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REVIEW ARTICLE

The Dawn of Mitophagy: What Do We Know by Now?

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Abstract: Mitochondria are essential organelles for healthy eukaryotic cells. They produce energy-rich phosphate bond molecules (ATP) through oxidative phosphorylation using ionic gradients. The presence of mitophagy pathways in healthy cells enhances cell protection during mitochondrial damage. The PTEN-induced putative kinase 1 (PINK1)/Parkin-dependent pathway is the most studied for mitophage. In addition, there are other mechanisms leading to mitophagy (FKBP8, NIX, BNIP3, FUNDC1, BCL2L13). Each of these provides tethering of a mitochondrion to an autophagy apparatus *via* the interaction between receptor proteins (Optineurin, p62, NDP52, NBR1) or the proteins of the outer mitochondrial membrane with ATG9-like proteins (LC3A, LC3B, GABARAP, GABARAPL1, GATE16). Another pathogenesis of mitochondrial damage is mitochondrial depolarization. Reactive oxygen species (ROS) antioxidant responsive elements (AREs) along with-antioxidant genes, including pro-autophagic genes, are all involved in mitochondrial depolarization. On the other hand, mammalian Target of Rapamycin Complex 1 (mTORC1) and AMP-dependent kinase (AMPK) are the major regulatory factors modulating mitophagy at the post-translational level. Protein-protein interactions are involved in controlling other mitophagy processes. The objective of the present review is to analyze research findings regarding the main pathways of mitophagy induction, recruitment of the autophagy machinery, and their regulations at the levels of transcription, post-translational modification and protein-protein interaction that appeared to be the main target during the development and maturation of neurodegenerative disorders.

Keywords: Mitochondria and mitophagy pathways, healthy cells, factors modulating mitophagy at the post-translational level, autophagy machinery, mitochondria and post-translational modification, protein-protein interaction and mitophagy, risk factors, central nervous system disorders.

1. INTRODUCTION

Mitochondria are essential cell organelles that participate in a plethora of processes maintaining ion and energy balance inside the cell and cellular homeostasis, as well as programmed cell death. This significance necessitated the development of highly regulated and reliable mechanisms of mitochondrial quality control. Mitochondrial damage affects not only their own function but also may injure other cell organelles, proteins, and membranes.

Mitochondrial autophagy, otherwise known as mitophagy, is the process of eliminating damaged mitochondria. It thereby maintains intracellular homeostasis [1]. ROS (reactive oxygen species)-dependent mitochondrial depolarization is one of the main factors inducing mitophagy [2-5]. In turn, this promotes the activation of various mechanisms at the transcriptional and protein levels. The result is the disposal of damaged mitochondria and maintenance of a stable ROS level.

There are several pathways of mitophagy induction. PINK1 (PTEN-induced putative kinase 1)/Parkin-dependent pathway is the dominant pathway in most cells [5, 6]. During this process, PINK1 stabilizes in the outer mitochondrial membrane, resulting in the recruitment of E3-ubiquitin ligase parkin [7-9]. Parkin recruitment mediates OMM (outer mitochondrial membrane) proteins ubiquitination, additional recruitment of parkin as well as autophagy apparatus to OMM [10-12]. Interaction between mitochondria and autophagy apparatuses may occur *via* polyubiquitinated proteins of OMM mediated by 'mediator' proteins (p62, OPTN, NDP52, *etc*.) [13-15] or through direct interaction with the OMM proteins referred to as *'mitophagy receptors'* of the PINK1/Parkin independent pathway [16-19].

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A significant reduction in the functionality of these pathways leads to diminished clearance of damaged mitochondria, resulting in lethal changes in the cell ROS homeostasis that damage subcellular organelles and membranes, thereby increasing the PCD (programmed cell death) rate. These alterations may cause a variety of diseases such as Parkinson's disease and parkinsonism [20-22] as well as Alzheimer's disease [22, 23]. Reduction in mitophagy may contribute to tumor progression [24, 25].

All together these factors give substantial grounds to consider mitochondria as a promising target for developing a novel generation of protective agents – mitoprotectors. In turn, these are promising means for treating various disorders, particularly neurodegenerative diseases [26-32].

The aim of this review is to investigate the roles of the different signal molecular pathways in mitophagy induction: PINK1/Parkin-dependent and PINK1/Parkin-independent, and involvement of autophagy machinery proteins in endoplasmic reticulum-specific autophagic process. The paper also explores the implication of transcription factors on the expression of pro- and anti-autophagic genes as well as the effect of post-translational modifications on the activity of the particular proteins.

2. MITOPHAGY INDUCTION

2.1. Chemical Mitophagy Inducers

In order to model the mitophagy process *in vitro*, a variety of chemical compounds may be used. Despite their diversity, only a few are widely used in experimental practice: primarily, CCCP (carbonyl cyanide m-chlorophenyl hydrazone), FCCP (carbonyl cyanide-p-trifluoromethoxyphenylhydrazone), oligomycin, and antimycin A.

The first pair of compounds (CCCP and FCCP) are structurally phenylhydrazones and could be classified as protonophores – lipophilic weak acids able to transfer protons through cellular membranes [33-36]. Proton leakage from intermembrane space leads to $\Delta\psi m$ reduction on the inner mitochondrial membrane (IMM), diminishing the ATP synthesis rate, increasing ROS production, and promoting subsequent mitophagy. Additionally, CCCP and FCCP usage is limited because of their potential to incorporate into not only IMM, but also other membrane structures, disrupting cellular metabolism [35]. It is noteworthy that an investigation by Berezhnov et al. has shown that mitochondrial depolarization might not be a major factor in mitophagy induction [37]. Since FCCP causes proton leakage not only from intermembrane space to the cytoplasm, but also from lysosomes, all these events result in the cytoplasmic acidification. According to these authors, cytoplasmic acidification might be the main factor leading to mitophagy induction [37]. This limitation gave rise to the development of the second generation protonophore BAM15, which exhibits lower cytotoxicity and higher selectivity to IMM [35, 38].

Oligomycin and antimycin A are referred to as antibiotics inhibiting electron flow on the electron transport chain (ETC) and are produced by bacteria of genus Streptomyces [39, 40]. Antimycin A inhibits complex III (cytochrome C-oxireductase) of the electron transport chain (ETC) and presents quite limited activity on mitochondrial depolarization [35, 39]. Therefore, since its effect may be quickly compensated by reverse ATP hydrolysis, antimycin A is used in combination with an antibiotic-macrolide oligomycin, which, in turn, inhibits ATP-synthase, thereby preventing reverse ATP hydrolysis.

2.2. Reactive Oxygen Species (ROS)

Mitochondrial depolarization induced by increasing ROS concentrations or uncouplers, such as CCCP or FCCP, appears to be the crucial factor for mitophagy induction [2-5]. ROS are considered indispensable in low concentrations for normal tissue and organ development, as well as vital cell activity in physiological and pathophysiological states [4, 41, 42]. Electron transport chain (ETC) has a major impact on ROS production [4, 43] mainly through the NADH-dehydrogenase (complex I) and coenzyme Q dehydrogenase cytochrome C reductase or complex III) [42]. During the course of this process, superoxide anions $O2^{\bullet-}$ are produced (Fig. **1**). According to some estimates, their concentration in the mitochondrial matrix should be 5-10-fold higher than in the nucleus and the cytoplasm [42, 44]. Superoxide molecules may be converted by superoxide dismutase (SOD) to hydrogen peroxide [45] or react with hydrogen peroxide molecules that already have been formed (Haber-Weiss reaction):

$$O_2^{\bullet-} + H_2O_2 \rightarrow OH^- + OH^{\bullet} + O_2$$

Moreover, superoxide anions may interact with nitrogen oxide II NO to form peroxynitrite anions $ONOO^-$. As a consequence, the accumulation of peroxynitrite anions initiates S-nitrosation and Fe-nitrosylation, leading to the inactivation of NADH dehydrogenase and cytochrome c oxidase and, subsequently, functional abnormalities [46, 47].

Hydrogen peroxide then either escapes to the cytosol or is reduced by the antioxidant defense system, which includes SOD, glutathione peroxidase (GPX) [48-50], and peroxiredoxin (PRXIII) [51, 52]. Hydrogen peroxide enters into a chemical reaction with iron divalent ion (Fenton reaction) and triggers the induction of ferroptosis [53, 54]:

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + OH^{\bullet}$$

As a result, oxidative damage caused by reactive oxygen and nitrogen species may lead to membrane injury, energy balance disorders, mutations, and abolishing enzyme function, as well damaging other proteins and eventually leading to cell death. However, potent cellular self-defense mechanisms can prevent impairment of vital functions and structures (Fig. **1**).

3. TRANSCRIPTIONAL REGULATION OF MITOPHAGY

3.1. NRF (Nuclear Factor Erythroid 2 (NFE2)-related Factor) Family

At the transcription level, the maintenance of cellular redox homeostasis is attained by ARE-recognizing transcriptional factors [55]. Proteins of nuclear factor erythroid 2 (NFE2)-related factor (NRF) family modulate the protein expression both in the antioxidant defense system and autophagy machinery.

