Article title: Glucocerebrosidase 1 and leucine-rich repeat kinase 2 in Parkinson disease and interplay between the two genes

Running title: GBA1 and LRRK2 in Parkinson Disease

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Abbreviations:

ALP, autophagy-lysosome pathway; ANK, Ankyrin; ARM, Armadillo repeats; COR, C-terminal of ROC; DA, dopaminergic; EGFR, epidermal growth factor receptor; ER, endoplasmic reticulum; *GBA1,* glucocerebrosidase 1 (gene); GCase, glucocerebrosidase 1 (protein); GD, Gaucher disease; GDP, guanosine diphosphate; GTP, guanosine triphosphate; LIMP-2, lysosomal integral

membrane protein type-2; *LRRK2*, Leucine-rich repeat kinase 2; PD, Parkinson disease; RAB, Ras-related in brain; ROC, Ras of complex; UPS, ubiquitin-proteasome system; WT, wild-type

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Glucocerebrosidase 1 and leucine-rich repeat kinase 2 in Parkinson disease and interplay between the two genes

Abstract

The glucocerebrosidase 1 gene (*GBA1*), bi-allelic variants of which cause Gaucher Disease (GD), encodes the lysosomal enzyme glucocerebrosidase (GCase) and is a risk factor for Parkinson Disease (PD). GBA1 variants are linked to a reduction in GCase activity in the brain. Variants in Leucine-Rich Repeat Kinase 2 (*LRRK2*), such as the gain-of-kinase-function variant G2019S, cause the most common familial form of PD. In patients without *GBA1* and *LRRK2* mutations, GCase and LRRK2 activity are also altered, suggesting that these two genes are implicated in all forms of PD and that they may play a broader role in PD pathogenesis. In this review, we review the proposed roles of *GBA1* and *LRRK2* in PD, focussing on the endolysosomal pathway. In particular, we highlight the discovery of Ras-related in brain (Rab) guanosine triphosphatases (GTPases) as LRRK2 kinase substrates and explore the links between increased LRRK2 activity and Rab protein function, lysosomal dysfunction, alpha-synuclein accumulation and GCase activity. We also discuss the discovery of RAB10 as a potential mediator of *LRRK2* and *GBA1* interaction in PD. Finally, we discuss the therapeutic implications of these findings, including current approaches and future perspectives related to novel drugs targeting *LRRK2* and *GBA1.*

Parkinson Disease

Parkinson Disease (PD) is a common neurodegenerative disorder that affects approximately 1% of the population over 60 years of age and 5% of the population over 85 years of age (Reeve, Simcox et al. 2014, Tysnes and Storstein 2017). Pathological hallmarks of PD include the progressive loss of dopaminergic (DA) neurons in the substantia nigra pars compacta and the accumulation of proteinaceous, alpha-synuclein-rich inclusions called Lewy bodies and neurites (Dehay, Bove et al. 2010). Clinical features involve motor symptoms such as bradykinesia, rigidity, tremor and posture and gait impairments, and non-motor symptoms encompassing autonomic dysfunction, cognitive and behavioural changes, olfactory dysfunction, sleep disturbances and fatigue (Schapira, Chaudhuri et al. 2017, Varadi 2020).

Genetic and possibly environmental factors determine the risk of developing PD. Several key biological pathways have been implicated, including the proteostasis network dysfunction (protein aggregation and intracellular protein and membrane trafficking), protein disposal by the ubiquitin-proteasome system (UPS), the autophagy-lysosomal pathway (ALP), synaptic structure, mitochondrial dysfunction and neuroinflammation (Balestrino and Schapira 2020). However, the exact pathogenic mechanisms underlying PD are unclear.

In the context of genetic risk factors, heterozygous mutations in the beta-glucocerebrosidase 1 gene (*GBA1*; OMIM 606463) encoding the lysosomal enzyme glucocerebrosidase (GCase) are the most common risk factor for PD (Sidransky, Nalls et al. 2009, Stoker, Camacho et al. 2020). *GBA1* variants are reported in around 5-15% of European PD patients and up to 25% in the Ashkenazi Jewish population (Zhang, Shu et al. 2018). *GBA1* variants may influence PD pathogenesis through multiple mechanisms: accumulation of misfolded GCase in the endoplasmic reticulum (ER) resulting in the dysfunction of the UPS and impaired protein degradation; accumulation of GCase substrates and lipid homeostasis disruption; impairment of the ALP (Menozzi and Schapira 2020).

Mutations in the leucine-rich repeat kinase 2 (*LRRK2*, OMIM 609007) gene are the most common cause of late-onset, autosomal dominant PD (Zimprich, Biskup et al. 2004). LRRK2 is a large, multidomain protein which is thought to play a role in several cellular processes, including mitochondrial function, signalling, synaptic function, immune inflammatory pathways and the ALP (Schapansky, Nardozzi et al. 2014, Roosen and Cookson 2016, Madureira, Connor-Robson et al. 2020). Recently, a subset of Ras-related in brain (Rab) guanosine triphosphatases (GTPases) have been identified as main phosphorylation substrates of LRRK2 (Roosen and Cookson 2016, Steger, Tonelli et al. 2016). Rab GTPases play key roles in intracellular vesicle trafficking (Eguchi, Kuwahara et al. 2018), and pathogenic mutations in *LRRK2* commonly enhance Rab GTPase phosphorylation.

Recent literature has highlighted the presence of an interaction between *GBA1* and *LRRK2.* The increased kinase activity that arises from *LRRK2* variants has been reported to reduce GCase activity levels (Fujiwara, Hasegawa et al. 2002, Ysselstein, Nguyen et al. 2019). Dried blood spots from PD patients carrying the LRRK2 mutation G2019S exhibit higher levels of GCase activity (Alcalay, Levy et al. 2015), and LRRK2-knockout mice show increased levels of ceramide in the brain, indicating a reduced level of ceramide metabolism as a result of reduced GCase activity (Ferrazza, Cogo et al. 2016). In contrast, constitutive LRRK2 kinase silencing in mice has been shown to increase GCase activity and impair macro- and chaperone-mediated autophagy (Albanese, Mercatelli et al. 2021). Therefore, there is currently not a clear consensus on the mechanisms by which LRRK2 may affect GCase activity. Thus, further understanding of the intersection of the LRRK2 and GBA1 pathways, in particular the role of Rab GTPases which may mediate the influence of LRRK2 on GCase, can provide important insights into the pathogenesis of two common genetic risks for PD.

