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REVIEW ARTICLE

The Role of PTEN-L in Modulating PINK1-Parkin-Mediated Mitophagy

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Abstract

An inherent challenge that mitochondria face is the continuous exposure to diverse stresses which increase their likelihood of dysregulation. In response, human cells have evolved sophisticated quality control mechanisms to identify and eliminate abnormal dysfunctional mitochondria. One pivotal mitochondrial quality control pathway is PINK1/Parkin-dependent mitophagy which mediates the selective removal of the dysfunctional mitochondria from the cell by autophagy. PTEN-induced putative kinase 1 (PINK1) is a mitochondrial Ser/Thr kinase that was originally identified as a gene responsible for autosomal recessive early-onset Parkinson's disease (PD). Notably, upon failure of mitochondrial import, Parkin, another autosomal-recessive PD gene, is recruited to mitochondria and mediates the autophagic clearance of deregulated mitochondria. Importantly, recruitment of Parkin to damaged mitochondria hinges on the accumulation of PINK1 on the outer mitochondrial membrane (OMM). Normally, PINK1 is imported from the cytosol through the translocase of the outer membrane (TOM) complex, a large multimeric channel responsible for the import of most mitochondrial proteins. After import, PINK1 is rapidly degraded. Thus, at steady-state, PINK1 levels are kept low. However, upon mitochondrial import failure, PINK1 accumulates and forms a high-molecular weight > 700 kDa complex with TOM on the OMM. Thus, PINK1 functions as sensor, tagging dysfunctional mitochondria for Parkin-mediated mitophagy. Although much has been learned about the function of PINK1 in mitophagy, the biochemical and structural basis of negative regulation of PINK1 operation and functions is far from clear. Recent work unveiled new players as PTEN-l as negative regulator of PINK1 function. Herein, we review key aspects of mitophagy and PINK1/Parkin-mediated mitophagy with highlighting the role of negative regulation of PINK1 function and presenting some of the key future directions in PD cell biology.

Keywords PINK1 · PTEN-L · Parkin · Mitochondrial quality control · Mitophagy · Protein degradation · Protein quality control · Neurodegeneration

Introduction

Cellular homeostasis is accomplished through a sustained balance between biogenesis and turnover. Defects in damaged organelles and protein aggregate removal can cause cellular stress and eventually cell death. Lysosomal-mediated degradation and intracellular component recycling are under a tight control of regulated, highly conserved process termed autophagy (Mizushima et al. 2008; Mizushima 2018). There are three forms of intracellular autophagy in mammalian cells, including macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA). Autophagy could be either a non-selective randomly uptake process (bulk autophagy) or a special process to remove or degrade specific organelles, aggregated proteins, DNA, and pathogens (selective autophagy). The classification of these forms depends on the size of the substrates to be removed, their lysosomal degradation scale, and the delivery mechanism of the substrates to the lysosome. Macroautophagy is considered to be the major route for cytoplasmic proteins and organelles degradation; it is orchestrated by a group of proteins encoded by autophagy-related genes (ATGs) (Nakatogawa et al. 2009). Subcellular components in macroautophagy are engulfed by double-membrane vesicles termed autophagosomes and be vulnerable to lysosomal enzymes. The second form of

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autophagy (microautophagy) arises through the entrance of cellular constituents (including whole organelles) to lysosome via the direct invaginations of lysosomal membranes (Li et al. 2012). The latter form of autophagy is chaperone-mediated autophagy, in which soluble cytosolic proteins containing a specific targeting motif are delivered by the cytosolic chaperone heat shock cognate 70 (HSC70) to the lysosomal surface (Kaushik et al. 2012). Several types of selective autophagy, specific for the substrate, have been found; for instance, mitochondria (mitophagy), lipids (lipophagy), pathogens (xenophagy), peroxisomes (pexophagy), ribosomes (ribophagy), and endoplasmic reticulum (reticulophagy or ERphagy) (Tasdemir et al. 2007; Weidberg et al. 2009; Bauckman et al. 2015; Eldeeb et al. 2021a).

Mitochondria are not only the powerhouse of the cell that provide energy for a variety of different processes, but also are key triggers for programmed cell death, regulators of calcium homeostasis, and providers of diverse cellular metabolic and chemicals for the cell (Lill 2009; Schmidt et al. 2010; Harbauer et al. 2014; Hou et al. 2017). To fulfill such multitasking, mitochondrial quality control must be tightly controlled to achieve normal cellular activities. One major aspect of evolutionarily conserved macroautophagy is mitophagy, which involves monitoring quality control of mitochondria, either by regulating their number or, specifically, by removing those that are damaged (De Duve et al. 1996; Lemasters 2005; Eldeeb et al. 2018; Eldeeb et al. 2020a, b, c; Eldeeb and Ragheb 2020). Owing to its pivotal function in sustaining mitochondrial homeostasis and strong association with multiple human diseases, such as Parkinson's disease (PD) and Alzheimer's disease (AD), the mitophagy machinery has gained considerable attention throughout the last two decades. Cells possess numerous non-redundant mechanisms of mitophagy which imply that different stimuli can trigger mitophagy via various signaling cascades (Fig. 1) (Palikaras et al. 2017). For instance, the PINK1/Parkin-dependent mitophagy is the main modulator of depolarized mitochondria turnover. Additionally, several mitochondrial proteins, such as BNIP3, NIX, and FUNDC1, could function as mitophagy receptors, and they are constitutively localized at the outer membrane of mitochondria

