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Genetic perspective on the role of the autophagy-lysosome pathway in Parkinson disease

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Abbreviations: ALP, autophagy-lysosome pathway; ATP, adenosine triphosphate; ATG5, autophagy-related 5; ATG7, autophagy-related 7; ATP6AP2, ATPase, H^+ transporting, lysosomal accessory protein 2; ATP13A2, ATPase type 13A2; CMA, chaperone-mediated autophagy; DNA, DNA, DNAJC13, DnaJ (Hsp40) homolog, subfamily C, member 13; FBXO7, F-box protein 7; FBXW7, F-box and WD repeat domain containing 7, E3 ubiquitin protein ligase; GAK, cyclin G associated kinase; GBA, glucosidase, β, acid; GD, Gaucher disease; GLA, galactosidase, α; GPNMB, glycoprotein (transmembrane) nmb; GSK3A, glycogen synthase kinase 3 α; GWAS, genome-wide association study; LAMP2, lysosomal-associated membrane protein 2; LAMP3, lysosomal-associated membrane protein 3; LRRK2, leucine-rich repeat kinase 2; MAPT, microtubule-associated protein tau; MCCC1, methylcrotonoyl-CoA carboxylase 1 (α); MEF2D, myocyte enhancer factor 2D; MFN1, mitofusin 1; MFN2, mitofusin 2; M6PR, mannose 6-phosphate receptor (cation dependent); mRMA, messenger ribonucleic acid; NPC1, Niemann-Pick disease, type C1; NPC2, Niemann-Pick disease, type C2; NUCKS1, nuclear casein kinase and cyclin-dependent kinase substrate 1; PARK2, parkin RBR E3 ubiquitin protein ligase; PARK7, parkinson protein 7; PARK16, Parkinson disease 16 (susceptibility); PINK1, PTEN induced putative kinase 1; PM20D1, peptidase M20 domain containing 1; RAB29, RAB29, member RAS oncogene family; RNAi, RNA interference; SCARB2, scavenger receptor class B, member 2; SLC41A1, solute carrier family 41 (magnesium transporter), member 1; SLC45A3, solute carrier family 45, member 3; SMPD1, sphingomyelin phosphodiesterase 1, acid lysosomal; SN, substantia nigra; SNCA, synuclein, α (non A4 component of amyloid precursor); SQSTM1, sequestosome 1; SREBF1, sterol regulatory element binding transcription factor 1; SREBF2, sterol regulatory element binding transcription factor 2; SYNJ1, synaptojanin 1; TFEB, transcription factor EB; TMEM175, transmembrane protein 175; UCHL1, ubiquitin carboxyl-terminal esterase L1 (ubiquitin thiolesterase); UPS, ubiquitin-proteasome system; VCP, valosin containing protein; VPS35, VPS35 retromer complex component); WASH1, WAS protein family homolog 1.

Parkinson disease (PD), once considered as a prototype of a sporadic disease, is now known to be considerably affected by various genetic factors, which interact with environmental factors and the normal process of aging, leading to PD. Large studies determined that the hereditary component of PD is at least 27%, and in some populations, single genetic factors are responsible for more than 33% of PD patients. Interestingly, many of these genetic factors, such as *LRRK2*, *GBA*, *SMPD1*, *SNCA*, *PARK2*, *PINK1*, *PARK7*, *SCARB2*, and others, are involved in the autophagy-lysosome pathway (ALP). Some of these genes encode lysosomal enzymes, whereas others correspond to proteins that are involved in transport to the lysosome, mitophagy, or other autophagic-related functions. Is it possible that all these factors converge into a single pathway that causes PD? In this review, we will discuss these genetic findings and the role of the ALP in the pathogenesis of PD and will try to answer this question. We will suggest a novel hypothesis for the pathogenic mechanism of PD that involves the lysosome and the different autophagy pathways.

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Introduction

Parkinson disease (PD) is a common, age-related, neurodegenerative movement disorder, characterized by degeneration of dopaminergic neurons at the substantia nigra pars compacta, and accumulation of the SNCA protein within aggregates termed Lewy-Bodies.[1] The lifetime risk for PD is 1–2%,[2] with various environmental and genetic factors that affect PD susceptibility.[1]

For the past 2 decades, major advancements have been made in the understanding of the genetic basis of PD, transforming our notion of PD as a sporadic disease in which "it appears unlikely that heredity is an important determinant"[3] into a disorder largely affected by genetics. Studies that aimed to determine the role of heredity in PD, suggested that at least 27% and up to 60% is attributed to genetic factors.[4-6] With the development of new genetic methods, we now know of numerous genes and genetic loci that cause or affect the risk for PD.

