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Mechanisms of Glucocerebrosidase Dysfunction in Parkinson's Disease

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Abstract

Beta-glucocerebrosidase is a lysosomal hydrolase, encoded by *GBA1* that represents the most common risk gene associated with Parkinson's disease (PD) and Lewy Body Dementia. Glucocerebrosidase dysfunction has been also observed in the absence of *GBA1* mutations across different genetic and sporadic forms of PD and related disorders, suggesting a broader role of glucocerebrosidase in neurodegeneration. In this review, we highlight recent advances in mechanistic characterization of glucocerebrosidase function as the foundation for development of novel therapeutics targeting glucocerebrosidase in PD and related disorders.

Graphical Abstract

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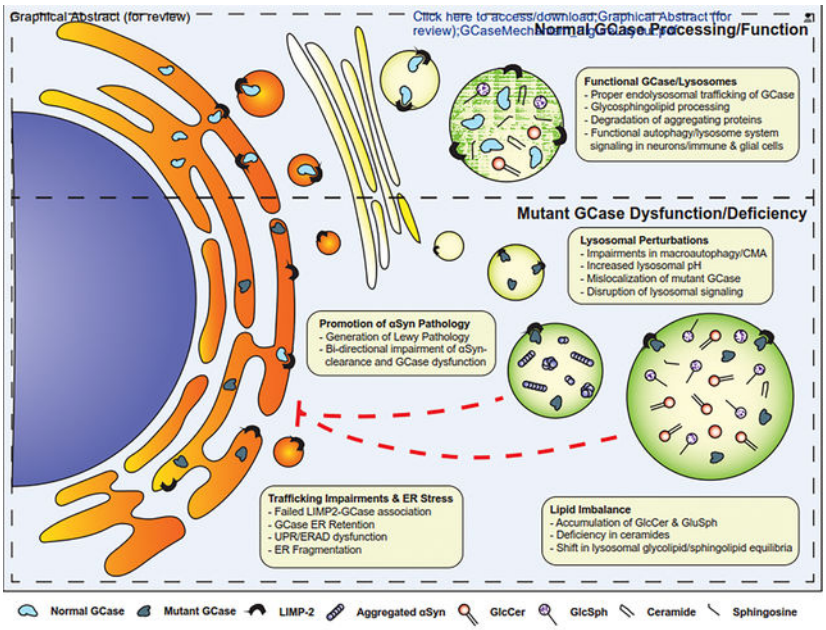
Declaration of interests

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: D.K. is the founder of Vanqua Bio, Lysosomal Therapeutics, Inc., and serves on the Scientific Advisory Board of Intellia Therapeutics, AcureX Therapeutics, Leal Therapeutics, The Silverstein Foundation and serves as a Venture Partner at OrbiMed.



Keywords

Glucocerebrosidase; GBA1; Parkinson's disease; neurodegeneration; lysosomes

Introduction

Parkinson's Disease (PD) is a debilitating neurodegenerative movement disorder that presents with a diverse array of symptomatology. The disease signature most notably associated with motor symptoms (bradykinesia, rigidity, postural instability, and tremor) is the selective degeneration of dopaminergic neurons in the substantia nigra [1]. However, PD is a progressive disorder that also affects other neuronal subpopulations leading to non-motor symptoms such as cognitive decline, behavioral and mood disorders, and autonomic dysfunction [2,3]. PD is pathologically characterized by eosinophilic inclusions known as Lewy bodies or Lewy neurites consisting of the aggregated protein alpha-synuclein (αSyn) [4].

Although predominantly known as an idiopathic disorder, approximately 15% of PD cases are considered familial with up to 10% inherited in Mendelian pattern [5]. Several genetic risk factors identified since the late 1990s have been studied to better understand convergent mechanisms potentially applicable to sporadic PD [6,7]. Interestingly, more than half of PD risk genes identified in GWAS studies are associated with putative variants linked to lysosomal storage disorders [8]. *GBA1*, the gene encoding for beta-glucocerebrosidase (GCase), is the most common genetic risk factor for PD that has been involved in PD pathogenesis [9,10]. Glucocerebrosidase is a member of the coordinated lysosomal expression and regulation (CLEAR) network that functions in glycosphingolipid processing and ceramide metabolism [11,12]. Given the established genetic link between *GBA1* and

PD, several studies have aimed to understand *GBA1*-based mechanisms that contribute to PD-related neurodegeneration.

Several excellent reviews have comprehensively described the link of GCase deficiency and dysfunction to PD. In this review, we provide an update on mechanistic studies exploring the role of GCase in PD, including how non-cell autonomous GCase dysfunction may contribute to PD pathogenesis, and highlight important considerations to better understand GCase-pathophysiology and effective targeting for therapeutic development.