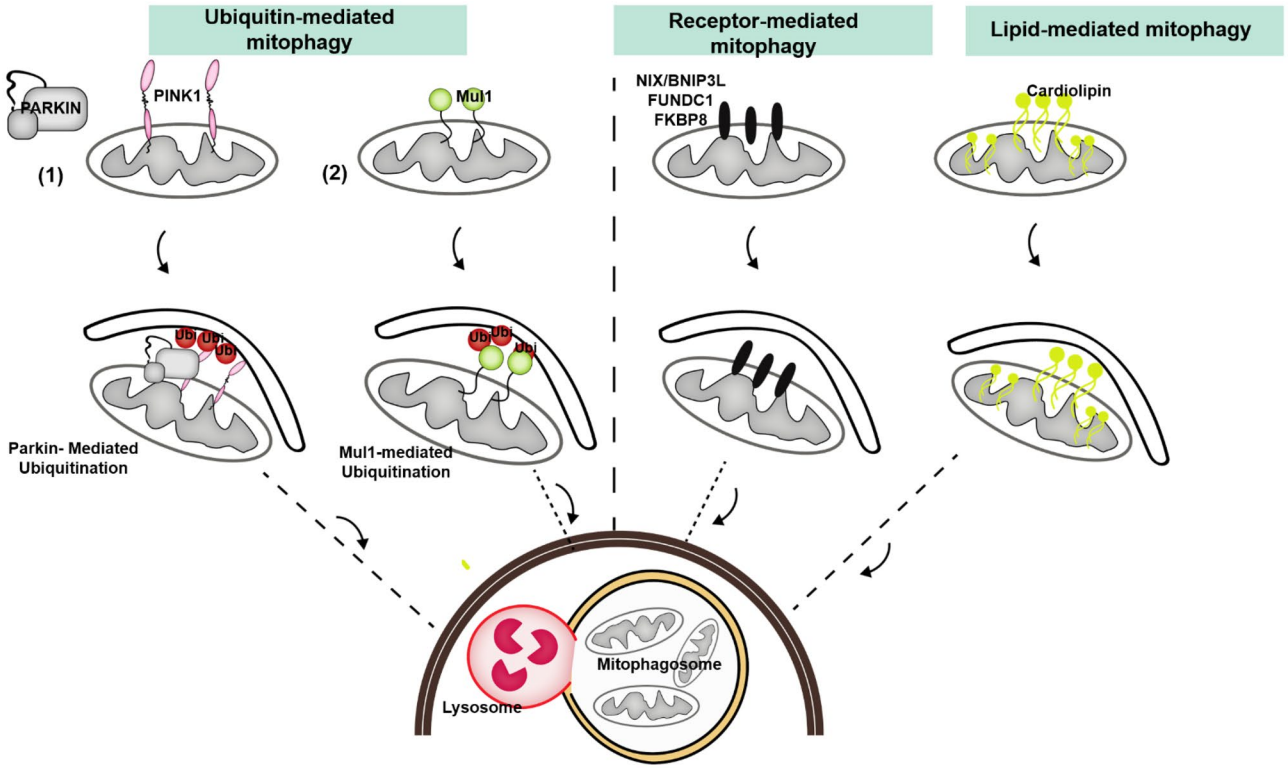

Fig. 1 The major pathways of mitophagy, including ubiquitin-mediated mitophagy (pathway 1, PINK1-Parkin-dependent mitophagy; and pathway 2, Parkin-independent mitophagy), receptor-mediated mitophagy, and lipid-mediated mitophagy. In PINK1-Parkin-dependent mitophagy, the stabilized PINK1 on the OMM of the damaged mitochondria facilitates the recruitment of Parkin from the cytosol to the OMM, resulting in the phospho-ubiquitination of proteins on the OMM via PINK1 and Parkin activities and finally the formation of mitophagosome. In ubiquitin-mediated Parkin-independent mitophagy, MUL1 (E3 ubiquitin ligase) located at damaged mitochondria can bind directly to GABAA receptor-associated protein (GABARAP), resulting in recruitment of phagophore to engulf damaged mitochondria. In receptor-mediated mitophagy, OMM receptors, such as BNIP3, NIX/BNIP3L, FUNDC1, and FKBP8, bind directly to LC3s allowing finally the formation of mitophagosome. In lipid-mediated mitophagy, cardiolipin is translocated from IMM to OMM, and binds directly to LC3s, resulting in mitophagy initiation

(OMM) and interact directly with autophagosomal membrane protein light chain 3 (LC3) to stimulate mitophagy. There are also lipid-mediated mitophagy and ubiquitin-mediated mitophagy (Chu et al. 2013; Strappazzon et al. 2015; Villa et al. 2018). Collectively, these pathways are deregulated in human diseases, including cancer, neurodegenerative disorders, metabolic disorders, and aging revealing the significance of mitophagy as a cellular housekeeping function (Valente et al. 2004; Narendra et al. 2008; Chourasia et al. 2015; Springer et al. 2016; Pickles et al. 2018a). In the current review, we provide an overview of the key pathways involved in mitophagy regulation, and we discuss the potential role of the newly identified PTEN isoforms, PTEN-Short, and PTEN-Long, in the fine-tuning of mitophagy.

