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Review Article

Diversity in the Regulation of Autophagy and Mitophagy: Lessons from Parkinson's Disease

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Selective mitochondrial degradation through autophagy (mitophagy) has emerged as an important homeostatic mechanism in a variety of organisms and contexts. Complete clearance of mitochondria can be observed during normal maturation of certain mammalian cell types, and during certain forms of neuronal cell death. In recent years, autophagy dysregulation has been implicated in toxin-injured dopaminergic neurons as well as in major genetic models of Parkinson's disease (PD), including α-synuclein, leucine-rich repeat kinase 2 (LRRK2), parkin, PTEN-induced kinase 1 (PINK1), and DJ-1. Indeed, PINK1-parkin interactions may form the basis of a mechanism by which dissipation of the inner mitochondrial membrane potential can trigger selective mitochondrial targeting for autophagy. Multiple signals are likely to exist, however, depending upon the trigger for mitophagy. Similarly, the regulation of basal or injury-induced autophagy does not always follow canonical pathways described for nutrient deprivation. Implications of this regulatory diversity are discussed in the context of neuronal function and survival. Further studies are needed to address whether alterations in autophagy regulation play a directly injurious role in PD pathogenesis, or if the observed changes reflect impaired, appropriate, or excessive autophagic responses to other forms of cellular injury.

1. Introduction

Macroautophagy represents an evolutionarily conserved response to nutrient stresses, which also plays an increasingly recognized role in basal cellular maintenance and in cellular responses to injury. The important role of macroautophagy in brain development and quality control was highlighted by observations that mice engineered for deficiency in key autophagy genes exhibit spontaneous neurodegeneration with ubiquitinated protein aggregates [1, 2]. Macroautophagy (hereafter, autophagy unless otherwise specified) is also implicated in mitochondrial quality control, as altered mitochondria accumulate under basal conditions of autolysosomal dysfunction [3–6], and mitophagy is further induced in cells exhibiting damaged mitochondria [7, 8]. Mitochondrial autophagy induced in response to mitochondrial damage or neuronal injury may play either prosurvival [7, 9] or prodeath roles [10, 11]. As mechanisms underlying different models of injury-induced autophagy and mitophagy are discovered, the concept of distinct regulatory inputs to a core autophagy pathway has emerged.

In sympathetic neurons, it was noted that the phosphoinositide 3-kinase inhibitor 3-methyladenine (3-MA) delayed apoptosis by reducing cytochrome c release and caspase activation [12]. Subsequent studies in the same system resulted in the first report of complete and selective clearance of mitochondria from neurons [13]. Combined with developmental observations of selective mitochondrial clearance in reticulocytes, lens, and lymphocytes [14, 15], these findings implicate the existence of specific mechanisms targeting mitochondria for autophagic clearance (although nonautophagic mechanisms may also contribute [16, 17]). Autophagy dysregulation is observed in a growing number of toxic/environmental and genetic models of Parkinson's disease (PD). Recent breakthroughs show a key role for two recessive Parkinsonian genes, PINK1 and parkin, in the specification of depolarized mitochondria for sequestration in aggresomes and/or autophagosomes [18, 19]. The potential

role of autophagy in PD models is reviewed in relation to diverse regulatory pathways feeding into the core autophagy machinery.

2. Autophagy Dysregulation in Parkinson's Disease

2.1. Sporadic PD. In PD patient tissues, evidence of apoptosis and of autophagy is observed in substantia nigra neurons [20]. Additional studies demonstrate mitophagy in the substantia nigra neurons of patients with PD spectrum diseases [21], and in Alzheimer's disease [22]. The ultrastructural observations of mitophagy in PD are correlated with a peculiar punctate/vesicular staining pattern for phosphorylated extracellular signal-regulated protein kinases (ERK1/2) [23, 24]. Although there have not been quantitative ultrastructural studies of autophagolysosomal structures in PD tissues, analysis of punctate/vesicular phospho-ERK1/2 indicates preferential involvement of the substantia nigra ventrolateral tier [21]. Incidental Lewy body disease, which is thought to represent a preclinical form of PD, exhibits an intermediate level of involvement [21]. In contrast, substantia nigra dopaminergic neurodegeneration associated with a distinct disease, progressive supranuclear palsy, do not show these changes (author's unpublished data), suggesting specificity for synucleinopathies.