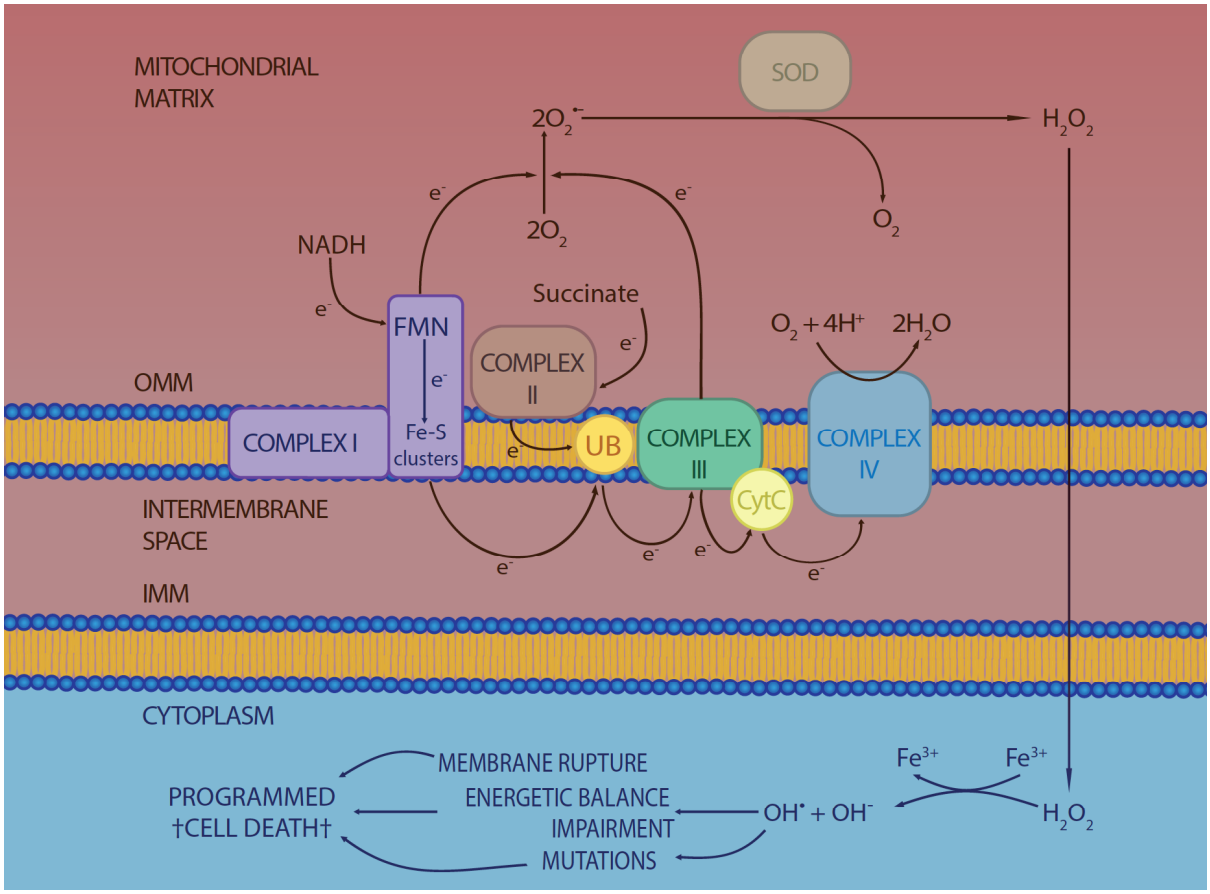

Fig. (1). Electron transport chain (ETC) structure and role in reactive oxygen species (ROS) production. NADH-dehydrogenase (complex I) and coenzyme Q dehydrogenase (cytochrome C reductase or complex III) are established to be the major ROS production sites, especially superoxide anion. Then it may be converted to hydrogen peroxide and afterwards escape from the matrix to the cytoplasm. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Transcription factor NRF1 is localized in the endoplasmatic reticulum (ER) membrane [56] and normally is ubiquitinated by ERAD-associated E3 ubiquitin-protein ligase HRD1 (in the ER) or beta-transducin repeat containing E3 ubiquitin protein ligase (β-TrCP) (in the nucleus) and undergoes proteasomal degradation (Fig. **2**) [57]. However, cellular stress conditions are reflected in the DNA-damage inducible 1 homology 2 (DDI2)-mediated cleavage of NRF1 [58]. Thus, having been released, NRF1 translocates to the nucleus and binds the AREs (antioxidant responsive elements) upregulating expression rates such genes as *MT1, MT2, HO-1, NQO1, ferritin* [55, 59].

It is well established that NRF2 plays the utmost role in neurodegenerative disorders pathogenesis [60-62]. In the normal state, NRF2 binds with Kelch-like ECH-associated protein 1 (KEAP1), which is a redox-regulated substrate adaptor for Cullin3-containing E3-ubiquitin ligase complex. It mediates NRF2 ubiquitination and its concomitant proteasomal degradation [63, 64]. Under stress conditions, stress-inducible factors modulate NRF2-KEAP1 complex dissociation [65, 66]. Released NRF2 translocates to the nucleus and upregulates expression of *NRF1, PINK1, p62, SOD2, GPX1, TFAM, TRXP2, NDP52, NDUFA4*, enzymes of the glutathione synthesis pathway, malic-enzyme, and factors of pentose phosphate pathway [55, 60, 66, 67].

Likewise, NRF1 and NRF3 are localized in the ER membrane and their activity is modulated by the same factors, as mentioned above, along with glycosylation [68, 69]. It has been reported that NRF3 is capable of activating the expression of *PRDX6, PPARG2, NFE2L2, NOX4, NQO1 in vitro* [55].

3.2. ATF-4

Activating transcription factor 4 (ATF4) is described as an important transcription factor of the cellular stress response to the unfolded proteins, ROS and amino acid deprivation. Under these conditions, kinases proline-rich receptor-like protein kinase (PERK) [70], protein-kinase R (PKR) and eukaryotic translation initiation factor (eIF-2α) kinase (GCN2) phosphorylate eIF-2α inhibit translation of most of mRNAs, whereas ATF4 mRNA is selectively translated [55, 71]. ATF4 binds CCAAT-enhancer-binding protein (C/EBP)-ATF response element (CARE) upregulating expression rates of *MAP1LC3B, ATG16L, ATG12, ATG3, BECN1, GABARAPL2* [70]. ATF4 is suggested to form heterodimers with C/EBP-homologous protein (CHOP), which enhance

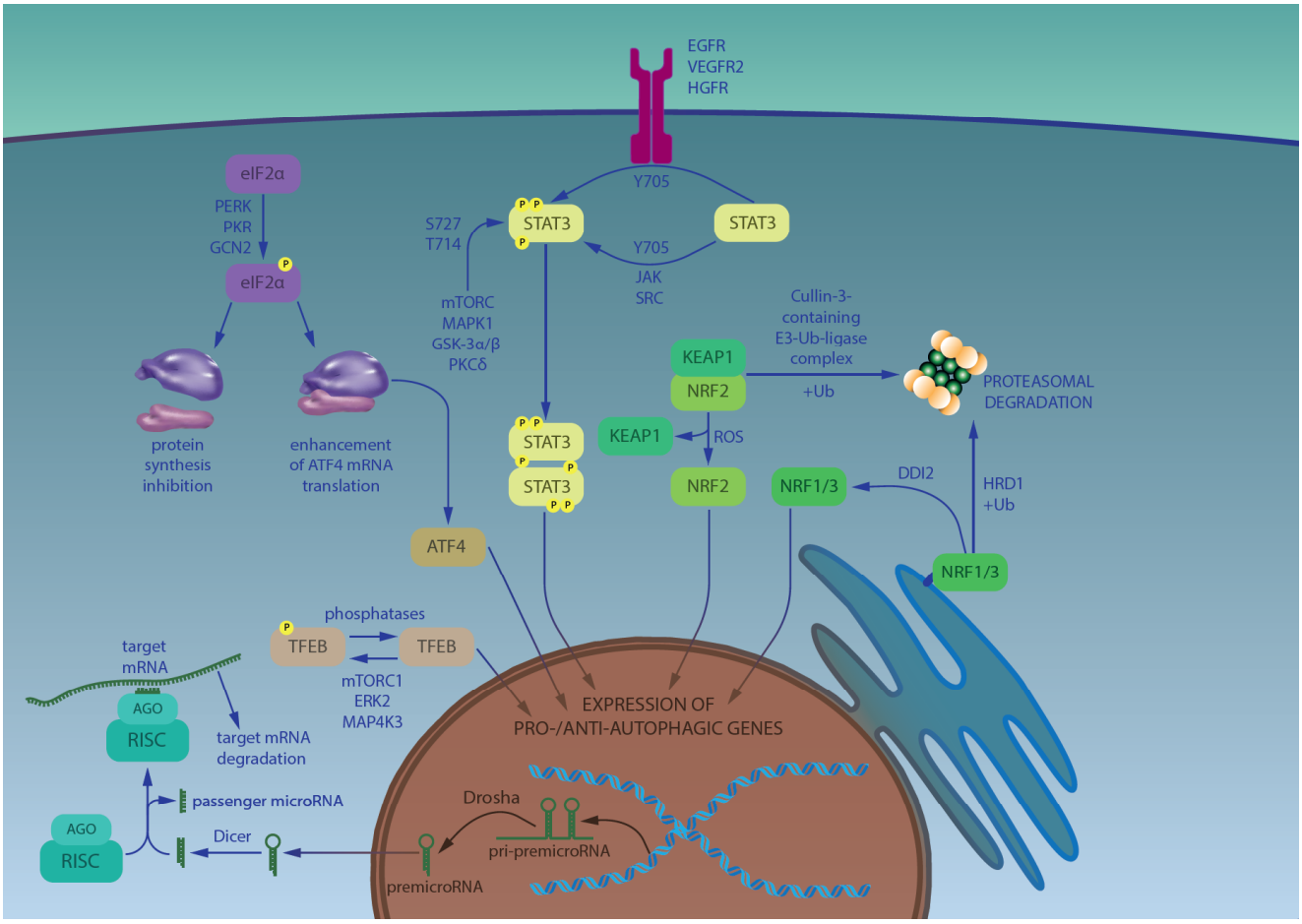

Fig. (2). Molecular mechanisms and signaling pathways promoting mitophagy. Autophagy is controlled through a variety of pathways. The control may be exercised *via* extracellular factors and internal factors. For instance, growth factors, such as epidermal growth factor EGF, vessel endothelial growth factor 2 VEGF2, and hepatocyte growth factor HGF, are referred to as extracellular 'actors'. Their effect may activate as well as repress pro-autophagy gene expression. On the other hand, increased levels of reactive oxygen species (ROS) may be a prerequisite to engage the mitophagy process. This process is described below. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

the expression of *p62, NBR1, ATG7* [70] and with NRF2 activating transcription of *HO-1, NQO1, GST* [72].

