

● INVITED REVIEW

The emerging role of autophagic-lysosomal dysfunction in Gaucher disease and Parkinson's disease

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Abstract

Gaucher disease (GD), the commonest lysosomal storage disorder, results from the lack or functional deficiency of glucocerebrosidase (GCase) secondary to mutations in the *GBA1* gene. There is an established association between *GBA1* mutations and Parkinson's disease (PD), and indeed *GBA1* mutations are now considered to be the greatest genetic risk factor for PD. Impaired lysosomal-autophagic degradation of cellular proteins, including α -synuclein (α -syn), is implicated in the pathogenesis of PD, and there is increasing evidence for this also in GD and *GBA1*-PD. Indeed we have recently shown in a *Drosophila* model lacking neuronal GCase, that there are clear lysosomal-autophagic defects in association with synaptic loss and neurodegeneration. In addition, we demonstrated alterations in mechanistic target of rapamycin complex 1 (mTORC1) signaling and functional rescue of the lifespan, locomotor defects and hypersensitivity to oxidative stress on treatment of GCase-deficient flies with the mTOR inhibitor rapamycin. Moreover, a number of other recent studies have shown autophagy-lysosomal system (ALS) dysfunction, with specific defects in both chaperone-mediated autophagy (CMA), as well as macroautophagy, in GD and *GBA1*-PD model systems. Lastly we discuss the possible therapeutic benefits of inhibiting mTOR using drugs such as rapamycin to reverse the autophagy defects in GD and PD.

Key Words: Gaucher disease; Parkinson's disease; *Drosophila*; autophagy; lysosome; glucocerebrosidase; *GBA*

The Link between Gaucher Disease and Parkinson's Disease

Homozygous loss-of-function mutations in the *GBA1* gene cause Gaucher disease (GD), the commonest lysosomal storage disorder. This gene encodes glucocerebrosidase (GCase), a lysosomal enzyme responsible for the hydrolysis of the glycolipid substrate glucosylceramide (GlcCer) to ceramide and glucose. Reductions in enzymatic activity result in the lysosomal accumulation of GlcCer, as well as glucosylsphingosine, within reticulo-endothelial cells, leading to the systemic sequelae of GD, including organomegaly, bone disease, anaemia and thrombocytopenia. The clinical spectrum of GD has historically been sub-divided into Type 1 GD, the so-called non-neuronopathic milder form of the disease, and Types II and III GD, which are severe acute and chronic neuronopathic forms respectively (Cox, 2010). In recent years heterozygous *GBA1* mutations have been identified as key

genetic risk factors for Parkinson's disease (PD), and increase the risk of developing PD by approximately 20-fold (Sidransky et al., 2009; Migdalska-Richards and Schapira, 2016).

The Role of Autophagy in Cellular α -Synuclein Degradation

The neuropathological hallmark of PD is the presence of proteinaceous intraneuronal inclusions, known as Lewy bodies, predominantly composed of aggregated α -synuclein (α -syn), in addition to other proteins such as ubiquitin and p62 (Zatloukal et al., 2002; Shults, 2006). α -syn is a presynaptic protein of unknown function, which is thought to play a central role in the pathogenesis of PD. Moreover, there is mounting evidence that soluble α -syn aggregation intermediates (so-called oligomeric or protofibrillar species) represent the most toxic form of the protein (Volles and Lansbury, 2003). α -syn is removed

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from the cell by both macroautophagy and chaperone-mediated autophagy (CMA) (Cuervo et al., 2004; Watanabe et al., 2012), and indeed α -syn aggregates accumulate in response to the pharmacological inhibition of autophagy in mice (Klucken et al., 2012). α -syn is a well-characterised substrate of CMA due to the presence of a CMA-specific pentapeptide sequence motif. It is selectively translocated across the lysosomal membrane in a complex with the heat shock cognate protein 70 (hsc70), a process dependent on lysosomal-associated membrane protein 2A (LAMP-2A). Furthermore pathogenic forms of α -syn inhibit CMA through the blockade of receptor-mediated uptake into the lysosome (Cuervo et al., 2004). Macroautophagy is a less selective degradative pathway, which is responsible for the bulk removal of defective organelles and mis-folded cytoplasmic proteins, including α -syn, from the cell. It involves the sequestration of the cytosolic contents into double-membrane autophagosomes, which are then delivered to the lysosome to form a single-membrane autophagolysosome. The cargo is then degraded by lysosomal hydrolases. Macroautophagy dysregulation is increasingly being recognized as a pathogenic factor in neurodegeneration, including in PD (Ravikumar et al., 2010). Consistent with this, the selective suppression of autophagy, through the neuronal loss of the autophagy genes *atg7* or *atg5*, results in a number of phenotypes in mice, including locomotor defects, accumulation of polyubiquitinated proteins and neurodegeneration (Hara et al., 2006; Komatsu et al., 2006).