In this review, we present the genetic, epidemiological and clinical features of PD patients carrying either *GBA1* and *LRRK2* variants, or compound mutation carriers, focussing on the mechanisms in which dysfunctional GCase and LRRK2 kinase activity influence PD pathobiology. We also explore the biological pathways that are thought to underlie the interplay between

these two genes, highlighting the ALP which is thought to be influenced by both genes, and discuss the therapeutic implications of these findings.

GBA1

Gene and protein

The human *GBA1* gene is located at the chromosomal region 1q21, consists of 11 exons and spans 7.6 kb in length (Horowitz, Wilder et al. 1989). A 5.7 kb untranslated *GBA1* pseudogene consisting of 11 exons is located 16 kb downstream (Horowitz, Wilder et al. 1989, Sorge, Gross et al. 1990). The Metaxin gene *MTX1* and its own pseudogene are also located in this region surrounding *GBA1* (Hruska, LaMarca et al. 2008).

The encoded GCase enzyme is responsible for the hydrolysis of the glycosphingolipid glucosylceramide into ceramide and glucose (Klein and Mazzulli 2018). GCase is normally synthesised on ER-bound polyribosomes and its entry into the ER is accompanied by leader peptide cleavage and N-linked glycosylation. When correctly folded, GCase exits the ER, is transported to the Golgi apparatus for further modifications, and then trafficked to the lysosomes with the aid of the receptor lysosomal integral membrane protein type-2 (LIMP-2) (Reczek, Schwake et al. 2007, Bendikov-Bar and Horowitz 2012).

GBA1 variants and Parkinson Disease: epidemiological and clinical features

Homozygous (bi-allelic) mutations in the *GBA1* gene cause the autosomal recessive lysosomal storage disorder Gaucher Disease (GD) (Hruska, LaMarca et al. 2008). Three clinical forms of GD have been identified – Type 1 is the most common form and is traditionally considered the only type in which patients do not routinely present primary neurological involvement. Types 2 and 3 are linked to neurological impairment of varying degrees and can result in fatality at a young age – in particular, Type 2 can present perinatally (Gupta, Oppenheim et al. 2011).

To date, over 300 pathogenic *GBA1* variants have been discovered, including point mutations, deletions, insertions, splice-site mutations and recombination events (Hruska, LaMarca et al. 2008). Most *GBA1* mutations are missense, resulting in reduced activity, possibly through structural changes (Do, McKinney et al. 2019). Misfolded GCase proteins that are unable to exit the ER undergo ER-associated degradation followed by translocation to the cytosol, where they undergo degradation in the UPS. The degree of ER-associated degradation and UPS-mediated

degradation has been proposed to contribute to the severity of GD and may ultimately explain the phenotypic heterogeneity of GD (Ron and Horowitz 2005). The most common GBA1 variant implicated in Type 1 GD and in the Ashkenazi Jewish population is the N370S missense mutation, whereas in Asians and Caucasians with no Ashkenazi Jewish ancestry, L444P is the most common (Grabowski and Horowitz 1997, Hruska, LaMarca et al. 2008).

Both heterozygous and homozygous *GBA1* variant carriers have an increased risk of developing PD, although the majority of *GBA1* variant carriers will not develop PD during their lifetime. In the heterozygous state, penetrance is age-dependent and is estimated to be around 5-10% by the age of 60, and 19-30% by the age of 80 (McNeill, Duran et al. 2012, Balestrino, Tunesi et al. 2020). Certain variants, for example L444P, are considered 'severe' and are therefore associated with a greater risk of developing PD and an earlier age at onset, whereas 'mild' variants, including N370S and R496H, are associated with a lower risk and a later age at onset (Gan-Or, Amshalom et al. 2015). *GBA1* variants not confirmed to cause GD in the homozygous state, such as E326K and T369M (Clark, Ross et al. 2007, Horowitz, Pasmanik-Chor et al. 2011, Duran, Mencacci et al. 2013), have also been reported as risk factors for PD (Alcalay, Levy et al. 2015).

Compared with non-carrier PD patients, patients carrying *GBA1* variants have been shown to have an earlier disease onset of 5 years, with a mean time to the development of dementia and postural instability of 5 and 2 years earlier, respectively (Gan-Or, Giladi et al. 2008, Mullin, Hughes et al. 2019, Stoker, Camacho et al. 2020). *GBA1*-PD patients also show stronger cognitive dysfunction and earlier mortality in comparison with non-carriers (Stoker, Camacho et al. 2020).

Other than PD, *GBA1* variants have also been associated with other neurodegenerative disorders, including multiple system atrophy (Mitsui, Matsukawa et al. 2015, Sklerov, Kang et al. 2017), although this remains inconclusive (Srulijes, Hauser et al. 2013), and dementia with Lewy bodies (Geiger, Ding et al. 2016).

Proposed mechanisms by which GCase dysfunction may mediate PD pathology

The mechanisms by which GCase dysfunction can influence PD pathogenesis has recently received much attention and although there appears to be a link between GD and PD, mechanistic insights remain unknown.