The Association of Gaucher Disease and *GBA1*-PD

Glucocerebrosidase is a 497-amino acid protein which functions within the acidic lumen of lysosomes to hydrolyze glycolipids and sphingolipids. Synthesized GCase is transported from the endoplasmic reticulum (ER) to the lysosome by the lysosomal integral membrane protein-2 (LIMP2) encoded by *SCARB2* [13]. Lysosomal GCase functions independently from homologous cytosolic glucosidases, glucocerebrosidase-2 and -3 (*GBA2*/*GBA3*), which do not have genetic associations with PD, but *GBA2* has been linked to hereditary spastic paraplegia [14]. Biallelic mutations in the *GBA1* gene are known to cause Gaucher Disease (GD), a rare, pan-ethnic lysosomal storage disorder that ranges in a broad spectrum of clinical presentations and ages of onset [15]. Although a majority of GD cases present as a disease of the peripheral organs (known as Type 1 GD), a small fraction of GD cases manifest in neuronopathic disease (Types 2 and 3) which features focal neurodegeneration and brainstem dysfunction [15,16]. A vast majority of GD associated mutations cause loss-of GCase activity which leads to substrate accumulation in lysosomes, most commonly observed in the form of engorged macrophages (termed “Gaucher Cells”) clustered in the spleen, liver, lungs, and bone marrow [16]. The severity and rate of progression of disease is variable amongst GD patients and associated to particular risk variants. For example, the most common missense mutation, p.N370S (now commonly referred to as p.N409S due to an updated annotation featuring an additional 39-residue leader sequence) typically is characterized by milder phenotypes associated with Type 1 GD [17,18]. The other common variant, p.L444P (i.e. p.L483P), is observed across all three subtypes of GD and is considered a more severe mutation. To date, almost 400 mutations in the *GBA1* locus have been identified throughout coding and non-coding sequences, possibly contributing to heterogeneity in disease course and progression [19].

In 1996, Neudorfer described six cases of GD-associated Parkinsonism with cardinal features including tremor, rigidity, bradykinesia, and speech impairment [20]. These findings were later validated in larger studies showing a higher propensity of GD patients to develop PD [18,21]. Interestingly, the higher incidence of Parkinsonism in GD patients was also observed in first- and second-degree family members of GD patients, indicating that GCase function, even in heterozygous carriers, may be an important factor in PD pathogenesis [22,23]. Sidransky et. al. confirmed the link between *GBA1* heterozygosity and PD in an international, multicenter study that compared 5691 PD and 4898 control subjects and found an odds ratio of 5.43 for GBA mutation carriers to develop PD [9]. Since then, multiple studies have reproduced these findings with the incidence of PD in GBA-mutant carriers ranging from 5–20% depending on the populations of interest. Several studies have provided

excellent summaries of the distribution mutations across ancestries [19,24,25]. Recent additional studies of carrier frequency were conducted in India, the Netherlands, Ireland, and New Zealand [26–29]. However, as exome-sequencing and whole genome sequencing for *GBA1* can be problematic due to a highly analogous pseudogene on *chr.1* (*GBAP1*) [30], utilizing refined methods to analyze comprehensive mutant status from populations is necessary to understanding the scope of *GBA1*-PD populations [31].

The distribution of mutations has been well reviewed in previous work [19,32,33]. However, new PD-associated mutations continue to be uncovered, most recently including the p.N227S mutation found in GD patients in Chinese population studies [34]. Although a majority of PD-associated variants overlap with causative GD mutations, several PD-selective variants have also been identified which are not considered pathogenic for GD (e.g. p.D443N, p.E326K, p.K7E, and p.T369M) [33,35–37]. The data suggest some risk variants may contribute specifically to the development of PD pathologies without inducing GD pathophysiological sequalae.

Interestingly, the calculated relative risk of developing PD is similar between GD patients and heterozygous *GBA1* mutation carriers (RR of 21.4 to 30, respectively) [38,39]. It is relevant to note that although GBA carriers have a substantially higher odds ratio of developing a synucleinopathy than the general population, mutations are poorly penetrant, and a vast majority of carriers do not manifest with disease [40]. Penetrance is hypothesized to be linked to a combination of genetic, epigenetic, and environmental modifiers that modulate GCase-linked pathologies.

Clinical Manifestations of *GBA1*-PD

GBA1-PD is marginally distinguishable from the classical PD. Disease onset in *GBA1*-carriers is accelerated by approximately 2–6 years, depending on variant and population [9,33,41]. The acceleration of motor dysfunction coincides with a shorter, but more prevalent, prodromal phase of disease that characteristically features anosmia, autonomic dysfunction, neuropsychiatric and behavioral disorders, and early motor dysfunction [42]. Honeycutt et. al. reported no change in the severity of motor prodrome in GBA-carriers, but indicated a more rapid conversion to PD or cognitive impairment from prodromal indications [43]. Data also suggest an association between the severity of variant and the acceleration of disease onset [44]. *GBA1*-PD patients are reported to experience faster motor symptom progression and a more rapid conversion to Hoehn and Yahr Stage 3 (onset to postural instability) [45,46]. A long-term, UK-based study of mutant carriers conducted by Stoker et. al. validated higher rates of dementia in mutant carriers and also indicated earlier mortality in patients carrying pathogenic, GD-associated mutations [47].

In addition to canonical PD symptomatology, *GBA1*-PD patients commonly develop non-motor symptoms at significantly higher rates than non-mutant carriers, including neuropsychiatric sequalae and cognitive deficit. Several studies have demonstrated a higher prevalence of cognitive decline and dementia in *GBA1*-PD compared to non-mutant carriers [33,46,48,49]. This disease progression is observed with higher frequencies of neocortical and limbic neuropathology. A recent study analyzed CSF GCase activity of PD patients

(with and without mutations) and control subjects and found GCase activity to be lower at the time of diagnosis in patients who develop dementia within 10 years compared to cognitively normal patients [50]. These data suggest CSF GCase activity may be an effective prognostic differentiator for newly diagnosed patients. Although the difference in PD prevalence is marginal between GD patients and *GBA1* heterozygotes, two studies in Ashkenazi Jewish populations indicate GD-PD patients demonstrate earlier ages-of-onset, and may develop more pronounced motor and non-motor deficits than *GBA1*-PD patients, suggesting a potential dose effect of GCase in the development of PD symptomatology [51,52].

