrate dehydrogenase and  $\alpha$ -ketoglutarate dehydrogenase. However, the uncontrolled increase in cytoplasmic Ca<sup>2+</sup> and mitochondrial Ca<sup>2+</sup> could drive cell death. Specifically, prolonged mitochondrial Ca<sup>2+</sup> overload triggers the opening of mPTP, leading to the release of pro-apoptotic molecules and activation of downstream CASPs [182]. Mitochondrial outer membrane is permeable to solutes and ions, while Ca<sup>2+</sup> across the inner membrane is highly regulated. Through the VDACS in the outer membrane, MCU (mitochondrial Ca<sup>2+</sup> uniporter) mediates the Ca<sup>2+</sup> transfer through the inner membrane. The close contacts between mitochondria and ER render the rapid Ca<sup>2+</sup> uptake by mitochondria from ER through ITPRs-VDACS-MCU.

Additionally, mitochondria could also export excessive Ca<sup>2+</sup> and thus ensure the mitochondrial Ca<sup>2+</sup> homeostasis. SLC8B1/NCLX (solute carrier family 8 member B1) is the mitochondrial Na<sup>+</sup>-Ca<sup>2+</sup> exchanger, mediates mitochondrial Ca<sup>2+</sup> efflux by catalyzing Na<sup>+</sup>- or Li<sup>+</sup>-dependent Ca<sup>2+</sup> export [183].

As a vital signal molecule, Ca<sup>2+</sup> could regulate the autophagic flux, although the mechanisms seem complicated and the effects are context-dependent [184]. Along with the downstream kinases, including PRKC/PKC (protein kinase C), CAMKK2 (calcium/calmodulin dependent protein kinase 2), CAMK (calcium/calmodulin-dependent kinase), MAPK1/ERK2 (mitogen-activated protein kinase 1)-MAPK3/ERK1 and PIK3C3/VPS34 (phosphatidylinositol 3-kinase catalytic subunit type 3), Ca<sup>2+</sup> could stimulate the autophagy induction [184]. However, several studies reported that Ca<sup>2+</sup> could antagonize the autophagic flux. Specifically, Ca<sup>2+</sup> is indispensable for CAPN1 (calpain 1)-mediated cleavage of ATG5, and this ATG5 cleavage inhibits ATG12-ATG5 conjugation and prevents autophagy induction [185]. By sustaining the mitochondrial bioenergetics, it is not unexpected that mitochondrial Ca<sup>2+</sup> could inactivate AMPK pathway and hence suppress the autophagy by supporting ATP production [186,187].

Ca<sup>2+</sup> could also modulate the selective mitophagy. The sequestering capacity of Ca<sup>2+</sup> by mitochondria is highly dependent on the membrane potential. During mitochondrial depolarization, Ca<sup>2+</sup> released from mitochondria is captured by RHOT2, a key component of the adaptor complex anchoring mitochondria to motor proteins. The phosphorylated (by PINK1) and Ca<sup>2+</sup>-binding RHOT2 realigns from tetramers to monomers on the mitochondrial outer membrane, and functions as a platform for the subsequent PRKN translocation

[188]. Besides, there is a similar mechanism for RHOT1.  $\text{Ca}^{2+}$ -binding RHOT1 promotes PRKN translocation, while RHOT1 mutations in the EF-hands essential for  $\text{Ca}^{2+}$  binding decrease glutamate-induced calcium-provoked mitophagy in neurons [189]. It has been widely recognized that the  $\text{Ca}^{2+}$ -binding of RHOT1 and RHOT2 arrests mitochondrial mobility [190]. Therefore,  $\text{Ca}^{2+}$  sensors RHOT1 and RHOT2 act as key modulators for the coordination of mitochondrial mobility and the PINK1-PRKN-dependent mitophagy. Due to a significant implication of mitochondrial  $\text{Ca}^{2+}$  in determining mitochondrial integrity and programmed cell death, it is of great value to further elucidate the relationship between mitochondrial  $\text{Ca}^{2+}$  and mitophagy, especially in related human disease pathogenesis.

### Glycolysis-TCA cycle associated metabolites and mitophagy

Mitochondria are located at the center for both catabolism and anabolism of bio-molecules. The cytosolic glycolysis breaks down glucose into pyruvate to fuel the TCA cycle. The following TCA cycle enzymatically catalyzes nutrients such as lipids, carbohydrates and amino acids to generate smaller units and metabolites, supporting the oxidative phosphorylation for ATP production. Normal mitochondrial functionalities are important for these cellular metabolisms. Reversely, the related metabolites are potent modulators of mitophagy (Table 1).

Glucose provides the major carbon source for cellular bioenergetics. However, high plasma glucose (or hyperglycemia) is one of the most causative factors of diabetes, and is strongly correlated with the diabetes-related complications by damaging a group of kidney cells, neurons and endothelial cells [191]. It was firstly reported by H. Crabtree in 1929 that high level of glucose could suppress the cellular respiratory flux, known as Crabtree effect [192]. A number of hypotheses on the mechanisms underlying the Crabtree effect have been formulated. Recently, it has been reported that high level of glucose could induce mitophagy in diabetic platelets [193] and neuronal cells [194]. Mechanistically, hyper-production of ROS due to the mitochondrial fission may trigger this mitophagy [195]. Furthermore, high level of glucose upregulates the HIF1A activity [196,197], and thus induces the expression of PINK1 [198] or BNIP3 [199] for mitophagy induction, leading to the decrease in oxidative phosphorylation and increase in glycolysis. Therefore, the mitophagy-driving capacity of glucose may partially contribute to the Crabtree effect, although some other studies suggested that high level of glucose could inhibit mitophagy in other types of cells.

Furthermore, several glucose metabolites as discussed below could also modulate mitophagy in corresponding circumstances.