3.3. FOXO Family

FOXO (forkhead box protein) family comprises 4 transcription factors: FOXO1, FOXO3, FOXO4 and FOXO6. FOXO1 acts as a pro-autophagic factor in the cytoplasm, its disruption of function entails the inhibition of p62 degradation and LC3II accumulation [73, 74] It has been reported that interaction between FOXO3 and ATG7 is indispensable for autophagy induction [73-75]. Another member of the family, FOXO3, performs its function in the nucleus and activates expression of pro-autophagic genes such as *BECN1, VPS34, GABARAPL1, MAP1LC3B, BNIP3, BNIP3L, ATG12L, ATG4B, ULK2, LC3* [73, 76-78]. Under normal conditions, serine/threonine-protein kinase mTOR (mammalian target of rapamycin) facilitates nuclear entry of forkhead box protein K1 (FOXK1) where interaction with paired amphipathic helix protein SIN3A occurs. All of this leads to pro-autophagic genes repression by restricting FOXO3-binding to promoters of autophagy genes [79].

3.4. STAT Family

The signal transducer and activator of transcription (STAT) family is a group of transcription factors localized in the cytoplasm in an inactive state that is involved in cytokine and growth factor signal transduction [80-82]. STAT3 is activated by receptor (epidermal growth factor receptor (EGFR), kinase insert domain receptor (KDR), hepatocyte growth factor receptor (MET)) or non-receptor (janus-kinase (JAK), SRC) tyrosine kinases mediated phosphorylation at Y705. Moreover, STAT3 is phosphorylated by serine-threonine kinases (mTOR, mitogene-associated protein kinase 1 (MAPK1), glycogen synthase kinase-3α/β (GSK-3α/β), protein kinase Cδ (PKCδ)) on S727 and T714, which are indispensable to enhance transcriptional activity [80, 83-88]. Afterwards, STAT3 homo- or hetero-dimerizes with other members of STAT-family that translocate to the nucleus [85-89]. STAT3-dimer is able not only to inhibit autophagy through activation of anti-autophagic factors (*BCL2, BCL2L2, MCL1, PIK3R1/p55α, PIK3R1/p50α*) expression and repression of autophagy genes (*BECN1* and *ATG3* through histone deacetylase 3 (HDAC3) and HDAC1 activa-

tion correspondingly) expression, but also to induce autophagy by increasing *HIF1α* and *BNIP3* expression [80, 82, 87, 88, 90-92]. In cytoplasm, STAT3 is capable of inhibiting eIF2α kinase 2, pFOXO1, and pFOXO3a to prevent autophagy induction [92-94]. In turn, STAT1 inhibits autophagy *via* the suppression of Unc-51 like autophagy activating kinase (ULK1) gene promoter activity and repression of ULK1 expression [95, 96].

3.5. TFEB

Transcriptional factor EB (TFEB) is responsible for regulating the expression of lysosome biogenesis and dynamics genes [97]. In nutrient-rich conditions, lysosome subcellular localization is controlled by mTORC1, extracellular signal-regulated kinase 2 (ERK2), MAP4K3 and glycogen synthase kinase-3 beta (GSK3β) *via* promoting its nuclear export and cytosolic relocalization [98-101]. Upon starvation, protein phosphatase 3 (PPP3)/calcineurin is activated as a result of mTORC1 inhibition. Consequently, TFEB is dephosphorylated and accumulated in the nucleus due to diminished TFEB nuclear export [102]. An increase in nuclear TFEB concentration leads to enhanced expression of lysosomal trafficking regulator factor type 1 phosphatidylinositol 4,5-bisphosphate 4-phosphatase (TMEM55B) [103], proteins of coordinated lysosomal expression and regulation network (CLEAR) and autophagy genes such as *UVRAG, WIPI, MAPLC3B, SQSTM1, VPS11, VPS18, ATG9B* [99].

3.6. Sirtuin-1

The sirtuin family of NAD+-dependent histone deacetylases utilizes cleavage energy of NAD+ and acts as receptors of the NAD+/NADH ratio. SIRT1 is localized in the nucleus, but it can shuttle between the nucleus and cytoplasm [104]. In the nucleus, SIRT1 deacetylates transcriptional factor PGC-1α enhancing mtDNA replication, expression of mitochondrial proteins and mitochondrial proliferation [105]. SIRT1 can act upstream of AMP-dependent kinase (AMPK) *via* deacetylation and activation of the AMPK by serine/threonine-protein kinase STK11 (LKB1) [106]. It has been reported that treatment with nicotinamide causes increased NAD+/NADH ratio and, thereby, SIRT1 activation and reduced electron flow to ETC Complex I. Concomitantly, there was a decrease in superoxide production and an increase in microtubule-associated protein 1A/1B light chain 3 (LC3) autophagosomes as well as mitochondrial fragmentation [107, 108]. Another group of researchers reported that the expression of Beclin-1 and mitochondrial localization of BCL2 interacting protein 3 like (BNIP3L) is inhibited in prostatic intraepithelial neoplasia (PIN) cells of SIRT1+/+ mice in contrast to PIN cells of SIRT1-/- mice [109]. Moreover, it has been shown that SIRT1 delayed Parkin translocation to mitochondria due to the reduction in the rate of ROS production and SOD2 activation [109].

3.7. microRNA-silencing

MicroRNAs are conserved small single-stranded non-coding post-transcriptional regulators of gene expression [110, 111]. At all stages of development, hundreds of microRNAs control the expression of thousands of mRNAs. MiRNAs are initially transcribed as a part of a complex molecule, which is made up of several stem-loop miRNA precursors called primary miRNA (pri-miRNA). The first step in pri-miRNA processing is splicing by ribonuclease III enzyme Drosha to form short pre-miRNA hairpin loops that are about 70 bp in length. Then miRNA precursor is exported out of the nucleus and undergoes the second step of processing. Cytoplasm endoribonuclease Dicer cuts away the loop of the hairpin structure, yielding double-stranded fragments about 19-25 bp in length. Usually, only one strand incorporates ('guide strand') into the RNA-induced silencing complex (RISC). The RISC can either promote mRNA degradation (in case of complete complementarity) or prevent mRNA translation (in case of incomplete complementarity) [112]. Myriad autophagy factors are regulated in this way, *e.g.*, the expression of the components of the mTOR complex and Beclin-1 is regulated by miR-30a [113], AMPKα1 subunit is regulated by miR-148b [114], miR20a and miR-10b control ULK1 expression [115], class III phosphatidylinositol 3-kinase (PI3KC3) is silenced by miR-338-5p [116], miR-145 regulates BCL2 interacting protein 3 (BNIP3) expression [117], NIX/BNIP3L is regulated by miR137, miR-133a, miR-302/367 [118], Parkin expression is regulated by miR-181a [119]. Therefore, we reasonably may conclude that the expression of pro- and anti-autophagic factors are strongly dependent not only on transcription factors but also on microRNA.

4. MITOCHONDRIAL QUALITY CONTROL AND MITOPHAGY

Mitochondria are pivotal organelles in cell viability, damage to which may cause energy imbalance as well as increased ROS and pro-apoptotic factors release such as cytochrome C and Smac. Consequently, mechanisms of mitochondrial quality control and elimination of damaged mitochondria are essential for cell stability and viability.

Mitochondrial membrane potential $\Delta\psi_m$ is known to indicate the intactness of mitochondria. By exposing cells to ionophores, such as CCCP and FCCP, or ETC complexes inhibitors (*e.g.*, antimycin A and oligomycin), reduction of Δψm could be reached in the experiment. Therefore, wide usage of these specific ionophores for studying mitophagy processes stems from the fact that these compounds may damage mitochondria inducing mitophagy [120-123].

4.1. PINK1/Parkin Pathway

One of the major factors reflecting on $\Delta\psi_m$ reduction and inducing mitophagy is a presenilins-associated rhomboid-like protein (PARL). PARL is an integral multipass peptidase that is localized in the inner mitochondrial membrane (IMM) [123]. PARL has been reported to be a part of large stomatin-like protein 2 (SLP2)–PARL–YME1L (SPY) supercomplexes [124]. PARL undergoes sequential α- and β-cleavage events during post-translational processing [123]. The site of α-cleavage is located between 52 and 53 amino acids, and the β-site lies between 77 and 78 amino acid residues [123]. The α-cleaved form of PARL is triphosphorylated at S65, T69, and S70 by PDH kinase 2 (PDK2) and cannot undergo β-cleavage [123, 125]. This form cleaves the major mitophagy regulator factors such as phosphatase and tensin homologue (PTEN)-induced putative kinase 1

(PINK1) [126] and phosphoglycerate mutase 5 (PGAM5) [127]. If PDK2 is inactivated due to low ATP/ADP ratio or increased ROS levels by means of mitochondrial damage, unphosphorylated PARL goes through β-cleavage [128]. During the β-cleavage event, 25-residual peptide pβ has been observed to be released (liberated). It is important to note that pβ peptide contains a nucleus-targeted sequence. However, the functions of pβ and β-cleaved PARL remain to be elucidated [129].