Alpha-synuclein is a small, presynaptic neuronal protein encoded by *SNCA* and is believed to play a role in synaptic-vesicle recycling (Murphy, Rueter et al. 2000). The degradation pathway of alpha-synuclein is still under debate, although it has been suggested to undergo degradation via the UPS under normal conditions *in vivo,* and via the ALP when in a pathogenic state (Webb, Ravikumar et al. 2003, Ebrahimi-Fakhari, Cantuti-Castelvetri et al. 2011, Stefanis, Emmanouilidou et al. 2019). Toxic oligomerisation of alpha-synuclein into pathogenic inclusions result from impaired degradation of the protein, leading to accumulation as well as generation of Lewy bodies that are associated with the death of DA neurons in various neurodegenerative disorders (Spillantini, Schmidt et al. 1997, Kim, Yun et al. 2018). The spread of alpha-synuclein aggregates within the brain in PD as disease progresses approximately correlates with the development of symptoms (Braak, Del Tredici et al. 2003), although it is debatable whether alpha-synuclein aggregation is a driver of PD or is a side effect of PD pathobiology. Nevertheless, rare, pathogenic mutations (point mutations or gene multiplications) in *SNCA* are a cause of familial and sporadic PD (Kasten and Klein 2013).

Most data appear to indicate a link between GCase dysfunction and alpha-synuclein accumulation (Gegg, Burke et al. 2012, Schapira and Gegg 2013) and this has been confirmed in some reports (Murphy, Gysbers et al. 2014) but not others (Parkkinen, Neumann et al. 2011). In cultured neurons, reduced GCase activity has been associated with a decreased rate of clearance of alpha-synuclein (Mazzulli, Xu et al. 2011) and increased toxic aggregation of insoluble alpha-synuclein fibrils in neuronal cultures (Kim, Yun et al. 2018, Gegg, Verona et al. 2020) and higher levels of monomeric alpha-synuclein in *GBA1*-deficient iPSCs (Yang, Gegg et al. 2020). 12-month-old mice that express the D409V knock-in allele (exhibiting significantly reduced GCase activity) display a subtle but statistically significant age-dependent increase of alpha-synuclein levels in the brain when compared with younger littermates (Cullen, Sardi et al. 2011). Interestingly, reduced GCase activity has been observed in PD brains of patients both with and without *GBA1*

mutations (Gegg, Burke et al. 2012). Similarly, low GCase activity has also been associated with increased levels of phosphorylated alpha-synuclein in the substantia nigra pars compacta of PD and Dementia with Lewy bodies patients with and without *GBA1* mutations (Gundner, Duran-Pacheco et al. 2019). This suggests that GCase activity may be involved in PD pathology beyond the pathogenicity of *GBA1* variants. On the other hand, it has also been shown that overexpression of alpha-synuclein may in fact inhibit lysosomal GCase trafficking and activity (Gegg, Burke et al. 2012), implying that there may be a bidirectional relationship between alpha-synuclein and GCase.

Alternatively, a different mechanism by which reduced GCase activity enhances neuronal susceptibility to pre-existing alpha-synuclein aggregation, but does not affect alpha-synuclein toxicity itself, has also been proposed (Henderson, Sedor et al. 2020). Furthermore, most homozygous and heterozygous *GBA1* mutation carriers do not develop PD – therefore, it is possible that reduced GCase activity is not the only factor leading to an increased risk of developing PD (Do, McKinney et al. 2019), and there may be multiple factors that regulate both GCase function and toxic alpha-synuclein aggregation. The idea that additional factors other than the reduction in GCase activity are responsible for the risk for PD comes from the observation that there is little if any difference in PD risk between bi-allelic and heterozygous *GBA1* variant carriers (Alcalay, Dinur et al. 2014).

Lipids have also been thought to modulate the propensity of alpha-synuclein aggregation. Patients with lysosomal storage disorders that arise from a mutation in lysosomal enzymes that metabolise lipids harbour an increased risk of developing PD (Robak, Jansen et al. 2017), and in those patients that develop PD, accumulation of lipids are associated with alpha-synuclein accumulation (Nelson, Tse et al. 2014, Smith, Santos et al. 2014). Lipid compositions of late endosome membranes, regulated by lysosomal enzymes such as GCase, may either impair alpha-synuclein degradation through altered endosomal micro-autophagy or trigger alpha-synuclein oligomerisation (Fecchio, Palazzi et al. 2018, Rivero-Ríos, Romo-Lozano et al. 2020). In lysosomes with reduced enzymatic activity, degradation of alpha-synuclein is also reduced (Klein and Mazzulli 2018). Glycosphingolipid-induced alpha-synuclein accumulation has also been found to

trigger cellular degeneration of human iPSC-derived midbrain neurons from patients with and without *GBA1* mutations, while glycosphingolipid-reducing agents reduces toxic alpha-synuclein assemblies in the neuronal cultures and improves synaptic localisation of alpha-synuclein (Zunke, Moise et al. 2018), further supporting a relationship between GCase and alpha-synuclein in PD.

GBA1 mutations are associated with loss of mitochondrial function which is observed in both PD and GD patients (Gegg and Schapira 2016). N370S and the frameshift mutation 84GG have been shown to cause prolonged mitochondria-lysosome contact, resulting in disrupted mitochondrial function and distribution (Kim, Wong et al. 2021). N370S has also been reported to lead to increased mitochondrial content and impaired mitochondrial turnover, possibly as a result of inhibited mitochondrial degradation via the ALP due to reduced GCase activity (Moren, Juarez-Flores et al. 2019). L444P is linked to impaired mitochondrial priming and autophagy and oxidative stress (Li, Ham et al. 2019). Impaired calcium homeostasis is also implicated in the drive of neurodegeneration in PD (Schapira 2013, Plotegher, Perocheau et al. 2020). For example, L444P has been shown to trigger increased levels of basal calcium in iPSC-derived DA neurons which is potentially linked to the increased susceptibility of *GBA1*-carrying DA neurons to cell death in PD (Schondorf, Aureli et al. 2014).

Genetic variations in LIMP-2 are associated with Lewy-body associated dementias, including PD (Do, Tung et al. 2011). LIMP-2 deficient mice show increased levels of alpha-synuclein accumulation in the brainstem, which results in inflammation and death of DA neurons (Zunke, Andresen et al. 2016). In these brains, protein levels of active GCase are significantly reduced relative to wild-type (WT), while mRNA levels remain unchanged, consistent with the knowledge that LIMP-2 and GCase protein trafficking is tightly linked. Furthermore, overexpression of LIMP-2 accelerates the intra-lysosomal clearance of alpha-synuclein by increasing GCase activity.