Lactate, previously regarded as the waste product of glycolysis, is gradually proved to serve as a major circulating carbohydrate fuel and a circulating redox buffer that equilibrates the NADH:NAD<sup>+</sup> ratio across cells and tissues in mammals [200]. Additionally, lactate could facilitate mitochondrial biogenesis *via* upregulation of PPARGC1A [201]. Lactate could block the autophagic flux and suppress the BNIP3-related mitophagy by blunting the expression of BNIP3 through the NR4A1 (nuclear receptor subfamily 4 group A member 1)-PRKDC (protein kinase, DNA-activated, catalytic subunit)-TP53 axis in vascular smooth muscle cells. This mitophagy inhibition aggregates the calcification of vascular smooth muscle cells in the presence of lactate [202,203].

Pyruvate, the C3 product of glycolysis, fuels the TCA cycle through decarboxylation and generation of acetyl-coenzyme A (acetyl-CoA) inside mitochondria. Pyruvate can be reduced to lactate and NAD<sup>+</sup> in the cytosol, thereby supporting the NAD<sup>+</sup> pool [204]. Early studies elucidated that both pyruvate administration and enhanced MPC (mitochondrial pyruvate carrier)-mediated mitochondrial pyruvate utilization facilitate mitochondrial biogenesis [205,206]. Recently, two independent groups reported that pyruvate could accelerate mitophagy by stabilizing PINK1. Ectopic expression of PDK4, a pyruvate dehydrogenase kinase phosphorylating and negatively determining the enzymatic activity of pyruvate dehydrogenase complex, leads to pyruvate accumulation and expedites mitophagy in response to mitochondrial depolarization. Supplementation of pyruvate alone facilitates PINK1 stabilization, drives PINK1 and MAP1LC3 recruitment onto mitochondrial surface and stimulates mitophagy induction [207]. The underlying mechanism was elaborated by Kim and colleagues. Pyruvate deprivation restrains the generation of NAD<sup>+</sup> (an important mitophagy inducer, which will be discussed below), leading to the inhibition of lysosomal acidification and mitophagy defect by increasing the acetylation of v-ATPase ATP6V0A1 [208].

Acetyl-CoA, the central cellular intermediate, is not only the catabolic product of the glycolytic pyruvate, fatty acids and branched-chain amino acids, but also the anabolic precursor for fatty acids, steroids and certain amino acids. Acetyl-CoA is the sole donor of acetyl groups for protein acetylation and thus extensively dominates the gene expression and cellular signaling. Furthermore, acetyl-CoA metabolism is regulated by compartmentalization, and mitochondria locate at the center [209]. It has been well understood that acetyl-CoA is a master

**Table 1.** Glycolysis-TCA cycle associated metabolites and mitophagy.

| Metabolite | Molecular Formula   | Metabolic Precursor   | Effect on Mitophagy  |
|------------|---|---|--|
| Lactate    | $\text{C}_3\text{H}_6\text{O}_3$                                      | Glucose (anaerobic glycolysis)  | Lactate antagonizes mitophagy through NR4A1-PRKDC-TP53-BNIP3 axis.   |
| Pyruvate   | $\text{C}_3\text{H}_4\text{O}_3$                                      | Glucose (aerobic glycolysis)  | Pyruvate accelerates mitophagy by stabilizing PINK1.<br>Pyruvate sustains the generation of NAD <sup>+</sup>   |
| Acetyl-CoA | $\text{C}_{23}\text{H}_{38}\text{N}_7\text{O}_{17}\text{P}_3\text{S}$ | Pyruvate (oxidative decarboxylation)<br>Fatty acid ( $\beta$ -oxidation)<br>Acetate | Acetyl-CoA exhaustion reduces mitochondrial acetylation, leading to PRKN-independent mitophagy.<br>Acetyl-CoA manipulates autophagy <i>via</i> dynamic acetylation of core autophagy proteins. |

autophagy regulator. Nutrient starvation causes a rapid depletion of acetyl-CoA and initiates the autophagy program, while replenishment of acetyl-CoA or dimethyl- $\alpha$ -ketoglutarate to complement sufficient amount of acetyl-CoA, could strongly suppress the starvation-induced autophagy. Mechanistically, acetyl-CoA determines the acetylated status of several core autophagy components by controlling the enzymatic activity of acetyltransferase EP300 [210]. Alternatively, acetyl-CoA also dominates the acetylation of RPTOR (regulatory associated protein of MTOR complex 1) and manipulates MTOR activation [211,212]. Given the significant role of acetyl-CoA in metabolism and signaling transduction, it is not unexpected that acetyl-CoA could manipulate mitophagy. During starvation, the mitochondrial acetyltransferase BLOC1S1/GCN5L1 (biogenesis of lysosomal organelles complex 1 subunit 1) is inactivated due to the rapid exhaustion of acetyl-CoA. The inactivation of BLOC1S1 leads to an extensive reduction in the acetylated modifications of mitochondrial protein, leading to a PRKN-independent mitophagy [213]. However, the exact mechanism by which mitochondrial acetylation manipulates mitophagy is still unknown. It is assumed that the deacetylations of mitochondrial proteins enable or facilitate the ubiquitination in an allosteric manner, which may signal to mitophagy induction [214].

Additionally, the TCA intermediate succinate could modulate mitophagy in certain circumstances [215]. Early studies revealed that succinate stabilizes the transcription factor HIF1A [216], boosts ROS generation [217], and modifies certain substrate proteins through succinylation [218]. It is still elusive whether HIF1A, ROS or succinylation is involved in succinate-induced mitophagy or not.