Regulation of PINK1 import into intermembrane space and consequential cleavage in the IMM are suggested to be an important part of the mitochondrial quality control process. It has been reported that translocase of outer membrane complex (TOMC)-dependent import of PINK1 requires TOM70 and TOM7 mitochondrial import receptor subunits [130, 131]. PINK1 import is shown to occur independently of $\Delta\psi_m$, if the TOM7 function is abrogated [131]. Having been transported into the intermembrane space, PINK1 interacts with mitochondrial import inner membrane translocase subunit TIM23 and undergoes processing by mitochondrial processing peptidase (MPP) [126, 129]. In contrast, another research team found that PINK1 is imported into intermembrane space in a $\Delta\psi_m$-dependent manner, but it is not cleaved by MPP [130]. Afterwards, PARL cleaves PINK1 within its TM-domain in a $\Delta\psi_m$-dependent manner [126, 127, 132], which is followed by PINK1 retro-translocation to the cytosol and subsequent proteasomal degradation targeted by the N-end rule pathway [133]. Thereby, mitochondrial depolarization may cause disruption of PINK1 processing and import into intermembrane space. Furthermore, this leads to the accumulation of PINK1 in the OMM [7], promoting RING-Between-RING E3-ubiquitin ligase recruitment to the OMM [8, 9]. PINK1 undergoes several autophosphorylation events at T257 [134], S465 [135], S228 [10, 136], S402 [10] sites and activates Parkin through the phosphorylation at S65 [134]. PINK1 autophosphorylation is required for Parkin recruitment, ubiquitin binding and ubiquitin kinase activity [reviewed in [11]]. The conjugation of ubiquitin-like protein NEDD8 to PINK1 and Parkin is shown to be crucial for PINK1/Parkin complex functioning [137]. PINK1-mediated ubiquitin phosphorylation at S65 is required for the E3-ubiquitin ligase activity of Parkin facilitation [12, 138, 139]. Having been activated, Parkin polyubiquitinates proteins localized to the OMM at K6, K11, K48, K63 and to a lesser extent at M1, K27, K29 sites [44]. According to the feed-forward model proposed by Ordureau et al. and Shiba-Fukushima et al. groups, PINK1 activates Parkin E3 ubiquitin ligase activity *via* phosphorylation at S65. Concomitantly, PINK1 phosphorylates ubiquitin at S65 strengthening Parkin binding to p-Ub of polyubiquitin chains, amplifying its E3 ubiquitin ligase activity, and promoting consequent OMM proteins ubiquitination [12, 139]. Subunits of proteasomes, voltage-dependent anion channels (VDAC), subunits of TIM-TOM complex, autophagy factors, mitochondrial fission and fusion regulators, metabolic proteins are described as a target of Parkin-mediated ubiquitination [140].

4.2. P62/SQSTM1

Polyubiquitin chain exposition to the cytosol allows mediator proteins (*e.g.*, p62, Optineurin, and the neighbor of BRCA1 gene 1 (NBR1)) to bind the chains and link damaged mitochondria to the autophagy apparatus (Fig. **3**) [13-15]. P62/SQSTM1 contains on its C-terminus ubiquitin-binding domain UBA, binding mostly to K63 and, to a lesser degree, to K48 polyubiquitin chains [13, 141-143]. Casein kinase 1 (CK1) and Sestrin-1/ULK1-mediated phosphorylation within the UBA domain increases p62 affinity to polyubiquitin chains [144, 145]. P62 activity is modulated by AMPK- mediated and PKC-δ-mediated phosphorylation at S294 [146] and at S349, respectively, in a vacuolar protein sorting 34 (VPS34)-dependent manner [147]. In addition to the UBA domain, p62 contains other noteworthy protein-protein interacting domains. For example, there are several important motifs located within the N- terminal arm of p62 protein, such as Phox and Bem1p-1 (PB1), which cause binding to atypical PKCs (aPKCs), ZZ zinc finger motif participating in TNFα-signaling and TBS domain, a binding site for TRAF6 [143]. P62 directly interacts with microtubule-associated protein LC3 (MAPLC3) through its LC3-interacting region (LIR) domain located in the interface between the N-terminus and C-terminal UBA domain [148, 149]. P62 binding to LC3 relies on the LC3-recognition sequence of p62 LIR motif, which comprises acidic cluster (337-339) DDD/DEE and hydrophobic cluster (340-343) WXXL/WXXV [150]. LRS is indispensable for interaction with other ATG8-family members (gamma-aminobutyric acid receptor-associated protein (GABARAP), gamma-aminobutyric acid receptor-associated protein-like (GABARAPL), gata transcription factor 13 (GATA13)) [150]. KEAP1-interacting region (KIR) within the p62 structure allows p62 to bind to KEAP1 in EGTE NRF2 domain manner disrupting the KEAP1-dependent NRF2 degradation pathway [reviewed in [151]]. Furthermore, the KEAP1/NRF2 pathway can be disrupted by binding of VPS34 to KEAP1, thereby enhancing p62 transcription rate and creating a positive feedback loop [147].

4.3. Optineurin

Optineurin acts as one of the key mediators that play an essential role in mitochondrial stability. Optineurin contains NF-κB-essential molecule (NEMO)-like domain, leucine scissors motif, coiled-coil (CC) motif, ubiquitin binding domain UBD, the LIR motif, and C-terminal zinc finger motif. Unlike Optineurin, p62 binds polyubiquitinated mitochondria at specific sites causing mitochondrial aggregation [152]. Optineurin modulates autophagosome formation by regulating the recruitment of Atg12-5-16L1 complexes [153], Tom1-positive vesicles transport to autophagosomes, and myosin IV activity as well [154]. TBK1 phosphorylates Optineurin at intrinsic LRS S177 residue, thus promoting interaction with LC3 [155]. Optineurin is also phosphorylated by TBK1 at S473 and enhances its p-Ub binding stability [154].

4.4. NDP52/CALCOCO2

Nuclear Domain 10 Protein 52 (NDP52, aka CALCOCO2) may play a role as an adapter in tethering mitochondrion to phagophore [156]. It contains SKICH-domain (indispensable for interaction with TANK-binding kinase 1 (TBK1), LC3C, and mitochondrial poly(A) polymerase (MTPAP), non-canonical LIR-motif CLIR, CC-domain (participates in auto-aggregation of NDP52) and C-terminal LIM-L domain bind-

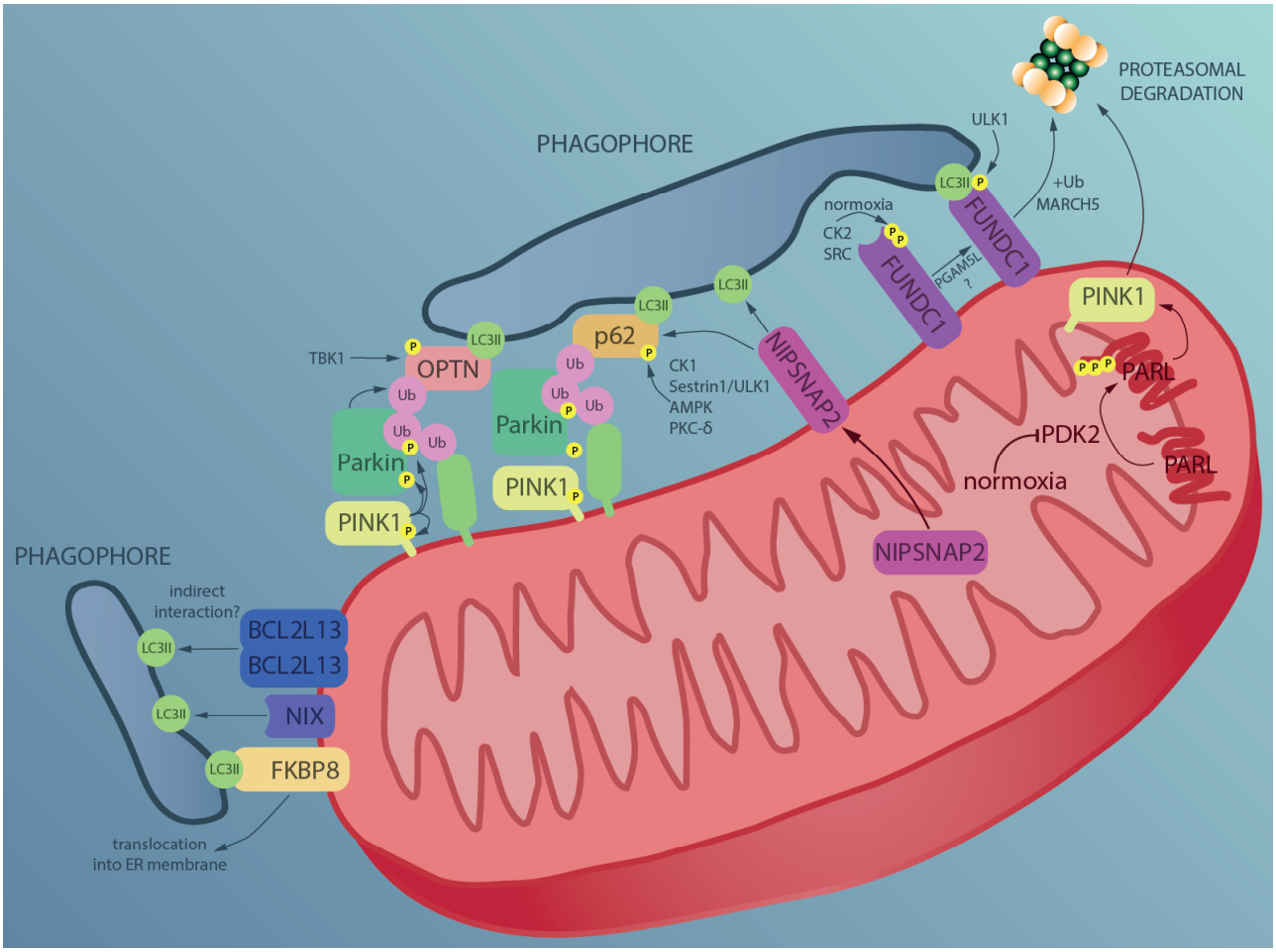

Fig. (3). The major factors exercising mitochondria quality control. Two different mechanisms that engender mitophagy have been referred to in the article: PINK1/Parkin-dependent and PINK1/Parkin-independent. PINK1/Parkin complex acts through mediator proteins, such as Optineurin, p62, NDP52, *etc*. Other mitochondrial mitophagy factors act *via* interaction with ATG8-like phagophore factors. These mitochondrial factors and PINK1/Parkin complex coincide to interact with ATG8-like proteins, which are described below. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