The Role of GCase Deficiency in PD

Both loss-of-function and toxic gain-of-function hypotheses have been put forward to explain the link between *GBA1* mutations and PD (Kinghorn, 2011; Migdalska-Richards and Schapira, 2016). There is growing evidence supporting the role of GCase loss-of-function in PD. The majority of *GBA1* mutations, including missense, nonsense and frame-shift mutations, insertions or deletions, are associated with reduced lysosomal GCase levels (Montfort et al., 2004; Sidransky et al., 2009). Moreover, milder mutations, associated with slightly diminished GCase levels, confer a much lower risk of PD than more severe mutations resulting in severe enzymatic dysfunction (Swan and Saunders-Pullman, 2013). Moreover, GCase protein levels and enzymatic activity are both decreased in the post-mortem brain tissue from patients with both idiopathic and *GBA1*-linked PD (Gegg et al., 2012). A number of mechanisms linking GCase loss-of-function with neurodegeneration have been demonstrated (Kinghorn, 2011; Migdalska-Richards and Schapira, 2016). Loss of GCase activity has been shown to lead to GlcCer accumulation, resulting in stabilisation of α -syn oligomers and α -syn ac-

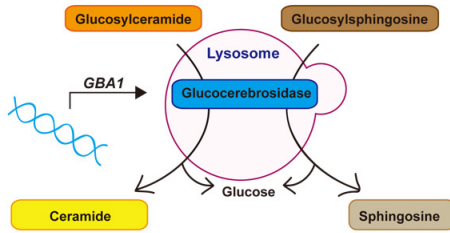
cumulation. The subsequent increase in α -syn may inhibit GCase ER-Golgi trafficking and lysosomal GCase levels, thus creating a bidirectional pathogenic loop (Mazzulli et al., 2012).

The Emerging Role of Autophagy-lysosomal Dysfunction in GD and PD

We recently investigated the role of the autophagy-lysosomal (ALS) system in neuronopathic GD using *Drosophila melanogaster* (Kinghorn et al., 2016). Employing homologous recombination techniques we developed a fly model lacking GCase in the brain. GCase-deficient flies displayed reduced lifespan, age-dependent locomotor abnormalities, as well clear evidence of synaptic loss and neurodegeneration. In keeping with the hallmark lysosomal dysfunction seen in GD cells, staining with LysoTracker[®] revealed numerous abnormally enlarged lysosomes in the brains of flies lacking GCase. This abnormal lysosomal pathology was associated with the accumulation of GlcCer, similar to that seen in neuronopathic GD brains (Conradi et al., 1984) (Figure 1).

Normal lysosomal functioning is required for the formation of autolysosomes and thus the autophagic removal of misfolded proteins and defective organelles from the cell (Ravikumar et al., 2010). During macroautophagy LC3-I is converted into its lipidated form, LC3-II, which is recruited to autophagosomal membranes (Ravikumar et al., 2010). We therefore probed macroautophagy function by measuring the levels of the fly homologue of LC3, Atg8, by western blot analysis. This demonstrated that both Atg8(LC3)-I and Atg8(LC3)-II are increased in the GCase-deficient fly brain, in addition to the ratio of Atg-II/Atg-I, suggestive of increased autophagosome number and a block in autophagy flux. This mirrors the increased LC3-II levels seen in the substantia nigra of PD patients (Dehay et al., 2010). In addition, we demonstrated increased accumulation in GCase-deficient fly brains of autophagy substrates, namely polyubiquitinated proteins and Ref(2)P, the *Drosophila* homologue of p62. Both ubiquitin and p62 are abundant constituents of protein inclusions associated with neurodegenerative diseases, including LBs in PD (Zatloukal et al., 2002; Bartlett et al., 2011). Further interrogation of autophagy at the regulatory level in fly brains revealed a decrease in the phosphorylation of p70S6 kinase, a substrate of the energy sensing mammalian target of rapamycin (mTOR)-complex 1 (mTORC1). mTORC1 plays a central role in macroautophagy by initiating the formation and elongation of the autophagosomal membrane (Ravikumar et al., 2010). Thus the decrease in mTORC1 activity seen in GCase-deficient fly brains likely represents a compensatory response to the autophagy block and is similar to that seen in fibroblasts derived from PD patients harbouring *GBA1* mutations (Magalhaes