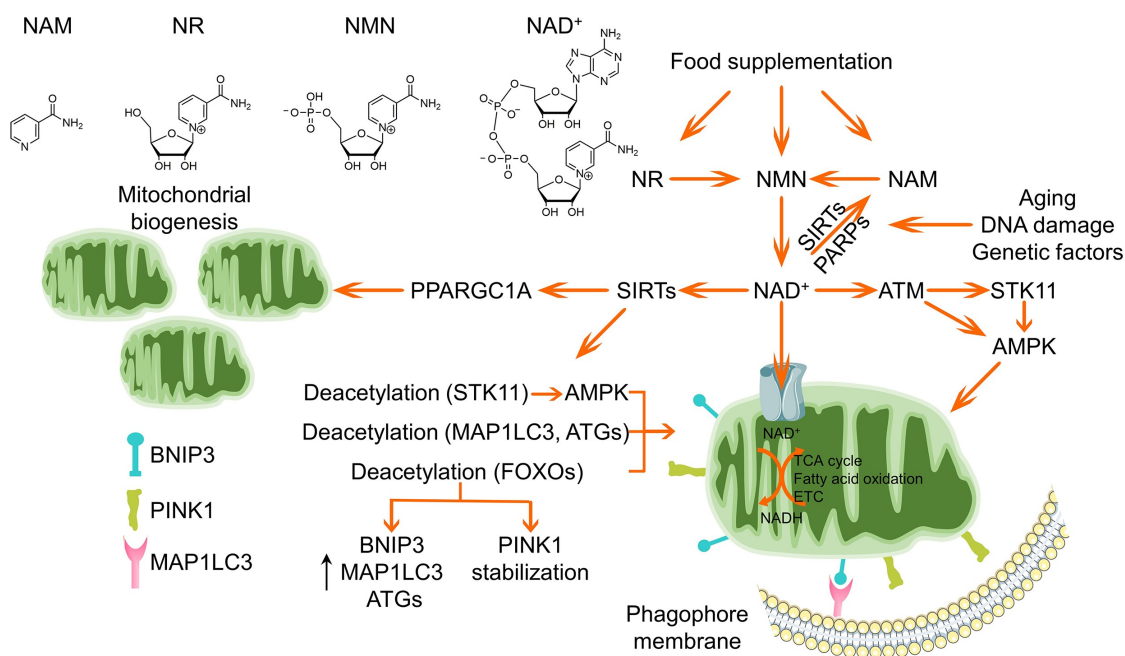
In conclusion, the glycolysis-TCA cycle associated intermediates are important to fuel oxidative phosphorylation for ATP production and supply certain intermediates for anabolism and redox determination. The anaerobically glycolytic lactate and the aerobically glycolytic pyruvate, as well as its downstream product acetyl-CoA could manipulate mitophagy as discussed above. It is assumed that the mitophagy-mediated metabolic remodeling confers the cellular adaption to the metabolic dynamics for maintaining the cellular homeostasis.

### NAD<sup>+</sup> and mitophagy

As a crucial co-enzyme important for hundreds of redox reactions and an essential co-factor for non-redox enzymes (including SIRT6 [sirtuins] and PARPs [poly(ADP-ribose) polymerases]), NAD<sup>+</sup> supports a group of metabolism pathways including glycolysis, TCA cycle, oxidative phosphorylation, and fatty acid oxidation, maintains the redox homeostasis by coordinating the generation and detoxification of ROS, sustains genomic stability, and manipulates gene expression [219,220]. Furthermore, a gradual decline in the cellular NAD<sup>+</sup> and prolonged disequilibrium of NAD<sup>+</sup> metabolism have been widely formulated in series of human diseases, especially aging associated metabolic disorders, cancers and neurodegenerative diseases, suggesting NAD<sup>+</sup> metabolism as a potential therapeutic target for these human diseases [220,221].

Although previous study implied that mitochondria could uptake cytosolic NAD<sup>+</sup>, it was just recently identified that SLC25A51 functions as the mitochondrial NAD<sup>+</sup> transporter and dictates the mitochondrial NAD<sup>+</sup> pool. SLC25A51 deficiency leads to increase in the mitochondrial mass but significant decrease in mitochondrial oxygen consumption rate, demonstrating a disturbed mitochondrial turnover during mitochondrial NAD<sup>+</sup> depletion [222]. NAD<sup>+</sup> repletion has been widely documented to ameliorate mitochondrial functionalities and protect against certain metabolic disorders [223–226]. Although the UPR<sup>mt</sup> conferring the retrograde signal from mitochondria to nucleus contributes to the beneficial effect of NAD<sup>+</sup> [223,226,227], it is not surprised that NAD<sup>+</sup> could modulate mitophagy to maintain the mitochondrial homeostasis (Figure 5). The challenge of nicotinamide (NAM), a metabolic precursor of NAD<sup>+</sup>, results in disturbed mitochondrial architecture and initiates mitophagy in a SIRT1-dependent manner. This mitophagy could be blocked by inhibition of NAM conversion to NAD<sup>+</sup> [228,229]. Xeroderma pigmentosum is a rare autosomal-recessive disorder with severe ultraviolet sensitivity and an increased risk of skin cancers due to the defective DNA repair. Xeroderma pigmentosum patient-derived cells present a clinical mitochondrial pathology, with mitochondrial dysfunction and mitophagy deficit. Mechanistically, the PARP1 hyperactivation due to the DNA damage leads to NAD<sup>+</sup> exhaustion, which results in mitochondrial hyper-polarization, excessive cleavage of PINK1, and disorder in the PINK1-PRKN-dependent mitophagy. Administration of NAD<sup>+</sup> precursors nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN) are able to restore the mitophagy and improve the mitochondrial functionalities in patient derived cells [230]. Furthermore, defects in ATM (ATM serine/threonine kinase), the master sensor and repairing regulator of DNA double-strand breaks, leads to a similar decline in NAD<sup>+</sup>. Damaged mitochondria accumulate in ATM-deficient neurons, mice, and worms. Treatment of NR or NMN complements NAD<sup>+</sup> levels and restores mitophagy in ATM-deficient cells through reestablishing SIRT1 activity. *dct-1*/BNIP3 and *pink-1*/PINK1 engage in this mitophagy pathway [231]. Additionally, it was also reported that NAD<sup>+</sup> replenishment could restore mitophagy, which is crashed in Alzheimer disease and Werner syndrome due to the depletion of NAD<sup>+</sup> [232,233]. Overall, these impressive studies collectively elaborated NAD<sup>+</sup> as an endogenous mitophagy inducer.