ing mono- and polyubiquitin [156-160]. Unlike canonical LIR-motif, the CLIR motif, located between the SKICH and CC domains, does not contain aromatic amino acids. Its LC3-recognition sequence comprises three hydrophobic amino acids LVV [157]. Besides the linkage of polyubiquitinated OMM proteins to ATG8-like protein LC3C, NDP52 may bind LC3C to the IMM mitochondrial poly(A) polymerase (MTPAP). The interaction occurs by OMM disruption at the start of mitophagy, and its (MTPAP) exposition to cytosol that results in LC3C and autophagy apparatus recruitment to the damaged mitochondrion [156]. Both Optineurin and NDP52 create positive feedback loops that amplify autophagy factors recruitment to depolarized mitochondria [157].

4.5. Prohibitin-2

Prohibitin-2 (PHB2) is another mitophagy factor that plays a role as an IMM scaffold protein and forms ring-like structures with PHB1 through their coiled-coil domains [161, 162]. PHB2 is vital for mitochondrial metabolism, stabilizing mtDNA and ETC complexes, participating in proteins translocation inwards to mitochondria and regulation of cardiolipin and phosphatidylethanolamine synthesis [163, 164]. Moreover, the PHB complex plays an important role in mitochondrial quality control and mitophagy; $\Delta\psi m$ reduction results in PHB complex-mediated PARL activity prohibition and stabilization of PINK1 on the OMM [162]. Consequently, this leads to OMM proteins ubiquitination, their proteasomal degradation and subsequent OMM rupture, which makes it possible for PHB2 to interact with LC3 through its LIR (YXXL) and to recruit phagophores to damaged mitochondria [162, 165]. Another possible mechanism of mitophagy promotion and phagophore recruitment might build on the interaction of PHB complex with P62 [166].

4.6. NIPSNAP1

Recent studies have identified the role of mitochondrial proteins NIPSNAP1 and NIPSNAP2 (4-Nitrophenylphosphatase domain and non-neuronal SNAP25-like protein homolog 1/2) in the mitophagy process [167]. These proteins normally occur in the mitochondrial matrix, but they were shown to translocate to the OMM and to bind ATG8-like proteins as

well as mediator proteins p62, NBR1, NDP52, TAX1-binding protein (TAX1BP1) acting as an "eat me" signal in CCCP-treated Parkin-expressing HeLa cells [158, 167]. Interestingly, NIPSNAP1 was shown to be a predominant form expressed in *Danio rerio* embryo head, in larval and adult zebrafish brains [167]. The crucial increase in ROS levels was observed in nipsnap1 mutant and NIPSNAP1-/- embryos [167]. Exogenous addition of L-DOPA rescues locomotor activity defect observed in nipsnap1 mutant and NIPSNAP1-/- zebrafish larvae revealing that the defect is due to a decrease in the number of dopaminergic neurons [167].

4.7. FUNDC1

The OMM-localized protein FUN14 domain-containing protein 1 (FUNDC1) regulates hypoxia-induced autophagy promoting mitophagy *via* interaction between its LIR-domain and LC3 [16]. Y18, the residue of LIR-motif (YXXL), and S13 are reported to act like switches regulated by phosphorylation. In normal conditions, FUNDC1 is phosphorylated by SRC at Y18 and by CK1 at S13, but upon hypoxia, the residues are dephosphorylated, so that FUNDC1 could interact with LC3 [16, 168]. Upon mitochondrial stress conditions, phosphatase PGAM5L (long isoform) dephosphorylates FUNDC1 at S13 [168]. Normoxia conditions recovery was observed to rescue mitochondrial membrane potential resulting in FUNDC1 phosphorylation [168]. It is important to note that Bcl-2-like protein 1 (BCL2L1) upon binding to PGAM5 disrupts FUNDC1 dephosphorylation at S13 and, consequently, stops mitophagy [169]. Curiously, ULK1-mediated phosphorylation of FUNDC1 at contiguous to LIR-motif S17 residue enhances FUNDC1-LC3B binding affinity threefold in contrast to dephosphorylated FUNDC1, while the FUNDC1 pS13 and FUNDC1 pY18 forms show threefold and tenfold decrease in the binding affinity, respectively [170, 171]. The increase in FUNDC1 pS17 binding affinity to LC3B is due to an additional hydrogen bond formed between LC3B K49 and FUNDC1 pS17 [170]. Phosphate group at S13 hinders the S13-R10/D14-R10 hydrogen bond formation leading to decreased affinity [170]. Importantly, mitochondrial E3 ubiquitin ligase MARCH5 (membrane-associated ring finger (C3HC4)), but not Parkin, has been reported to fine-tune hypoxia-induced mitophagy by interacting with and ubiquitinating FUNDC1 which promotes its proteasomal degradation [172]. Apart from mitochondria tethering to the autophagy apparatus, FUNDC1 plays a crucial role in mitochondrial dynamics contributing to mitochondrial fission during mitophagy [173]. Under hypoxia conditions, FUNDC1 accumulates at ER-mitochondria tethering sites (MAMs – mitochondrion associated membranes) and associates with ER protein Calnexin, but their interaction is likely to be indirect. ER forms tubular structures that wrap around mitochondria to mark a fission site. Afterwards, FUNDC1-Calnexin complex dissociates, so that FUNDC1 can recruit mitochondrial fission GTPase DRP1 to promote mitochondrial fragmentation and subsequent mitophagy [173].

4.8. AMBRA1

Activating molecule in BECN1-regulated autophagy protein 1 (AMBRA1) may be added to this group of PINK1/Parkin-independent mitophagy mediators. Structurally, AMBRA1 is an intrinsically disordered protein. Similar to other LC3-interacting proteins, it contains the LRS (WXXL) on its C-terminus [174-176]. Interestingly, like FUNDC1, AMBRA1 affinity to LC3 depends on IKKα- mediated phosphorylation at S1046, which is in the close proximity upstream of the LIR motif [177]. AMBRA1 is well-known as a factor cross-linking cell proliferation and autophagy signaling pathways [178]. Upon starvation, ULK1 phosphorylates AMBRA1, which in turn, activates ULK1 by modulating its ubiquitination [179]. Herewith, mTORC1 plays as a negative regulator and prevents this interaction *via* AMBRA1 phosphorylation [179]. AMBRA1 may also interact with PPP2/PP2A leading to MYC pS62 dephosphorylation and thus impede cell proliferation [180]. Since AMBRA1 partially occurs on mitochondria, it provides the HUWE1 (HECT, UBA and WWE Domain Containing E3 Ubiquitin Protein Ligase 1) translocation towards OMM and OMM proteins ubiquitination in Parkin-independent fashion [177]. In addition, since AMBRA1 contains its own LIR-domain, it has the ability to interact with LC3 and rescue mitophagy in penta KO (OPTN-/-, NDP52-/-, p62-/-, TAX1BP1-/-, NBR1-/-) cells in independently of PINK1/Parkin [177, 180]. MCL1 (myeloid cell leukemia 1), a member of BCL2-family, appears to be one of the major AMBRA1 activity regulators [181]. It acts as a negative modulator of AMBRA1 and decreases ubiquitination levels, mitochondria aggregation and, as a consequence, AMBRA1-mediated mitophagy [181]. Noteworthy, mutual AMBRA1 and GSK-3β activity promotes HUWE1-dependent MCL1 ubiquitination and consequent proteasomal degradation [181].

4.9. BCL2L13

BCL2L13 is localized to the OMM. It is involved not only in apoptosis but also in PINK1/Parkin-independent mitochondrial quality control. Although BCL2L13 is described to comprise WXXL/I LC3-recognition sequence (LRS)-motifs, ULK1 was shown to be indispensable for BCL2L13 and LC3B association, implying that their interaction is indirect [182, 183]. Specifically, BCL2L13 overexpression can promote mitochondrial fragmentation and mitophagy, but its mechanism remains to be determined [182].

4.10. BNIP3 and NIX/BNIP3L

The BNIP3 [17, 77, 184, 185], BNIP3L/NIX [77, 113, 186] and FKBP8 [122] pathways could be referred to as PINK1/Parkin independent pathways. BNIP3 dimer phosphorylation at S17 is essential for LC3 binding *via* its LIR-domain [17, 184, 185]. Aside from this interaction, BNIP3 is able to bind other ATG8-like protein, GATE-16, but with weak binding affinity [185]. This interaction requires BNIP3 to be phosphorylated at S17 and S24 flanking the LIR-domain [185]. In contrast to NIX, BNIP3 was observed to be expressed in a delayed manner emphasizing its important role in redundant mitophagy [184]. After OGD/RP (oxygen-glucose deprivation and reperfusion) injury, a decrease in proapoptotic factor levels and apoptosis rate has been observed as along with general autophagy enhancement in BNIP3 KO mice neurons [184]. Apoptotic cascade damage could ensue due to decreased excessive mitophagy and absent BNIP3 proapoptotic function [184], its role in apoptosis

[reviewed in [187]]. It is important to note that BNIP3 has been found in ER fraction denoting its ER localization and possible role in ER autophagy [17]. In addition to apoptosis induction, BNIP3 is released into the cytoplasm by implementing mitochondria elimination [185].