2.2. Toxin Models of PD. Autophagy has been implicated in neurotoxin and environmental toxin models of dopaminergic cell death. Early and late autophagosomes can be identified by ultrastructural analysis, or by monitoring autophagosome-associated microtubule-associated protein 1 light chain 3 (LC3). Cytosolic LC3 migrates as an LC3-I band; upon stimulation of autophagy, LC3 is covalently conjugated to phospholipids, resulting in a faster migrating LC3-II band and correlating with punctate redistribution of the LC3 immunofluorescent signal. Increased autophagosomes have been described in acute injury models involving methamphetamine [25, 26], high doses of dopamine [27], 1-methyl-4-phenylpyridinium (MPP+) [10], 6-hydroxydopamine [11], the environmental toxicants rotenone [28], and paraquat [29]. In the case of toxins that are weak bases, it is not clear whether increased autophagosomes reflect increased autophagy induction or impaired completion of autophagic degradation from lysosomal pH elevation. Moreover, the role of autophagy in cell survival and cell death has been model-dependent. In some cases the "autophagy inhibitor" 3-MA exacerbated cell death [26] and autophagy stimulation conferred protection [28], but in other cases 3-MA ameliorated cell death [27, 30].

3-MA is a phosphoinositide 3-kinase (PI3K) inhibitor, which acts to inhibit autophagy by blocking the activity of the beclin 1-Vps34/class III PI3K complex. Interpretation of increased cell death in the presence of 3-MA, however, is complicated due to the ability of 3-MA to inhibit not only the class III PI3K involved in beclin 1-dependent autophagy pathways, but also the neuronal survival kinase Akt that is downstream of class I PI3K [12]. Due to opposite effects of class I and class III PI3Ks on autophagy [31], 3-MA can reduce or promote autophagy depending on the relative activation state of the two pathways [32]. 3-MA also has direct effects on glucose/glycogen metabolism independent of its autophagy-modulating effects and elevates lysosomal pH in living hepatocytes, but not isolated lysosomes [33]. Thus, it is essential to verify that 3-MA inhibits autophagy in the particular experimental condition being studied, and confirmation using more selective molecular inhibition of autophagy may be preferable.

While neuroprotective effects of autophagy in toxin models have been correlated with α-synuclein sequestration [26], noncanonical beclin 1-independent autophagy/mitophagy contributes to MPP+ toxicity, as shown by RNA interference knockdown of Atg7 and LC3/Atg8 [10]. This implicates excessive activation of autophagy, since the participation of beclin 1 in autophagy is downregulated by binding to Bcl-2 [34] or rubicon [35, 36]. Blunting the autophagy response has also been shown using dominant negative Vps34 to prevent hydrogen peroxide-mediated lysosomal leakage and caspase activation [37]. Likewise, a compound that activates mTOR to suppress autophagy confers protection from oxidative stress in neurons [30] while rapamycin exacerbates toxicity in this system and in primary neurons treated with MPP+ [38].

2.3. Genetic Models of PD. The dominant PD-linked protein α-synuclein exhibits consensus motifs for lysosomal degradation by chaperone-mediated autophagy (CMA), which is distinct from macroautophagy in its regulation. Mutant forms of α-synuclein bind the CMA receptor but are not internalized, inhibiting this degradative pathway in isolated liver lysosomes [39]. Moreover, dopamine-oxidized forms of α-synuclein show the same effect [40]. Both CMA and macroautophagy are involved in degrading wild-type α-synuclein in neurons [41], and A53T α-synuclein expression impairs CMA in living cells [42]. While upregulation of macroautophagy can mediate clearance of α-synuclein aggregates in metabolically intact cells [43], reports that α-synuclein can affect mitochondrial metabolism [44] and macroautophagy efficiency [45] raise additional questions. Indeed, CMA impairment induces upregulation of macroautophagy, which appears to contribute to neuron cell death [42]. Interestingly, low-dose application of the fusion inhibitor bafilomycin can protect against α-synuclein pathology in *C. elegans* [46]. The reciprocal cross-regulation of autophagy and of α-synuclein complicates analysis and creates the possibility of damaging feed-forward cycles.

One of the prominent phenotypes attributed to the dominant and sporadic PD-implicated protein LRRK2 is modulation of the neuritic arbor. Increased LRRK2 activity and PD-linked LRRK2 mutants cause simplification and shortening of neuritic projections while knockdown of LRRK2 expression results in enhanced neuritogenesis [47]. LRRK2-G2019S elicits neuritic autophagy, which mediates neurite shortening in retinoic acid-differentiated SH-SY5Y cells [48] and in primary cortical neurons [49]. LRRK2 associates with multivesicular bodies, and LRRK2-R1441G

elicits increased autophagosomes attributed to disrupted autophagic flux in HEK-293 cells [50]. Whether cell type differences or somatic versus neuritic differences affect flux responses to mutant LRRK2 remain to be established, as estimates of autophagy induction and flux rates are inferred unless pulse-chase techniques are used.