LRRK2

Gene and protein

Figure 1. LRRK2 domain structure and pathogenic mutations.
Catalytic domains, protein-protein interaction regions and most common pathogenic mutations are indicated. ANK, Ankyrin; ARM, Armadillo repeats; COR, C-terminal of ROC; LRR, Leucine-rich repeats; MAPKKK, kinase; ROC, Ras of complex; WD40, Trp-Asp-40 repeat.

LRRK2 is a large gene located at chromosome 12q12 consisting of 51 exons (Takanashi, Funayama et al. 2018). *LRRK2* encodes a multidomain protein of 2527 amino acids (figure 1) harbouring the MAPKKK kinase domain which catalyses phosphorylation of substrates such as Rab GTPases (Steger, Tonelli et al. 2016), the Ras of complex (ROC) GTPase domain which catalyses the hydrolysis of GTP-guanosine diphosphate (GDP), and the C-terminal of ROC (COR) which is thought to be involved in dimerization of LRRK2 (Guaitoli, Raimondi et al. 2016). Structural studies *in situ* have shown that the GTPase and kinase domains are located in close proximity to each other, suggesting possible interactions between the two that may influence kinase and GTPase activity (Watanabe, Buschauer et al. 2020). LRRK2 also contains protein-protein interaction domains, such as an armadillo repeat domain (ARM), an ankyrin repeat domain (ANK), a leucine-rich repeat domain (MAPKKK) and a Trp-Asp-40 (WD40) domain (Cookson 2010, Mills, Mulhern et al. 2012, Kuwahara, Inoue et al. 2016) which could be involved in modulating LRRK2 kinase activity (Guaitoli, Raimondi et al. 2016).

The LRRK2 protein is ubiquitously expressed in the brain, including in astrocytes and microglia (Henry, Aghamohammadzadeh et al. 2015), substantia nigra, kidneys, lungs (Biskup, Moore et al. 2007, Li, Tan et al. 2007, Gardet, Benita et al. 2010) as well as in peripheral immune cells (Maekawa, Kubo et al. 2010). In the cell, LRRK2 is predominantly distributed in the cytoplasm but about 10% is associated with the outer mitochondrial membrane (West, Moore et al. 2005). The broad range of cells and tissues that LRRK2 resides in highlights its variable roles in the body, but its precise physiological roles and how it influences PD pathology is still unclear.

LRRK2 variants and Parkinson Disease: epidemiological and clinical features

Over 50 different *LRRK2* variants have been associated with late-onset autosomal dominant PD (Lill, Roehr et al. 2012, Atashrazm and Dzamko 2016). The most prevalent *LRRK2* variant associated with PD is G2019S which resides in the kinase domain. In the UK, G2019S accounts for around 0.8% of familial PD and around 0.4% of sporadic PD (Tan, Malek et al. 2019). Worldwide, G2019S accounts for around 4% of all familial PD and around 1% of all sporadic PD cases (Haugarvoll, Rademakers et al. 2008, Healy, Falchi et al. 2008). Unlike other pathogenic *LRRK2*

variants illustrated in Figure 1, G2019S displays a reduced penetrance that increases with age (Goldwurm, Zini et al. 2007). Ethnicity is also thought to be important in penetrance. For example, penetrance of G2019S in the Ashkenazi Jewish population has been reported to be lower than in other populations (Marder, Wang et al. 2015). Other common variants include R1441G in the ROC domain which is most common in the Basque population (Simón-Sánchez, Martí-Massó et al. 2006), and G2385R in the WD40 domain which is most frequent in the Asian population (Ho, Jang et al. 2016). Patients carrying R1441G/C variants also reportedly have an earlier average age of symptom onset compared to patients carrying the G2019S (González-Fernández, Lezcano et al. 2007, Healy, Falchi et al. 2008).

Although there is no distinctive feature which has been described in association with *LRRK2*-PD patients, these individuals have been reported to exhibit lower levels of depression, anxiety, cognitive impairment and olfactory dysfunction compared with non-*LRRK2* PD patients and generally have milder motor progression (Kestenbaum and Alcalay 2017, Saunders-Pullman, Mirelman et al. 2018, Omer, Giladi et al. 2020)

Proposed mechanisms by which *LRRK2* variants mediate PD pathology

Independent studies in a variety of model systems have shown that LRRK2 influences late-stage endocytosis, lysosomal trafficking and synaptic vesicle endocytosis (Rivero-Ríos, Madero-Pérez et al. 2016, Connor-Robson, Booth et al. 2019). However, the direction in which LRRK2 variants affect the ALP are not completely understood (Wallings, Manzoni et al. 2015, Manzoni 2017).

G2019S lies in a conserved region that commences the activation loop which regulates LRRK2 kinase activity. A computational study showed that G2019S decreases the flexibility and increases the compactness of the kinase domain, allowing it to remain in an active conformation for a longer period of time (Agrahari, Doss et al. 2019) and thus increasing kinase activity and hyper-phosphorylation of substrates about two to three fold (Jaleel, Nichols et al. 2007). In primary mouse astrocytes, the pathogenic variants G2019S, R1441C and Y1699C reduce lysosomal capacity per cell and increased lysosome size (Henry, Aghamohammadzadeh et al.

2015) and G2019S reduces lysosomal pH, which is also thought to account for dysfunctional lysosomal enzymatic activity.

Familial mutations located in the ROC and COR domains, including R1441C/G and Y1699C, have been reported to reduce LRRK2-mediated GTP hydrolysis (Li, Tan et al. 2007, Daniels, Vancraenenbroeck et al. 2011, Liao, Wu et al. 2014). However, these mutations appear to only inconsistently increase kinase activity and, in some cases, only slightly modulate kinase activity (Greggio and Cookson 2009). It has been also suggested that the GTPase domain regulates the kinase domain through binding of GTP to ROC and may influence neuronal death in PD, although the mechanisms by which this occurs remain uncertain (Ito, Okai et al. 2007, Taymans, Vancraenenbroeck et al. 2011, Biosa, Trancikova et al. 2013).