Molecular Pathways of Mitophagy

PINK1-Parkin-Mediated Ubiquitin-Driven Mitophagy

Ubiquitin (ub) is a small protein that plays crucial role in multicellular processes including protein degradation and immune system signaling. Among the ubiquitin enzymes, ubiquitin-activating enzyme (E1), ubiquitin-conjugating enzyme (E2), and ubiquitin ligase (E3), E3 Ub ligases are the most abundant which designates that E3 ligases are the principal factors affecting the substrate specificity essential to the ubiquitin pathway (Scheffner et al. 1995). Parkin (encoded by the *PARK2* gene) is an E3 Ub ligase, which was discovered in 1998, and it contains five domains: an N-terminal Ub-like domain (UBL), a RING1 domain, an IBR domain, a RING2 domain, and a RING0 domain which is a Parkin unique domain (Hristova et al. 2009; Trempe et al. 2013; Walden et al. 2017) and has important roles in the pathogenesis of autosomal recessive Parkinson's disease (ARPD) (Kitada et al. 1998; Lucking et al. 1998; Abbas et al. 1999). Another ARPD-associated gene, PINK1 (PTEN-induced putative kinase 1) which encoded by *PARK6* gene and was discovered in 2001 (Unoki et al. 2001), encodes a mitochondrial serine/threonine kinase that regulates Parkin activity via phosphorylation cascades. PINK1 comprises of different domains, including an N-terminal mitochondrial targeting sequence (MTS) and a transmembrane domain (TMD) followed by a serine/threonine kinase domain and a regulatory domain at the C-terminal (Okatsu et al. 2015). Considering mitochondrial quality maintenance, the PINK1/Parkin-pathway is considered to play a key role in the removal of dysfunctional mitochondria and to constitute a mitochondrial quality-control system via PINK1-Parkin-mediated mitophagy initiation (Harper et al. 2018; Pickles et al. 2018a; Wang et al. 2020). The discovery of PINK1-Parkin-mediated pathway has been persuasive due to its contributions in understanding the key molecular mechanisms of mitophagy (Narendra et al. 2008, 2010; Vives-Bauza et al. 2010).

In normal healthy condition, Parkin is located in the cytosol and is in an autoinhibited state. Also, PINK1 is regularly maintained at a low level owing to mitochondrial import, protease cleavage, and proteasomal degradation, where PINK1 gets imported by the translocase of the outer membrane (TOM) complex into the inter membrane space (IMS) and the mitochondrial inner membrane (MIM), and then degraded by matrix processing peptidase (MPP), presenilin-associated rhomboid like (PARL), and the proteasome at the N-terminal part between Ala103 and Phe104 (Jin et al. 2010; Deas et al. 2011; Lazarou et al. 2012). The resulting N-terminal destabilizing amino acid is constitutively recognized by N-end rule E3 ubiquitin ligases (UBR1, UBR2, and UBR4) for protein degradation (Eldeeb and Ragheb 2018; Yamano et al. 2013). However, reduced potential of mitochondrial membrane results in accumulation of PINK1 on the outer mitochondrial membrane (OMM), and the accumulated PINK1 then undergoes dimerization and autophosphorylation at Ser228 and Ser402 thus resulting in its activation (Okatsu et al. 2012, 2013; Aerts et al. 2015; Rasool et al. 2018). Therefore, PINK1 functions as a mitochondrial damage sensor resulting in mitophagy propagation. Once activated, PINK1 leads to downstream phosphorylation events including Ser65 in the UBL domain of Parkin. Unfortunately, this alone is not enough to fully induce mitophagy, so PINK1 phosphorylate free ubiquitin as well as (poly-ubiquitin) chains at Ser65, which are already present on OMM proteins. Phosphoubiquitin (pSer65-Ub) then serves as a key receptor to initiate Parkin recruitment from cytosol to mitochondria (Okatsu et al. 2013; Kane et al. 2014; Kazlauskaite et al. 2014; Koyano et al. 2014; Shiba-Fukushima et al. 2014). Subsequently, activated Parkin linked more Ub onto OMM proteins for PINK1 phosphorylation that modulates more rounds of Parkin translocation to mitochondria, thereby forming a positive feedforward loop of PINK1, pSer65-Ub, and Parkin to trigger mitophagy. Intriguingly, PINK1-mediated pSer65-Ub is not the only identified phosphorylation; multiple other PINK1-independent phosphorylation Ub sites, including pSer20-Ub, pThr7-Ub, and pSer57-Ub, have been recognized (Wauer et al. 2015). Between them, it has been reported that pSer57-Ub hyperactivate Parkin (George et al. 2017).

After fully activation, Parkin polyubiquitylates different proteins on OMM such as Mfn1/2, TOM20/40/70, and VDAC 1 (Geisler et al. 2010; Sarraf et al. 2013). The bulk ubiquitylation of OMM proteins facilitates two main downstream events: recruitment of receptor proteins and activation of the ubiquitin–proteasome system. Receptor proteins, such as p62, interact on one side with the polyubiquitin chains directly and on the other side with LC3s or GABARAPs (Stolz et al. 2014). Initially, p62 was identified as the main adapter for Pink1/Parkin-mediated mitophagy (Geisler et al. 2010). Recently, comprehensive