Parkin deficiency causes different phenotypes in different model systems. In parkin knockout mice, the primary defect relates to neurotransmission [51, 52]. In Drosophila, however, prominent mitochondrial degeneration in flight muscles and sperm is observed [53]. A pivotal discovery for parkin function was made in HeLa cells treated with the mitochondrial depolarizing agent FCCP or CCCP [18]. Parkin translocation to FCCP-depolarized mitochondria results in their eventual clearance through Atg5-dependent mechanisms, and this observation has led to an explosion of papers on the subject, each of which sheds additional insight into molecular mechanisms of mitochondrial cargo specification (discussed below). While overexpressed parkin enhances mitophagy in FCCP-treated cells [18] and in PINK1-deficient cells [7], the role of endogenous parkin in this setting is less clear. Translocation of tagged parkin to mitochondria and its ubiquitinating activity is essential for enhanced mitochondrial autophagy in FCCP/CCCP-treated cells. However, parkin monoubiquitination of Bcl2 enhances the ability of Bcl2 to bind beclin 1 and suppress autophagy, and RNAi knockdown of parkin increases the LC3-II band in 293, SH-SY5Y, and primary neuron cultures [54]. Thus, depending on subcellular localization and/or target accessibility, parkin can act to either promote mitochondrial specification for autophagy or to downregulate general autophagy.

PINK1 knockdown cells exhibit mitochondrial functional and morphological abnormalities [7, 55–57], with enhanced autophagic clearance of mitochondria [7]. On the other hand, overexpressed, full-length PINK1 reduces unconjugated LC3 [58] and increases parkin localization to mitochondria ([59, 60] and discussed below). Endogenous PINK1 in SH-SY5Y cells is predominantly processed [7], and PINK1 is processed in Drosophila by the membrane protease Rhomboid-7 [61]. As mitochondrial protein import and processing depends upon an intact inner mitochondrial membrane potential, stabilization of full-length PINK1 at the surface of depolarized mitochondria initiates PINK1-dependent mitophagy enhancement [62, 63].

Mitochondrial dysfunction observed in DJ-1 null cells is accompanied by a baseline decrease in the activated LC3-II band [6, 64]. However, whether this reflects increased or decreased autophagic flux remains controversial, and an increase in markers of compensatory mitophagy was recently reported in DJ-1 shRNA-expressing neuroblastoma cells [65]. DJ-1 null fibroblasts show reductions in expression of rapamycin-induced autophagosome markers in one study, interpreted as indicative of decreased autophagic induction [6]. Based on decreased basal levels of the autophagy substrate and cargo adaptor p62, however, another study concluded increased autophagic flux [64]. Flux analysis of autophagy or mitophagy can be technically challenging, but it is also possible that DJ-1 has different effects on basal versus induced autophagy. Interestingly, DJ-1 null cells exhibited decreased phosphorylation of ERK1/2 [6], which mediates autophagy/mitophagy in several systems [10, 11, 48, 66, 67]. DJ-1 siRNA has also been reported to inhibit paraquat-induced autophagy [68].

3. Diversity in the Regulation of Autophagy

3.1. Canonical Pathway of Starvation-Induced Autophagy. The identification of yeast genes necessary for autophagy, and related membrane trafficking events revolutionized the study of mitophagy in health and disease [69]. In brief, amino acid signals and insulin signals converge in turning on the mammalian target of rapamycin (mTOR), which suppresses autophagy. Amino acids also suppress ERK1/2 signaling. Loss of insulin signals, loss of amino acids, or direct inhibition of mTOR then serve to derepress autophagy induction, while 5′ adenosine monophosphate-activated protein kinase (AMPK) senses low energy to turn on autophagy. Beclin 1-Vps34-mediated changes in lipid composition are needed to define the phagophore and nucleate the membrane deposition of ubiquitin-like proteins Atg12 and LC3 in response to deprivation of growth factors or nutrients. Because beclin 1 can be found in several competing protein complexes [34–36], beclin 1-dependence has been proposed to serve a potential rheostat role in fine tuning levels of autophagy.