There is also evidence that suggests pathogenic *LRRK2* variants may reduce the efficiency of alpha-synuclein clearance. A study in *Caenorhabditis elegans* showed that expression of wild-type LRRK2 protects DA neurons from the toxic effects of human alpha-synuclein (Yuan, Cao et al. 2011), while G2019S induces ER-stress in α-synuclein–treated brain astrocytes of mice (Lee, Han et al. 2019). Again, inhibition of G2019S-LRRK2 kinase has been reported to reduce alpha-synuclein inclusions and promote autolysosome formation and lysosomal activity (Obergasteiger, Frapporti et al. 2020). However, alpha-synuclein pathology is not always present in LRRK2-PD patients (Martí-Massó, Ruiz-Martínez et al. 2009, Kalia, Lang et al. 2015, Takanashi, Funayama et al. 2018). Additional pathology, for example tau, has also been reported in LRRK2 carriers (Henderson, Sengupta et al. 2019). It is therefore likely that *LRRK2* influences PD pathology through multiple pathways beyond the association with alpha-synuclein.

LRRK2 variants have also been linked with various mitochondrial alterations such as mitophagy, respiration and morphology (Macdonald, Barnes et al. 2018, Grunewald, Kumar et al. 2019). G2019S *LRRK2* has been associated with mitochondrial uncoupling in fibroblast and neuroblastoma cells (Papkovskaia, Chau et al. 2012). Distorted and aggregated mitochondria have been found in Lewy body formations in patients alongside lipids and lysosomal structures (Shahmoradian, Lewis et al. 2019), and mitochondrial dysfunction in the SN have been linked to

neuronal loss (Schapira, Cooper et al. 1989, Schapira, Cooper et al. 1990, Flones, Fernandez-Vizarra et al. 2018). LRRK2 has been implicated in the regulation of voltage-gated calcium channels (Bedford, Sears et al. 2016), and mouse cortical neurons expressing the LRRK2 G2019S or R1441C mutations demonstrate calcium buffering deficiencies, where excess cytosolic or mitochondrial calcium may trigger mitochondrial dysfunction as well as dendritic shortening (Cherra, Steer et al. 2013). Thus, *LRRK2* variants might modify normal mitochondrial function and calcium homeostasis that underlie PD pathology, warranting further investigation.

Rab GTPases are key mediators of LRRK2 activity

Figure 2. Schematics of LRRK2 and Rab GTPases interactions that may underlie PD pathology.
Rab29 recruits LRRK2 to the *trans*-Golgi apparatus, triggering downstream phosphorylation events including the phosphorylation and deactivation of Rab29 itself – LRRK2 is thought to influence its own activity in this way. Rab10 has been implicated in influencing GCase enzymatic activity – phosphorylation of Rab10 by LRRK2 has been shown to decrease GCase activity without altering GCase protein levels. Rab35 has also been associated with alpha-synuclein propagation. Some studies have suggested that alpha-synuclein accumulation inhibits the lysosomal trafficking of GCase, while others suggest that decreased GCase activity triggers alpha-synuclein accumulation, implying that there may be a bi-directional relationship between GCase activity and alpha-synuclein. Activation of Rab7 by LRRK2 is thought to be mediated through Rab8, and Rab7 and Rab8 have both been implicated in endolysosomal trafficking and the ALP. It is possible that Rab7 and Rab8 may both influence alpha-synuclein degradation – there has also been evidence to suggest Rab8 may influence lipid storage and alpha-synuclein aggregation.

Rab GTPases are critical regulators of vesicular trafficking, including the endocytosis of extracellular material and autophagy of intracellular components (Eguchi, Kuwahara et al. 2018). For example, early endosomes are marked by RAB5 while late endosomes are marked by RAB7 (Poteryaev, Datta et al. 2010). The recent discovery of Rab GTPases as LRRK2 substrates highlights LRRK2's involvement in lysosomal function (Roosen and Cookson 2016, Steger, Tonelli et al. 2016). Systematic proteomic analysis of LRRK2 has shown that RAB1, RAB3, RAB5, RAB8, RAB10, RAB12, RAB29 (also known as RAB7L1), RAB35 and RAB43 can all be phosphorylation substrates of LRRK2, with some phosphorylated at least upon LRRK2 overexpression (Steger, Diez et al. 2017). Figure 2 illustrates interactions between LRRK2 and Rab GTPase substrates and how these might underlie PD pathology. Proposed interactions between LRRK2 protein and GCase, which might play a role in PD pathogenesis, will be thoroughly presented later in this review.

RAB29 recruits LRRK2 to the *trans*-Golgi network and activates kinase activity

The gene encoding RAB29 resides in the *PARK16* locus which is associated with increased risk of developing PD (Tucci, Nalls et al. 2010, Lill, Roehr et al. 2012). It is thought that RAB29 recruits LRRK2 to the *trans*-Golgi network to activate LRRK2 kinase activity, leading to phosphorylation of

other Rab GTPases such as RAB8, RAB10 and RAB12 (Liu, Bryant et al. 2018, Purlyte, Dhekne et al. 2018). R1441G/C and Y1699C LRRK2 mutants enhance GTP binding to the ROC domain and are more readily recruited to the Golgi and activated by RAB29 than wild-type LRRK2 (Purlyte, Dhekne et al. 2018).

Knockdown of RAB29 in rat primary neurons results in lysosomal defects, such as lysosomal enlargement and deficiency of the lysosomal mannose 6-phosphate receptor (which is required to recruit lysosomal hydrolases), pathological effects similarly seen in G2019S-carrying neurons (MacLeod, Rhinn et al. 2013). Overexpression of RAB29 supresses lysosomal abnormalities in G2019S mutant neurons. However, knockout of both *LRRK2* and RAB29 in mice does not result in behavioural changes (Mazza, Nguyen et al. 2020), and neither knockout nor overexpression of RAB29 affect basal phosphorylation of RAB10 and RAB12 by LRRK2 kinase *in vivo* (Kalogeropulou, Freemantle et al. 2020). This suggests that RAB29 is not a mediator of basal or pathogenic LRRK2 phosphorylation activity. However, there is a possibility that RAB29 can influence LRRK2-mediated phosphorylation of other Rab GTPases, and it is also likely there are other currently uncharacterised proteins that can interact with LRRK2 and regulate its activity.