NIX (otherwise known as BNIP3L) is involved in reticulocyte maturation and is implicated in apoptosis that leads to either PCD or mitophagy [188]. As a consequence of M40 serving as an alternative translation initiation site, NIX is present in both short- and full-length forms [188, 189]. NIX comprises the LIR motif (WXXL) on its N-terminus to bind ATG8-like proteins, so that NIX can act as a receptor of mitophagy [186]. By contrast to BNIP3, NIX recruits to mitochondrial membrane gamma-aminobutyric acid receptor-associated protein-like 1 (GABARAP-L1) upon stress conditions [186]. Noteworthy, phosphorylation of S34 and S35 residues adjacent to the LIR domain enhances NIX affinity to LC3a and LC3B one-hundredfold [190]. Zhang J et al., in their study, found that LIR motif deletion (36-39 amino acids) slightly diminishes its activity, whereas truncation of 70-86 amino acids completely abolished NIX function [189]. This region does not interact with LC3 and comprises four hydrophobic amino acids M70, I73, L74, L75 flanked by polar amino acids [189]. NIX affects the development of other tissues apart from reticulocyte maturation. For instance, NIX regulates mitochondria, ER, Golgi apparatus (GA) elimination during eye lens organelle-free zone formation [18]. It has been revealed in this study that NIX can co-localize with ER and GA [18]. In patients with Parkinson's disease caused by disruption of the PINK1/Parkin pathway, NIX acts as a neuroprotector rescuing mitophagy and increasing neuronal cells and fibroblast viability [191]. Identical results were obtained by another group studying the role of NIX in PINK1/Parkin independent mitophagy in a murine model of cerebral ischemia *in vivo* and mouse cortical neurons *in vitro* [192].

4.11. FKBP8/FKBP38

Calcineurin inhibitor FKBP8 (FKBP38, FK506-binding protein) initially was characterized as a marker in the mouse schwannoma model and later described as a PINK1/Parkin-independent mitophagy receptor [19, 193]. FKBP8 is primarily expressed in the liver, kidneys, and brain, especially in hippocampal formation [172]. In contrast to other members of FKBP-family, FKBP8 co-localizes with BCL2 and BCL-X_L in the OMM, as confirmed by the finding that FKBP8 TM-domain deletion with and without CAAX-sequence insertion resulted in the redistribution of these proteins [19]. FKBP8 contains LIR-domain (FXXL) on its N-terminus with a predominant affinity to LC3A-II [194]. After LC3A-II recruitment and autophagy promotion, FKBP8 and BCL2, but not BCL-XL, escape from the OMM to the ER membrane *via* microtubule-associated vesicular transport during PINK1/Parkin-dependent and independent mitophagy as well [194, 195]. This translocation can prevent apoptosis in murine embryonic fibroblasts (MEFs) under CCCP-induced stress [195].

4.12. Cardiolipin

Cardiolipin (CL) is a dimeric phospholipid of the inner mitochondrial membrane in eukaryotic cells. In the case of mitochondrial damage by rotenone or 6-OHDA, CL can translocate from the inner to the outer mitochondrial membrane by means of phospholipid scramblase-3 (PLS3), mitochondrial creatine kinase (MtCK), Nm23-H4 and tBid [196–199]. PLS3 is responsible for changing the conformation of CL, MtCK acts as a bridge for transporting cardiolipin through the intermembrane space, Nm23-H4 performs lipid transfer function as well [197-200]. The oxidized CL interacts with the CTD of Beclin-1 and N-terminal helices of the LC3-II, which play a pivotal role in autophagosome biogenesis, but interaction with CTD of Beclin-1 scarcely contributes to mitophagy promotion [196].

5. PHAGOPHORE FORMATION

The phagophore formation process begins with the formation of the Ω-shaped structure omegasome. However, the biogenesis of omegasome is controversial. It is reliably known that phosphatidylinositol-3-phosphate (PI3P) plays the main role in omegasome framing. According to one of the models, omegasomes are formed in certain sites on the ER. First, a disk-like structure is formed, and then at the edges of it, the zinc finger FYVE domain-containing protein 1 (DFCP1) binds to phosphatidylinositol 3-phosphate (PI3P). Next, the disk increases in size and, at a certain point, LC3II begins to be accumulated on the membrane. The omegasome reaches its maximum diameter and begins to form a cup-shaped structure, which then closes, forming an immature autophagosome [201]. Accordingly, this process produces IMATs (isolation member-associated tubular/vesicular structures) that connect the edges of the phagophore and ER [202]. Phosphatidylinositol 3-kinase complex type 3 (PI3KC3) is one of the main protein complexes that are responsible for PI3P synthesis [203]. The activation of this complex is accomplished by serine-threonine kinase Unc-51, such as autophagy activating kinase ULK1. In turn, this is activated by the inhibition of mTORC1 complex upon starvation and amino acid deprivation, as well as by the activation of AMPC [203–206]. The kinase complex consists of ULK1 kinase, scaffold protein FIP200, ATG13, ATG101 [205]. However, ULK1 activation can occur without inhibiting the mTORC1 complex, since the Huntingtin protein causes dissociation of the mTORC1-ULK1 complexes and, as a result, driving autophagy [207].

5.1. ULK1 Complex Regulation

In some instances, the ULK1 complex is subjected to diverse post-translational modifications: phosphorylation/autophosphorylation [206, 208], reactivation of the complex by PP2A-mediated dephosphorylation at S637 [209], PP1-mediated dephosphorylation at S757 [210], GSK3/TIP60-mediated acetylation [211] and the mTORC1-dependent K63-linked ubiquitination by AMBRA1/TRAF6-complex. Taken together, all this leads to the ULK1 complex activation [212], concomitant NEDD4L-ubiquitination at K923 and K925 that is dependent on the status of ULK1 CTD phosphorylation, and KHLH20/Cul3-ubiquitination of ULK1 and ATG13 upon starvation. Both modifications induce proteasomal degradation [213] for the avoidance of uncontrollable autophagy [214]. Under starvation conditions, ULK1, after S757- dephosphorylation and AMPK-mediated phosphorylation at S317 and S555, undergoes O-GlcNAc transferase

subunit p110 (OGT)-mediated O-GlcN-acetylation at T754 (that being close to the mTOR-mediated S757 phosphorylation site), that positively modulates its activity [210]. Under hypoxic conditions, AMPK is able to phosphorylate ULK1 at S555, resulting in translocation complex to mitochondria and phosphorylation of FUNDC1 [215]. The complex ULK1 is necessary for directing lysosomes to mitochondria during mitophagy, its localization on the surface of mitochondria is controlled by FUNDC1 pS17 [171, 216]. ULK1 regulates the phosphoinositide 3-kinase class 3 (PI3KC3) through Beclin-1 phosphorylation at S14 [217]. ULK1's kinase activity in relation to PI3KC3 is positively modulated by ATG14L proteins in response to interaction with ULK1 [217]. To ensure the activity of the PI3KC3 complex, beclin-1 needs to be phosphorylated by ULK1/2 kinases at S30 (and to a lesser extent ULK2) in complex with ATG14L, but not with UV radiation-resistant associated protein (UVRAG) [218]. It has been noted that the ATG14L phosphorylation at S29 by kinase ULK1 is required for VPS34 activity in the cellular model of Huntington's disease [219]. Interestingly, ATG14L phosphorylation is mTOR-dependent (*i.e.*, in response to amino acid deprivation), but not glucose and concurrently Beclin-1 is indispensable for phosphorylation [219]. Kinase with-no-lysine (WNK) and its substrate SPS/STE20-related proline-alanine-rich kinase (SPAK) are mTORC1-independent and diminish autophagy progression by inhibiting T172- phosphorylation AMPK, AMPK-mediated phosphorylation of ULK1 at S555-site and by direct interaction with UVRAG [220].

5.2. PI3KC3 Structure and Modulation

In mammalian cells, there are three classes of phosphoinositide 3-kinase (PI3K). PI3KC1 uses $PI4,5P_2$ as substrates to form $PI3,4,5P_3$; PI4P and PI are substrates for PI3KC2 and PI3KC3, respectively. Both substrates are used to form $PI3,4P_2$ and PI3P [203, 221]. VPS34 forms two types of complexes involved in autophagy: Beclin-1/ATG14L/VPS34/VPS15 complex and Beclin-1/UVRAG/VPS34/VPS15 complex [222]. PI3K VPS34 consists of three C2 domains, spiral and kinase domains [223, 224]. C2 domain plays a role in the binding domain interacting with the other three subunits within the complex, in particular, C2 domain fragment (C2 helical hairpin (C2HH)) interacts with WD40 domain of VPS15 [224]. In fact, VPS15 plays the role of both positive and negative modulators of VPS34 activity by regulating the dynamics displacement of the catalytic domain VPS34 [225]. VPS34 activity is regulated *via* various post-translational modifications. Lysine acetyltransferase p300 achieves a negative regulation of VPS34 and Beclin-1 activities by VPS34 acetylation at K29, K771 and K781, there is profoundly important that K771 is in the catalytic domain, thereby acetylation at K771 breaks the PI binding and acetylation at K29 breaks interaction with Beclin-1, while Beclin-1 acetylation at K430, K437 leads to autophagy inhibition stimulating association with Rubicon protein [226, 227].