study reported the importance of five well-known receptors: TAX1BP1, NDP52, NBR1, p62, and OPTN. Among them, NDP52 and OPTN were found to be the most important receptors for PINK1/Parkin-dependent mitophagy (Lazarou et al. 2015). The recruitment of autophagy receptors such as NDP52 and OPTN to damaged mitochondria is TANK-binding kinase 1 (TBK1)-dependent process (Heo et al. 2015; Lazarou et al. 2015; Richter et al. 2016). TBK1 is a serine/threonine kinase that enhances the binding ability of autophagy receptors to various Ub chains through their phosphorylation (Heo et al. 2015; Richter et al. 2016). In the presence of PINK1 and Parkin, TBK1 activation also requires OPTN binding to Ub chains (Heo et al. 2015; Richter et al. 2016). In the current mitophagy model, OPTN and NDP52 recruit phagophore onto mitochondria by directly binding to LC3 through their LC3-interacting region (LIR) domain after binding to polyubiquitin chains (Gatica et al. 2018; Palikaras et al. 2018). A very recent study has highlighted the role of NDP52 in the recruitment of ULK1 complex to damaged mitochondria (Vargas et al. 2019). NDP52 directly interacts with FIP200 in a TBK1-dependent manner to recruit ULK1 complex, leading to autophagosome biogenesis on damaged mitochondria and initiation of autophagy machinery. Therefore, receptor proteins ensure the removal of mitochondria by autophagosomes.

Receptor-Mediated Mitophagy

BNIP3/NIX-Mediated Mitophagy

Several mitophagy receptors, such as ATG32 in yeast (Okamoto et al. 2009) as well as BNIP3 (BCL2 and adenovirus E1B 19-kDa-interacting protein 3) (Hanna et al. 2012), NIX (also known as BNIP3L) (Chen et al. 2010), and FUNDC1 in mammalian cells, have recently been identified. One major characteristic of mitophagy receptors is that they contain LIR that interacts with LC3, thereby enhancing the mitochondrial sequestration into phagophore (Wei et al. 2015; Bhujabal et al. 2017). The mechanism of BNIP3- and NIX-mediated mitophagy is distinguished from that of the Parkin/PINK1 pathway in that these proteins act as direct adaptors targeting mitochondria to the autophagosome. BNIP3 (a member of pro-death BCL2 family proteins) (Boyd et al. 1994) and NIX (a homolog of BNIP3 with ~ 56% sequence similarity) (Matsushima et al. 1998) have BH3 domain and C-terminal transmembrane domain (TMD), which is crucial for their proapoptotic functions and mitochondrial localization (Yasuda et al. 1998; Imazu et al. 1999). Furthermore, BNIP3 and NIX have an identical N-terminus LIR domain exposed to the cytosol that facilitate interacting with LC3s (microtubule-associated protein 1A/1B light chain) for both receptors, or to GABARAP (gamma aminobutyric acid receptor-associated protein) for NIX, leading to recruitment of autophagosomes to induce mitophagy (Novak et al. 2010; Hanna et al. 2012; Birgisdottir et al. 2013). In these stress response pathways, the expression of BNIP3 is transcriptionally regulated by HIF-1, PPARγ, Rb/E2F, FoxO3, activated Ras, and p53, whereas NIX is regulated by HIF-1 and p53 (Sowter et al. 2001; Mammucari et al. 2007; Zhang et al. 2008). Although BNIP3 and NIX are predominantly under transcriptional control, they are post-translationally modified for their mitophagic activity. Evidently, it has been shown that serine phosphorylation at positions 17 and 24 adjacent to the LIR of BNIP3 and at positions 34 and 35 in the LIR domain of NIX enhances the interaction of these receptors with LC3 augmenting mitophagy (Rogov et al. 2017). LIR motif mutation prevents the BNIP3/NIX interaction with LC3 and thus mitigates the mitochondrial removal (Novak et al. 2010; Hanna et al. 2012; Zhu et al. 2013), while LIR motif phosphorylation promotes the interaction with LC3 and enhances mitophagy (Zhu et al. 2013; Rogov et al. 2017). NIX is implicated in the clearance of mitochondria from reticulocytes which is a crucial step for the red blood cell maturation, and it was confirmed as mitochondria were not cleared in reticulocytes when NIX is deficient (Diwan et al. 2007; Schweers et al. 2007; Zhang et al. 2008).

Furthermore, recent studies emphasized that both BNIP3 and NIX have a significant role in the progression of cancer and metastasis (Chourasia et al. 2015). In addition, it is believed that BNIP3-mediated mitophagy delays the metastatic disease progression. It is accepted that mitophagy, in general, is a tumor suppression mechanism (Bernardini et al. 2017; Roperto et al. 2019).

BNIP3 and NIX are implicated in hypoxia-induced tumor cell death. BNIP3 was identified in a subtractive hybridization screen in Chinese hamster ovary-K1 cells exposed to hypoxia, and hypoxia strongly induced BNIP3 mRNA (Bruick 2000). Furthermore, BNIP3 protein was induced by hypoxia in these cells, and the kinetics of induction correlated with cell death. The BNIP3 promoter has two HIF-1α-binding sites, and the site at − 234 relative to the translational start codon is required for transactivation by hypoxia and HIF-1α. In another study, hypoxia induced BNIP3 expression in tumor cell lines, and BNIP3 was expressed in the perinecrotic areas of several epithelial cell carcinomas (Sowter et al. 2001). In this study, BNIP3 was suppressed by Von Hippel-Lindau protein in a renal cell carcinoma cell line, consistent with its regulation through the HIF-1α pathway. Hypoxia in tumors is a negative prognostic indicator; accordingly, deregulation of BNIP3 expression is associated with aggressive disease (reviewed by Burton and Gibson (Burton et al. 2009).