LRRK2 may influence downstream RAB7 activity through RAB8

RAB7 is thought to be crucial in lysosomal positioning, function and reformation, as well as autophagosome maturation and trafficking of some signalling receptors (Jäger, Bucci et al. 2004, Ceresa and Bahr 2006, Rojas, van Vlijmen et al. 2008, Yu, McPhee et al. 2010, Guerra and Bucci 2016). Gómez-Suaga et al reported that overexpression of pathogenic LRRK2 in *LRRK2*-mutant cells and fibroblasts from G2019S-*LRRK2*-PD patients decreased RAB7 activity, resulting in impaired degradation of the epidermal growth factor receptor (EGFR) through delayed endosomal trafficking. This was reversed upon LRRK2 kinase inhibition and overexpression of RAB7 (Gómez-Suaga, Rivero-Ríos et al. 2014).

RAB7 does not appear to be a direct phosphorylation substrate of LRRK2 (Steger, Tonelli et al. 2016, Steger, Diez et al. 2017) and RAB7 levels in G2019S-*LRRK2*-PD patients do not differ from non-carriers (Gómez-Suaga, Rivero-Ríos et al. 2014). Therefore, RAB7 activity may be influenced

by LRRK2 via other Rab proteins. One mechanism in which this could occur is via RAB8. RAB8 has been implicated in endolysosomal trafficking (Braun, Hendrick et al. 2015), and interacts with rabin8 to trigger subsequent downstream vesicular trafficking events (Westlake, Baye et al. 2011). Expression of active RAB8 or upregulation of the RAB11-rabin8 cascade rescues deficits in endolysosomal membrane trafficking mediated by G2019S-LRRK2 (Rivero-Ríos, Romo-Lozano et al. 2019). Conversely, loss of RAB8 mimics deficits in endolysosomal function and impairs EGFR degradation, effects similar to those from reducing RAB7 activity. Loss of RAB8 also reduces RAB7 activity, suggesting a relationship between the two, as well as implying RAB7 activity to be downstream from RAB8.

LRRK2 can act through RAB35 and RAB8 to influence alpha-synuclein propagation

RAB35 is a LRRK2 substrate that is localised on the plasma membrane and endocytic compartments to control endocytic recycling (Kouranti, Sachse et al. 2006). A study on cell culture, nematode and murine models of G2019S-LRRK2-PD reported that increased LRRK2 kinase activity enhanced propagation of alpha-synuclein, mediated through LRRK2 phosphorylation of RAB35 (Bae, Kim et al. 2018). In the same study, functional inhibition of LRRK2 to reduce kinase activity reduced levels of both RAB35 and alpha-synuclein. However, the direction in which LRRK2 affects RAB35 levels is unclear – for example, it is possible that the reduction in RAB35 levels is due to increased RAB35 degradation upon LRRK2 inhibition. It is also equally as likely that LRRK2 inhibition reduces RAB35 synthesis.

RAB8 has also been suggested to promote the storage of lipids and lipid droplets (Yu, Arshad et al. 2018). As previously discussed, lipid composition may influence alpha-synuclein aggregation. Therefore, there is a possibility that increased LRRK2 kinase activity results in hyper-phosphorylation of Rab substrates to modify lipid composition, inhibit lipid storage and influence alpha-synucleinopathy and PD pathogenesis.

***GBA1* and *LRRK2* crosstalk in Parkinson Disease: From Bed to Bench**

Recent evidence has suggested an interaction between *GBA1* and *LRRK2* in PD. From a clinical perspective, patients carrying both a *GBA1* variant and G2019S-*LRRK2* present a higher risk of developing PD and a non-significant trend towards an earlier age of symptom onset compared to

patients carrying just one mutation in either gene or sporadic PD patients (Yahalom, Greenbaum et al. 2019, Ysselstein, Nguyen et al. 2019). Patients carrying mutations in both genes have also been reported to be phenotypically similar to *LRRK2*-PD patients and show milder motor symptoms and olfactory dysfunction when compared to *GBA1*-PD patients, as well as lower depression when compared to sporadic PD and *GBA1*-PD patients (Omer, Giladi et al. 2020, Ortega, Wang et al. 2021). This might suggest a possible protective effect of *LRRK2* on *GBA1* mutants which may result in a milder PD phenotype, despite the apparent increased risk. However, it may also argue that compound variant carriers may only exhibit the more dominant *LRRK2*-associated PD symptoms due to the variable penetrance of *GBA1* mutations.

At a biochemical level, gain-of-function *LRRK2* variants, such as G2019S, R1441C or R1441G, have been shown to reduce lysosomal GCase activity in DA neurons (Fujiwara, Hasegawa et al. 2002, Ysselstein, Nguyen et al. 2019), which is somehow unexpected given the milder phenotype observed in patients carrying compound variants. Correction of the point mutations G2019S and R1441C with CRISPR/Cas9, as well as LRRK2 kinase inhibition, reverses the GCase loss-of-activity to a level similarly seen in controls. Inhibition of LRRK2 also rescues other PD-related phenotypes such as reducing accumulated DA oxidation products and phospho-Ser129 alpha-synuclein, which is a major component of aggregated alpha synuclein. In addition, LRRK2 activity has been shown to affect cytokine production. *GBA1* mutant astrocytes showed a reduction in the expression of several pro-inflammatory cytokines compared to controls. Upon LRRK2 kinase inhibition, lysosomal dysfunction in astrocytes was normalised and cytokine production partially restored (Sanyal, DeAndrade et al. 2020). However, as mentioned earlier, Alcalay et al reported that G2019S increases GCase activity in dried blood spots. Taken together, these studies indicate that the interplay between *GBA1* and *LRRK2* in PD is complex and may also influence PD pathogenesis beyond the functionality of GCase and LRRK2 proteins. By impacting on other systems, such as the immune system, the biochemical effects of compound variants, indeed, warrant further investigation.

