

## Review

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# Decoding Parkinson's Disease Pathogenesis: The Role of Deregulated mRNA Translation

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**Abstract.** Mutations in a number of genes cause rare familial forms of Parkinson's disease and provide profound insight into potential mechanisms governing disease pathogenesis. Recently, a role for translation and metabolism of mRNA has emerged in the development of various neurodegenerative disorders including Parkinson's disease (PD). In PD, preliminary evidence supports a role for aberrant translation in the disease process stemming from mutations in several genes. Translation control is central to maintaining organism homeostasis under variable environmental conditions and deregulation of this may predispose to certain stressors. Hypothetically, deregulated translation may be detrimental to neuronal viability in PD through the misexpression of a subset of transcripts or through the impact of excessive bulk translation on energy consumption and burden on protein homeostatic mechanisms. While compelling preliminary evidence exists to support a role for translation in PD, much more work is required to identify specific mechanisms linking altered translation to the disease process.

## INTRODUCTION

Protein homeostasis (hereafter referred to as proteostasis) is fundamental to cell viability and promotes favorable conditions for organismal development and somatic maintenance [1]. At its core, protein homeostasis is achieved through balancing the synthesis, folding and effective trafficking of proteins with their degradation through proteasomal or autophagy-mediated pathways [2]. Each of these processes is tightly controlled based on nutrient availability and cellular requirements while their deregulation has been hypothesized as a major driver

of aging and disease. For neurodegenerative diseases, there is substantial evidence supporting a central role for the misfolding and aggregation of proteins in disease development [3]. Given that a breakdown of proteostasis is observed in these diseases, it comes as no surprise that inappropriate mRNA translation and metabolism can contribute to the establishment of disease. Loss of translation control has previously been implicated in a number of diseases including cancer, obesity, diabetes and growth disorders [4]. Considering the high energetic cost of protein synthesis to the cell, its coordinated regulation is key to organismal development and homeostasis in response to rapidly changing environmental conditions [4]. Under nutrient abundance, anabolic processes such as protein synthesis are favored while low nutrient conditions oppose global translation to conserve resources and favors expression of proteins important in stress response and organism survival. Hence,

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tightly regulated translation is crucial for cellular function and survival in response to adverse conditions and loss of this control may predispose to disease. A growing body of evidence now also highlights an important role for loss of translation control in neurodegenerative diseases including Parkinson's disease. The purpose of this review is to present evidence from the recent literature describing the contribution of mRNA translation to the pathogenesis of Parkinson's disease. For introductions to eukaryotic translation [5, 6] and genes linked to Parkinson's disease [7], the reader is directed to a number of excellent reviews on these topics.

### **ALTERED mRNA TRANSLATION IN NEUROLOGICAL DISEASE**

A number of neurodegenerative diseases have roots in genetic mutations or cellular pathology that affects mRNA translation. Large poly-glutamine expansions in Ataxin-2 cause dominantly-inherited spinocerebellar ataxia type 2 while intermediate-length polyQ expansions have been associated with an increased risk for developing amyotrophic lateral sclerosis (ALS) [8]. Ataxin-2 interacts with multiple RNA-binding proteins with roles in RNA processing and also to poly(A)-binding protein PABPC1, mediating its association with polyribosomes [9–12]. Ataxin-2, PABPC1 and ribosomes are localized to stress granules under cell stress conditions, suggesting that Ataxin-2 may play a role in the adaptation of mRNA processing and translation to stress in a manner that could be perturbed via Ataxin-2 mutations [13]. Dominant mutations in five transfer RNA (tRNA) synthetases, which catalyze the aminoacylation of tRNAs with appropriate amino acids, result in axonal Charcot-Marie-Tooth (CMT) neuropathy. In a *Drosophila* model of CMT, disease-associated mutations in glycyl-tRNA synthetase (GARS) or tyrosyl-tRNA synthetase (YARS) cause a decrease in protein synthesis rates in motor and sensory neurons [14], although this does not appear to be linked to altered aminoacylation activity and mechanisms underlying this effect are unknown. Neurodegeneration can also result from a tRNA synthetase mutation that impairs its proofreading ability to incorporate the correct amino acid. This mutation was shown in a mouse model to result in cerebellar Purkinje cell death and ataxia highlighting the consequences of impaired translation fidelity on neuronal viability [15]. A role for globally reduced