Accordingly, autophagy is regulated by the epidermal growth factor receptor (EGFR) Tyr-kinase, which activates by binding of caveolin-1 (CAV-1) or epithelial growth factor. As a result, autophosphorylation of the receptor and Beclin-1 binding occurs. This leads to a decrease in the autophagy level that is important for cell survival in tumor progression [228]. The formation of the PI3K complex also disrupts the transcription factor (high mobility group box 1 (HMGB1)), which has a higher affinity to Beclin-1 [229]. Interestingly, VPS34 deacetylation triggers autophagy even in $AMPK^{-/-}$, $ULK1^{-/-}$, $FIP200^{-/-}$, $TSC2^{-/-}$ (permanently highly active mTORC1) cells, but not in Beclin-1-/- cells [227]. Activation of PI3K Vps34 is promoted by acetyl-hsp70 and KAP1-dependent SUMOylation E3 ligase at K840 [230]. The regulation of PI3KC3 complexes activity is carried out by protein-protein interactions. For example, transcription factor NRBF2 binds to VPS15 in the composition of PI3KC3 type 1, thus positively modulating the autophagy process [231]. However, other research has shown that binding of the same protein NRBF2 in the N-terminal domain with the Beclin-1 and by the interaction of CC domains with the ATG14L leads to the inhibition of PI3K activity [232]. Golgi-specific protein, progestin and adipoQ receptor family member 3 (PAQR3), is an essential protein in the PI3KC3 complex as it plays a role in the stability of PI3KC3-C1 that can be accomplished through interaction with Beclin-1 and ATG14L in the cavities associated with the Golgi, as well as during the formation of autophagosomes [233].

Dapper-1 protein (Dpr1) is a Wnt-pathway inhibitor that induces the PI3KC3 type 1 assembly on the insulating membrane and stimulates its PI3K activity [234]. Dpr1-association with PI3KC3 type 1 does not affect its activity, while interaction with a Rubicon-PI3KC3 type 2 autophagy-inhibiting complex leads to negative modulation of its activity [234]. PI3P-enriched membrane leads to its binding to WIPI-family proteins (WD-repeat protein interacting with phosphoinositides), including 4 representatives (WIPI1-4), of which only three WIPI1, WIPI2 and WIPI4 are necessary for autophagy [235]. All of these proteins bind to PI3P, but nevertheless, perform various functions: WIPI1 bridges the adaptor protein p62 to the phagophore membrane, WIPI2 proteins provide LC3 lipidation participating in the non-canonical autophagy pathway, WIPI4 is required for autophagosomes maturation [235, 236].

5.3. ATG-family and Phagophore Formation

During autophagy, ubiquitin-like proteins (ubiquitin-like, Ubls) play an instrumental role in phagophore formation. These include ATG8-family proteins (LC3A, LC3B, LC3C, GABARAP, GABARAPL, GATE-16) and ATG12 protein. One of the most important steps in phagophore formation is the formation of the ATG5-ATG12 complex and its associated ATG16L. ATG12 is a ubiquitin-like protein whose conjugation with ATG5 occurs through an enzymatic cascade similar to those that catalyze the ubiquitin-ligase complex. The ATG7 protein is an E1-like enzyme that activates ATG12, forming the ATG7- (C507-G186) -ATG12 thioester bond [237-239]. Moreover, ATG10 interacts with the ATG7-ATG12 complex as an E2-like enzyme facilitating the transfer of ATG12 and the formation of the ATG10-ATG12 conjugate [237-239]. However, the transfer of ATG12 to the target protein ATG5 is carried out without an E3-like enzyme [237, 238]. The binding of ATG12 to ATG5 occurs through the formation of isopeptide bond at the ε-amino group of lysine residues [240]. The ATG5-ATG12 conjugate

can be attached to ATG3, exhibiting E3-like activity that is necessary for conjugation of phosphatidylethanolamine (PEA) and Atg8-like protein LC3 [237, 240, 241]. LC3B--PEA (phosphatidylethanolamine) conjugation is implemented by ATG7/ATG3/ATG5-ATG12 ubiquitin ligase-like complex [237].

The first step in the LC3B conjugation process is the ATG4B-mediated processing, in which cysteine protease ATG4B cleaves the LC3B resulting in exposure of glycine residue at the C-terminus [242, 243]. ATG4B activity can be reduced by ULK1 kinase complex-mediated phosphorylation at S316, while phosphoprotein phosphatase 2A (PP2A) can reactivate the ATG4B [244]. At the next step, ATP-dependent conjugation of the E1-like enzyme (ATG7) to LC3B occurs [245]. The ATG7 homodimer interacts with LC3 *via* the C-terminal flexible tail, and then transfers it through the crossover loop (CL) domain and the α17 helix to the adenylation domain (AD), thereby leading to the adenylation reaction and thioester bond formation [245]. These processes occur within the limits of one $ATG7^{CTD}$ protomer of the homodimer, whereas $ATG7^{NTD}$ of another protomer recruits an E2-like (ATG3) enzyme, promoting transthiolation reaction in trans [246, 247]. In the presence of E3-like ATG5-ATG12 conjugate, the ATG3 catalytic center is rearranged, allowing conjugation of LC3 and phosphatidylethanolamine (PEA) [248-250]. At the same time, ATG5-ATG12 interacts with PEA-containing liposomes and ATG3, ATG3, but does not with LC3 [249]. Likewise, Ubl GABARAP lipidation is accomplished [251]. LC3 lipidation does not necessarily associate with autophagy; therefore, caution should be exercised in the utilization of only the LC3-I/LC3-II ratio as an indicator of the autophagy level [252]. After autophagosome formation, ATG8 protein deconjugation is an important process since conjugation is accomplished by a group of ATG4 proteins [239, 244]. ATG5-ATG12 conjugate is associated with ATG16L *via* ATG5 interaction with ATG16L to form 800 kDa-complexes, although part of ATG5-ATG12 is still in the free state in the cytoplasm [253]. According to the one model, PI3P-binding protein (WIPI2B) is implicated in recruiting the ATG12-ATG5-ATG16L complex *via* interaction with ATG16L on PI3P-enriched membrane [254]. ATG16L occurs in complexes on the membrane during the phagophore formation. It subsequently dissociates from the autophagosome membrane [253]. ATG5 immediately interacts with the phagophore membrane and determines membrane localization of the full complex [253, 255]. ATG12-ATG5-ATG16L membrane complexes specify LC3 lipidation at the membrane sites of the forming phagophore [256].

ATG16L splicing isoforms are tissue-specific: ATG16Lα- and ATG16Lβ-isoforms are expressed in embryonic stem cells (ES) and hepatic cells, ATG16Lγ-isoform is specific for brain cells [253]. There is ATG16L2 isoform, the gene of which is located on human chromosome 11q13.4, which has a structure similar to ATG16L1. In turn, it forms a complex with ATG12-ATG5, having E3-like activity; but it does not affect the formation of the phagophores due to differences in the M-region, presumably participating in the process negative feedback [257]. By interacting with the M-region, Golgi-resident small GTPase Rab33B involved in retrograde Golgi-ER membrane traffic can bind free ATG16L1 and ATG12-ATG5-ATG16L1 complexes [258], while ATG16L2 forms unstable complexes with Rab33B [257]. ATG8-like proteins are not necessary for autophagosome biogenesis around mitochondria [259]. During PINK1/Parkin-dependent mitophagy, Optineurin/NDP52-dependent ULK1 recruitment to depolarized mitochondria occurs, which is accompanied by the transport of ATG9A-vesicles to ULK1 and subsequent PI3P-dependent ATG9A dissociation [6, 260]. TKO (triple knock-out) LC3 cells did not differ in the mitophagy level from WT-cells, while hexa KO cells could assure a successful mitophagy flux, but their mitophagosomes were significantly smaller than WT-cells mitophagosomes [259].

6. MITOPHAGY IN THE CONTEXT OF NEURODEGENERATION

Mitochondria are extremely vulnerable organelles; so, they often play a key role in a number of pathological disorders and neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD). Importantly, there currently is no scientific consensus on the causes of AD; however, mitochondria are conjectured to play a central role in both mitochondrial cascade and amyloid cascade hypotheses. [N.B. These are reviewed in [261]]. Reductions in several bioenergetic flux-related enzymes, such as α-ketoglutarate dehydrogenase complex (α-KGDHC) and pyruvate dehydrogenase complex (PDHC), as well as cytochrome-C oxidase (COX), are reported to be the main mitochondrial alterations [262]. Deficiency of these enzymes inevitably leads to a decline of mitochondrial ATP synthesis, elevated ROS levels, and, ultimately, mitochondrial depolarization. Accumulation of 8-oxoGMP in neurons is known to be an important indicator of not only AD and PD but also Huntington disease (HD) [263, 264]. 8-oxoG abundance in DNA causes G-to-T transversion mutations because of its ability to pair with both adenine and cytosine [265, 266]. Moreover, the mitochondrial genome may contain only a few non-coding regions ipso facto increasing the odds of ROS-induced mutagenesis in coding regions [266].

Due to mitochondrial dysfunction and ROS accumulation, nuclear DNA could be oxidized as well. For example, oxidative damage to the p62 promoter region and consequent decreased expression of p62, autophagy disruption resulted in an AD-like phenotype in mice [267, 268]. 4977bp mtDNA deletion is reported to be another important indicator of AD development [269, 270]. This deletion causes the loss of genes coding subunits of ETC enzyme complexes as well as genes coding mitochondrial tRNAs that lead to demolishing mitochondrial ETC function and ROS accumulation [271, 272]. These factors are implicated in mitochondrial dysfunction and depolarization as well. This is evidenced by studies reported apropos of elevated mitophagy levels in AD [273, 274]. In addition, mitochondrial over-proliferation and fragmentation, apparently is a result of dynamin-related protein (DRP1) enhanced expression and its interaction with Aβ and p-Tau [275, 276]. This mechanism appears to be a defense reaction encouraging the elimination of dysfunctional mitochondria and engendering intact mitochondria proliferation. Elimination of disruption as a consequence of autophagy machinery dysfunction can aggravate the situation [277].