LRRK2 phosphorylates RAB10 to influence GCase activity

LRRK2 kinase has been reported to phosphorylate and deactivate RAB10 function by preventing binding to Rab guanosine diphosphate- (GDP) dissociation inhibitor factors, inhibiting membrane delivery and recycling (Di Maio, Hoffman et al. 2018). Ysselstein et al recently reported a 50% increase in phosphorylated RAB10 in G2019S-*LRRK2* gain-of-function PD patients relative to non-carriers (Ysselstein, Nguyen et al. 2019). They also reported that knock-down of RAB10 reduced GCase activity while overexpression of RAB10 raised GCase activity. Interestingly, this did not alter GCase protein levels. Inhibition of LRRK2 kinase using MLi-2 was also shown to reduce levels of phosphorylated RAB10 but again did not affect GCase protein levels. Together, this might suggest LRRK2 does not influence GCase activity through altering GCase protein expression but via a different pathway, possibly mediated through RAB10. However, it must be noted that the level of GCase protein were measured from the total lysate and not from the lysosomes, so any unmeasured changes in the lysosomes could have still accounted for the altered GCase activity.

Furthermore, Ysselstein also showed that knockdown of wild-type LRRK2 in DA neurons reduced RAB10 protein levels as well as GCase activity, implying that the influence of LRRK2 on RAB10 protein levels may be via a kinase-independent mechanism. For example, it has been suggested that LRRK2 interacts with RAB10 through increased molecular proximity rather than kinase activity (Kuwahara, Funakawa et al. 2020). However, Ysselstein also showed that the G2019S mutation, residing in the kinase domain, raised RAB10 levels. Therefore, the direct relationship between LRRK2 and RAB10 is still unclear. GCase deficiency was reported to reduce levels of phosphorylated RAB10, suggesting GCase activity may influence LRRK2 kinase activity. Further studies that demonstrate interactions between RAB10 and GCase will be required.

Implications of Rab GTPases in PD pathology: a summary

These studies have emphasised the importance of Rab proteins in lysosome exocytosis and the maintenance of lysosomal homeostasis, as well as highlighted connections between LRRK2 and Rab GTPases. These findings have also hinted at possible pathways in which gain-of-function LRRK2 mutations might facilitate PD pathology.

Phosphorylation of RAB8 and RAB10 leads to their inactivation (Steger, Tonelli et al. 2016, Di Maio, Hoffman et al. 2018) – if this assumed for all Rab GTPases, we can hypothesise that hyperphosphorylation of Rab GTPases by LRRK2 inhibits Rab activity, causing endolysosomal deficits that could result in impaired degradation and accumulation of alpha-synuclein, analogous to the degradation deficits of EGFR as mentioned earlier. Alpha-synuclein accumulation can then impair GCase activity by inhibition of intracellular trafficking of the protein. It is however still unclear whether altered GCase function influences alpha-synuclein degradation (Sanyal, DeAndrade et al. 2020). It is also possible that GCase deficiencies in lysosomes may result in lysosomal stress that triggers increased RAB10 phosphorylation by LRRK2 kinase via a separate pathway. These proposed series of events may give rise lysosomal defects, dysregulation of alpha-synuclein homeostasis, mitochondrial and calcium signalling dysfunction and DA neuronal death in PD pathology.

The influence of LRRK2 on alpha-synuclein aggregation through RAB8 and the lipid pathway is also an interesting area to research in the context of *LRRK2-GBA1* interplay. The future of lipidomics could provide crucial insight into possible relationships between *GBA1* and *LRRK2*, as well as their individual involvement in PD in the context of lipids, in the road to recognising novel therapeutic targets and biomarkers for early disease detection.

It must also be noted that, as previously discussed, alpha-synuclein pathology is not always present in LRRK2-PD subjects. This suggests that there are multiple pathways by which LRRK2 may act in PD.

GBA1, LRRK2 and Rab GTPases in the diagnostic and therapeutic strategies of PD

Most of the research on LRRK2 kinase inhibition as a form of PD treatment has been conducted primarily on cell culture models and transgenic rodent models, but results have been promising. First generation inhibitors such as staurosporine and sunitinib have been demonstrated to inhibit LRRK2 kinase activity, although non-specifically (Deng, Dzamko et al. 2011). Second generation compounds are more selective and yield promising results *in vivo*, but LRRK2 inhibition in the brain was found to be limited (Estrada, Chan et al. 2014, Saez-Atienzar, Bonet-Ponce et al. 2014).

Newer compounds that are highly selective, potent and have high penetrance through the brain are currently in clinical development, such as the inhibitor DNL151 (ClinicalTrials.gov Identifier: NCT04056689 and NCT04557800). In addition, compounds such as LRRK2 inhibitors that target LRRK2 kinase could also be trialled in PD patients carrying *GBA1* mutations to determine if they could rescue the effects of GCase deficiency and potentially halt or even reverse pathologies such as alpha-synuclein aggregation, mitochondrial and lysosomal dysfunction and calcium dyshomeostasis. However, the G2019S variant has been reported to be more resilient towards kinase inhibition compared with the WT variant, posing another challenge for drug development (Kelly, Wang et al. 2018).

The discovery of Rab GTPases as direct LRRK2 substrates not only allows scientists to get a clearer understanding of the physiological roles of LRRK2 but also provides opportunities to develop novel research tools in PD. Monoclonal antibodies designed to specifically detect RAB10 phosphorylation by LRRK2 in a variety of cells are already in development (Lis, Burel et al. 2018), and antibodies displaying broad sensitivity to a variety of Rab GTPases, including RAB8A and RAB10, have also been identified. These antibodies could be deployed in both basic and clinical settings. For example, phosphorylated GTPases could serve as clinical markers to understand the effectiveness of drugs, such as LRRK2 inhibitors, on PD patients. Monoclonal antibodies could also be used to detect Rab phosphorylation levels resulting from different pathogenic *LRRK2* variants. In addition, as previously mentioned, overexpression of functional, dephosphorylated RAB8 has also been shown to reverse trafficking deficits associated with G2019S, and overexpression of RAB10 appears to also rescue GCase activity deficits. This suggests possible targeting of certain Rab GTPases in PD patients, although this has not yet been readily explored. Nonetheless, the implications of Rab GTPases in therapeutic intervention are still unclear as its molecular mechanisms that underlie PD remain elusive.