AMPK locates at the center of NAD<sup>+</sup>-induced mitophagy. As a major metabolic regulator, AMPK is one of the most important guardians for mitochondrial homeostasis, including dynamics, biogenesis and mitophagy [165]. Specifically, AMPK phosphorylates MFF, the primary receptor for DNM1L translocation onto mitochondrial outer membrane, leading to mitochondrial fission [234]. Furthermore, AMPK phosphorylates ULK1 to stimulate mitophagy induction [235]. AMPK activity is suppressed in NAD<sup>+</sup>-deficient cells, while NAD<sup>+</sup> replenishment could restore AMPK activation [232]. Mechanistically, ATM-mediated activation of STK11/LKB1 (serine/threonine kinase 11), the upstream kinase responsible for AMPK phosphorylation, is involved in NAD<sup>+</sup>-mediated AMPK activation and mitophagy induction. ATM could also



**Figure 5.**  $\text{NAD}^+$  boosts mitophagy. Cellular  $\text{NAD}^+$  could be complemented by food supplementation of the metabolic precursors including NAM, NR and NMN, or synthesized *de novo*. SIRT1 and PARPs are two major  $\text{NAD}^+$ -dependent enzymes catalyzing the  $\text{NAD}^+$  to yield NAM, which is gradually elevated during aging, DNA damage and other genetic or environmental insults.  $\text{NAD}^+$  is imported into mitochondria to sustain several mitochondrial metabolisms. It was reported that  $\text{NAD}^+$  facilitates mitochondrial biogenesis via SIRT1-PPARGC1A axis. Additionally,  $\text{NAD}^+$  activates AMPK kinase through supporting SIRT1 deacetylation of STK11, or through ATM-STK11-AMPK or ATM-AMPK axes. Alternatively, the activated SIRT1s could mediate deacetylation of autophagy core components MAP1LC3, ATG5 and ATG7, as well as deacetylation of FOXOs to promote the expression of BNIP3, MAP1LC3 and ATGs, or enhance PINK1 stabilization, which collaboratively strengthen the mitophagy program.

directly phosphorylate AMPK [236]. Furthermore,  $\text{NAD}^+$  could activate AMPK by sustaining SIRT1 deacetylation of STK11 [237]. However, other pathways are likely involved in the  $\text{NAD}^+$ -induced mitophagy, as knockdown of AMPK is unable to completely ablate the  $\text{NAD}^+$ -induced mitophagy [232]. The elevation of  $\text{NAD}^+$  supports the enzymatic activity of SIRT1, a master mitophagy regulator by finely tuning the acetylated status of MAP1LC3 [238], ATG5 and ATG7 [239], or activating the *daf-16/FOXO-dct-1/BNIP3* pathway [231].  $\text{NAD}^+$  also shapes mitochondrial morphology by manipulating the dynamics proteins [226]. Moreover, this  $\text{NAD}^+$ -mediated mitophagy is mitochondria- and cell-protective. As a group of aging-related diseases are manifested by  $\text{NAD}^+$  exhaustion due to the elevated DNA damage, genetic or epigenetic insults and environmental toxins, replenishment of  $\text{NAD}^+$  by supplementation of the metabolic precursors provides a highly potent therapeutic design for these diseases.

### Amino acids associated metabolites regulating mitophagy

Amino acids are the metabolic blocks for protein synthesis. They could also fuel cellular bioenergetics as carbon source, and certain amino acids are dedicating to signaling transduction as signal molecules. Specifically, amino acids are sensed by the corresponding sensors, leading to the activation of MTOR and suppression of autophagic flux [240]. It has been reported some amino acids associated metabolites as

mitophagy regulators in corresponding circumstances (Table 2).

Glutamine, the most abundant amino acid, functions as the nitrogen source for the bio-synthesis of nucleotides, amino acids, and hexamine, as well as carbon source to fuel the TCA cycle for bioenergetics through glutaminolysis [241]. During glutaminolysis, glutamine is converted to  $\alpha$ -ketoglutaric acid ( $\alpha$ -KG) and ammonia, which is catalyzed by mitochondrial GLS (glutaminase). Ammonia was previously identified as a diffusible autophagy-inducing molecule in cancer cells [242]. Ammonia supplementation increases the expression of BNIP3, PINK1, and PRKN, leading to the increased mitophagy in mammalian cells. Inhibition of GLS activity and glutamine withdrawal reduce the expression of BNIP3 [243]. Mechanistically, ammonia exposure facilitates HIF1A stabilization and elevates the transcription of the target genes (including BNIP3) under normoxic conditions [244]. Glutamate, the deamidated product of glutamine during glutaminolysis, was reported to facilitate PRKN translocation onto mitochondria. Excessive glutamate could trigger mitochondrial  $\text{Ca}^{2+}$  entry and  $\text{Ca}^{2+}$  binding to RHOT1, which leads to the arrest of mitochondrial mobility and PRKN recruitment onto mitochondria for the initiation of mitophagy, as discussed above [189,245].

$\gamma$ -Aminobutyric acid (GABA), a well-recognized inhibitory neurotransmitter, is a four-carbon non-protein amino acid, which is synthesized primarily from glutamate catalyzed by GAD (glutamate decarboxylase). The disorders in GABA metabolism are manifested in diverse human neurological diseases