Recently, the largest genetic study of PD thus far—a large scale meta-analysis of genome-wide association studies (GWAS), analyzed data from more than 19,000 PD patients and over 100,000 controls—identified 24 genetic loci across the genome that are associated with PD.[7] Most of these genetic markers were identified in previous large GWASs,[4,8-13] and 6 of them were

novel. Interestingly, out of these 24 loci, at least 11 genes are involved in or disrupt various functions of the autophagy-lysosome pathway (ALP), namely *SNCA*,[14] *GBA*,[15,16] *LRRK2*,[17,18] *SCARB2*,[19,20] *LAMP3*,[21] *RAB29/RAB7L1*,[17,22,23], *MAPT*,[24-26] *GAK*,[27,28], *SREBF1*,[29] *GPNMB*,[30,31] and potentially *TMEM175*.[32]

Prior to and during the GWAS era, the study of familial parkinsonism and candidate gene approaches in clinical settings, led to the discovery of additional genes that cause PD or parkinsonian syndromes. The first gene that was identified was *SNCA* (synuclein, α [non A4 component of amyloid precursor]), in an Italian family with PD,[33] followed by the identification of the *PARK2*,[34] *PINK1*[35] and *PARK7/DJ-1*[36] genes in young onset recessively inherited PD. Additional autosomal recessive mutations that lead to atypical parkinsonism syndromes were identified in the genes *ATP13A2*,[37] *ATP6AP2*,[38] and *SYNJ1*,[39,40] and mutations in *DNAJC13* were suggested to cause autosomal dominant familial PD.[41] Disease-causing mutations with reduced penetrance were also identified in familial settings and cohort studies in the *LRRK2*[42-45] and *GBA*[46] genes, which are now recognized as the 2 most common genetic causes of PD worldwide. More recently, mutations in the *VPS35*[47,48] and *SMPD1*[49,50] genes were also suggested to cause PD. All of these genes are also involved in various functions of the ALP.

The importance of the ALP in neuroprotection and neurodegeneration in general is well established.[51] For example, ATG5 and ATG7, 2 important proteins in the ALP,[52,53] are crucial for neuronal maintenance. Deficiency of ATG5 in mice leads to motor function deficiency and accumulation of neuronal inclusion bodies.[54] Similarly, mice with selective ATG7 deficiency in the central nervous system have motor impairment, severe neurodegeneration, and formation of inclusion bodies from polyubiquitinated proteins.[55] Whole-brain ATG7 deficiency results in accumulation of the PD-related proteins SNCA and LRRK2.[56] *SQSTM1*/p62 also plays a central role in autophagy and may be involved in neurodegeneration.[57-59] However, it is still not clear if the *ATG5*, *ATG7* and *SQSTM1* genes have a direct role in PD in humans, as no mutations or genetic risk markers have been found in these genes in PD patients.

In this review we will discuss the findings in human genetic studies and their suggested roles in the ALP and in PD pathogenesis (**Fig. 1**). We will attempt to answer the question of whether these genes are involved in a specific ALP-related function that may lead to PD, or whether it is more probable that several ALP-related functions are involved. We will conclude by suggesting a novel hypothesis for one possible mechanism by which ALP dysfunction may lead to PD.

The Autophagy-Lysosome Pathway

Autophagy is a cellular degradation pathway involved in various processes in normal and diseased cells. The normal function of the ALP involves the transfer of various components into the lysosome for degradation, by 3 main pathways: chaperone-mediated autophagy (CMA), microautophagy, and macroautophagy (**Fig. 1**).[51] CMA involves chaperone proteins that bind and direct specific targets (e.g., SNCA) to receptors on the lysosomal membrane (e.g., LAMP2A, to be discussed later), which in turn internalize these targets into the lysosome for degradation. Microautophagy is the engulfment and internalization of cytoplasmic components by the lysosomal membrane, a relatively less studied mechanism. Macroautophagy is a complex mechanism, characterized by the creation of a phagophore, a double-lipid bilayer that engulfs cellular cargo, such as proteins and organelles, to create an autophagosome, which in turn fuses with the lysosome for the degradation of its content.[51] This process includes mitophagy, the selective degradation of mitochondria via a pathway involving specific signals.[60]

Genes Involved in Lysosomal Storage Disorders and Parkinson Disease

GBA—Gaucher disease

Mutations in the *GBA* gene may lead to the autosomal recessive Gaucher disease (GD) when inherited from both parents. GD is a lysosomal storage disorder that can be further classified into neuropathic (GD type II or III) or non-neuropathic (GD type I). In GD, the lysosomal enzyme encoded by the *GBA* gene, glucosidase β, acid/glucocerebrosidase, has a reduced or null activity, which leads to accumulation of glucocerebroside and lysosomal dysfunction. Thus far, approximately 300 *GBA* mutations have been described, including missense, frame-shift, splice-sites, and stop mutations, as well as recombinant alleles caused by recombination with the nearby and highly homologous pseudogene.[61] The association between *GBA* mutations and PD was first suggested after several clinical reports described GD patients who developed PD.[62] Although initially this association was controversial,[63,64] it is now clear that *GBA* mutations are among the most common genetic factors for PD worldwide, found in about 3–20% of the patients in various populations, most common among Ashkenazi-Jews, but also found in Asians, Europeans, North and South Americans, and Africans.[46,65] The classification of *GBA* mutations as "severe" or "mild" according to the type of GD that they lead to (severe mutations lead to the neuropathic GD types and mild mutations lead to the non-neuropathic type),[66] is also valid for PD, as carriers of severe *GBA* mutations have higher risk and earlier onset compared to mild *GBA* mutation carriers.[67]

It is still unclear how *GBA* mutations lead to PD, and several hypotheses have been raised, including mechanisms involving loss-of-function or gain-of-function mutations.[68] First, it was demonstrated that chemical inhibition of GBA can lead to accumulation of SNCA,[69] a finding that was later replicated in other models with *GBA* mutations.[70-73] In brains of PD patients without *GBA* mutations, reduction of GBA enzymatic activity is associated with increased SNCA.[74] It was also demonstrated that *GBA* dysfunction leads to increased cell-to-cell transmission of SNCA.[75] A possible mechanism suggested to explain the accumulation of SNCA and PD development is a positive feedback loop, in which *GBA* depletion increases SNCA accumulation, which in turn inhibits