3.2. Mitophagy Regulation during Nutrient-Deprivation-Induced Autophagy. Starvation-induced autophagy is traditionally thought of as a nonselective bulk degradation process, with nonselective or bystander engulfment of mitochondria. However, yeast studies suggest a degree of mitochondrial recognition even in this process. The clearance of presumably undamaged mitochondria during nitrogen starvation requires the presence of an outer mitochondrial membrane protein Uth1p, [70], which does not have a clear mammalian homolog. Efficient mitochondrial autophagy in stationary-phase yeast are also regulated by an intermembrane space protein Aup1p [71]. Yeast cells grown in lactate undergo mitochondrial autophagy. Recently, the mitochondrial protein Atg32 was identified as a yeast mediator of selective mitophagy [72]. Atg 32 binds to Atg11, a known adaptor protein for selective autophagy in yeast. This system recruits mitochondria to autophagosomes, but does not directly regulate macroautophagy induction itself.

3.3. Beclin 1-Independent Injury-Induced Autophagy. Mitophagy is induced in neuronal cells and primary neurons injured with MPP+. Interestingly, in this system, autophagy induction proceeds even in the presence of PI3K inhibitors or siRNA knockdown of beclin 1 [10]. PI3K inhibitors are also unable to inhibit the selective clearance of photodamaged mitochondria in hepatocytes [73]. Beclin 1-independent mitophagy would no longer be negatively regulated by Bcl2 or rubicon, and thus, is more likely to allow a harmful level of autophagy activation. While the mechanism of beclin 1-independent autophagy has not been defined, it could reflect

alternative enzymatic means of increasing localized membrane concentrations of phosphatidylinositol 3-phosphate (PI(3)P) [38]. Alternatively, there could be other pathways of nucleation in which membrane changes mediated by ROS or kinase activation can substitute for PI(3)P in recruiting Atg18–Atg2 [74] or Atg16L to membranes.

Beclin 1-independent autophagy has been described in several model systems. As inhibition of autophagy is protective in these models [10, 48, 75–77], these observations support the concept of harmful overactivation of autophagy. It remains to be determined whether this is accidental, or forms part of a programmed cell death pathway.

3.4. Quality Control Autophagy and Cargo Regulation. Other variations from classic rapamycin-induced autophagy are beginning to emerge. Both basal autophagy and injury-induced autophagy play roles in organellar and protein quality control. A key feature of quality control-related autophagy relates to the ability of the cellular autophagy machinery to selectively remove damaged proteins and organelles while sparing their normal counterparts.

Interestingly, studies of quality control autophagy reveal requirements for HDAC6 and actin remodeling for maturation and completion of autophagy [78]. HDAC6-dependent retrograde transport of autophagy substrates and mediators to the perinuclear region is necessary for degradation of aggregated huntingtin [79], and selective transport may represent one mechanism of cargo enrichment. For protein aggregates, another mechanism of cargo recruitment involves direct adaptor protein interactions mediated by p62, which bridges ubiquitin on the cargo with LC3 on the autophagic membrane [80, 81]. Other adapter proteins that have been identified include NBR1, which can cooperate with p62 [82], and Nix, which binds to GABARAP-L1 [83]. While specific proteins may differ between yeast and mammals, the general concept of cargo receptors and adapter proteins that link into the autophagy machinery represents a rapidly emerging area of research.

3.5. Depolarization-Induced Mitophagy. One of the exciting developments in mitophagy regulation is the use of chemically depolarized mitochondria to dissect proteins needed for mitochondrial clearance. With nutrient deprivation, depolarization of mitochondria can occur after sequestration by GFP-LC3 [84], preceding their entry into acidic lysosomal compartments in rat hepatocytes [85]. Live imaging studies also show that mitotracker-labeled mitochondria disappear within 8 minutes of entering lysotracker-stained lysosomes in hepatocytes [86]. Thus, the observation of "mitophagosomes" is a transient event, most readily observed when elicited by synchronized chemical insults, or with inhibition of autophagosome maturation [11, 87].

The past year has witnessed significant advances in delineating mechanism(s) by which depolarization promotes mitophagy, subsequent to the original observation that the ubiquitin ligase parkin translocates to mitochondria in FCCP/CCCP-treated cells to mediate their clearance [18]. Of note is the observation that parkin functions only in the cargo recruitment step of mitophagy, but other mechanisms involving Nix mediate the induction of autophagy by depolarization [8]. Subsequent discussion will focus on surface changes on depolarized mitochondria that could mediate their autophagic recruitment in the depolarization model.