protein synthesis in the etiology of prion disease has been proposed based on mouse models of disease [16, 17]. The accumulation of misfolded prion protein in mouse brain triggers ER stress, prolonged activation of PERK and PERK-mediated eIF2 $\alpha$  phosphorylation in the unfolded protein response. The resulting repression of protein synthesis has been suggested to cause neurodegeneration through loss of synaptic proteins leading to eventual synaptic failure [17]. Finally, a growing body of literature indicates that microsatellite expansions in a number of genes can lead to repeat-associated non-ATG (RAN) translation, wherein cap-independent translation of protein fragments is initiated downstream of these expansions [18, 19]. It is currently unclear how expanded repeats cause translation initiation although there is evidence that triplet expansions known to express RAN proteins form hairpins or G-quadruplexes, providing possible secondary structure to recruit ribosomes in a process that may be analogous to cap-independent translation [18, 19]. RAN proteins have been reported in an increasing number of diseases, including spinocerebellar ataxia type 8 (SCA8) [20], myotonic dystrophy type 1 (DM1) [20], Fragile-X tremor ataxia syndrome (FXTAS) [21], and C9ORF72 amyotrophic lateral sclerosis (ALS)/frontotemporal dementia (FTD) [22]. While there is some evidence that RAN proteins accumulate in degenerating neurons (e.g. SCA8 polyAla RAN protein in Purkinje cells), more work is needed to determine their contribution to neurodegeneration.

### **DEREGULATED TRANSLATION IN PARKINSON'S DISEASE**

Accumulating evidence indicates an important role for mRNA translation in Parkinson's disease pathogenesis resulting from disease-linked mutations in genes including LRRK2, pink1, parkin and DJ-1. This evidence is presented below followed by a discussion on current hypotheses addressing the contribution of translation to the disease process.

LRRK2 (leucine-rich repeat kinase 2) is a large multi-domain protein with enzymatic RAS-like GTPase and kinase domains in which numerous disease-linked mutations are clustered [23]. Mutations in LRRK2 segregate with familial PD with age-related penetrance [24, 25] and are also found in sporadic PD [26–28], indicating a broad role for LRRK2 dysfunction in PD neurodegeneration. Mutations in LRRK2 results in clinical phenotypes

very similar to late-onset PD although Lewy body pathology is not always present [29, 30]. It is now well established that the common G2019S mutation in LRRK2 results in enhanced kinase activity (autophosphorylation and exogenous substrate phosphorylation) that is instrumental in neuronal toxicity, as observed in several *in vitro* and *in vivo* models [31–49]. There is currently debate about how other disease-segregating mutations affect kinase activity, although fairly good consensus exists that the I2020T mutation also increases kinase activity [38, 42, 45, 49–53]. It is less clear how ROC-COR domain mutations affect LRRK2 kinase activity, as the number of studies reporting an increase, decrease or no change in kinase activity is much more evenly spread [32–34, 39, 42, 45, 47, 48, 54]. These inconsistencies may reflect variable methodology used across these studies and results from *in vitro* kinase assays may not necessarily accurately represent the effects of these mutations on *in vivo* kinase activity which awaits clarification. A number of studies on *Drosophila* expressing kinase-enhancing mutations in human LRRK2 or its fly ortholog (dLRRK) support a functional interaction of LRRK2 with the translation machinery that may be altered by these mutations. Early evidence indicated that LRRK2 genetically interacts with the TOR (target of rapamycin) pathway in flies [38]. Loss of dLRRK worsens phenotypes associated with downregulated TOR signaling caused by overexpression of a constitutively-active form of 4E-BP1 (eIF4E-binding protein 1) or co-overexpression of TSC1 and TSC2. The stimulatory effects of TOR signaling on general translation are mediated in part via phosphorylation of 4E-BP1 which disrupts its eIF4E binding activity, thereby promoting cap complex formation through binding of eIF4G to free eIF4E (Figure). Both human LRRK2 and dLRRK were reported to phosphorylate 4E-BP1 and hence kinase-enhancing mutations that hyper-phosphorylate 4E-BP1 were suggested to promote PD-related phenotypes via eIF4E-dependent translation initiation [38]. Contrastingly, in LRRK2-transfected HEK cells or mammalian brain, 4E-BP1 does not appear to be a direct LRRK2 substrate [40, 55] and increased phosphorylation of 4E-BP1 is not found in G2019S LRRK2 knock-in mice but, conversely has been reported in LRRK2 knock-out mice and LRRK2 kinase-dead transgenic mice [56]. Another study sought to identify specific transcripts with altered translation in the presence of LRRK2. While numerous targets were identified, the authors concentrated on e2f1 and dp1 upregu-

