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Parkinson's Disease Shares the Lysosome with Gaucher's Disease

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Summary

The second most common neurodegenerative disorder, Parkinson's disease (PD) is an age dependent progressive neurodegenerative disorder that affects movement. While many of the causes of PD remain unclear, a consistent finding in PD is the abnormal accumulation of α -synuclein that has led to the widely held notion that PD is a synucleinopathy. In a recent *Cell* manuscript Mazzuli et al., provide a potential mechanistic link between Gaucher's disease, a glycolipid lysosomal storage disorder due to Glucocerebrosidase (GBA) deficiency and PD. The authors reveal a reciprocal connection between the loss of GBA activity and accumulation of α -synuclein in the lysosome establishing a bidirectional positive feed back loop with pathologic consequences. These findings should stimulate further work on role of the lysosome in PD pathogenesis and the identification of new treatment strategies for PD.

Body

Parkinson's disease (PD) is common neurodegenerative disorder characterized by the age-dependent progressive degeneration of substantia nigra dopamine (DA) neurons that leads to the major clinical manifestations of the disease including slowness of movement, rigidity and tremor (1). In addition, there is the accumulation of non-degraded products of the neurodegenerative process including α -synuclein, ubiquitin and other proteins into structures designated, Lewy neurites and Lewy bodies (2, 3). α -Synuclein, which has a propensity to assemble into oligomers and fibrils is the major component of Lewy neurites and Lewy bodies (4). Although the majority of PD is thought to be sporadic in nature with

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no known cause, there are several genes that when mutated can cause PD through autosomal dominant (*α-synuclein* and *LRRK2*) or autosomal recessive (*parkin*, *PINK1*, *DJ-1*) mechanisms (5-7). In addition to these Mendelian inheritance patterns that cause PD in some patients, there are mutations in these and other genes and/or regulatory elements that increase the relative risk of developing PD (5, 8). Recent studies indicate that mutations in glucocerebrosidase (GBA), which has traditionally been clinically linked to the lysosomal storage disorder Gaucher's disease, is the most common genetic risk factor for PD (9).

The first hints that Gaucher's disease and PD might be linked were case reports that Ashkenazi Jewish patients with Gaucher's disease had parkinsonism (10, 11). Subsequent genetic studies indicated that there was a several fold higher risk for PD in patients of different ethnic backgrounds with common and rare GBA variants that cause Gaucher's disease (8, 12-14). Moreover, there was a higher than expected incidence of parkinsonism in Gaucher's disease carriers (15). The clinical phenotype of GBA associated PD ranges from drug-responsive PD to a range of parkinsonian phenotypes including treatment refractory PD (15, 16). Neuropathologic studies indicate that patients with GBA mutations develop widespread Lewy body pathology characterized by α -synuclein accumulation and aggregation and loss of DA neurons (13, 17).

How might Gaucher's disease and PD, two disorders that on the surface seem to be completely unrelated to one another, be linked? On the one hand Gaucher's disease is a glycolipid lysosomal storage disorder, that accumulates glucosylceramide and PD on the other hand is a protein accumulation disorder characterized by α -synuclein aggregation and toxicity. In a recent paper in *Cell* Mazzuli et al., provide a potential mechanistic link between Gaucher's disease and PD. They show that a loss of GBA activity in primary cultures and human iPS neurons causes a preferential accumulation of α -synuclein by interfering with lysosomal protein degradation. What makes the results particularly striking is that they also show a bidirectional positive feedback loop, in which α -synuclein inhibits GBA leading to a feed forward mechanism of neurodegeneration (Fig. 1).

Lysosomes contain a variety of acidic lysosomal hydrolases, which degrade macromolecules and organelles in a process termed autophagy. Proteins, protein complexes, protein oligomers and fibrils that are not degraded by the ubiquitin proteasome system (UPS) due to their size, lack of appropriate ubiquitination signals and the subsequent failure to enter the proteasome or when the UPS is inhibited are degraded by autophagy (18, 19). α -Synuclein appears to utilize both systems for its degradation. Both the UPS and the autophagic system are impaired in PD with disease causing α -synuclein mutations or aggregated α -synuclein contributing to the impairment of both systems (20, 21). In the degenerative process of PD, it is difficult to know which system is impaired first, but one could envisage that α -synuclein that is not degraded by the UPS would be shuttled to the autophagic system. The failure of both systems would ultimately contribute to the demise of neurons.

α -Synuclein that fails to be degraded by the UPS is catabolized by chaperone-mediated autophagy (CMA), microautophagy and macroautophagy (20). CMA utilizes heat-shock cognate protein of 70 kDa and the lysosomal membrane receptor, lamp2a to transport α -synuclein and other proteins into the lysosome. Wild type α -synuclein is cleared by CMA,

but mutant and postrationally modified α -synuclein inhibits CMA possibly contributing the buildup of proteins that utilized the CMA pathway for degradation(22, 23). Microautophagy mediates the turnover of long-lived cytosolic proteins and organelles through poorly characterized mechanisms by lysosomal membrane sequestration of whole regions of the cytosol (18). Macroautophagy mediates the degradation of a variety of cytosolic proteins and organelles via uptake into double membrane bound structures known as autophagosomes that merge with lysosomes to single membrane bound autophagolysosomes that contain acidic lysosomal hydrolases (18, 19). The lysosome is probably where the majority of α -synuclein is degraded and where GBA resides.