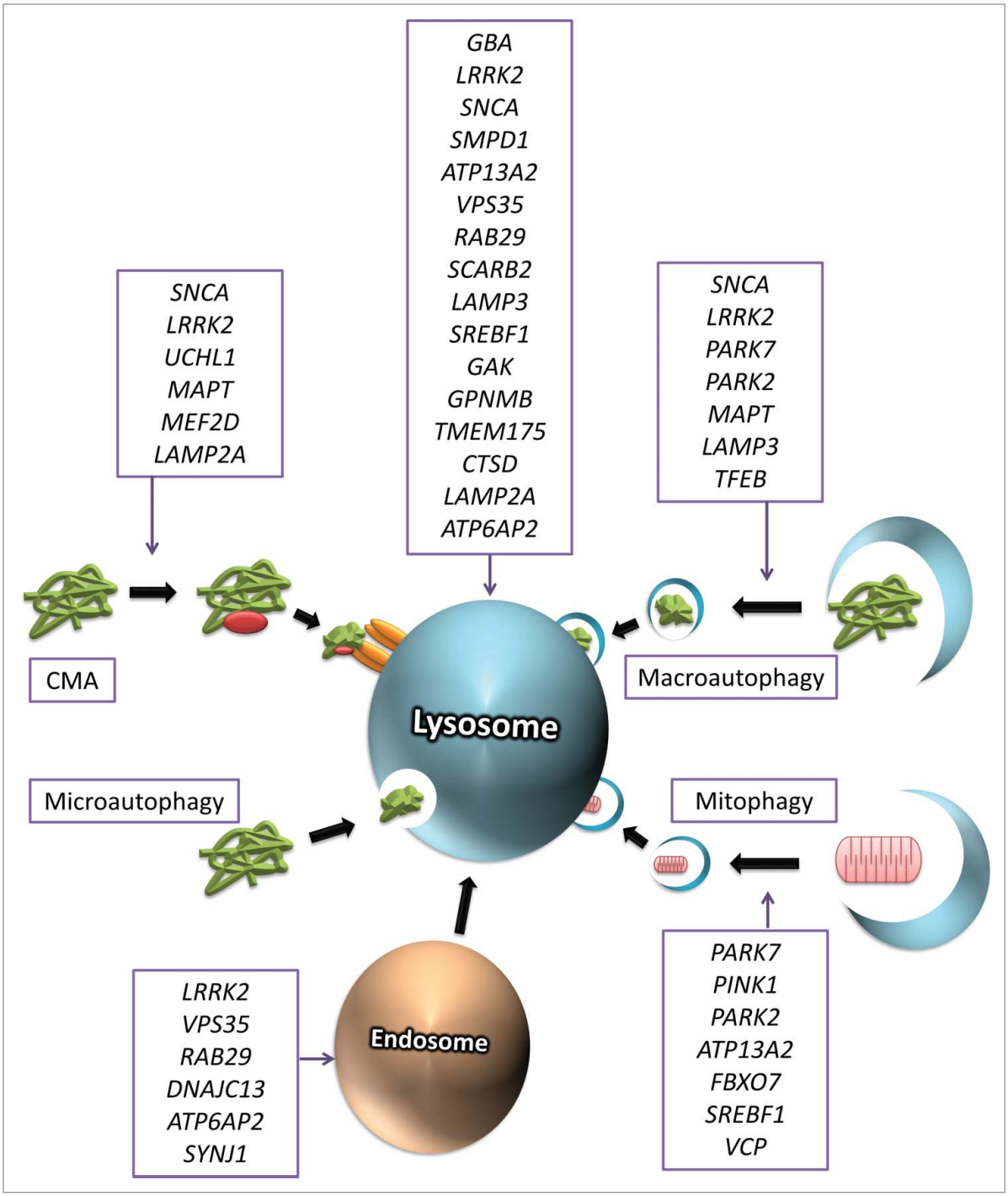

Figure 1. Genes involved in Parkinson disease and in the autophagy-lysosome pathway. **Figure 1** depicts genes that are associated with Parkinson disease and their area of effect in the autophagy lysosome pathway. Genes that are also involved in any lysosomal function that is not one of the forms of autophagy are depicted above the lysosome.

the function of normal GBA, causing additional aggregation of SNCA.[71] Alternatively, toxic gain-of-function mechanisms were suggested,[68,76] for example by causing ER stress.[76] However, GBA toxic gain of function, although it can contribute to PD development, is less likely to have an essential role in the disease development. This can be explained by the fact that null *GBA* mutations, which result in lack of expression of GBA, also cause PD.[67] Hence, if no protein is produced, it cannot cause a toxic effect, and loss of function is more likely to be the cause of increased susceptibility for PD.