Under hypoxic conditions, NIX level is fine-tuned by various post-transcriptional and post-translational mechanisms (Bruick 2000; Sowter et al. 2001; Fei et al. 2004). For instance, in U2OS osteosarcoma cells, NIX abundance appear to be regulated transcriptionally and post-transcriptionally by two factors including hypoxia and p53 (Fei et al. 2004). Although the transcriptional mechanism by which NIX levels is regulated appears to involve

HIF-1α-dependent recruitment of CBP to the *Nix* gene, followed by recruitment of p53, the post-transcriptional mechanism remains yet to be fully elucidated. In line with this, it was found that repressing NIX level experimentally augments the growth of these cells in a tumor transplant model, underscoring a potential role for NIX in restraining tumor growth upon hypoxic circumstances. Tellingly, in studies of human cancer, hypermethylation of the BNIP3 promoter was found in pancreatic cancer (Okami et al. 2004), and the *Nix* gene was found to be mutated in a panel of primary breast and ovarian tumors (Lai et al. 2003). Thus, BNIP3 and NIX are regulated by hypoxia in tumor cells, and their expression is associated with tumor cell death.

In heart muscle, the BNIP3 and NIX have been shown to play a regulatory role in pathological cell death and this has been demonstrated in rat cardiomyocytes (Guo et al. 2001; Kubasiak et al. 2002; Regula et al. 2002).

Numerous researches suggest a possible crosstalk between BNIP3/NIX receptor-mediated pathway and PINK1-Parkin-mediated axis (Ding et al. 2010; Lee et al. 2011); NIX was connected to Pink1/Parkin-mediated mitophagy as a substrate of Parkin that recruits NBR1 to the mitochondria (Gao et al. 2015). Additionally, BNIP3-induced mitophagy is reduced in Parkin-deficient cells (Lee et al. 2011) and BNIP3 can stabilize PINK1 on OMM and inhibit PINK1 proteolytic degradation (Zhang et al. 2016). These results indicate that these pathways could cooperate with each other to ensure effective mitophagy.

FUNDC1-Mediated Mitophagy

FUN14 domain containing 1 (FUNDC1), an integral mitochondrial outer-membrane protein, is another important receptor for hypoxia-mediated mitophagy. FUNDC1 composed of three TMD and an LIR domain in its N-terminus exposed to the cytosol which interacts with LC3 for autophagosome recruitment (Liu et al. 2012). Like other key regulators of mitophagy, the activity of FUNDC1 is also fine-tuned by phosphorylation and dephosphorylation. The phosphorylation states of the three key residues, Ser13, Ser17, and Tyr18, in the outer membrane region of FUNDC1 have been reported to play essential roles in impacting the binding affinity for LC3 and controlling mitophagy (Chen et al. 2014; Wu et al. 2016). Under normal conditions, the LIR motif of FUNDC1 is phosphorylated at Ser13 by CSNK2/CK2 kinase and at Tyr18 by SRC kinase, which leads to inhibition of its interaction with LC3 and prevents mitophagy. Conversely, hypoxia elicits dephosphorylation of FUNDC1, which can then bind to LC3 and provoke mitophagy (Chen et al. 2014; Lv et al. 2017).

Another study showed that hypoxia leads to upregulation of ULK1 and initiates its translocation to damaged mitochondria; ULK1 directly phosphorylates FUNDC1 at serine-17, which is required for FUNDC1 and LC3 binding leading to mitophagy (Chen et al. 2014). Furthermore, Chen et al. confirmed that phosphoglycerate mutase family member 5 (PGAM5) dephosphorylates Ser13 upon induction of hypoxia in mitochondria, which results in the enhanced interaction of FUNDC1 with LC3, and eventually selective removal of dysfunctional mitochondria, while (casein kinase 2) CK2 phosphorylates the Ser13 of FUNDC1 in normal cells to reverse the effect of PGAM5 in mitophagy activation (Chen et al. 2014).

Many studies have demonstrated that contact between the mitochondria and the ER plays a crucial role in mitochondrial fission (Friedman et al. 2011; Murley et al. 2013; Naon et al. 2014). During physiological mitochondrial fission, several mitochondrial receptors, including MFF, MID49/51, and FIS1, have been reported to recruit DRP1, a highly conserved dynamin-related GTPase which is essential for the mitochondrial fission process (Smirnova et al. 2001). In contrast, mitochondrial fission under hypoxic conditions is still elusive, and thus, further studies are warranted to enhance our understanding of the molecular mechanisms of mitochondrial fission upon hypoxia (Kim et al. 2011).

Interestingly, it was reported that FUNDC1 integrates mitophagy and mitochondrial fission at the interface of the ER–mitochondrial contact site (MAM) through the association with ER-membrane protein calnexin to recruit DRP-1 (Wu et al. 2016). Another interactor of FUNDC1 is the mitochondrial E3 ligase MARCH5 (known as MITOL), which is a mitochondrially localized RING-finger E3 ligase that is involved in mitochondrial dynamics by ubiquitylating Fis1 (Yonashiro et al. 2006), Mfn1 (Park et al. 2014), and Mfn2 (Sugiura et al. 2013). Recently, MARCH5 was found to play a role in ubiquitin-mediated degradation of MiD49 and recruitment of Drp1 (Xu et al. 2016). The MARCH5/FUNDC1 interaction mediate FUNDC1 ubiquitylation at lysine 119 for subsequent degradation hence reducing mitophagy activity. Therefore, the regulation of MARCH5/FUNDC1 axis desensitizes mitochondrial degradation and prevents improper clearness of undamaged mitochondria.