The prevalence of non-motor symptomatology in *GBA1*-PD, most notably cognitive decline, raises question of the association of GBA mutations with other synucleinopathies or neurodegenerative illnesses that feature non-motor pathologies. GWAS studies have suggested an even stronger association between *GBA1* variants and Dementia with Lewy Bodies (DLB) than with PD, with an adjusted odds ratio observed to be 8.28 [53]. Similarly, *GBA1* was identified amongst a subtype of Alzheimer's disease patients with concomitant DLB pathology (LBD-AD), providing further evidence that cortical and hippocampal neurons are susceptible to GCase pathologies [54]. One clinical study investigated the *GBA1*-PD specific variants p.E365K and p.T408M and highlighted lower cognitive performance and neuroimaging signs of more advanced disease in variant carriers vs wild-type PD patients [55]. Interestingly, it has been suggested that mutant status may exacerbate cognitive deficits in patients undergoing deep brain stimulation in the subthalamic nucleus (STN-DBS) [56].

A recent GWAS analysis also identified *GBA1* as a significant risk allele for REM sleep and behavioral disorder (RBD), the most predictive prodromal syndrome of conversion to synucleinopathy with >80% of diagnosed patients developing PD, DLB or multiple system atrophy (MSA) [57,58]. Interestingly, the study also identified GWAS hits in the loci of *SNCA*, *TMEM175*, and *SCARB2*, all of which directly associate with GCase or mediate GCase function within the lysosome [57]. Collectively, these data suggest a potent association with pathways involved in lysosomal GCase function and the development of neuronal synucleinopathies. Mutations have also been linked to the oligodendroglial synucleinopathy, MSA, [59], although data on the association is conflicting with some studies suggesting no genetic association between variants and MSA [60,61].

Although a majority of mutant carriers will not go on to develop PD, there are lines of evidence that suggest non-manifesting GBA mutant carriers experience subtle clinical changes that may indicate preliminary PD conversion. A study from the Parkinson's Progression Markers Initiative (PPMI) investigated a longitudinal cohort of GBA non-manifesting carriers and found higher scores in the Movement Disorders Society-Unified Parksinson's Disease Rating Scale (MDS-UPDRS) in carriers (9.5) vs control subjects (4.6) indicating a subtle clinical dysfunction that may precede DAT deficits [62]. Neuroimaging studies of non-manifesting carriers, however, have shown highly-variable and conflicting evidence of a prodromal PD signature [63]. Similarly, studies in discordant siblings have shown no development of clinical Parkinsonism in non-manifesting carriers [64,65]. These data caution against over-interpreting non-penetrant *GBA1*-mutation carriers as eventual

converters to PD, and suggest the need for more comprehensive longitudinal studies to better evaluate the penetrance of *GBA1*-PD.

Glucocerebrosidase and Alpha-synuclein

Neuropathological studies and concordant clinical presentation of non-motor symptoms have suggested a strong association with GCase and alpha-synuclein (αSyn) pathology. Unlike other common PD risk variants such as *LRRK2* or *PRKN*, Lewy pathology (LP) is commonly seen in *GBA1*-PD. LP has also been observed in the brainstem, cortex, and hippocampal regions of GD patients that develop DLB-like phenotypic dysfunction and Parkinsonism, suggesting a prominent association between GCase and αSyn [16]. αSyn is an intrinsically disordered 140-amino acid protein most prevalently found in synaptic compartments of neurons. Although the precise function and requirement of αSyn remains unclear, studies suggest αSyn plays a role in synaptic vesicular dynamics and transmission [66,67]. αSyn belongs to a class of amyloidogenic proteins which have a propensity to aggregate and induce proteopathic templating of naïve protein under pathologic conditions.

Since the near parallel discoveries of αSyn as a causative gene for PD [68] and its predominance as a protein constituent in LP [69], a substantial body of work has characterized mechanisms by which αSyn may cause cellular toxicities and neurodegeneration [4]. Several mutations [70–74] and multiplications [75,76] of the *SNCA* locus further confirmed the genetic association of αSyn and PD. Gunder et. al. demonstrated increased αSyn levels in the substantia nigra of post-mortem patients with GBA mutations [77]. These findings coincide with data illustrating decreased GCase activity in the substantia nigra of PD and DLB patients [78]. GWAS analysis of modifiers identified variants near the *SNCA* locus amongst two candidate loci that may have a significant role in GBA1-PD penetrance, indicating a potential genetic interaction in addition to protein interactions [79].