Several studies have also suggested that *GBA* dysfunction may lead to general lysosomal dysfunction and disruption of

autophagy.[74,75,77] Moreover, it was suggested that in PD patients without *GBA* mutations, there is a reduced function of GBA. For example, a study on brains of PD patients with wild-type *GBA*, the GBA levels and its enzymatic activity were reduced, which led to reduced lysosomal chaperone-mediated autophagy, increased SNCA levels and reduced ceramide levels.[74] This observation implies that factors other than *GBA* mutations, whether genetic or environmental, can affect the activity of GBA. Identifying these factors could be of great importance for the understanding of PD pathogenesis. In a cellular model with *GBA* null mutations, there is a general lysosomal impairment, demonstrated by the accumulation of SQSTM1 and polyubiquitinated proteins, as well as increased LysoTracker-positive structures, reduced degradation of dextran and accumulation of vacuoles.[75]

Interestingly, one of the genes that is repeatedly implicated in GWASs, the *SCARB2* gene, associated with a 10–20% reduced risk for PD ($p < 8 \times 10^{-10}$).[4,7] *SCARB2* encodes the scavenger receptor class B, member 2, which is responsible for the transport of GBA to the lysosome.[19] SCARB2 deficiency can lead to reduced GBA activity and SNCA accumulation.[20] Mutations in *SCARB2* cause autosomal recessive progressive myoclonus epilepsy, in which reduced GBA activity is also noted.[78] Both *SCARB2* and *GBA* are also strongly associated with another synucleinopathy, Lewy body dementia,[79-81] further supporting the effect of these genes on SNCA aggregation, and suggesting that *SCARB2* variants may affect *GBA* and lysosomal function. It will be important to examine the effects of *SCARB2* variants on transport of GBA to the lysosome and on its function in PD-relevant models. At the end of this review, we propose a novel mechanism that can explain how *GBA* mutations impair lysosomal function and increase susceptibility to PD.

SMPD1—Niemann-Pick type A and B

The *SMPD1* gene codes for the lysosomal enzyme sphingomyelin phosphodiesterase 1, acid lysosomal, and carriage of homozygous or compound heterozygous mutations in this gene may lead to the lysosomal storage disorder Niemann-Pick type A or B. Since the end product of both GBA and SMPD1 is ceramide, which was previously implicated in PD,[82] and since both are causing closely related lysosomal storage disorders, the potential role of the *SMPD1* gene in PD was also examined. Two studies identified rare *SMPD1* mutations that are associated with increased risk for PD;[49,50] however, more studies are needed to determine the significance of the *SMPD1* gene in PD.

Similar to *GBA*, it is possible that SMPD1 deficiency may lead to more general disruption of the lysosome and autophagy. For example, fibroblasts from patients from Niemann-Pick type A show accumulation of autolysosomes, and an excess of sphingomyelin, caused by *SMPD1* deficiency, which affects autophagy regulation.[83] In addition, SMPD1 also regulates autophagy in smooth muscle of mice.[84] Therefore, it will be of interest to examine the effects of *SMPD1* mutations on lysosomal activity in general and on the internalization and processing of SNCA specifically.

Other lysosomal storage disorder genes

Several other lysosomal storage disorders may be associated with PD. Limited evidence exists suggesting that the Fabry disease gene *GLA*, encoding the lysosomal enzyme galactosidase, α, may also have a role in PD. One case study of a patient with Fabry disease presenting with parkinsonism was described.[85] Reduced activity of GLA is observed in leukocytes of PD patients,[86] and a subsequent study showed a reduced expression of *GLA* both in the mRNA level and in the protein level in PD patients.[87] However, there is little evidence that *GLA* genetic variants can be associated with PD,[88] therefore the role of *GLA* in PD is still to be determined.

A possible association of Niemann-Pick type C with PD, caused by mutations in the *NPC1* or *NPC2* gene, was also suggested, although the evidence for this association is also not strong. In a study of 563 PD patients, 1.1% had *NPC1* mutations, which was only slightly higher than controls (0.8%) and not statistically significant.[89] A case series of 3 heterozygous carriers[90] and a case report of an additional carrier[91] of *NPC1* disease-causing mutations with parkinsonism, further support a potential role for *NPC1* in PD. Some pathological evidence from autopsies of Niemann-Pick type C patients' brains, suggest that SNCA may be aberrantly phosphorylated and aggregate in Lewy bodies.[92,93] Although none of these genes was implicated in human genetic studies, it is possible that rare mutations in these genes can be found in PD; therefore, sequencing of *GLA* and *NPC1* in different PD cohorts is important for determining if they have a role in PD.

Autosomal Dominant PD Genes and Autophagy

LRRK2

LRRK2 mutations, together with *GBA*, are the 2 most common genetic risk factors for PD. Both are dominant with reduced penetrance, i.e., heterozygous carriage of a mutation increases the risk for the disease, but other genetic or environmental factors are required for PD to develop. Although *LRRK2* was initially identified in several familial PD cases,[45,94] it is a common cause of sporadic PD, found in more than 30% of Arab-Berber PD patients,[95,96] more than 12% of Ashkenazi-Jews with PD,[97] and in many other patient populations worldwide with various frequencies, mostly ranging between 1–5%.[98]

Evidence from recent years suggests that *LRRK2* has an important role in autophagy as a part of the pathogenic mechanism leading to PD. While the wild-type LRRK2 protein is degraded by CMA, the common LRRK2^{G2019S} mutation impairs this degradation.[99] Moreover, it was demonstrated that the interaction between the mutated LRRK2 and the CMA receptor, LAMP2A, disturbed the multimerization of the receptor, resulting in accumulation of its substrates, including SNCA.[99] These findings suggest a possible mechanism linking *LRRK2* mutations to defective autophagy and subsequent accumulation of SNCA. Other studies suggest a role for *LRRK2* also in general lysosomal function and in macroautophagy. In a cellular model transfected with the gene encoding the LRRK2^{G2019S} mutation, an accumulation