**Table 2.** Amino acids associated metabolites regulating mitophagy.

| Metabolite              | Molecular Formula   | Metabolic Precursor                      | Effect on Mitophagy   |
|-------------------------|---|--|---|
| Ammonia                 | NH <sub>4</sub> <sup>+</sup>  | Amino acid (oxidative deamination)       | Ammonia promotes the expression of BNIP3, PINK1 and PRKN, thus facilitates mitophagy.   |
| Glutamate               | C <sub>5</sub> H <sub>9</sub> NO <sub>4</sub>                                       | Glutamine (glutaminolysis)               | Glutamate induces Ca <sup>2+</sup> entry leading to RHOT1-dependent PRKN translocation and mitophagy.   |
| GABA<br>NO              | C <sub>4</sub> H <sub>9</sub> NO <sub>2</sub><br>NO                                 | Glutamate<br>Arginine (catalyzed by NOS) | GABA activates MTOR and inhibits mitophagy.<br>NO triggers S-nitrosylation of PRKN and PRKN translocation to initiate mitophagy.<br>S-nitrosylation of PINK1 and PRKN impairs mitophagy.<br>NO disturbs phagophore formation to suppress mitophagy.   |
| Spermidine              | C <sub>7</sub> H <sub>19</sub> N <sub>3</sub>                                       | Arginine                                 | Spermidine activates ATM kinase-dependent activation of PINK1-PRKN pathway.<br>Spermidine induces the expression of BECN1, MAP1LC3, PINK1, PRKN, ULK1, ATGs, AMPK activation and MTOR inhibition.   |
| Melatonin               | C <sub>13</sub> H <sub>16</sub> N <sub>2</sub> O <sub>2</sub>                       | Tryptophan                               | Melatonin suppresses ROS-mediated EIF2AK4-ATF4-BNIP3 axis-dependent mitophagy.<br>Melatonin antagonizes mitophagy <i>via</i> PPARG-FUNDC1 axis in platelet and alleviates cardiac ischemia-reperfusion injury.<br>Melatonin antagonizes mitophagy <i>via</i> suppression of mitochondrial fission-VDAC1-HK2-mPTP-mitophagy axis in cardiac microvasculature. Melatonin activates ALDH2-CGAS-STING1-TBK1 signaling to restore mitophagy in cardiomyocytes of mice with Alzheimer disease.<br>Melatonin activates mitophagy <i>via</i> NR4A1-PRKDC-TP53-BNIP3 axis and improves mitochondrial quality in hepatocytes of nonalcoholic fatty liver disease. |
| H <sub>2</sub> S<br>GSH | H <sub>2</sub> S<br>C <sub>10</sub> H <sub>17</sub> N <sub>3</sub> O <sub>6</sub> S | Cysteine<br>Glutamate cysteine glycine   | H <sub>2</sub> S facilitates PINK1-PRKN mediated mitophagy <i>via</i> sulfhydrylation of PRKN and USP8.<br>GSH inhibits mitophagy by suppression of Atg32 in yeast.   |

[246]. It was reported that the increase in endogenous GABA level could inhibit the pexophagy (a selective type of autophagy degrading peroxisomes) and mitophagy, but not other autophagy related pathways in yeast. This deficit in pexophagy and mitophagy could be restored by supplementation of rapamycin, indicating a TOR activation-dependent manner of GABA restraining pexophagy and mitophagy. Furthermore, supplementation of GABA, or genetic ablation of ALDH5A1 (aldehyde dehydrogenase 5 family member A1; which catalyzes GABA to succinate to fuel the TCA cycle, leading to the decrease in endogenous GABA) leads to the accumulation of morphologically abnormal mitochondria and defective mitophagy in mammalian cells. This study elaborates the mitophagy-restraining activity of GABA, which may implicate in the pathogenesis of GABA disorder associated diseases [247].

Nitric oxide (NO) is a lipophilic, highly diffusible, and short-lived metabolite of NOS (nitric oxide synthase) that catalyzes the conversion of arginine into citrulline. It has been well understood that NO acts as a signaling molecule and plays the pleiotropic patho-physiological roles both in normal and diseased circumstances. Specifically, NO dictates S-nitrosylation of the target substrates and engages in the post-translational regulation and signaling transduction [248]. Excess NO is converted to the toxic reactive nitrogen species, which could bind to the electron transport chain components, leading to the disruption of mitochondrial functionalities [249]. NO could initiate the PINK1-PRKN-mediated mitophagy. The exposure of NO donor triggers PRKN translocation onto mitochondria even in PINK1 depleted cells. This NO-induced mitophagy facilitates PINK1-null dopaminergic neuronal cells to recover from mitochondrial damage [250]. It is assumed that S-nitrosylation of PRKN at Cys323 enhances the E3 ligase activity and accelerates mitophagy [251]. However, other studies reported that S-nitrosylation of PINK1 or PRKN leads to significantly reduced PRKN translocation onto mitochondria [252,253]. Besides, NO was proved to disturb autophagosome formation

through distinct mechanisms [254]. Therefore, it seems more complicated for NO manipulating mitophagy. Further mechanistic studies are needed.

Spermidine is another arginine derived polyamine metabolite. For mammals, spermidine could be obtained *via* autonomous synthesis by using arginine as the precursor, synthesis by the gut microbiota and uptake from dietary supplementation. Spermidine was previously identified as an anti-aging molecule in yeast, worms, flies, mice, and human cells through an autophagy-dependent manner [255–257]. Specifically, spermidine performs highly cardiac-protective properties. Administration of spermidine stimulates mitophagy in cardiomyocytes, maintains the mitochondrial functionalities and delays cardiac aging in mice [258,259]. Furthermore, exposure of spermidine also reestablishes mitophagy and leads to the reverse of senescence in muscle stem cell [260]. Mitophagy induction by spermidine has been linked to ATM kinase-dependent activation of PINK1-PRKN pathway [261]. Additionally, spermidine elevates autophagy- and mitophagy-related components including BECN1 (beclin 1), MAP1LC3, PINK1, PRKN, ULK1, and ATG proteins, and promotes AMPK activation and MTOR inhibition [262]. However, these studies mainly utilized exogenous administration of spermidine as models. The exact function and mechanism of endogenous spermidine in mitophagy are less characterized.