Our group has demonstrated a bi-directional association between GCase and αSyn, whereby GCase impairment leads to accumulation of αSyn in iPSC-derived dopaminergic neurons [10]. Furthermore, accumulated GlcCer from GCase deficiency can stabilize intermediate aggregate structures to drive the generation of high-molecular weight αSyn species [10]. Conversely, aggregated αSyn was observed to decrease GCase activity in iPSC-derived neurons and post-mortem brains of patients with idiopathic forms of disease, illustrating a positive feedback mechanism of αSyn-GCase toxicity [10]. These data suggest that this feedback loop would lead to decreased activity of wild-type or mutant GCase in any cell that accumulates αSyn. However, this mechanism does not explain preferential vulnerability of midbrain dopaminergic neurons in PD. Our subsequent work suggested that the activity of wild-type or mutant GCase can be decreased by accumulation of oxidized dopamine in dopaminergic neurons [80]. While the effects of αSyn on trafficking of GCase can affect GCase activity in dopaminergic and non-dopaminergic cells, the effect of oxidized dopamine would be seen only in dopaminergic populations. Mitochondrial oxidant stress and dysfunctional synaptic vesicle endocytosis contribute to increased oxidized dopamine in PD patient dopaminergic neurons [81]. Since oxidized dopamine and neuromelanin were

detected in human but not mouse dopaminergic neurons, our data highlight the importance of human models for studying dysfunction of nigral dopaminergic neurons in PD.

We have also observed decreased GCase activity and concomitant PD pathology in neurons derived from patients with alternative familial PD mutations, including *LRRK2*, *PRKN*, and *DJ-1*, implicating convergent GCase-αSyn pathology across PD subtypes [82]. Collectively, these results suggest that direct targeting of wild-type glucocerebrosidase may improve pathogenic phenotypes across synucleinopathies. To this end, we identified allosteric GCase modulators increase wild-type GCase activity in dopaminergic neurons from patients with various forms of PD [82]. These modulators improved lysosomal dysfunction, lowered oxidized dopamine, αSyn, and glucosylceramide in patient neurons. Activation of wild-type GCase may serve as a potential therapeutic target for multiple synucleinopathies that exhibit decreased GCase activity.

The direct interaction between GCase and αSyn is still relatively unknown. A study from Yap et. al. identified C-terminal interactions between αSyn and GCase at sub-cytosolic pH, which was tempered by p.N370S mutant GCase [83]. Thus, αSyn may feature a direct binding motif that facilitates processing. However, it is uncertain how aggregated forms of αSyn modify binding capacity with or without the presence of GCase mutations. Kuo et. al. observed that misfolded mutant GCase is aberrantly bound to the lysosomal membrane in post-mortem brains of PD patients [84]. This mislocalization leads to interference and disruption in chaperone-mediated autophagy (CMA) and consequently leads to αSyn aggregation and induced DA neurodegeneration, thus providing an indirect mechanism for the GCase-αSyn pathological cascade [84]. A recent study of *GBA1*-PD fibroblasts used a shotgun lipidomic method to differentiate p.L444P-patients from control subjects and sporadic PD cases [85]. Lipid extracts from the p.L444P fibroblasts rapidly accelerated αSyn aggregation upon co-incubation, indicating a permissive lipid profile for αSyn pathology that may be promoted through impaired GCase activity [85].

Several studies have utilized animal models to understand how mutations may affect αSyn seeding, propagation, and toxicity. One study in a drosophila model of αSyn neurodegeneration confirmed several loss-of-function enhancers of αSyn toxicity, including *SCARB2*, *SMPD1*, *CTSD*, all of which are associated with lysosomal function, or more directly, GCase function [86]. In the p.D409V transgenic mouse model, heterozygous animals showed no histopathological aggravation of αSyn pathology or behavioral insults compared to wild-type littermates after unilateral injection of αSyn pre-formed fibrils (PFFs) into the olfactory bulb [87]. However, two independent studies injecting PFFs into the striata of p.L444P heterozygous mice show enhanced formation and spread of αSyn inclusions compared to control subjects [88,89]. Mahoney-Crane et. al. reported pathological exacerbation specifically in the hippocampus, whereas the rate of nigrostriatal and cortical pathologies was unaffected [89]. Previous reports have demonstrated the diversity of αSyn pathology profiles are contingent to the site of PFF injection and the corresponding neural networks associated with the target brain region [90–92]. However, these studies in *GBA1*-mutant model systems also suggest GCase modification of αSyn aggregation kinetics may be dependent on the particular pathogenic variant. In studies in both primary murine neuronal cultures and mouse models, Henderson et. al. show GCase inhibition

does not induce αSyn aggregation, but is permissive to already initiated pathological processes in which pathological αSyn attenuates GCase activity [93]. Intriguingly, the indirect association between αSyn seeding and GCase activity has also been tested in peripheral tissues. In a study modeling gut-to-brain pathological αSyn spread, delivery of a peripheral-targeting AAV carrying *GBA1* was efficient in reducing enteric nervous system αSyn pathology and highlighted potential therapeutic benefit of restoring active GCase in peripheral tissues [94]. It is hypothesized that a fraction of PD pathologies may initiate from peripheral induction points with CNS contacts such as the gut [95]. Studies exploring these axes of pathological initiation and transfer are useful in understanding what role peripheral GCase deficiencies may play in CNS disease.

The imbalance of lipid pathways upon glucocerebrosidase deficiency

The primary known function of GCase is the hydrolysis of glucosyl residues from glucosylceramide (GlcCer) and glucosylsphingosine (GlcSph), although several other glycosphingolipid moieties may also be substrates specific to lysosomal GCase. Mutation-induced impairment in GCase activity thus shifts the stoichiometry of glycosphingolipid processing causing an abundance of unprocessed lysosomal substrates and changes in ceramide levels. However, the specific role of how substrate-product imbalance contributes to *GBA1*-PD pathophysiology has been conflicting and difficult to resolve.