of autophagic vacuoles is observed.[100] Similar responses are noted in cells with another common mutation, LRRK2^{R1441C},[101] in mice with the LRRK2^{G2019S} mutation,[102] and in *Drosophila* with *Lrrk2* loss of function.[103] Knockdown of *LRRK2* increases autophagic activity and reduces cell death;[101] however, independent studies demonstrated that either *Lrrk2* mutations or knockout of *Lrrk2* result in the reduction of the autophagic marker LC3-II (although this could be attributed to accelerated autophagic flux).[104,105] In addition, increased GTPase activity of the LRRK2 protein impairs endocytic vesicular trafficking and autophagy.[106] Collectively, these results raise the issue of gain vs. loss of function in *LRRK2*-associated PD. While it was demonstrated that the mutations that occur in PD patients can cause gain of the kinase or GTPase functions,[54] the above experiments demonstrate that both loss and gain-of function have similar deleterious effects on autophagy. The reduction in the autophagic marker LC3-II occurs in both gain- (*Lrrk2* mutations)[104] and loss-of-function (knockout) models of *LRRK2*-associated PD. Likewise, accumulation of autophagic vacuoles is observed in both gain- (mutated mice)[102] and loss-of-function (*Drosophila*)[103] models. This could be explained by differences between species and models, but it is also possible that while *LRRK2* mutations cause a gain of kinase/GTPase activity, they also cause loss of another function at the same time, and therefore this issue should be further studied.

A recent study also suggested an effect of the LRRK2^{G2019S} mutation on induction of mitophagy by interacting with the mitochondrial membrane protein BCL2.[107] *LRRK2* also interacts with *RAB29* and affects PD risk and lysosomal dysfunction; these interactions will be discussed in the *RAB29* section. While there is clear evidence that *LRRK2* is involved in various forms of autophagy and lysosomal functions, the exact mechanisms are not fully understood and necessitate more study. Interestingly, *LRRK2*-associated PD is not always characterized by accumulation of SNCA, and it can be associated with deposition of MAPT/tau protein or ubiquitin-positive inclusions.[108] It was suggested that LRRK2 dysfunction may be upstream to the accumulation of SNCA and MAPT, and that other genetic or environmental factors determine which pathology will develop;[109] however, more evidence is needed to support this hypothesis.

SNCA and autophagy

SNCA is the main component of Lewy bodies. Duplications, triplications,[110,111] and point mutations [33,112-114] in the *SNCA* gene cause PD or parkinsonian syndromes, and genetic markers in its locus are associated with PD in various populations.[4,7,8,13,115] Since SNCA oligomers are toxic in neurons, a leading paradigm in PD research suggests that SNCA accumulation, resulting from its overexpression or lack of degradation, is one of the important mechanisms causing degeneration of dopaminergic neurons.[116]

Early reports suggested that both ALP and the ubiquitin-proteasome system (UPS) are responsible for SNCA degradation,[117] but it seems that the main cellular mechanism responsible for its degradation is the ALP, as SNCA accumulation results from inhibition of the ALP, but not the UPS.[118] CMA internalizes SNCA into the lysosome,[14] but macroautophagy also takes part in SNCA clearance.[118,119]

Chaperone-mediated autophagy and SNCA degradation

CMA of wild-type SNCA is mediated by the LAMP2A lysosomal receptor and the chaperone molecule HSPA8.[14,118,120] Interestingly, the mutant forms of SNCA that cause PD, SNCA^{A53T} and SNCA^{A30P}, are poorly degraded by CMA,[14,121] although they have high affinity to LAMP2A.[14] This observation may suggest that these mutant forms attach to the receptor and prevent it from internalizing wild-type or mutant SNCA, resulting in SNCA accumulation and cellular toxicity. Furthermore, dopamine can modify SNCA, and as a result the CMA of SNCA is blocked by the dopamine-modified form of the protein.[122] This finding may explain the higher sensitivity of dopaminergic neurons to SNCA accumulation, as observed in PD. Additional effects of SNCA on CMA and neurodegeneration may be mediated by the neuronal survival factor MEF2D. Both wild-type and mutant SNCA inhibit the CMA of MEF2D, accompanied by a decline of MEF2D function and survival of neuronal cells.[123] Of note, the *UCHL1* gene product, whose role in PD is still under debate, interacts with LAMP2 and increases SNCA levels, suggesting that it affects the CMA of SNCA.[124]

Wild-type SNCA is also degraded by macroautophagy, and inhibition of this process causes SNCA accumulation, in contrast to inhibition of the UPS.[118] In addition, following dysfunction of the CMA pathway in cells with the SNCA^{A53T} mutation, a subsequent activation of the macroautophagy pathway occurs.[121] The same phenomenon follows inhibition of CMA with dopamine,[122] or overexpression of wild-type SNCA or SNCA^{A53T},[125] suggesting that macroautophagy may be a compensatory mechanism for dysfunctional CMA of SNCA. It was further demonstrated that induction of autophagy can induce degradation of SNCA and rescue neurons from cell death. For example, trehalose, a dissacharide that induces macroautophagy, accelerates the degradation of the SNCA^{A30P} and SNCA^{A53T} mutant forms of SNCA,[126] and induction of autophagy by the transcription regulator of the ALP, TFEB,[127] rescues dopaminergic neurons from SNCA toxicity.[128]