lation and report that pathogenic LRRK2 represses the activity of let-7 and miR-184, respectively to result in these effects [57]. The inhibitory effects of mutant LRRK2 on miRNA function are proposed to occur through two independent mechanisms. First, pathogenic LRRK2 associates with *Drosophila* Argonaute-1, a key component of the RNA-induced silencing complex, leading to decreased Argonaute-1 levels by an unknown mechanism. Second, mutant LRRK2 stimulates the association of phospho-4E-BP1 with human Argonaute-2 thereby impairing its function [57].

More recently, LRRK2 was found to interact with and directly phosphorylate a number of ribosomal proteins through interactor and kinase screening in series [42]. Phosphorylation of ribosomal protein s15 is enhanced by G2019S and I2020T mutations in the kinase domain of LRRK2, and this was identified as a key mediator of mutant LRRK2 toxicity in primary neuron and *Drosophila* models of LRRK2 toxicity. Reporter assays revealed that mutant LRRK2 stimulates both cap-dependent and cap-independent mRNA translation in an s15-dependent manner. Additionally, G2019S LRRK2 transgenic *Drosophila* exhibit elevated bulk protein synthesis which was shown to be important in age-related neurodegenerative phenotypes through rescue experiments with the protein synthesis inhibitor anisomycin. These data corroborate previous findings implicating that LRRK2 has a stimulatory effect on mRNA translation. Currently unresolved are how s15 phosphorylation affects mRNA translation and whether there are specific translational targets that mediate LRRK2 toxicity. Interestingly, G2019S LRRK2 was also found to positively regulate levels of numerous ribosomal protein transcripts in mouse brain when compared to the brains of LRRK2 KO mice, raising the possibility that altered levels of ribosomal proteins and potentially whole ribosomes could be another mechanism whereby LRRK2 impacts mRNA translation [58]. Considering the clinical and pathological overlap between LRRK2-linked PD with sporadic cases, it will be informative to determine if excess mRNA translation as a route to PD pathogenesis is also supported in sporadic PD, for example by examining if s15 or 4E-BP1 phosphorylation are elevated in postmortem brain tissue from these patients.

A role for the initiation step of mRNA translation in PD is supported by the identification of rare missense mutations in eIF4G1 proposed to cause autosomal-dominant disease [59, 60]. While PD-causing mutations in a translation initiation factor