GlcCer has been demonstrated to directly mediate αSyn aggregation dynamics [10]. However, post-mortem assessment of GlcCer levels in the brains of synucleionpathy patients show conflicting data, with one study suggesting age-dependent accumulation in PD patients [96] and others showing no changes compared to control subjects [97,98]. Some evidence suggests GlcSph levels may also have an association with PD pathology. Taguchi et. al. showed *in vitro* GlcSph specifically induces seed-competent αSyn oligomerization that can template naïve αSyn in neurons [99]. They further show GlcSph accumulation to precede GlcCer accumulation in a PD mouse model generated from GD mice crossed with αSyn transgenic mice [99]. Recent data quantifying lipid content in plasma from p.N370S carriers in PD and non-PD populations showed increases in GlcSph in mutant carriers compared to controls, but were unable to differentiate the PD from non-PD cohort [100].

Methods to detect lipid accumulation in post-mortem brains have several potential confounding variables that may generate lower signal-to-noise ratios. For example, different cell types have large distributions of GCase expression and activity. Isolating neuronal glycosphingolipid content from glial fractions is technically challenging and may not present the most relevant lipid profiles for neurodegeneration. Also, the mass spectra signal of GlcCer and GlcSph may be contaminated by enantiomeric glycosphingolipids such as galactosylceramides which are prevalent in CNS tissue. Additionally, lipid content is subject to variability due to post-mortem intervals and tissue processing methods. Other studies have investigated substrate accumulation profiles from CSF, but have similarly found conflicting or negative results from *GBA1*-PD patients [98,101]. Thus, it is problematic to establish conclusions of substrate accumulation in *GBA1*-PD from the current literature, and studies to validate GBA-substrate/product ratios will require larger cohorts and more consistent methodology than have previously been utilized [102].

Although the evidence of GCase substrate accumulation from PD patient data has been conflicting, evidence from animal models of substrate accumulation led to the development of Venglustat, a small molecule inhibitor of glucosylceramide synthase, for the treatment of *GBA1*-PD [103]. Phase II clinical data (ClinicalTrials.gov Identifier: NCT02906020) suggested effective target engagement and lowering of CSF GlcCer at 4 weeks (a decrease of 72% from baseline in Japanese patients and 74.3% from baseline in non-Japanese patients at highest treatment dose) [104]. However, treated patients showed no signs of improvement in UPDRS part II or III [104]. Although the phase II study was not powered to detect meaningful clinical changes, further development of Venglustat for treatment of *GBA1*-PD was suspended. These findings suggest GlcCer accumulation may not be an ideal pharmacological target for effective therapy, or may indicate substrate reduction therapy to be ineffective in combating *GBA1*-PD.

GCase impairment may also contribute to impaired ceramide processing, which may play a significant role in cellular health and function. Ceramides are important constituents in lipid membrane stabilization and signaling [105]. In a recent study, our group showed lysosomal ceramides activate Cathepsin B which, in turn, promotes cleavage of prosaposin to saposin C, the coactivator of lysosomal GCase [106]. In *PRKN*-mutant models of PD, deficient ceramide levels correlated with impaired GCase activity [106]. Conversely, treatment with an inhibitor of acid ceramidase to upregulate ceramide rescued Cathepsin B activation [106]. However, clinical data of ceramide levels in *GBA1*-PD are conflicting. One study comparing brain ceramide levels in patients with Lewy Body Disease (LBD) vs age-matched controls showed elevations of ceramide in LBD regardless of variant status [107]. Indeed, these data collectively suggest altered sphingolipid processing in patients with Lewy Body Disease, but does not show clean directionality on ceramide levels.

It is also possible that GCase mediated lipid dysregulation may be challenged beyond ratios of specific GCase substrates, suggesting greater lipid imbalances that may influence pathologies. Interestingly, several other proteins involved in glycosphingolipid enzymatic processing have also been implicated as PD risk genes, specifically functioning in the ceramide metabolism pathway (e.g. *GALC*, *GLA*, *SMPD1*, *ASAH1*) [6,8,108]. These findings suggest a collective dysregulatory network which may lead to lipid imbalances and cellular dysfunction. Recent data suggests that plasma multiple glycosphingolipid levels may be abnormal in PD patients with or without select GBA mutations, nominating lipid dyshomeostasis as a convergent phenomenon across PD subtypes [109]. Studies using unbiased lipidomic analyses across glycosphingolipid processing with respect to GCase activity may provide insight into functional requirement and makeup of lipid profiles with respect to disease progression and tissue type.

Glucocerebrosidase and the Autophagic Lysosomal System

Lysosomal network genes and enzymes function in a carefully regulated and coordinated manner as part of cellular autophagy-lysosome system. As such, many hypotheses of GCase-related cellular dysfunction connect GCase-induced impairments to global lysosomal/autophagic dysfunction. Several studies have explored and documented global impairments in the autophagy lysosomal system as a product of GCase deficiency [110–112]. GCase

deficiency has also been associated with disruption to chaperone-mediated autophagic programs [84].

However, autophagic responses to GCase damage may differ depending on model system. One study investigating the role of proteasomal turnover and autophagic regulation in mutant flies with *gba1b* deficiency (the drosophila ortholog of *GBA1*) showed no GCase-associated perturbation in global autophagy or other protein regulation systems [113]. The study did find higher levels of extracellular vesicle synthesis and release in *gba1b* mutants, indicating a potential pathologic role in vesicle cycling and protein aggregation [113]. One study investigating post-mortem brain tissue assessed sphingolipid hydrolase activity to determine whether network sphingolipid dysregulation contributed to PD decline [96]. The study identified GCase impairment to be accompanied by a network of dysfunctional hydrolase activities, leading to impairments in complex ganglioside concentrations [96]. Importantly, sphingolipid processing impairments were correlated with aging in control subjects, but were more pronounced in PD subjects. These findings suggest the concept of lysosome enzymatic fatigue as a product of aging, which may provide important context in the malignancy and penetrance of GBA mutations.