Mazzuli et al., (24) show that reducing GBA activity either via shRNA or in human iPS cells from a patient with Gaucher's disease preferentially reduces the lysosomal degradation of α -synuclein. Moreover, reducing GBA activity promotes the neurotoxicity of α -synuclein through polymerization-dependent mechanisms by selectively promoting the formation of toxic soluble and insoluble, as well as, high molecular weight forms of α -synuclein. The accumulation of toxic soluble α -synuclein species occurs through stabilization of soluble oligomeric forms of α -synuclein by the substrate of GBA, glucosylceramide in the acidic environment of the lysosome. It is known that α -synuclein strongly binds to brain derived glycosphingolipids that contain glucosylceramide as their core structure (25). This stabilization of soluble oligomeric forms of α -synuclein by glucosylceramide occurs at the expense of delaying fibril formation, but once fibrils form there is a 2 to 3 fold increase in fibril formation. Reduced GBA activity in *C. elegans* or in mouse models of Gaucher's disease also leads to soluble and insoluble α -synuclein accumulation. More importantly, there is accumulation of soluble and insoluble α -synuclein in a Gaucher's disease patient with atypical PD and patients that were homozygous or heterozygous for GBA mutations with a diagnosis of Lewy body dementia, but no accumulation of α -synuclein in asymptomatic Gaucher's disease patients.

The authors also report that the reduction of GBA levels leading to the stabilization of soluble oligomeric forms of α -synuclein by glucosylceramide leads to neurotoxicity. The mechanism of neurotoxicity was not explored. However, the authors did report that overexpression of α -synuclein preferentially inhibits the intracellular trafficking of GBA resulting in decreased lysosomal GBA activity and increased ER retention of GBA. The authors suggest that this may occur by α -synuclein's ability to impede ER-Golgi trafficking of GBA via inhibiting the formation of soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) protein complexes (26, 27), although it was not shown that GBA utilizes this system for ER-Golgi trafficking. The levels of ER retained GBA correlate with α -synuclein levels in human post-mortem brain with high α -synuclein levels occurring in the setting of high levels of ER retained GBA suggesting that the normal variation of α -synuclein levels modulates the maturation and subsequent activity of lysosomal GBA. In patients with PD there was a significant reduction in GBA activity further supporting the notion that there is a reciprocal regulation of GBA activity and α -synuclein levels. Thus elevated levels of α -synuclein that occur in PD and related α -synucleinopathies impairs the activity of lysosomal GBA, which leads to further stabilization and propagation of α -synuclein creating a feed-forward mechanism of

pathogenicity (Fig. 1). One could envisage that impairment of lysosomal GBA and accumulation of soluble oligomeric and fibrillar forms of α -synuclein ultimately lead to the disruption of the lysosome and the subsequent release of lysosomal proteases, into the cytosol setting in motion an irreversible death cascade. Consistent with the notion of lysosomal dysfunction is the observation that autophagosomes accumulate in PD (28). The most likely explanation for this is that lysosomes are not functioning to degrade autophagosomes. Support for this idea come from studies in which, autophagosomes accumulate and lysosomal permeabilization occurs in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mouse model of PD through the ectopic release of lysosomal proteases into the cytosol (29). Other lysosomal storage disorders accumulate α -synuclein and mutations in *ATP13A2* cause parkinsonism consistent with the notion that lysosomal function is intimately linked to α -synuclein (30, 31).

Prior and contemporaneous work by some of the coauthors of this paper confirm that α -synuclein accumulates in knockin mouse models of Gaucher's disease associated GBA mutants (32). Chemical inhibition of GBA promotes α -synuclein accumulation and overexpression of wild type GBA lowers α -synuclein levels consistent with a loss of function of GBA activity (33, 34). However, Cullen et al also reported that that overexpression of GBA mutants in cell lines in a time and dose-dependent manner promoted α -synuclein accumulation *in vitro* without effecting GBA activity (32). Thus, there appears to be more to the story than simply lowering GBA activity and accumulation of glucosylceramide as reported by Mazzulli et al., (24). Future studies focused on measuring glucosylceramide and other glycosphingolipids will need to be performed to explain these seemingly paradoxical findings.

Can these findings be translated into new therapies for PD. As Mazzulli et al., suggests strategies focused on enhancing lysosomal GBA activity could show particular promise by reversing the pathogenic feed forward cycle of α -synuclein toxicity and lysosomal GBA impairment in PD and related α -synucleinopathies (24). Dissecting the molecular components of the reciprocal regulation of lysosomal function and α -synuclein levels seem particularly important for understanding the pathogenesis of PD.

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Figure 1.

Pathologic α -synuclein signaling. Homeostatic mechanisms regulate the expression of α -synuclein (α -syn) through two pathways for degradation of excess or defective protein, the ubiquitin proteasome system and the autophagic system. Under normal conditions α -synuclein is degraded by the proteasome, chaperone mediated autophagy (CMA) or microautophagy. Mutations in α -synuclein or modifications from mitochondrial stress, reactive oxygen species (ROS) or nitrosative stress from nitric oxide (NO) trigger α -synuclein to oligomerize and fibrillize, which can cause the proteasome and CMA to become dysfunctional thereby forcing the microautophagic and macroautophagic pathway to be the major default mechanism for α -synuclein clearance. α -Synuclein fibrils can be engulfed in an autophagosome and targeted to the lysosome. In their recent paper in *Cell* Mazzulli et al. add a new twist to the understanding of α -synuclein pathology. They show that increased α -synuclein results in retention of glucocerebrosidase (GBA) in the endoplasmic reticulum initiating a feed forward cycle of increased α -synuclein expression and GBA retention. Mutations in GBA (GC Mutations) result in a decreased activity of GBA in lysosomes resulting in an increase in the GBA substrate, glucosylceramide (GlcCer) promotes the stabilization of soluble α -synuclein oligomers, which fuels the feed forward mechanism. Although this initially delays fibril formation, when fibrils form there is a 2-3 fold increase in expression. Excess α -synuclein fibrils may lead to lysosomal dysfunction, the release of lysosomal proteases, and ultimately neuronal cell death and neurodegeneration.