VPS35 and other genes in the lysosomal-endosomal pathway

Mutations in *VPS35* (VPS35 retromer complex component), are a rare but well validated cause of autosomal dominant PD, the most common mutation being VPS35^{D620N}.[47,48,129-131] In a meta-analysis of mRNA expression in the substantia nigra (SN), there was a highly significant decrease in VPS35 levels, which was further replicated in dopaminergic neurons that were laser-microdissected from the SN of PD patients.[17] VPS35 is a component of the retromer complex, which mediates endosome-to-Golgi transport of proteins, for recycling and reuse or for further degradation. One of these proteins is M6PR (mannose 6-phosphate receptor [cation dependent]), which is responsible for transporting many of the lysosomal hydrolases to the lysosome.[132] Therefore, retromer dysfunction may lead to lysosomal dysfunction. It was recently shown that the VPS35^{D620N}

mutation leads to reduced association with the WASH1/Wiskott–Aldrich syndrome homolog complex,[133] which is a complex of proteins essential for the process of endosomal actin polymerization and facilitation of protein sorting.[134] The reduced association of mutated VPS35 with the WASH complex, further reduce its recruitment to endosomes, which leads to impairment of autophagy.[133] In addition, knockdown or mutated VPS35 in neuronal cell cultures leads to reduced colocalization of the M6PR with the Golgi apparatus and with late endosome/lysosome markers.[17] Interestingly, 2 additional genes that cause rare autosomal recessive atypical parkinsonism, *ATP6AP2*,[38] and *SYNJ1*,[39,40] and the dominant PD gene *DNAJC13*,[41] are also involved in the endosomal pathway. Similar to VPS35, DNAJC13 is also associated with the WASH complex by binding to the FAM21 protein.[135] Atp6ap2 regulates endolysosomal trafficking in *Drosophila*[136] and it is essential for the acidification of lysosomes.[137] SYNJ1 also has an important role in endolysosonal trafficking of synaptic proteins,[138] together with the involvement of the other PD-related genes in this pathway, including *LRRK2* and *RAB29* (discussed separately), emphasizing its important role in PD.

Autosomal Recessive PD Genes, Autophagy, and Mitophagy

Carriage of homozygous or compound heterozygous mutations in 3 genes: *PARK2*,[34] *PINK1* [35] and *PARK7*,[36] causes young or early onset PD, with motor symptoms usually occurring between the first and sixth decades of life. *PARK2* is the most common autosomal recessive PD-causing gene, accounting for most cases of young onset PD, followed by *PINK1*.[108] Interestingly, these genes are all involved in the process of selective mitochondria engulfment by autophagosomes and their degradation within the lysosome, termed mitophagy. Pathologically, *PARK2*-associated PD is often limited to the substantia nigra, mostly without Lewy bodies,[108] suggesting that the pathogenic mechanism is downstream of the accumulation of SNCA. This could mean that ALP dysfunction that leads only to mitophagy dysfunction may be sufficient for the development of PD, or a sub-type of PD.

PARK2 and PINK1 in mitophagy

Initially, PARK2 was identified as a cytosolic E3 ubiquitin ligase, but it was later shown that when mitochondria are depolarized, PARK2 is selectively recruited to their surface and ubiqitinates other proteins on the outer mitochondrial membrane, such as MFN1 and MFN2.[139,140] The translocation of PARK2 to the mitochondrial membrane and the recruitment and ubiqitination of mitochondrial proteins initiates mitophagy, and this process requires PINK1 expression and kinase activity. PINK1 has low levels of expression on healthy mitochondria, whereas on dysfunctional mitochondria it rapidly accumulates and recruits PARK2 to induce mitophagy.[141-143] Furthermore, PD-causing mutations in *PINK1*[144] and *PARK2*[145] disrupt PARK2 recruitment to the mitochondria and the induction of mitophagy. Overexpression of *PARK2* has a protective effect in cells deficient for *PINK1*, and overexpression of *PINK1* suppresses autophagy or mitophagy induced by toxins.[146] It is possible that lysosomal dysfunction in lysosomal storage disorders can also affect PARK2-mediated mitophagy.[147] Studies of other genetic conditions in which parkinsonism is a part of the disorder may also shed more light on the importance of mitophagy in PD. For example, mutations in the *VCP* gene cause a multisystem degenerative disorder in which one of its many clinical features is parkinsonism.[148] A recent study demonstrated that the pathogenic mutations in *VCP* also impair the clearance of damaged mitochondria via the PINK1/PARK2 pathway.[149]

PARK7 and mitophagy

Interestingly, PARK7 acts under conditions of oxidative stress in a parallel pathway to that of PINK1 and PARK2 to sustain mitochondrial function and mitophagy, and overexpression of PARK2 protects against PARK7 loss and prevents mitochondrial damage.[150] In another study, Park7 overexpression rescues the phenotype of Pink1 loss of function in *Drosophila*.[151] Altogether, these studies demonstrated that the PD-related genes *PARK2, PINK1*, and *PARK7* have an important role in mitophagy, suggesting that impairment of this mechanism has a role in PD pathogenesis. Impaired mitochondria processing by mitophagy due to mutations in any of these genes, may lead to excess production of reactive oxygen species, cause excessive oxidative stress, and contribute to cell death and neurodegeneration.[152]