Deficiencies in other lysosomal-associated proteins have been shown to induce GCase pathologies. We and others have found that patients with progranulin mutations (*GRN*) that develop frontal temporal dementia (FTD) show lower levels of GCase activity [114,115]. Using iPSC-derived cortical neurons, we showed *GRN*-mutations fail to convert prosaposin into saposin-C, a critical activator of functional GCase [114]. *GRN*-deficits in GCase activity have also been reported to be a product of incompletely glycosylated GCase protein [115]. These findings were replicated in *GRN* KO mice, with evidence that GCase activity deficits in neurons can be corrected through administration of AAV-progranulin [115]. It has been suggested that progranulin regulates GCase activity through a number of different mechanisms. Progranulin has been shown to directly bind to GCase and regulate lysosomal compartmentalization of GCase [116,117]. In additional to failed GCase activation through saposin C, progranulin deficiency also causes dysregulation of bis(monoacylglycerol)phosphate (BMP), an anionic phospholipid that has been associated with GCase regulation [118].

GCase function has also been intriguingly linked with another common PD risk gene, *LRRK2* (which encodes for leucine-rich repeat kinase-2). Similar to *GBA1*, *LRRK2* dysregulation is linked to both genetic and sporadic forms of PD. Our group has shown that *LRRK2*-mutant iPSC-derived dopaminergic neurons show lower GCase activity that can be rescued through LRRK2 inhibition, primarily through Rab10-mediated regulation of lysosomal GCase [119]. A study investigating p.D409V murine astrocytes also showed rescue of lysosomal pathologies through inhibition of LRRK2 [120]. Studies in transgenic mice have shown a significant depletion of GCase protein in LRRK2 KO mouse brains [121]. Clinical studies have recently highlighted an interaction in compound heterozygous and *LRRK2* mutant carriers indicating a potential role for LRRK2 to modify dysfunction. A study monitoring patient performance on the Montreal Cognitive Assessment (MoCA) indicated *LRRK2*/*GBA1*-mutant carriers had slower rates of decline than *GBA1*-mutant carriers [122]. Yahalom et. al. described similar data from a smaller cohort that showed

lower incidence of RBD, dementia and psychosis in the dual mutant *LRRK2*/*GBA1* cohort [123]. The interaction between *LRRK2* modulation of *GBA1* requires further study to understand mechanistic links between the two proteins in relevant cell types.

Impairment of Glucocerebrosidase Trafficking and ER Stress

Over the last decade, studies have described the role of ER stress in PD pathophysiology. One prominent hypothesis is that mutant misfolded GCase, due primarily to the prevalence of nonsynonymous missense mutations, fails to traffic to the lysosomal compartment and induces proteostatic stress signaling and ER-associated degradation (ERAD) causing ER stress. Bendikov-Bar et. al. showed over 50% of p.L444P mutant GCase in GD-patient derived fibroblasts was retained in the ER and polyubiquitinated for proteasomal degradation [124]. Similarly, using p.N370S patient-derived fibroblasts, Thomas et. al. showed GBA haploinsufficiency to be accompanied by lower LIMP2 expression levels, thus decreasing efficiency of GCase trafficking to the lysosome [125]. Another study used heterozygous p.N370S patient-derived iPSCs differentiated into dopaminergic neurons to show upregulated unfolded protein response (UPR) and ER-stress markers compared to control DA neurons [126]. The study also highlighted a retention of high-molecular weight GCase isoforms, most likely attributed to improper GCase glycosylation processing in the golgi due to ER retention [126].

Other studies have also shown human cellular models of GCase inhibition and dysfunction to lead to ER stress, including several that link αSyn dysregulation and aggregation as a cause and consequence of ER-mediated GCase impairment and failure to reach lysosomes. Smith et. al. showed ER-GCase retention and ER stress was specific to the p.L444P variant compared to the p.E326K mutation in patient fibroblasts [127]. Certain mutant variants of GCase may induce improper folds or negatively impact LIMP2 binding which may promote ER retention and stress. Correcting GCase misfolding has been an attractive target for therapeutic intervention, as multiple studies have investigated the efficacy of molecular chaperones to rescue GCase pathologies. The repurposed chaperone molecule Ambroxol was previously shown to enhance GCase levels in mutant fibroblasts from GD and GBA1-carrier PD patients and healthy controls [128]. Subsequent *in vivo* validation studies confirmed Ambroxol increased GCase activity in the brains of rodents and non-human primates [128,129]. Most recently, after the successful completion of both phase I [130] and phase II clinical trials (ClinicalTrials.gov Identifier: NCT05287503), a large-scale, multi-center phase III clinical trial was confirmed, indicating evidence of potential clinical utility for chaperone-based pharmacological agents. Several other small molecule chaperones have also progressed through various stages of clinical development for the treatment of both GD and *GBA1*-PD [131].