N-Acetyl-5-methoxytryptamine (melatonin) is a tryptophan-derived pleiotropic endogenous hormone exclusively synthesized in pineal gland. Melatonin is mainly supporting the optimal coordination of daily and seasonal rhythms. Harboring a prominent mitochondria-protective property, melatonin could improve mitochondrial integrity and protect against a wide variety of cardiovascular and neurodegenerative diseases. Melatonin could detoxify ROS, suppress ROS-mediated EIF2AK4/GCN2 (eukaryotic translation initiation factor 2 alpha kinase 4)-ATF4 (activating transcription factor 4)-BNIP3 axis-dependent mitophagy in placental trophoblasts

and relieve cadmium-induced fetal growth restriction [263]. Furthermore, emerging evidence indicated that melatonin antagonizes mitophagy in platelet *via* PPARG (peroxisome proliferator activated receptor gamma)-FUNDC1 axis, which could inhibit mitochondrial energy production, suppress platelet hyperactivity and alleviate cardiac ischemia-reperfusion injury [264]. However, how the PPARG signaling regulates FUNDC1-dependent mitophagy is elusive. Melatonin also antagonizes mitophagy in cardiac microvasculature *via* suppression of mitochondrial fission-VDAC1-HK2-mPTP-mitophagy axis. Specifically, melatonin activates AMPK, facilitates DNM1L phosphorylation at Ser37 but dephosphorylation at Ser616, blunting the DNM1L-dependent mitochondrial fission. The maintenance of mitochondrial architecture restores VDAC1-HK2 interaction to prevent mPTP opening and the PINK1-PRKN activation, eventually block mitophagy and alleviate ischemia-reperfusion-induced cardiac injury [265]. However, the same group also reported that melatonin activates ALDH2 (aldehyde dehydrogenase 2)-CGAS (cyclic GMP-AMP synthase)-STING1 (stimulator of interferon response cGAMP interactor 1)-TBK1 (TANK binding kinase 1) signaling axis and restores mitophagy in cardiomyocytes in mice model with Alzheimer disease [266]. Melatonin could negate the increased expression of NR4A1, therefore block the activation of PRKDC and TP53, leading to BNIP3 upregulation, mitophagy reconstruction and improving mitochondrial functionalities in hepatocytes during the pathogenesis of nonalcoholic fatty liver disease [267]. Therefore, the effect of melatonin on mitophagy seems complicated and context-dependent.

Besides supporting the biosynthesis of melatonin, tryptophan could also be mobilized to fuel the kynurenine pathway, the sole metabolism for *de novo* NAD<sup>+</sup> synthesis. Disorder in kynurenine pathway is a potential causative factor for numerous aging diseases. The enzymes involved in this pathway are gradually inactivated with aging and mitochondrial dysfunction. The endpoint products of the kynurenine metabolism, kynurenic acid and NAD<sup>+</sup>, as well as several intermediate metabolites in the metabolic branches, are potential intervention targets of these diseases [268,269]. As a potent mitophagy inducer as discussed above, NAD<sup>+</sup> *de novo* synthesis through the kynurenine pathway is critically important for the maintenance of mitochondrial integrity. Increase in NAD<sup>+</sup> production by tryptophan supplementation or enhanced metabolic flux enhances mitochondrial function, leading to the increased lifespan and delayed pathology in *C. elegans* [270], while loss of function of the kynurenine pathway associated critical enzymes results in congenital organ malformations [271]. Moreover, it is worth noting that the kynurenine pathway also modulates the mitochondrial integrity independent on metabolites. KMO (kynurenine 3-monooxygenase), one of the rate-limiting enzymes in the kynurenine pathway, localizes in the mitochondrial outer membrane. A genome-wide RNAi screen identified KMO as a modulator of mitochondrial morphology and PRKN-dependent mitophagy [272]. The increase in mitochondrial mass but decrease in respiratory capacity in *cn/KMO*-deficient flies supports the notion that KMO may regulate mitophagy. *Drosophila* studies showed that *cn/*

*KMO* genetically interacts with *Pink1*, *park* and *Drp1/DNM1L* in a manner independent on kynurenine metabolism [273]. However, the underlying mechanism is elusive.

Cysteine and methionine are primary sulfur-containing amino acids, which substantially maintain the cellular redox homeostasis by detoxifying free radicals and ROS [274]. Therefore, it is not unexpected that both cysteine and methionine could impinge on the mitophagy activity. Hydrogen sulfide (H<sub>2</sub>S), derived from cysteine by CTH (cystathionine gamma-lyase) and CBS (cystathionine beta-synthase), is an important gasotransmitter and plays a critical role in regulating cardiovascular functions [275]. Although lower concentration of H<sub>2</sub>S is beneficial for body fitness, higher level of H<sub>2</sub>S is toxic, especially to mitochondria by interfering the oxidative phosphorylation or sulphydrating certain mitochondrial proteins [276]. It was reported that exogenous H<sub>2</sub>S facilitates PRKN recruitment onto mitochondria and enhances the PINK1-PRKN-mediated mitophagy [277]. H<sub>2</sub>S-mediated sulphydration of PRKN and mitophagy associated deubiquitinase USP8 enhances the corresponding enzymatic activity and facilitates the PINK1-PRKN-mediated mitophagy [278,279]. However, other study demonstrated that the elevation of the endogenous H<sub>2</sub>S by CBS, CTH, and MPST triple gene therapy mitigates mitophagy in endothelial cells [280].

Glutathione (GSH), the  $\gamma$ -L-glutamyl-L-cysteinyl-glycine tripeptide as a key determinant of cellular redox homeostasis, is assembled by GCL (glutamate cysteine ligase) ligating cysteine to glutamate to produce  $\gamma$ -glutamylcysteine, and following by GSS (glutathione synthetase) catalyzing glycine and  $\gamma$ -glutamylcysteine to yield GSH [281]. GSH is converted into GSH disulfide (GSSG) and detoxifies oxidative stress by GSH-dependent peroxidases. Although GSH is not *de novo* synthesized in mitochondria, a line of evidence has been raised that multiple mitochondria associated GSH carrier proteins could mediate the mitochondrial transport of cytosolic GSH and determine the redox homeostasis inside the mitochondria [282]. In yeast, decrease in endogenous GSH induced by chemical or genetic manipulation initiates selective mitophagy but not general autophagy, and this mitophagy could be suppressed by supplementation of a cell-permeable form of GSH or antioxidant N-acetyl-L-cysteine to normalize the cellular GSH abundance [283]. Mechanistically, suppression of Atg32 expression by GSH leads to the mitophagy deficit [284]. However, it is still elusive whether GSH could modulate mitophagy in mammalian cells.