such as eIF4G1 would represent a strong link between aberrant translation and disease, it should be noted that several recent studies have suggested that these mutations may rarely cause disease or not at all [61–63]. eIF4G1 is a large protein which acts as a scaffold for the binding of eIF4A and eIF4E to form the mRNA cap complex, required for initiating cap-dependent translation [5]. eIF4G additionally binds PABP at the poly A tail to circularize mRNA which stabilizes it and activates it for translation [5]. While eIF4G1 has an important role in translation initiation, it is yet to be described whether the mutations associated with PD cause a gain, loss or toxic gain of function to the individual protein or cap-complex and how this affects translation initiation. There is, however, evidence for a genetic interaction between eIF4G1 and another PD gene, VPS35. The VPS35 protein is a retromer complex component that mediates retrograde protein transport from endosomes to the trans-Golgi network [64, 65]. eIF4G1 overexpression is reportedly toxic in yeast lacking VPS35 or expressing mutant D620N VPS35 associated with PD, suggesting that this toxicity may be due to loss of retromer function [64]. Additional experiments suggest that toxicity is further related to proteotoxic stress, ER stress and the unfolded protein response [64]. This study highlights the interconnectedness of protein synthesis and transport in preventing protein misfolding and also provides clues to how gain-of-function mutations in eIF4G1 (consistent with an autosomal dominant mode of inheritance) could potentially impact neuronal function. Similarly, a link between protein trafficking and LRRK2 in the context of PD is suggested by other studies. LRRK2 was found to interact with RAB7L1 in a co-complex that additionally includes BCL2-associated athanogene 5 and Cyclin-G-associated kinase that may promote the autophagic clearance of *trans*-Golgi-derived vesicles [66]. RAB7L1 is a candidate sporadic PD risk factor identified by genome-wide association studies [27, 28]. Expression of constitutively active RAB7L1 was found to rescue mutant LRRK2-induced loss of neurites in neuronal cultures and loss of dopamine neurons in flies while knock-down of RAB7L1 in dopamine neurons causes neurodegeneration [67]. RAB7L1 localizes heavily to the Golgi and a link to defective retromer function in these phenotypes is supported by evidence that both VPS35 and VPS29 levels are decreased by expression of mutant LRRK2 or knock-down of RAB7L1 while VPS35 overexpression rescues dopamine neuron viability in both of these conditions [67].

Translational suppression may also be neuroprotective in the context of other PD mutations. Genetic interaction studies in flies showed that overexpression of 4E-BP is protective against loss of dopaminergic neurons in pink1 and parkin mutants [68]. 4E-BP overexpression is expected to enhance eIF4E sequestration thereby inhibiting binding to eIF4G and mRNA cap complex formation. An upregulation of un-phosphorylated 4E-BP can also be achieved via the mTOR kinase inhibitor rapamycin, and indeed, rapamycin treatment phenocopies the neuroprotective effect of 4E-BP upregulation in flies [68]. Consistent with this, another study showed that knock-down or overexpression of S6K ameliorated or exacerbated muscle degeneration in pink1 mutant flies, respectively, and that S6K overexpression also worsened dopamine neuron loss [69]. Interestingly, in both of these studies there was evidence of downregulated Akt/TORC1 signaling (levels of phospho-4E-BP, phospho-Akt and phospho-S6K) in pink1 and parkin mutants. Collectively, these results suggest that the Akt/TORC1 pathway is suppressed in these mutants typical of a protective stress response and that augmenting this blockade of TOR signaling may be an effective strategy to prevent degenerative phenotypes [68, 69]. The TORC1 pathway in which 4E-BP1 and S6K reside regulates numerous intracellular processes including autophagy, transcription, metabolism, cell survival and translation [70]. Given that specific manipulations of 4E-BP1 and S6K expression modulate pink1 and parkin phenotypes without need for whole TORC1 pathway inhibition, it is reasonable to postulate that protection occurs via a reduction in translation. Downregulation of protein synthesis typically occurs in response to cellular stress and in the case of pink1/parkin mutants may be important in lowering energy consumption under conditions predisposing to loss of mitochondrial quality control and mitochondrial dysfunction.

In contrast with LRRK2, there is no direct evidence to suggest that pink1 or parkin regulate global mRNA translation in a manner that goes awry in Parkinson's disease. Screening for parkin interactors in mammalian cells revealed many ribosomal proteins and translation initiation/elongation factors [71]. Despite this, validation of these interactions and evidence to support a functional role of parkin on mRNA translation is currently lacking. Similarly, the p38/AIMP2 scaffolding protein required for tRNA synthetase complex assembly is a substrate of parkin's E3 ubiquitin ligase activity [72]. AIMP2 levels accumulate in the brain of PD patients