However, it is still unclear whether ER stress is driven primarily through direct GCase interaction or through secondary GCase mechanisms such as αSyn aggregation and lysosomal dysfunction. Stojkovska et. al. demonstrated that aggregated αSyn induced ER fragmentation and disrupted proper protein folding in midbrain dopaminergic cultures [132]. These pathologies could be rescued through the use of small-molecule drugs that promote ER proteostasis and trafficking [132]. These findings also add to the notion

that many PD pathophysiologies are driven through impaired proteostatic machinery, both in the autophagy-lysosomal and the ubiquitin-proteasomal systems, suggesting a class of mechanistic targets that may be relevant to multiple PD subtypes.

Glucocerebrosidase Deficiency in Immune Cells

Mechanistic studies exploring the link of GCase deficiency and PD pathogenesis have largely centered on cell-autonomous neuronal dysfunction. However, recent work has highlighted how GCase abnormalities and impaired lysosomal function in immune cells and glia may contribute to neurodegenerative processes. Indeed, the prominence of dyslipidemic Gaucher Cells in GD suggests a particular vulnerability in myeloid cells to GCase impairment [133]. Lysosomes are critical sensors in scavenging/antigen-presenting cell populations such as myeloid cells and lymphocytes. Lysosomes drive cellular uptake programs like phagocytosis and modulate gene expression to mediate local microenvironments and induce appropriate cytokine/chemokine signaling. Thus, dysfunctional GCase, or associated enzymes like LRRK2 and progranulin with high expression in immune cells, may have significant impact on disease.

Neuroinflammation is a universal signature in the pathophysiology of synucleinopathies. PD neuropathology in accompanied by recruitment of both reactive microglia and astrocytes to primary sites of lesions [134]. Neuroimaging PET tracer studies also validate the localization of activated microglia to the substantia nigra of idiopathic PD patients [135,136]. Temporal post-mortem analysis of PD brains that received therapeutic transplants of fetal stem cells have also suggested that the temporal development of naïve LP is preceded by focal recruitment of CD45+ microglia, indicating a role in microglial signaling and reactivity in the development in pathology [137]. Recent studies in animal models of αSyn seeding have also demonstrated inflammatory glial processes to modify the kinetics of αSyn pathology [138,139]. Aside from CNS glial populations, both peripheral macrophages and T-cells have been implicated in PD pathogenesis [140,141]. T-cells from PD patients have been shown to bind to αSyn antigenic epitopes and may play a role in directly interacting with resident glial populations or dopaminergic neurons presenting MHC Class I [141].

There are several linking factors which implicate the role of GCase impairment in immune and inflammatory cell modification of neuronal pathologies. Microglial activation and cytokine release have been prominently associated with multiple animal models of GCase deficiency [142–144]. Studies utilizing the nestin-CRE floxed mouse modeling GCase impairment in neurons demonstrate engagement of lipid-engorged mac-2+ microglia in regions preceding neuronal loss and behavioral deficits [145,146]. Mutant mice as well as mice treated with CBE show microglial reactivity [144,147,148]. Soria et. al. generated a mouse with selective KO in dopaminergic neurons and observed prominent microglial activation without overt neurodegeneration or αSyn aggregation [149]. These data suggest a contribution in glial-specific GCase impairment in the degenerative thresholding of dopaminergic neurons. Astrocytic pathologies have also been observed in *GBA1*-PD models. Primary murine astrocyte cultures with p.D409V mutations show decreased lysosome counts and higher lysosomal pH than control astrocytes [120].

Peripheral monocytes and lymphocytes are also potent reservoirs of lysosomal hydrolase activity, including prominent GCase expression and activity [150,151]. Impaired glycosphingolipid processing can activate peripheral myeloid cells and induce cytokine production and release through GlcCer accumulation [152]. Studies have shown peripheral monocytes collected from both idiopathic PD and *GBA1*-PD patients have significantly dampened GCase activity, potentially highlighting a robust source for biomarker development and, ultimately, target engagement. Recently, Wallings et. al. described a multiplexed flow-cytometry based readout for GCase and LRRK2 activity from PD patient PBMCs, suggesting their utility as a reliable tandem biomarker for immune-related deficiencies associated with PD pathophysiology [153]. Longitudinal studies monitoring peripheral GCase enzyme activity correlated with disease course are ultimately needed to determine whether peripheral immune cells can serve as a surrogate measure for brain GCase activity.

Stemming from evidence in GD of differential secretion patterns of cytokines and chemokines, several groups have investigated cytokine release as a function of GCase activity. One study investigating *GBA1*- and *LRRK2*-mutant carriers showed no discernable differences in CSF or peripheral cytokine levels between groups [154]. These findings are in contrast to other studies that have found differential cytokine release profiles in *GBA1*-PD patients [155,156]. Assays to measure cytokine levels have markedly variable sensitivities and may generate conflicting results. Larger scale studies with consistent methodologies are necessary to resolve the pattern of cytokine/chemokine release related to GCase pathology.

Although there are convincing pathologies relevant to immune/inflammatory involvement in *GBA1*-PD, the relative contributions of GCase impairment in these cells, or their mechanisms associated with neuronal dysfunction are enigmatic. Furthermore, studies have shown clear disparities in immune cell signatures and function in humans vs animal model systems [157,158]. Thus, studies exploring human-cell based interactions of these cell types, perhaps through co-culture methods or organotypic/organoid modeling systems, will be important to highlight how compounded GCase pathologies in multiple cell types may cause neurodegenerative disease.