Physiological conditions



Pathological conditions

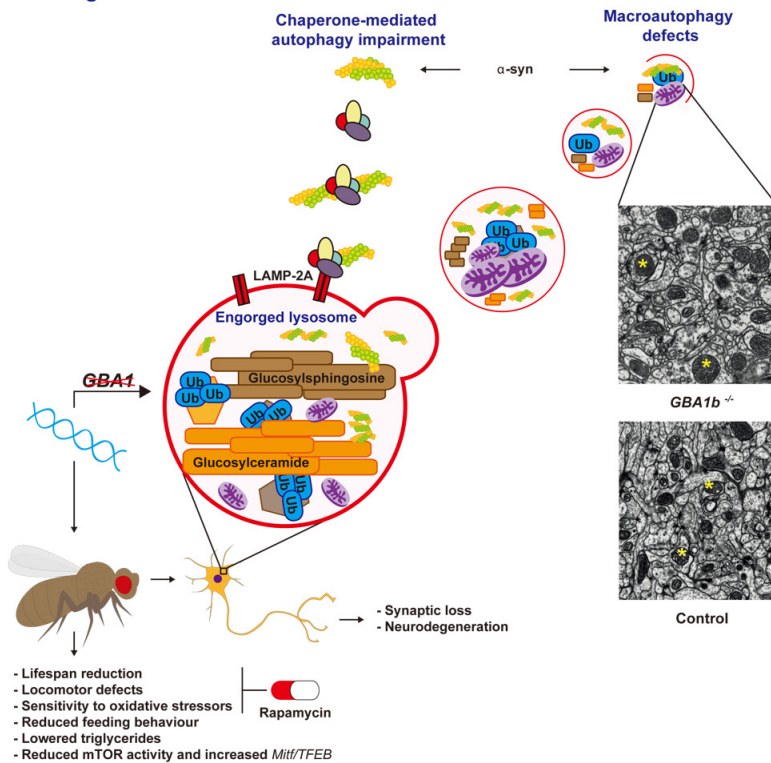


Figure 1 Glucocerebrosidase (GCase) deficiency results in autophagy-lysosomal system (ALS) dysfunction.

Under normal physiological conditions GCase hydrolyses glycolipid substrates (glucosylceramide and glucosylsphingosine) within the lysosome. Normal lysosomal function is required for the autophagic clearance of defective cellular organelles and mis-folded proteins. Mutations in the *GBA1* gene result in GCase loss-of-function and accumulation of its substrates. This leads to lysosomal dysfunction and subsequent defects in both macroautophagy and chaperone-mediated autophagy (CMA), with the consequent accumulation of α -synuclein (α -syn). ALS dysfunction in a fly model of neuronal GCase deficiency was associated with the accumulation of abnormal giant mitochondria (representative giant mitochondria in *GBA1* knockout (*GBA1b^{-/-}*) and healthy mitochondria in wild type control fly brains are shown with yellow asterisks, shown under identical magnification), accumulation of autophagy substrates (p62 and polyubiquitinated proteins), in addition to neurodegeneration and synaptic loss. These neuropathological defects resulted in a number of neurotoxic phenotypes, including reduced lifespan, locomotor abnormalities and decreased resistance to oxidative stress. Likely as a compensatory response to the autophagy block, mammalian target of rapamycin (mTOR)-complex 1 (mTORC1) activity was decreased and *Mitf/TFEB* gene expression was up-regulated in the brains of GCase-deficient flies. The mTOR inhibitor rapamycin was able to functionally rescue the lifespan, locomotor and oxidative stress phenotypes of the GCase-deficient flies, highlighting the potential therapeutic benefits of rapamycin and other inhibitors of mTORC1 in Gaucher disease (GD) and Parkinson's disease (PD) (Kinghorn et al., 2016). LAMP-2A: Lysosomal-associated membrane protein 2.

et al., 2016). In keeping with the impaired autophagy, abnormal giant mitochondria were observed in the brains of GCase-deficient flies, a reflection of the inability of the cells to clear aged and defective mitochondria by autophagy (the process of mitophagy). Interestingly GCase-deficiency in flies appeared to phenocopy *Mitf*-knockdown. *Mitf* (microphthalmia transcription factor) is the fly homologue of mammalian *TFEB* (transcription factor EB), the master regulator of lysosomal biogenesis. It has many conserved functions in the fly including regulation of the lysosomal-autophagy pathway and lipid metabolism (Bouche et al., 2016). GCase deficiency in the fly was also associated with *Mitf* gene up-regulation, likely in response to the lysosomal-autophagy block. Lastly treatment of GCase-deficient flies with the mTOR inhibitor rapamycin resulted in a significant rescue of the lifespan and locomotor phenotypes, as well as resistance to oxidative stress (Figure 1).