with Parkin mutations and ventral midbrain of Parkin knockout mice, yet studies in AIMP2 overexpressing mice suggest that global translation is normal [73]. Studies on *Drosophila*, however, implicate a role for pink1 and parkin in the local translation of nuclear-encoded respiratory chain complex transcripts on the mitochondrial outer membrane [74]. It has been suggested that pink1 and parkin may recruit targeting of these transcripts to the mitochondrial outer membrane and also displace translational suppressors such as Pumilio and Glorund/hnRNP-F to enable translation. Impairment of this process in pink1/parkin mutants could lead to defects in oxidative phosphorylation and underlie mitochondrial pathology in PD. There is, however, data to suggest that pink1 may be important in the upregulation of cap-dependent and cap-independent translation under hypoxia conditions *in vitro* [75]. Loss of pink1 had a greater impact on cap-independent translation and specifically, the production of HIF-1 $\alpha$  and hypoxia-responsive gene upregulation, possibly through loss of hypoxia-induced 4E-BP1 dephosphorylation.

While DJ-1 is best characterized to have a role protecting against oxidative stress and mitochondrial dysfunction, it may also impact translation. The PI3K/Akt pathway that activates mTORC1 signaling which in turn promotes mRNA translation is negatively regulated by the PTEN tumor suppressor [76]. DJ-1 was originally identified as a putative oncogene that transforms NIH3T3 cells cooperatively with ras [77]. It was subsequently revealed that DJ-1 acts as a suppressor of PTEN function in a *Drosophila* screen and its expression was found to correlate with the extent of PKB/Akt phosphorylation in mammalian cells and primary breast cancer samples [78]. Hence, it is possible that through its stimulatory effects on Akt activation, DJ-1 could be indirectly involved in regulating mRNA translation in a manner impaired by loss-of-function mutations. Although DJ-1 lacks canonical RNA binding motifs, it has been reported to bind to several mRNA targets including glutathione peroxidases, the selenoproteins necessary to produce glutathione peroxidase and members of the PTEN/PI3K pathway by a poorly understood mechanism [79]. Pathogenic variants of DJ-1 exhibit deficits in this ability to bind mRNA. Interestingly, DJ-1 has been proposed to partially inhibit mRNA translation upon mRNA binding and dissociate under conditions of oxidative stress [79], suggesting that it could in theory act to regulate specific antioxidant defenses in response to intracellular oxidative stress cues. It would be interesting to further investigate whether

DJ-1 acts as both redox sensor and regulator of antioxidant defenses in cells through regulating translation of antioxidants such as glutathione peroxidase.

Collectively, the evidence presented above indicates a significant role for mRNA translation in the pathogenesis of PD linked to several genes (Table). It is important to note, however, that the field is in the very early stages of describing this relationship and many of the recently-published studies presented here await independent confirmation. Further investigation into the role of mRNA translation in PD warranted by these studies will also be necessary to go beyond initial observations and pinpoint specific mechanisms by which deregulated mRNA translation might play a role in dopamine neuron degeneration. A common theme for several of these genes (LRRK2, pink1 and parkin) is that translational suppression can be neuroprotective against pathology. Downregulation of global protein synthesis prevents mutant LRRK2-induced neurodegeneration while reducing TOR-mediated translation can block pink1 and parkin pathology. These findings give rise to a number of possible hypotheses that may be investigated further. For example, the increase in global protein synthesis rates observed in LRRK2 transgenic *Drosophila* are directly linked to neuronal toxicity as multiple independent methods to reduce translation are neuroprotective. Possible mechanisms linking an increase in bulk translation to neurodegeneration may be generally categorized into (i) an upregulation of pathogenic translational targets or downregulation of neuroprotective proteins resulting from loss of translational control and (ii) an overall loss of protein homeostasis leading to neuronal dysfunction and death. Of course, these mechanisms may act in combination to promote neurodegeneration and may also be interdependent. Identifying translational targets of LRRK2 in dopamine neurons and then determining the impact of their elevated expression on mutant LRRK2 neurotoxicity, e.g. through knock-down screening assays, will test the hypothesis that upregulation of key translational targets mediates LRRK2 toxicity. On the loss of protein homeostasis, an overall excess in synthesized proteins could conceivably place an overwhelming burden on protein chaperone, trafficking and turnover capacity in a manner that promotes ER stress, protein misfolding and aggregation. LRRK2 has previously been linked to protein turnover via autophagy (reviewed in [80]). PD-causing mutations result in complex effects on the autophagy/lysosomal pathway which are poorly understood and may rep-