Inherited mutations in the PSEN1 gene are known to be one of the factors for mitophagic flux impairment [278]. Note that PS1, a product of PSEN1 expression, positively regulates PINK1 transcription in a Parkin-dependent manner, while PS2 is reported to act as an antagonist [279]. Mitophagy disruption may occur in inherited Parkinson's disease due to mutations in SNCA, PARK2 and PARK6 genes that code α-synuclein, Parkin, and PINK1 correspondingly [21, 22]. Other studies confirm that α-synuclein associates with mitochondria affecting its dynamics and functioning, but its role remains to be established [280, 281]. Accumulation of α-synuclein oligomers in astrocytes has been observed to cause outer and inner mitochondrial membrane rupture resulting in a decline in ATP synthesis [282]. In contrast, another scientific group found the overexpression of α-synuclein in H4 human neuroglioma cells and noted α-synuclein protects mitochondria from oxidative damage [283].

CONCLUSION

Mitophagy is known to be an evolutionarily conserved process, vital for both lower and higher eukaryotes. A plethora of parallel mitochondrial quality control pathways have evolved to assure cell protection against ROS in case of mitochondrial damage. PINK1/Parkin-dependent and -independent ('receptor') pathways appear to be the main mitophagy pathways. Owing to the laborious work of the scientific community towards understanding the process of mitophagy, the main mechanisms have been studied well, but important questions remain to be answered.

The PINK1/Parkin-dependent pathway is one of the most studied mitophagy pathways. Mitochondria depolarization stabilizes PINK1 kinase on the outer mitochondrial membrane [7]. Recent studies have shown this process to be dependent on the TIM/TOM complex, but the mechanism of the translocation is not understood well [130, 131]. Another unresolved issue is the mechanism of Parkin recruitment to OMM. What is a starting point of Parkin translocation to mitochondria: PINK1-mediated ubiquitin phosphorylation or Parkin recruits to outer mitochondrial membrane ahead of this event? The model proposed by Shiba-Fukushima et al. [139] describes PINK1-mediated ubiquitin phosphorylation as an initial event inevitably leading to the next questions: what is the molecular mechanism of this ubiquitination, which ubiquitin ligase mediates this process and do PINK1/Parkin-pathway factors affect its action?

Some recent studies have queried whether p62 is crucially important in mitophagy flux. For instance, Lazarou and coworkers have shown p62 to be dispensable for mitophagy progress, while Optineurin is vital to promote mitophagy [6, 152]. Another line of inquiry that remains to be answered is the nature of the interaction between LC3 and NIX. Since NIX contains the LIR motif, it would be reasonable to assume that NIX interacts with LC3 *via* its LIR domain. However, Zhang J et al. indicated that LIR-domain deletion slightly decreases its function, while the 70-86 amino acid region was observed to be of utmost importance for their interaction [189].

There are still many areas of research to be undertaken. The following features need immediate attention to establish the mitophagy theory for protecting the healthy cells such as a) evolutionary conserved process, b) Parkin recruitment to OMM, c) molecular mechanism of ubiquitination, d) the role of p62 in mitophagy, and e) interaction between LC3 and NIX during the development of neurodegenerative disorders such as AD and PD.

LIST OF ABBREVIATIONS

AD	=	Alzheimer's disease
AMBRA1	=	Activating molecule in BECN1-regulated autophagy protein 1
AMPK	=	AMP-dependent kinase
APP	=	Amyloid precursor protein
AREs	=	Antioxidant responsive elements
ATF4	=	Activating transcription factor 4
ATG-family	=	Autophagy related genes family
BCL2-family	=	B-cell lymphoma 2 protein family
BECN1	=	Beclin 1
BNIP3	=	BCL2 interacting protein 3
BNIP3L/NIX	=	BCL2/adenovirus E1B 19 kDa protein-interacting protein 3-like
BRCA1	=	Breast cancer type 1 susceptibility protein
C2HH	=	C2 helical hairpin
CARE	=	CCAAT-enhancer-binding protein-ATF response element
CAV-1	=	Caveolin 1
CC	=	Coiled coil domain
CCCP	=	Carbonyl cyanide m-chlorophenyl hydrazone
CK1	=	Casein kinase 1
CL	=	Cardiolipine
CLEAR	=	Coordinated lysosomal expression and regulation network
CLIR	=	Non-canonical LC3-interacting region
DDI2	=	DNA-damage inducible 1 homology 2
DFCP1	=	Zinc finger FYVE domain-containing protein 1
DPR1	=	Dapper-1 protein
DRP1	=	Dynamin-related protein 1
EGFR	=	Epidermal growth factor receptor
eIF2α	=	Eukaryotic translation initiation factor 2α
ER	=	Endoplasmic reticulum
ETC	=	Electron transport chain
FCCP	=	Carbonyl cyanide-p-trifluoromethoxy-phenylhydrazone

FKBP8 = FK506-binding protein FOXK1
FOXO = Forkhead box protein
FUNDC1 = FUN14 domain-containing protein 1
GA = Golgi apparatus
GABARAP = Gamma-aminobutyric acid receptor-associated protein
GATA13 = Gata transcription factor 13
GCN2 = General control nonderepressible 2
GPX = Glutathione peroxidase
GSK3β = Glycogen synthase kinase-3 beta
GST = Glutathione S-transferase
HD = Huntington's disease
HDAC = Histone deacetylase
HMGB1 = High mobility group box 1
HRD1 = ERAD-associated E3 ubiquitin-protein ligase
HUWE1 = HECT, UBA and WWE Domain Containing E3 Ubiquitin Protein Ligase 1
IMM = Inner mitochondrial membrane
KEAP1 = Kelch-like ECH-associated protein 1
KIR = KEAP1-interacting region
KO = Knock-out
L-DOPA = L-3,4-dihydroxyphenylalanine
LIR = LC3-interacting region
LKB1 = Serine/threonine-protein kinase STK11
LRS = LC3-recognition sequence
MAP4K3 = Mitogen-activated protein kinase kinase kinase kinase 3
MAPK/JNK = c-Jun NH2-terminal kinase
MAPLC3 = Microtubule-associated proteins 1A/1B light chain 3
MARCH5 = Membrane-associated ring finger (C3HC4) 5
MCL1 = Myeloid cell leukemia 1
MET = Hepatocyte growth factor receptor
miRNA = microRNA
MPP = Mitochondrial processing peptidase
MTOR = Mammalian target of rapamycin complex 1
MTPAP = Mitochondrial poly(A)-polymerase
NBR1 = Neighbor of BRCA1 gene 1
NDP52/ CALCOCO2 = Nuclear domain 10 protein 52
NQO1 = NAD(P)H quinone dehydrogenase 1
NRBF2 = Nuclear receptor binding factor 2
NRF = Nuclear factor erythroid 2 (NFE2)-related factor
OGD/RP = Oxygen-glucose deprivation and reperfusion
OMM = Outer mitochondrial membrane
P62/SQSTM1 = P62/Sequestosome 1
PAQR3 = Progestin and adipoQ receptor family member 3
PARL = Presenilins-associated rhomboid-like protein
PB = Phox and Bem1p-1
PCD = Programmed cell death
PD = Parkinson’s disease
PDK2 = PDH kinase 2
PEA = Phosphatidylethanolamine
PERK = Proline-rich receptor-like protein kinase
PGAM5 = Phosphoglycerate mutase 5
PHB = Prohibitin
PI = Phosphatidylinositol
PI3K = Phosphatidylinositol-3-kinase
PI3KC1-3 = Phosphatidylinositol-3-kinase complex type 1-3
PIN = Prostatic intraepithelial neoplasia cells
PINK1 = PTEN-induced putative kinase 1
PKC = Protein kinase C
PKR = Protein kinase R
PLS3 = Phospholipid scramblase-3
PP2A = Phosphoprotein phosphatase 2A
PRX = Peroxiredoxin
PS = Presenilin
RISC = RNA-induced silencing complex
ROS = Reactive oxygen species
SIRT = Sirtuin
SKICH = Skeletal muscle and kidney-enriched inositol phosphatase carboxyl homology domain
SLP2 = Stomatin-like protein 2
SOD = Superoxide dismutase
SPAK = SPS/STE20-related proline-alanine-rich kinase
STAT = Signal transducer and activator of transcription
TAX1BP1 = Tax1-binding protein 1
TBK1 = TANK-binding kinase 1
TFEB = Transcriptional factor EB

TIMC	=	Translocase of inner membrane complex
TKO	=	Triple knock-out
TMEM55B	=	Lysosomal trafficking regulator factor type 1 phosphatidylinositol 4,5-bisphosphate 4-phosphatase
TOMC	=	Translocase of outer membrane complex
TRAF6	=	TNF receptor associated factor 6
UBA	=	Ubiquitin-binding domain
ULK1	=	Unc-51 like autophagy activating kinase
UV	=	Ultraviolet
UVRAG	=	UV radiation resistance-associated protein
VDAC	=	Voltage-dependent anion channels
VPS34	=	Vacuolar protein sorting 34
WIPI	=	WD-repeat protein interacting with phosphoinositides
WNK	=	Kinase with-no-lysine
ZZ	=	ZZ-type zinc finger domain

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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