Besides cysteine, methionine is another sulfur-containing amino acid. The methionine residues in proteins are susceptible to oxidation. Therefore, it was assumed that the methionine constitutes an important antioxidant defense mechanism and substantially contributes to the cellular redox homeostasis [274,285]. The methionine-restricted diet could dramatically extend the healthspan of a variety of model organisms. Mitophagy is required for this lifespan extension [286]. Significant increases in PRKN and phosphorylated ubiquitin are observed during methionine restriction, suggesting that the PINK1-PRKN axis is involved in this mitophagy [287]. Mechanistically, S-adenosylmethionine, the most important methyl donor derived from methionine metabolism, facilitates

the methylation of the catalytic subunit of PPP2/PP2A (protein phosphatase 2), leading to the deficiency in autophagy and selective mitophagy [288].

### **Fatty acids associated metabolites regulating mitophagy**

Fatty acids are major energy source and important constituents of membrane lipids. Mitochondria play a dominative role in fatty acid metabolism, especially  $\beta$ -oxidation. Furthermore, the mitochondria derived citrate could shuttle to cytosol, where it is used to synthesize acetyl-CoA for lipogenesis. Mitochondria can also synthesize several phospholipids autonomously. Reversely, several fatty acids and the associated metabolites have been characterized to impinge on mitophagy activity to subsequently regulate the mitochondrial metabolism. Specifically, cardiolipin and ceramide are two well-characterized mitophagy receptors as discussed above. Furthermore, hyperlipemia could suppress mitophagy in a number of tissues *via* multiple mechanisms, suggesting a pathological role of the mitophagy suppression in obesity associated metabolic disorders [289,290].

Cholesterol, a key lipid molecule, is a metabolic precursor for the bio-synthesis of the steroid hormones, bile acids, and vitamin D. As mentioned above, mitochondria derived citrate could transport to cytosol and convert to acetyl-CoA for cholesterol *de novo* synthesis through the mevalonate pathway. Lysosomal storage disease Niemann-Pick type A (NPA) is characterized by the lysosomal cholesterol accumulation in diseased tissues including brain, spleen and liver, due to the genetic susceptibility or chemical interference. It has been reported that the fusion of mitochondria-containing autophagosomes with lysosomes is restrained in NPA hepatocytes, leading to the impaired mitophagy and aggregating acetaminophen induced liver injury [291]. The similar phenomenon is also observed in NPA neuron where lysosomal cholesterol accumulates [292]. Lysosomal cholesterol accumulation facilitates the hyper-activation of MTORC1 signaling, leading to the disruption of mitophagy program. Genetic or pharmacologic inhibition of MTORC1 could restore the lysosomal degradation of mitochondria, and ameliorate mitochondrial integrity in NPA neurons [293]. Alternatively, cholesterol overload aggravates the oxidative damage to promote the formation of OPTN aggregates, thereby blocking the OPTN translocation onto mitochondria for the PINK1-PRKN-mediated mitophagy [294]. These studies thus collectively highlight the mitophagy-restraining capacity of cholesterol.

Phosphatidylcholine (PC) is the predominant phospholipid class and required for the buildup of cell membrane. An overwhelming majority of PC is synthesized *via* the Kennedy pathway by using choline as the substrate. Deacceleration of PC *de novo* bio-synthesis by genetic ablation of choline kinase leads to mitochondrial damage, as evidenced by the impaired oxidative phosphorylation, decreased ATP production and increased ROS generation. Furthermore, PRKN, PINK1, MAP1LC3, polyubiquitin and SQSTM1/p62 are localized to these damaged mitochondria to initiate mitophagy [295]. Xiong et al. reported a strong association between aberrant choline-PC metabolism and mitophagy in diffuse large B-cell lymphoma [296]. Declined

choline uptake and disordered PC bio-synthesis lead to the remodeling of mitochondrial lipidomic signature, decrease in ATP production and AMPK activation, which are critical for mitophagy initiation [297]. Collectively, these studies thus shed light on a pathomechanistic link between choline-PC metabolism and mitophagy induction. Additionally, other studies reported that coenzyme Q [298,299] and bile acid [300] could also impinge on mitochondrial autophagy in the corresponding models.