Depolarization inhibits membrane potential-dependent proteolytic processing of PINK1 [88]. This, in turn, causes full-length PINK1 to accumulate at the surface of mitochondria [62, 63], which is necessary for stable and global association of parkin with mitochondria in the FCCP/CCCP treated cells. From here, several mechanisms have been described that could specify parkin-bearing mitochondria for mitophagy. Parkin ubiquitination of mitofusins serve to promote fission [60, 89], which is necessary for mitophagy [87]. Parkin has also been reported to polyubiquitinate voltage-dependent anion-selective channel protein 1 (VDAC1) [90], which may explain PINK1-parkin-dependent perinuclear aggregation of mitochondria [19, 91]. VDAC1 interacts with a dynein light chain [92], although it is unknown whether or not ubiquitination modulates this. PINK1 may also interact directly with LC3 [59]. Finally, the p62 adaptor discussed above is recruited to parkin-ubiquitinated mitochondria, although its role in aggregation versus mitophagy recruitment is controversial [90, 93].

3.6. Alternative Mechanisms Relating to Mitophagy. Mitophagy can be initiated prior to depolarization of the mitochondrial membrane potential in several model systems. In starvation-induced mitophagy in hepatocytes, mitochondria remain polarized until after they are encircled by GFP-LC3 [84]. Likewise, mitochondrial depolarization occurs downstream of autophagosome formation in reticulocytes during Nix-dependent developmental mitophagy [94]. Indeed, depolarization-independent, Nix-dependent mitophagy may involve direct interactions of Nix with an LC3 homolog GABARAP [83], indicating alternative signaling for mitochondria recognition during autophagosome formation.

Parkin also compensates for PINK1 deficiency [95, 96]. While this could be mediated by nonmitophagy-related mechanisms, increased parkin expression causes increased autophagy in PINK1-deficient cells [7], and parkin-mediated protection from cell death is substantially diminished by RNAi knockdown of autophagy mediators [9]. Whether or not stable parkin recruitment to mitochondria is necessary for its compensatory effects is unknown, but hydrogen peroxide can recruit parkin to mitochondria through a mechanism not requiring mitochondrial targeting of PINK1 [97]. Finally, a parkin mutant that is deficient in translocating to mitochondria can be rescued in this function by the DnaJ/Hsp40 chaperone HSJ1a [98]. Besides ubiquitination, phosphorylation or changes in lipid composition could conceivably also trigger loss of mitochondria [99].

It is reasonable to assume that these mechanisms would allow for selective removal of irreversibly damaged mitochondria while sparing normal mitochondria, but this has not yet been robustly demonstrated. FCCP- or CCCP-treated cell lines exhibit rather global changes of parkin

translocation, perinuclear aggregation, and clearance. Likewise, selective autophagy of mitochondria with mtDNA mutations is inferred from studies showing that fibroblasts from patients with mitochondrial DNA diseases exhibit higher rates of mitophagy upon amino acid deprivation than those containing normal mitochondria [100], but selective autophagic engagement of individual mitochondria with high burdens of mtDNA mutations was not assessed. Cells expressing mitochondrial DNA deletions exhibit elevated transcripts for Atg proteins [101], and thus generalized elevations in autophagic capacity may also result in greater mitophagy for stochastic reasons. Live imaging studies such as those demonstrating that relatively depolarized mitochondria show decreased fusion [102], or preferential retrograde axonal transport [103], could be used to further establish selective recognition of abnormal mitochondria on an organelle-by-organelle basis.

4. Summary

Autophagy has emerged as a central response observed in multiple models of Parkinsonian neurodegeneration. In several chronic models, autophagy induction plays beneficial roles in clearing protein aggregates or damaged mitochondria. Autophagy can also play a harmful role in neurons subjected to acute injury such as ischemia-reperfusion or neurotoxin treatment. As understanding of mechanisms underlying autophagy and mitophagy develops, it will be interesting to determine whether distinct regulatory inputs to the core autophagy machinery underlies differences in the degree and outcome of autophagy or mitophagy induction. Just as pathways are emerging that show differences between autophagy induced for quality control and in response to trophic/nutrient deprivation, variations on the depolarization-initiated PINK1-parkin pathway are likely to emerge. Cell type specific mechanisms must also be considered, as parkin translocation is not observed in CCCP-treated cortical and striatal/midbrain neurons [104]. Redundancy in mechanisms that underlie the removal of damaged mitochondria may account for the relatively minor symptoms observed in knockout mice and form the basis for future therapies to heighten neuroprotective responses in PD patients.

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