PTEN-Short as a Negative Regulator of Mitophagy

PTEN (phosphatase and tensin homolog deleted on chromosome ten) was shown to be instrumental for several signal transduction networks. PTEN contains 403 amino acids with a N-terminal phosphatidylinositol (4,5)-bisphosphate [PI(4,5)P2]-binding domain (PBD), a catalytic phosphatase domain, a C2 domain, a C-tail domain, and a PDZ-binding motif (Lee et al. 1999). PTEN is a potent tumor suppressor with both lipid phosphatase and protein phosphatase

activity, which was identified in 1997 (Li et al. 1997; Li et al. 1997; Steck et al. 1997). In addition, it is the second most common tumor suppressor, after P53, and is closely associated to tumorigenesis (Nakamura et al. 2000). Furthermore, PTEN is also widely expressed in the central nervous system (Song et al. 2012), and plays an important role in the development of the nervous system and maintenance of its normal functions. Concomitantly, its deregulation has been implicated in neurological disorders, such as Alzheimer's disease (Sonoda et al. 2010). Previous studies demonstrated that autophagy signaling depends upon the activity of the tumor suppressor PTEN. Crucially, the role of PTEN in controlling autophagy is dependent upon its lipid phosphatase activity, which downregulates the inhibitory effect of the PI3-K/AKT pathway on the autophagic pathway by dephosphorylating phosphatidylinositol 3,4,5-trisphosphate (PIP3) to phosphatidylinositol-4,5-bisphosphate (PIP2) (Cantley et al. 1999; Arico et al. 2001; Ueno et al. 2008; Rodon et al. 2013).

Previous studies identified Ser72 in RAB7A, a RAB linked with mitophagy pathway, as influential target of TBK1 during mitochondrial depolarization. RAB7A could be a direct target for phosphorylation by TBK1 at Ser72 and provoke PINK1-Parkin-mediated mitophagy, but non-phosphorylated RAB7A failed to initiate mitophagy (Heo et al. 2018). PTEN has been suggested to regulate RAB7A dephosphorylation in the context of epidermal growth factor receptor (EGFR) signaling through the endosome (Shinde et al. 2016). Based on the findings of previous studies (Erland et al. 2018), mitophagy can be activated by Mitofusin-2 (Mfn2) and helps injured mitochondria fuse with the lysosome (Chandra et al. 2018). Furthermore, other studies have also indicated that Mfn2 is primarily activated by the AMPK pathway (Daniel et al. 2018), which increases the phosphorylation of CREB, a transcriptional promoter (Edwards et al. 2018). Phosphorylated CREB translocates into the nucleus where it interacts with and activates the promoter of Mfn2, leading to the upregulation of Mfn2 expression and mitophagy activity (Fernández Vázquez et al. 2018). Inhibition of PTEN could promote endothelial survival via activating the AMPK–CREB–Mfn2-mitophagy signaling pathway providing a beneficial influence on mitochondrial homeostasis, cellular survival, and endothelial migration (Li et al. 2020). A recent study by W Tang et al. concluded that inhibition of PTEN function induced by bv (phen)-suppressed PINK1/Parkin-mediated mitophagy, which resulted in an increased apoptosis and release of mitochondrial Cytochrome C in H/R-injured H9c2 cells (Tang et al. 2019). Another study has also suggested that inflammation-induced PTEN downregulation resulted in TLR4-JNK-Bnip3-mitophagy pathway activation, which eventually amplified the cellular death signals in nasal epithelial cells(Li et al. 2018).