ATP13A2 lysosomal function and autophagy/mitophagy

ATP13A2 codes for a lysosomal transmembrane protein that functions as P-type ATPase on the lysosome and late endosome, and is highly expressed in the substantia nigra, as well as in other parts of the brain.[153] Mutations in *ATP13A2* cause Kufor-Rakeb syndrome, which is a rare autosomal recessive disorder characterized by early-onset parkinsonism with pyramidal degeneration and dementia.[37] Studies on fibroblasts from these patients demonstrated that, as compared to controls, there are high rates of mitochondrial DNA damage, decreased ATP synthesis rates and increased fragmentation of the mitochondrial network, all suggesting an effect of mitochondrial quality control. When wild-type *ATP13A2* is overexpressed, this mitochondrial phenotype is rescued.[154] Similarly, silencing of *ATP13A2* induces fragmentation of mitochondria in a neuronal cell model, and its overexpression delays mitochondrial fragmentation.[155] These and similar findings[156] suggest a role for *ATP13A2* in quality control of mitochondria, probably through mitophagy. A more general role in lysosomal function and autophagy was suggested for *ATP13A2*, as fibroblasts from patients with Kufor-Rakeb syndrome as well as mouse primary neurons with ATP13A2 deficiency lead to reduced capacity of lysosomal degradation, resulting in SNCA accumulation and neurotoxicity.[157]

FBXO7 and mitophagy

Homozygous and compound heterozygous mutations in the *FBXO7* gene can cause a parkinsonism disorder that can be

clinically similar to *PARK2*-associated PD,[158,159] or to typical PD.[160] Interestingly, just like the other autosomal recessive forms of PD, it was suggested that *FBXO7* is involved in mitophagy.[161] Given its similar phenotype to *PARK2*-associated PD, the interaction of FBXO7 with PARK2 was examined, and it was shown that reduced expression of FBXO7 leads to reduced translocation of PARK2 to the mitochondria. FBXO7 directly interacts with PARK2 and recruits it to the mitochondria, and it is also involved in mitophagy of mitochondria treated with carbonyl cyanide m-chlorophenylhydrazone.[161] Overall, it seems that the PD autosomal recessive genes may all converge into a subpathway of the ALP, mitophagy. It may suggest that severe impairment of mitophagy can elicit PD or a similar disease. Why this impairment affects mainly dopaminergic neurons at the substantia nigra and the exact mechanism by which this impairment occurs is still to be determined.

Genes Identified in GWAS and their Potential role in the Autophagy-Lysosome Pathway

RAB29

Two GWASs identified a region on chromosome 1, termed *PARK16*, which includes 5 genes: *PM20D1*, *SLC41A1*, *RAB29*/*RAB7L1*, *NUCKS1*, and *SLC45A3*.[12,13] Minor alleles in this region are associated with a 30–40% reduced risk for PD, a finding that was later replicated by several other studies in different populations.[162-166] A particularly reduced risk was demonstrated in the Ashkenazi Jewish population, demonstrating that a haplotype that included SNPs in the promoter of *RAB29* is associated with a 10-fold reduced risk. Furthermore, one of the promoter SNPs, rs1572931, has the strongest association and is found in both haplotypes with a protective effect.[162] Subsequently, it was demonstrated that the same SNP is associated with alternative splicing of *RAB29*, where the protective allele is associated with increased inclusion of exon 2, while the risk allele is associated with exon skipping.[17] A second SNP within the promoter region of *RAB29*, rs823114, has the strongest epistasis with *LRRK2*, jointly affecting the risk for PD.

These 2 proteins, RAB29 and LRRK2, not only genetically interact, they also physically interact, as shown in an unbiased screen using protein-protein interaction arrays.[17,22] This interaction was further supported in a study where *RAB29* overexpression inhibits the known effect of *LRRK2* mutations on neurite length.[17] In relation to the ALP, knockdown of RAB29 leads to swelling of lysosomes and to reduction of M6PR accumulation in the lysosome, and it was suggested that these changes may be secondary to altered retromer-mediated trafficking between the lysosome and the Golgi apparatus.[17] It was further confirmed that RAB29 has an important role in the retrograde trafficking of M6PRs to the Golgi apparatus.[23] M6PRs are needed for recruitment and transport of lysosomal hydrolases to the lysosome; therefore, disruption of this function may lead to lysosomal dysfunction.[17] Identifying the specific mechanism underlying the protective effect of RAB29, as well as other protective genetic factors, should be a priority, since they may provide clinicians with crucial information for treatment or prevention of PD.

SREBF1

The association between the *SREBF1* gene, encoding the sterol regulatory element binding transcription factor 1, and PD was initially identified in a GWAS,[4] and it was recently replicated in the largest GWAS performed to date.[7] In both GWASs, the minor allele is associated with a reduced risk for PD, with an estimated effect of 5–15% reduced risk. Recently, in a whole genome RNAi screen that aimed to identify factors that promote mitophagy mediated by PARK2, the lipogenesis pathway was implicated with 4 genes of this pathway, *SREBF1*, *SREBF2*, *FBXW7* and *GSK3A*, among the top hits.[29,167] Knockdown of *SREBF1* blocks both the translocation of PARK2 to the mitochondria and the consequent mitophagy, an effect that is independent of *PINK1* expression levels.[167] Therefore it is hypothesized that reduced SREBF1 expression my lead to reduced mitophagy and risk for PD.

SREBF1 also regulates the expression levels of the *NPC1* gene (which is associated with the lysosomal storage disorder Niemann-Pick Type C), by binding to its promoter and increasing its transcription. Downregulation of this pathway may induce the sequestration of cholesterol within late endosomes and lysosomes,[168] and the transcriptional activity of SREBF1 is enhanced in models of lysosomal storage disorders, leading to increased transcription of LDLR (low density lipoprotein receptor).[169] These findings suggest that *SREBF1* has a role in mitophagy, as well as in regulation of lysosomal lipid accumulation, and more studies of its potential interactions with *PARK2*, *PARK7*, and *PINK1* are necessary.