Challenges in Resolving Glucocerebrosidase Function in Disease

Several challenges exist to better understand how GCase dysregulation and impairment may contribute to the development of PD pathophysiology. A primary barrier to functional genomic understanding of GCase has been species disparities in GCase regulation, function, and mutational output depending on model system. For example, the p.N370S mutation most commonly found in PD patients causes embryonic lethality in mice [159]. Similarly, the frequently used transgenic animal model for GCase therapeutic targeting, p.D409V, has not been associated with the development of PD (although the p.D409H mutation associated with PD has also been used to monitor pathological effects of mutant GCase) [160,161]. Further development of GCase mutant transgenic lines and mutation-specific pathologies may illuminate key gaps in functional understanding and associations to genotype-specific pathophysiology. Studies employing both animal model systems in conjunction with human-cell based paradigms may be advantageous in clarifying GCase biology.

Another critical roadblock is poor penetrance of mutations and the development of disease. Recent efforts have utilized patient derived iPSCs to determine genetic modifiers of GCase penetrance. A large-cohort GWAS study investigating genetic risk loci for GBA-risk and age-of-onset identified variants near the *SNCA* and *CTSB* loci to be the most significant modifiers of GCase, although without very prominent effects [79]. One study on genetic modification of the *GBA1* locus interrogated regulatory interactions and suggests expression in the CNS (SN and cortex) is mediated through trans-regulatory action from other chromosomes, whereas peripheral GCase expression is mediated through cis-regulatory elements [162]. Another study screened 305 PD patients vs 207 controls to identify GBA variant modifiers and found the strongest interactors to be an alternate variant in the *GBA1* locus and variants in genes that cause mucopolysaccharidoses [163]. Better understanding of specific SNPs or loci that modify CNS GCase expression will be necessary to understand differential expression in tissue/cell types as well as identify genetic targets for intervention. Recent advances in pooled and arrayed CRISPR screening methods should be employed to determine how modified or shut-down expression across the genome may impact GCase activity and function. However, a significant challenge with current methods is accounting for epigenetic and environmental triggers and facilitators that contribute to modified penetrance. As iPSCs largely lose epigenetic regulatory signals during the reprogramming phase, recent efforts have turned to direct fibroblast-neuron differentiation programs to better understand genetic regulatory tags in patient-derived material [164,165].

Recent efforts to enhance the probing of patient GCase function have highlighted the importance of higher resolution, more selective assays in clinical characterizations of *GBA1*-PD. GCase activity assays feature non-specific noise from extra-lysosomal glucocerebrosidases (*GBA2*) as well as activity from other glucosidase family enzymes. The development of flow-cytometry based probes specific to lysosomal compartmentalization have improved the target signal of GCase activity detection, but can still be noisy. Methods for optimizing readouts of GCase activity have been discussed in previous reviews [166]. A recent study from Deen et. al. describes the development of lysotropic GCase fluorophores (LysoFQ-GBA) to be used for enhanced and targeted GCase activity measurements specifically in lysosomes of patient-derived tissues [167]. Similarly, multiplexed fluorescent probe systems to monitor GCase activity in tandem with other PD-associated enzymatic activity (LRRK2) may provide more appropriate context in the relative role of lysosomal GCase activity with other convergent pathologies identified in PD patients [153].

Lastly, integrating GCase dysfunction across relevant cell types will be critical moving forward, particularly with respect to therapeutic targeting. For example, it is still unclear what role GCase activity in CNS glia or peripheral monocyte and lymphocyte populations plays in facilitating neurodegenerative pathologies. Furthermore, new studies, particularly including scRNA and snRNA datasets, continue to confirm the level of heterogeneity found in these cell types and their potential roles in mediating CNS microenvironments. Current efforts for GCase replacement, either through enzyme replacement therapy or gene therapy, may be limited by ineffective comprehensive targeting of the appropriate cell types. For example, AAV serotypes currently in clinical use for the treatment of PD and other neurological disorders feature poor microglial tropism which may be necessary for effective target engagement. Establishing better GCase and lysosomal functional profiles across these

cell types, as well as their potential interactions with neurons, will be important to know to guide targeting strategies for improved GCase function.

Conclusions

Our knowledge of *GBA1*-PD has increased significantly over the course of the past two decades. Although the genetic link of GBA and PD has been well established, understanding how GCase plays a role in PD and related disorders has been limited by the lack of adequate model systems and the tools to accurately measure the activity of lysosomal GCase. Despite these barriers, important recent work has provided better insight into GCase function in different cell types across both the central nervous system and the periphery. This expanded picture of GCase dysfunction provides a platform to evaluate GCase-associated mechanisms in the context of other pathogenic pathways that have been implicated in PD. Hopefully, this will lead to improved translational studies for the development of effective therapeutic strategies for PD and other related neurodegenerative diseases.

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Research Highlights

- Mutations in GBA1 are the most prevalent genetic risk factor for Parkinson's disease.
- Lysosomal GCase dysfunction is a conserved mechanisms across genetic and idiopathic forms of disease.
- Enhancing GCase activity and function, in both normal and mutant protein, may be a powerful therapeutic avenue.
- Methods to analyze lysosomal GCase activity and function require standardization and higher signal-to-noise ratios for proper assessment of pathology.
- Identifying modifiers of GBA-PD penetrance will be critical to understand GCase dysfunction in disease.
- Non-neuronal glucocerebrosidase dysfunction, particularly in immune and glial cells, may contribute to neurodegeneration and requires future assessment.