PTEN-Long as a Pivotal Regulator of PINK1–Parkin-Mediated Mitophagy

PINK1-mediated phosphorylation and Parkin-mediated ubiquitination are the two key molecular events positively regulating mitophagy. The PINK1/Parkin pathway of mitophagy is subject to intricate regulation, primarily via the action of a number of deubiquitinating enzymes (DUBs), including USP15, USP30, USP35, and PTEN-L (PTENα) (Bingol et al. 2014; Cornelissen et al. 2014; Wang et al. 2015; Wang et al. 2018a, b). Unlike PTEN which is typically initiated at AUG codons (Kozak 1999), PTEN-L translation initiation occurs at non-AUG codons, which enhances genome coding capacity and protein diversity (Hann et al. 1988; Németh et al. 2007; Gerashchenko et al. 2010). Besides the same five functional domains with the canonical PTEN, PTEN-L contains an alternatively translated region (ATR) adding 173 amino acids at the N-terminus that encode a secretion signal sequence that allows this enzyme to be secreted into the extracellular environment (Fig. 2) (Hopkins et al. 2013). The extended ATR of PTEN-L consists of a secreted polyalanine signal sequence (Poly-A), a cell permeable polyarginine motif (Poly-R), a nuclear localization sequence (NLS), and a membrane-binding α-helix (MBH) (Hopkins et al. 2013; Malaney et al. 2013; Masson et al. 2016; Shen et al. 2019). In addition, PTEN-L may modify distinct substrates compared with PTEN as most parts of the ATR contain various post-translational modification sites and protein-binding motifs (Malaney et al. 2013; Masson et al. 2016). Significant proportion of PTEN-L is present in the mitochondrial fraction which enhances the possible regulatory role of PTEN-L in mitophagy (Wang et al. 2018a, b). PTEN-L is a canonical PTEN isoform located at outer mitochondrial membrane (OMM) and dephosphorylates Ub, hence may act to oppose PINK1/Parkin-mediated mitophagy. PTEN-L serves as the phosphatase to dephosphorylate pSer65-Ub mediated by PINK1, which is the key step for subsequent events including Parkin translocation, phosphorylation, conformational changes, and E3 ligase activation and ultimately mitophagy. Thus, PTEN-L-mediated dephosphorylation of pSer65-Ub eventually disrupts the feedforward loop and suppresses mitophagy (Fig. 3). In vitro analysis showed the role of PTEN-L on pSer65-Ub chains, a key element in the feed-forward mechanism in mitophagy, and PTEN-L dephosphorylates pSer65-mono-Ub, pSer65-tetra-Ub, and pSer65-poly-Ub chains (Wang et al. 2018a, b). PTEN-L was found to be involved in many cell functions; for instance, PTEN-L was found to be regulating mitochondrial energy metabolism. Concomitantly, somatic deletion of PTEN-L impairs mitochondrial respiratory chain function, as it is involved in the electron transfer reaction and ATP production, likely through regulation of COX activity, the rate-limiting enzyme in the respiratory chain. Multiple mechanisms may be involved in PTENα

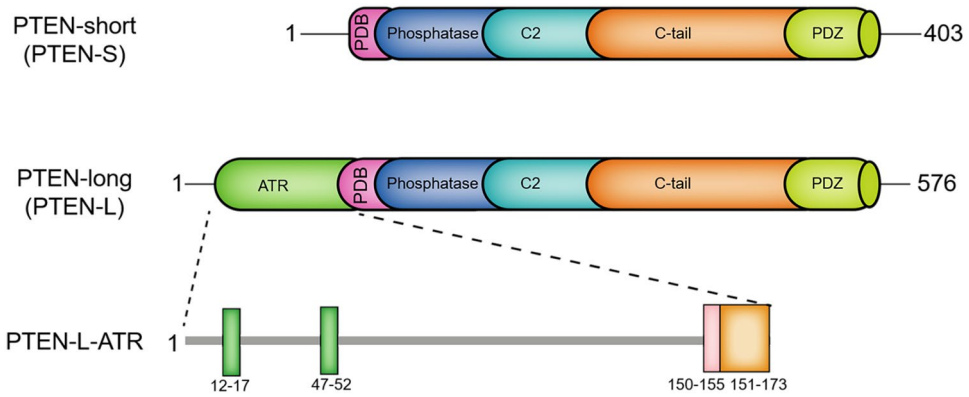

Fig. 2 Protein domain structure and isoforms of phosphatase and tensin homolog (PTEN). (A) PTEN-short (canonical PTEN) consists of five functional domains: a PIP2-binding domain (PBD), catalytic phosphatase domain, C2 lipid/membrane-binding domain, C-tail domain, and PDZ-binding motif. Canonical PTEN is translated from AUG start codon. (B) PTEN-long (PTEN-L) composed of the same five functional domains of the canonical PTEN and an alternatively translated region (ATR) which adds 173 amino acids to the N-terminus. PTEN-L is translated from a CUG start codon upstream from the classic AUG start codon. (C) ATR region structure of PTEN-L contains a polyalanine signal sequence (Poly-A), a cell permeable polyarginine stretch (Poly-R), a nuclear localization sequence (NLS), and a membrane-binding a-helix (MBH)

regulation of COX activity (Liang et al. 2014). Based on previous studies, PTEN-L is proposed to be a membrane-permeable lipid phosphatase that is released from cells and then taken up into other cells. PTEN-L antagonized PI3K signaling and induced tumor cell death in vitro and in vivo. Recently, studies report that PTEN-L is a required component of MFN1-Bak