Table  
Summary of PD genes linked to neuronal toxicity through mRNA translation

Gene	PD locus	Mode of Inheritance	Relationship to mRNA Translation
LRRK2	PARK8	AD	Kinase-enhancing mutations stimulate bulk translation linked to toxicity
eIF4G1	PARK18	AD	Implicated by eIF4G1 being constituent of mRNA cap complex, effect of mutations unknown
PINK1	PARK6	AR	Translation suppression prevents pathology, pink1 may regulate translation of nuclear-encoded respiratory chain mRNAs
Parkin	PARK2	AR	Translation suppression prevents pathology, pink1 may regulate translation of nuclear-encoded respiratory chain mRNAs
VPS35	PARK17	AD	Genetically interacts with eIF4G1, important in protein trafficking
RAB7L1	PARK16	ND	Genetically interacts with LRRK2, important in protein trafficking
DJ-1	PARK7	AR	Interacts with certain mRNAs, potentially to suppress their translation

AD, autosomal dominant; AR, autosomal recessive; ND, not determined.

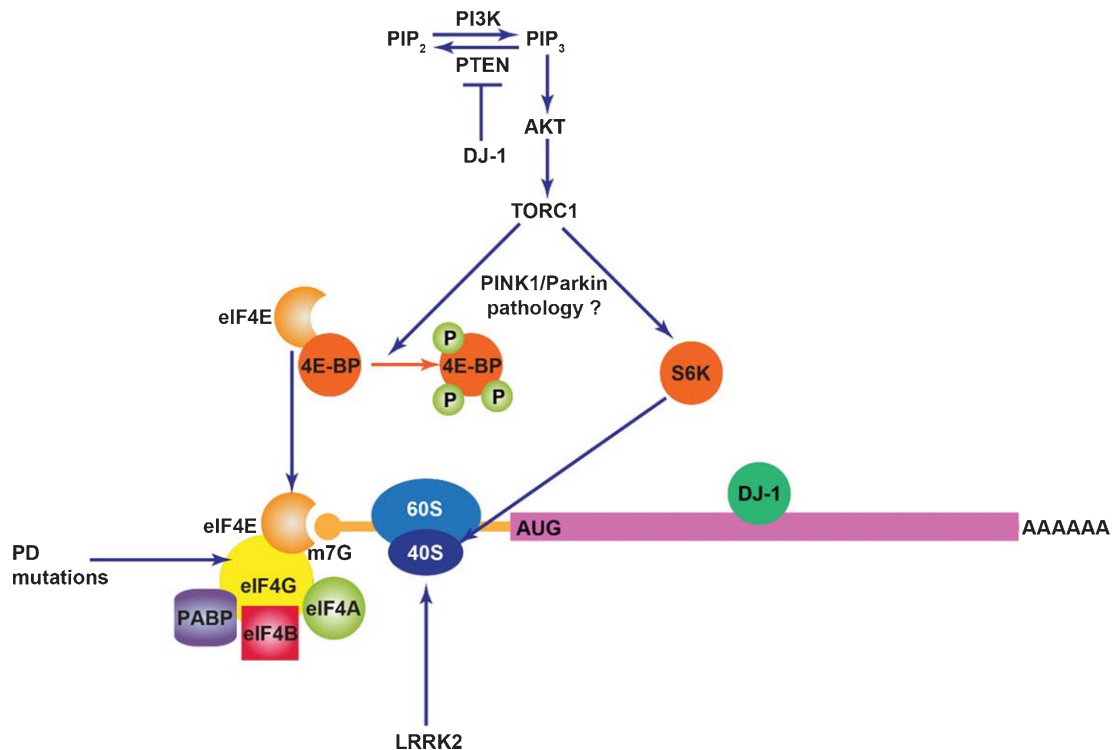


Figure. The impact of PD proteins on mRNA translation. DJ-1 inhibits PTEN, a negative regulator of PI3K/Akt signaling and also binds to certain mRNA transcripts in a manner that inhibits their translation. TORC1 activity may contribute to PINK1/Parkin pathology potentially through mRNA translation. Mutations in the translation initiation factor eIF4G1 likely cause PD. LRRK2 stimulates mRNA translation through interaction with the ribosome and phosphorylation of s15.