ALS dysfunction is increasingly being implicated in

the pathogenesis of GD and PD, and has been identified in several GD and GCase-deficient PD models. Autophagy defects, in association with inflammasome activation, were observed in GD macrophages (Aflaki et al., 2014). Pharmacological inhibition of GCase in mice, through the chronic systemic treatment with conduritol- β -epoxide, lead to the accumulation of insoluble α -syn aggregates and neurodegeneration, in addition to an increase in the CMA-associated protein LAMP-2A and the macroautophagy marker LC3-II (Rocha et al., 2015b). GCase siRNA knockdown in cell culture also inhibited macroautophagy flux with a rise in LC3-II and p62, and *GBA1* knockout in mouse embryonic fibroblasts lead to a compromise in CMA. Furthermore the autophagy defects were associated with loss of autophagic lysosomal reformation and maturation of endosomes. They also observed a decrease in functional acidified lysosomes within GCase-deficient cells (Magalhaes et al., 2016). Enlargement of the lysosomal compartment, as observed

in GCase-deficient fly brains, was also seen in *GBA1* mutant PD induced pluripotent stem cell (iPSC)-derived dopamine neurons, in association with autophagy defects and accumulation of intracellular p62 (Fernandes et al., 2016).

It has been suggested that both GD patients and *GBA1* mutation carriers display a similar risk of developing PD (Schapira, 2015). Consistent with this, *in vitro* work has shown that the degree of autophagy inhibition and α -syn accumulation is comparable in iPSC-derived neurones from GD patients and *GBA1* mutation carriers with PD (Schöndorf et al., 2014). Moreover, autophagic lysosomal reformation defects in GCase-deficient cellular models were also similar in heterozygote and homozygote mutant *GBA1* models (Magalhaes et al., 2016). These observations are in keeping, at least in part, by the complex interplay between the loss and toxic gain-of-functions of GCase activity, the ageing cellular degradative machinery, including the ALS, and additional genetic risk factors predisposing to PD. Work in our GCase knockout fly model, as well as in other cellular and mouse models, has demonstrated that loss of GCase activity is sufficient to cause neurodegeneration, even in the absence of α -syn, when GCase levels are sufficiently low (Kinghorn et al 2016). As already mentioned, α -syn can further potentiate GCase deficiency through the generation of a bidirectional feedback loop, leading to lysosomal dysfunction and the generation of toxic oligomeric α -syn species (Mazzulli et al., 2012). In addition to the effects of GCase loss-of-function, the cellular sequelae of aging undoubtedly play a role. Indeed both lysosomal and autophagic function decline with age (Martinez-Vicente et al., 2005; Cuervo, 2008). During ageing GCase activity also declines in the substantia nigra and putamen of healthy controls, and is comparable to the enzymatic activity in PD patients with *GBA1* mutations (Rocha et al., 2015a). This suggests that an age-dependent reduction in GCase activity may lower the threshold for developing PD, and contribute to the lysosomal dysfunction that occurs in ageing and PD. Therefore moderate reductions in GCase activity in *GBA1* mutation carriers, in addition to the age-related decline in the ALS, and other cellular perturbations secondary to additional genetic and environmental risk factors, may be sufficient to promote α -syn accumulation and neurodegeneration. Further studies are required to better characterize the relationship between specific pathogenic *GBA1* mutations, their corresponding GCase activity and ALS function, in addition to their dose effect and clinical PD phenotypes. Such studies will undoubtedly aid our understanding of the variable penetrance of *GBA1* mutations, in both the heterozygous and homozygous state, in causing PD.

Targeting Autophagy in GD and PD using the mTOR Inhibitor Rapamycin

The beneficial effects of rapamycin, demonstrated in our GCase knockout fly model, suggest that the inhibition of mTORC1 may represent an additional therapeutic strategy in the treatment of GD and PD, as well as other neurodegenerative disorders, in which there is significant ALS dysfunction. In support of this, rapamycin increased the clearance of exogenously expressed human wild-type and mutant α -syn in an inducible cell model (Webb et al., 2003) as well as endogenous α -syn in *GBA1*-knockdown primary cortical neurons (Du et al., 2015). Rapamycin has also been shown to mediate neuroprotective effects in other neurodegenerative diseases, including in a TDP-43-expressing amyotrophic lateral sclerosis mouse model (Bové et al., 2011; Wang et al., 2012). However, inhibition of mTOR by rapamycin is not invariably protective in all *GBA1* mutant models, and indeed rapamycin was found to trigger cell death in GD iPSC-derived neuronal cells harboring a *GBA1* mutation (Awad et al., 2015). Furthermore chronic rapamycin treatment aggravated the pathology and muscle weakness in a mouse model of VCP (valosin containing protein)-associated myopathy, despite a defect in mTOR signaling (Ching and Weihl, 2013). Thus the effects of inhibiting mTORC1 activity appear to vary depending on disease pathology, the model organism, and also likely the timing of the therapy. Further studies in mammalian models are now required to verify the benefits of rapamycin, and other inhibitors of mTOR, in ameliorating the neuropathology in GD and PD. It is likely that the clinical success of pharmacological mTOR inhibitors will rely on the precise titration of mTOR activity, in order to stimulate autophagy appropriately in the face of ALS dysfunction, minimalizing unwanted side effects.

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Conflicts of interest: None declared.

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