GCase replacement therapy and substrate reduction therapy have both been successful for GD patients but have not yet yielded an improvement in reversing neurological deficits (Stirnemann, Belmatoug et al. 2017). A trial of the substrate inhibitor venglustat showed no benefit in delaying motor progression in *GBA1*-PD (ClinicalTrials.gov Identifier: NCT02906020). Nonetheless, genetic

screening could help identify effective treatments for patients carrying GBA1 variants. For example, in patients carrying variants that are known to affect GCase stability and function, such as N370S and L444P, (Thirumal Kumar, Eldous et al. 2018, Thirumal Kumar, Iyer et al. 2019), chemical chaperones may be able to stabilise GCase and enhance its trafficking from the ER to increase its activity (Sawkar, Cheng et al. 2002). A GCase chaperone, ambroxol, has also been found to increase GCase activity in the brain of mice (Migdalska-Richards, Daly et al. 2016) and non-human primates (Migdalska-Richards, Ko et al. 2017), and has also been shown to increase alpha-synuclein levels in the cerebral spinal fluid of PD patients with and without *GBA1* mutations (ClinicalTrials.gov Identifier: NCT02941822). Therefore, ambroxol has potential to be a neuroprotective compound in PD patients (Mullin, Smith et al. 2020). Evidence of any influence of *GBA1* on *LRRK2* are currently limited and must be further explored to identify any potential effects of chemical chaperones and other drugs that target *GBA1* on LRRK2 kinase and GTPase activity.

Future perspectives

Both *GBA1* and *LRRK2* have been reported to influence PD pathology, and this review has focussed on the mechanisms by with both genes can alter alpha-synuclein homeostasis via Rab GTPases and the lysosomal pathway. Other possibilities in which the genes could act on alpha-synuclein in PD is through lipid storage and composition and the mitochondria. Current data suggest that, within the Rab GTPase family, RAB10 may be the most likely mediator of *LRRK2-GBA1* interaction in PD, but additional research must be conducted to confirm its relationship with *GBA1*, *LRRK2* and alpha-synuclein homeostasis. However, there may be some form of redundancy between the Rab GTPases, where more than one Rab protein could perform the same role. Further research on the influence of LRRK2 on GCase activity, as well as GCase activity on LRRK2 phosphorylation and possibly even GTPase activity, and ultimately how these mechanisms translate to clinic, are also required.

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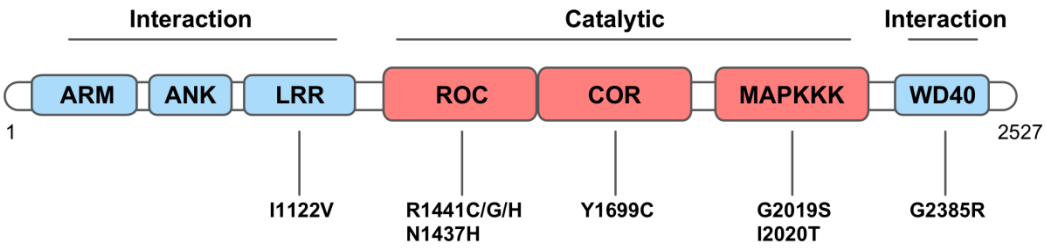

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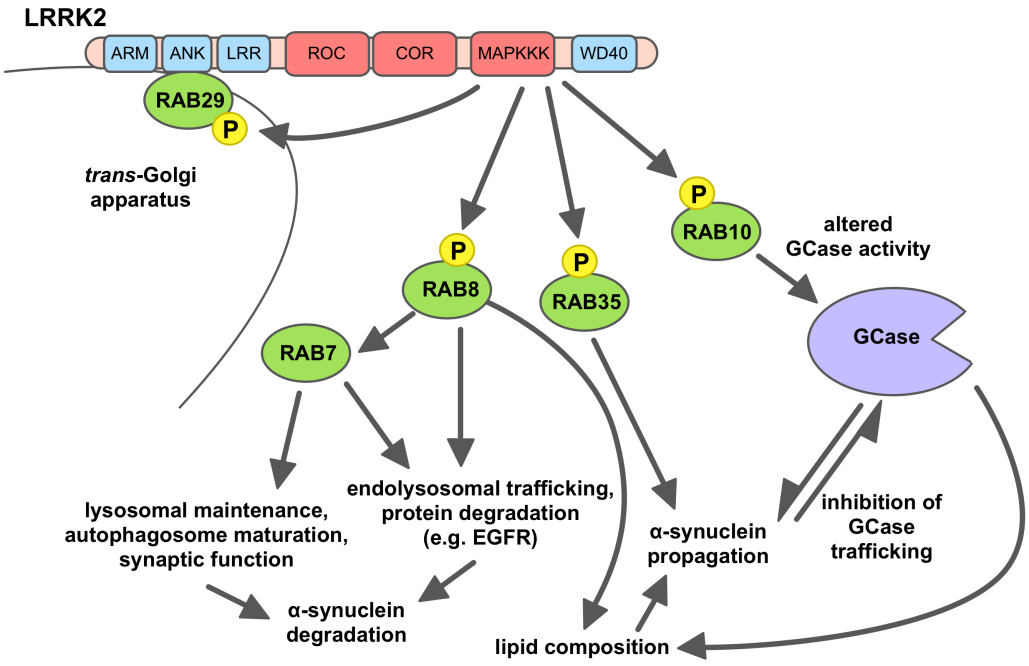

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