resent either increased autophagic flux or conversely, an impairment of autophagosome fusion with lysosomes resulting in autophagy arrest. While these effects may be mediated at least in part through direct impact of LRRK2 on the function of autophagosomes [81–83] or lysosomes [67, 82, 84–86] it is also possible that LRRK2's stimulatory effect on protein synthesis could have downstream consequences on protein degradation pathways. For mutant LRRK2, an overall increase in protein synthesis could conceivably result in depletion of the pool of free amino

acids in cells that simulates nutrient starvation conditions. One anticipated outcome of depleted amino acids might be an upregulation of autophagy in order to restore amino acid homeostasis. Increased global protein production may also require a counterbalancing increase in protein turnover through autophagy, especially if the increased burden on protein homeostatic mechanisms predisposes to an accumulation of misfolded or damaged protein. Along these lines, it will be informative to determine if the autophagy phenotypes observed via mutant LRRK2 expres-

sion can be blocked through suppression of protein synthesis.

As an accumulation of misfolded protein is an established hallmark of PD pathology, deficient proteostasis is an attractive hypothesis to link excess protein synthesis with neurotoxicity. More broadly, if insufficient protein trafficking, chaperone capacity or protein turnover are important contributors to pathology, then it may be possible to ameliorate neurodegeneration through bolstering these processes in an attempt to restore proteostasis as suggested by some studies. It may be hard, however, to reconcile this with the specific vulnerability of dopamine neurons in PD, unless the excess burden on proteostatic mechanisms does not directly result in toxicity but predisposes to one or more insults that dopamine neurons are particularly vulnerable to, such as oxidative stress. Hence, a slightly modified hypothesis from the one stated above is that translational reprogramming necessary for cellular adaptation under conditions of stress is impaired by LRRK2 mutations that predisposes dopamine neurons to dysfunction and death. An accumulation of oxidative damage to intracellular macromolecules and a decline in mechanisms to handle and eradicate reactive oxygen species are observed in aging organisms, including in brain. This may represent a major driving force for the decline in cognitive function with advanced age. Dopamine neurons are reported to be particularly susceptible to oxidative stress caused by dopamine metabolism and their autonomous pacemaking activity which promotes mitochondrial dysfunction [87, 88]. An age-related decline in antioxidant defenses coupled to an impaired ability to downregulate anabolic processes such as translation in the face of oxidative stress might predispose neurons in aged organisms to LRRK2 mutations. This hypothesis could conceivably account for a role of aging in Parkinson's disease linked to these mutations. Pervasively high levels of mRNA translation may also be detrimental through consumption of energy, given that protein synthesis is one of the major energy-consuming process. Neurons consume high levels of energy during active processes such as intraneuronal transport, neurotransmitter release and synaptic plasticity. Depleted energy reserves may also affect the ability of neurons to perform these activities. Neurons with mutations in *pink1* or *parkin* that lead to mitochondrial dysfunction and reduced energy output may be especially vulnerable to robust levels of protein synthesis, and this may account for the observation that lowering

translation through altered TOR signaling can prevent age-related neurodegeneration.

## CONCLUSIONS

A number of studies implicating translation in the pathogenesis of PD have recently emerged in conjunction with an increased recognition for the role of deregulated mRNA translation and metabolism in neurodegenerative diseases. There is a compelling need for more detailed investigation into the relationship between translation and PD in order to better understand the role of proteostasis decline in disease and with the ultimate goal of providing significant advances in the development of diagnostic tools and therapeutics.

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## CONFLICT OF INTEREST

The author has no conflict of interest to report.

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