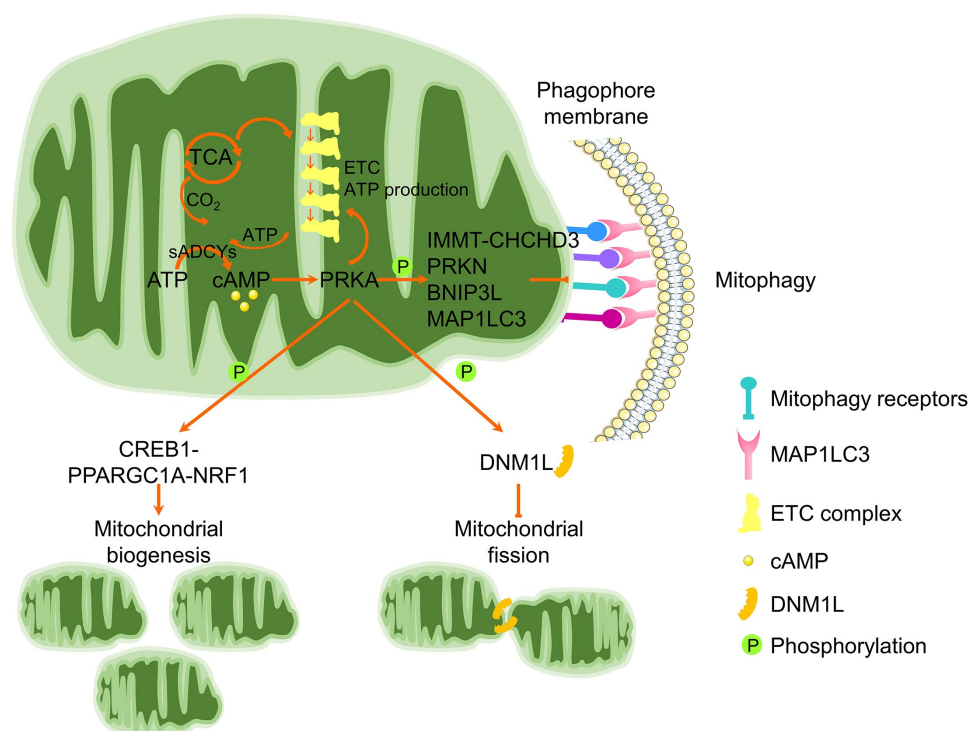
### **cAMP and mitophagy**

cAMP (cyclic adenosine 3',5'-monophosphate) is the first identified second messenger and plays fundamental roles in cellular signaling transduction, mainly by supporting the PRKA-CREB1 (cAMP responsive element binding protein 1) axis. ADCYs (adenylate cyclases), including transmembrane ADCYs (tmADCYs) and soluble ADCYs (sADCYs), are responsible for converting ATP into cAMP, while PDE (phosphodiesterase) catalyzes the hydrolysis of intracellular cAMP. It was reported that sADCYs reside at multiple subcellular organelles, including mitochondria [301]. sADCYs-mediated cAMP synthesis inside mitochondria sustains the mitochondrial bioenergetics through supporting PRKA-dependent phosphorylation of respiratory chain complexes [302]. Conversely, mitochondrial ATP,  $\text{Ca}^{2+}$  and bicarbonate could finely tune the enzymatic activity of sADCYs and facilitate the cAMP synthesis. Therefore, the mitochondrial health determines mitochondrial cAMP production and *vice versa*.

More than 100 mitochondrial proteins have been identified as potential PRKA substrates [303]. Specifically, PRKA could phosphorylate DNM1L and restrain its translocation onto the mitochondrial surface [304,305]. During starvation, cellular cAMP increases and supports DNM1L phosphorylation by PRKA, leading to mitochondrial elongation and protecting mitochondria from autophagic degradation [66,306,307]. The cAMP-PRKA also phosphorylates IMMT and CHCHD3/MIC19 (coiled-coil-helix-coiled-coil-helix domain containing 3), destabilizes PINK1 on the depolarized mitochondria, leading to the defect of the PINK1-PRKN-mediated mitophagy [36]. Furthermore, PRKN could be directly phosphorylated by PRKA. Similarly, this phosphorylation prevents the recruitment of PRKN onto mitochondria, resulting in defective mitophagy [308]. BNIP3L was recently reported as another PRKA substrate. PRKA phosphorylating BNIP3L abrogates BNIP3L-mediated mitochondrial fission and mitophagy [115]. Additionally, cAMP-PRKA axis also suppresses general autophagy by phosphorylating MAP1LC3 at its N-terminal region and abrogating MAP1LC3 recruitment to autophagosomes [309]. Collectively, these studies suggest a multifaceted modulation of mitophagy by the cAMP-PRKA axis (Figure 6).

### **Concluding remarks and perspective**

Mitochondria are highly dynamic organelles with constant fusion, fission, mobility, biogenesis and removal. These mitochondrial behaviors are coordinated to maintain the proper mitochondrial quality and quantity [8]. As mentioned above,



**Figure 6.** cAMP-PRKA signaling antagonizes mitophagy. Mitochondrial sADCYs are responsible for the biosynthesis of cAMP, which supports the PRKA activity. cAMP-PRKA phosphorylates CREB1 and activates the transcription of major mitochondrial biogenesis-associated factors. Mitochondrial fission protein DNM1L could be phosphorylated by PRKA, and this phosphorylation prevents its translocation onto the mitochondrial surface for mitochondrial fission. Furthermore, PRKA also phosphorylates IMMT, CHCHD3, PRKN and BNIP3L, abrogating PRKN- and BNIP3L-mediated mitophagy. MAP1LC3 phosphorylation by PRKA represses its translocation onto phagophores, thus inhibits general autophagy.

distinct pathways are sensing different mitochondrial stresses to coordinate mitophagy for mitochondrial quality control, suggesting a strict necessity to maintain a proper mitophagy activity for the cellular homeostasis [15].

Programmed mitophagy refers to the physiological routine to remove partial or all mitochondria in certain developmental, metabolic and physiological circumstances. Specifically, BNIP3L-mediated mitophagy is physiologically important for the maturation of red blood cells [111], while elimination of paternal mitochondria after fertilization is critical for the zygote development post fertilization and supports the maternal inheritance of the mitochondrial genome [310]. Besides, basal mitophagy, referred to the continuous removal of damaged mitochondria under steady-state level, was revealed by two transgenic mouse models to detect mitophagy *in vivo*, while its activity is highly tissue- and cell-dependent [311,312]. The induced mitophagy has attracted tremendous concerns. Although numerous studies utilized distinct mitochondrial toxins to trigger mitophagy, it is worth noting that the metabolic dynamics could impinge on mitophagy program due to the altered metabolites as mentioned above. Conversely, the induced mitophagy could finely tune the mitochondrial integrity including quality and quantity, and subsequently remodel the cellular metabolism. However, a group of previous studies aimed to explore the physiological

relevance of endogenous metabolites in mitophagy mainly rely on the exogenous administration of these metabolites or the metabolic precursors. These supplementations largely exceed the endogenous levels in some cases. Therefore, the exact physiological role of the endogenous metabolites in mitophagy regulation needs further investigations. The patients-derived cells with altered metabolic programs and metabolites are ideal models for these studies.

The defective mitophagy due to genetic susceptibility or environmental insults is manifested in several disease pathogenesis. Targeted normalization of proper mitophagy is believed to be a potent therapeutic design for these diseases. Exercise training is an effective nonpharmacological approach to resist pathogenesis. It has been reported that exercise could activate mitophagy to remove the damaged mitochondria and stimulate mitochondrial biogenesis to improve the mitochondrial functionalities in multiple tissues [313,314]. Furthermore, exercise-induced mitophagy is essential to reverse the high-fat diet-induced mitochondrial dysfunction [315]. The ATP-AMPK-ULK1 and NAD<sup>+</sup>-SIRT6 axes are involved in this mitophagy, although the exact mechanism is complicated and exercise type-dependent [316]. Nevertheless, the optimal manipulation of endogenous metabolites as mentioned above could drive a proper level of mitophagy, which provides ideal nutritional designs for intervention of related diseases.



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