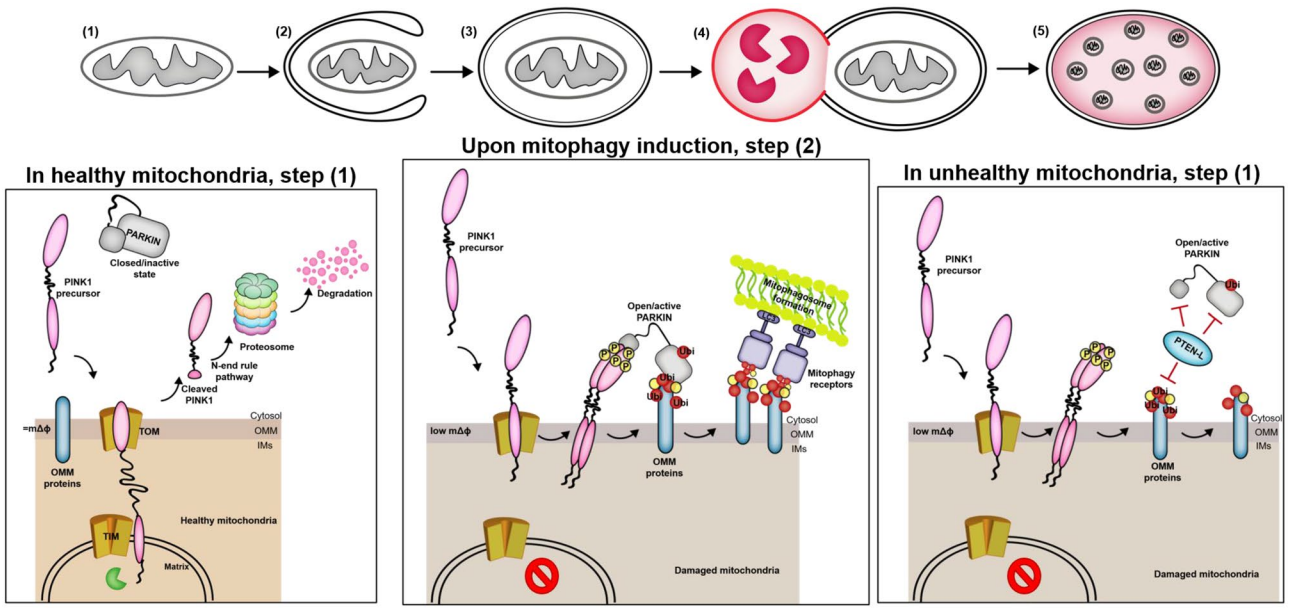

Fig. 3 Key effectors involved in mitophagy machinery during healthy and damaged phases of mitochondria. Under basal mitochondrial healthy condition, PINK1 is imported into the mitochondria, cleaved by proteases, and degraded by proteasome, while Parkin keeps in an inactive conformation in the cytosol. Upon mitochondrial deregulation, PINK1 is stabilized and activated at the outer mitochondrial membrane (OMM), which leads to the phosphorylation of its downstream targets, such as ubiquitin (Ub). Parkin has a high affinity to phosphorylated Ub (pSer65-Ub), which recruits Parkin from cytosol to mitochondria. Several other factors, such as mitofusin 2 (MFN2), Miro, Rab7A, and BCL2/adenovirus E1B 19 kDa protein-interacting proteins 3 (BNIP3), are also involved in Parkin mitochondrial recruitment. Binding to pSer65-Ub releases the Ub-like (UBL) domain of Parkin from RING1 domain, partially activating Parkin. Then, PINK1 phosphorylates the UBL domain at Ser65, which drives the phospho-UBL to rebind fully activation of Parkin. On the other hand, PTEN-L located at OMM dephosphorylates Ub to suppress mitophagy

signaling for apoptosis which resulted in mitochondrial fragmentation. This study, in conjunction to the Pink1-Parkin mitophagy-associated functions of PTEN-L, further solidifies a role for PTEN-L in regulating the targeted elimination of dysfunctional mitochondria (Sivakumar et al. 2020). Thus, understanding this novel function of PTEN-L provides a key missing piece in the molecular mitophagy pathway, a critical process in several human diseases.

Intriguingly, recognition of PTENα helps understand the complexity of PTEN function. Tellingly, previous studies revealed that PTENα and PTEN-L have distinct functions in response to stress and might be involved in different molecular mechanisms of neuroprotection (Jochner et al. 2019). PTEN family proteins are not only involved in the regulation of PINK1-Parkin-mediated Ub-driven but also implicated in BNIP3-mediated mitophagy. Additional studies to further understand the key tenets of PTEN family proteins are thus needed. These future studies would evaluate the potential role of targeting PTEN-L as potential molecular therapeutic targets in the regulation of mitophagy to benefit mitophagy-related human diseases.

Concluding Remarks and Future Perspectives

Optimal mitochondrial functioning is critical for cellular homeostasis, and abrogation of mitochondrial operation have long been widely linked to the pathogenesis of neurodegenerative diseases such as AD, PD, and ALS. Nevertheless, the detailed molecular mechanisms by which mitochondrial integrity is compromised in neurodegeneration are still far from clear.

To combat mitochondrial damage and maintain healthy mitochondrial operation, mammalian cells have evolved sophisticated mitochondrial quality control mechanisms. In neuronal cells, mitophagy represents a major quality control strategy for the clearance of aged and deficient mitochondria through lysosomal proteolysis. While the molecular mechanisms governing mitophagy have been extensively studied in the past decade, ablation in mitophagy progression has emerged recently as a pivotal hallmark in aging-linked neurodegeneration. Importantly, approaches to enhance protection of mitochondrial function have been recently recognized as a potential practical strategy to promote neuroprotection and halt disease pathology (Eldeeb et al. 2021b). For instance, mitochondrially targeted antioxidants have been proposed to exert protective effect against neurodegeneration in mice models. Remarkably, the antioxidant MitoQ, a redox active ubiquinone targeted to mitochondria, has been demonstrated to exhibit protective role in several of aging and neurodegenerative disorders (Kelso et al. 2001; McManus et al. 2011; Miquel et al. 2014; Ng et al. 2014).

Importantly, given the findings that PTEN-L is negative regulator of mitophagy, targeting PTEN-L could be another promising target for future drug discovery investigations. Lastly, further detailed molecular studies to elucidate mitophagy in physiological-relevant cellular models not only advance our understanding of molecular basis of diseases, but also unearth novel strategies to circumvent neurodegeneration (Cai et al. 2020).

Author Contribution MAE conceived the idea of the article. MAE, ME, MH, and MAR wrote the article. ME and MAE crafted the figures. All authors edited the article.

Declarations

Conflict of Interest The authors declare no competing interests.

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