MAPT

MAPT is one of the most intriguing genes in neurogenetics, as it is associated with different neurological conditions in different ways. *MAPT* codes for the microtubule-associated protein tau, which aggregates in Alzheimer and other diseases, generally termed tauopathies. In some of these diseases, such as progressive supranuclear palsy,[170] corticobasal degeneration,[171] and argyrophilic grain disease,[172] *MAPT* variations play an important role. Additionally, *MAPT* mutations may cause fronto-temporal dementia with parkinsonism[173] and lower motor neuron disease.[174] However, the association between *MAPT* variations and the most common tauopathy, Alzheimer disease, is still not clear, although several studies suggest such an association.[175-177] *MAPT* haplotypes, such as the H1 haplotype, were identified in various studies as important risk factors for PD,[4,7-9,12,13] in which tau does not accumulate. Furthermore, *MAPT*-associated SNP is the second strongest risk factor in PD GWAS, with an OR of 0.77 and $p = 2 \times 10^{-48}$.[7] Considering all these findings, it is clear that *MAPT* plays a critical role in the nervous system.

MAPT is both affected by and affects the function of the lysosome, since it is being degraded by it and at the same time is important to its function.[178-181] It is possible that the H1 haplotype is associated with impaired autophagy, or with dysfunction of

MAPT, which may lead to autophagy impairment.[26] However, this hypothesis still needs to be supported by future research.

Other GWAS hits with a possible role in the autophagy-lysosome pathway

A locus that contains 2 genes, *LAMP3* and *MCCC1*, was repeatedly identified in GWASs of PD, with an estimated risk reduction of 13–20%.[4,7,8] *LAMP3* encodes the lysosomal-associated membrane protein 3, which has a role in the unfolded protein response, and is expressed in immune system cells, mainly dendritic cells.[182] Since the immune system is also suggested to be involved in PD pathogenesis,[183] it is possible that the role of *LAMP3* in PD is related to the lysosomal function in these cells. It was recently shown that LAMP3 is involved in autophagy, as its knockdown reduces the ability of cells to complete the autophagic process, and cells with high *LAMP3* expression show increased basal autophagy levels.[21] However, not much is known about this potential function, and since the risk locus for PD includes both *LAMP3* and *MCCC1*, it is possible that it is *MCCC1* that is involved in PD. Although MCCC1 functions at the mitochondria as a subunit of the 3-methylcrotonyl-CoA carboxylase enzyme,[184] it is currently not known if it has any role in mitophagy or mitochondrial quality control. Studying the potential relationship of *MCCC1* with other mitochondrial-related genes that are involved in PD, such as *PARK2*, *PARK7*, *PINK1* and *SREBF1* may help determining if it is the *LAMP3* gene or *MCCC1* that affects the risk for PD in this locus.

GAK is another gene that was identified in the largest GWASs, with an estimated effect of 14–30% on risk for PD.[4,7,8] *GAK* encodes the cyclin G associated kinase, and RNAi-mediated depletion of GAK results in diminished sorting of CTSD (cathepsin D),[27] an important lysosomal hydrolase that is also responsible for the degradation of SNCA.[185,186] Introducing RNAi-resistant GAK following RNAi restores the proper lysosomal sorting of CTSD.[27] Therefore, it is possible that *GAK* is involved in PD through its effect on the lysosomal activity of CTSD and subsequent SNCA degradation, and more studies are necessary to examine this hypothesis. In another model, it was demonstrated that knockout of *GAK* results in destabilization of the lysosomal membrane and leakage of iron, causing DNA damage.[28]

Genetic markers around *GPNMB* were identified and replicated in several GWASs, with approximately 10% risk reduction.[7,9] Interestingly, *GPNMB* is an important gene in melanoma,[187] a skin malignancy that is associated with PD.[188] The GPNMB protein localizes mainly to melanosomes and to a lesser extent to lysosomes in melanoma cells; however, in other cells it localizes to lysosomes.[31] Furthermore, GPNMB is involved in phagocytosis, and is essential for recruitment of the autophagy protein LC3-II to the phagosome. In addition, GPNMB is necessary for the fusion of the lysosome with the phagosome leading to the degradation of the phagosome content.[30] Another gene associated with PD in GWAS, *TMEM175* (same locus and effects on risk as *GAK*), is found in the lysosomal membrane, but its function is unknown.[32]

Lysosomal Membrane Properties, Autophagy, and Parkinson Disease: A Novel Hypothesis

SNCA is the major constituent of Lewy bodies, the neuropathological hallmark of PD, and mutations and gene dosage variations in *SNCA* cause PD.[33,110-114] It was suggested that overexpression or accumulation of SNCA is toxic to cells, contributing to the development of PD.[189] The association between *GBA* mutations or dysfunction with SNCA accumulation,[46,69-73] in addition to other findings, prompted us to hypothesize a novel mechanism that may explain *GBA*-associated PD, but may also explain sporadic PD (**Fig. 2**).

The receptor for CMA of SNCA is LAMP2A, a lysosomal transmembrane protein.[14] In order to transport SNCA into the lysosome for further degradation by CTSD,[186] the LAMP2A protein must form complexes on the lysosomal membrane.[190] In its monomeric state, LAMP2A is found in specific membrane lipid microdomains, and the protein-complex formation process requires LAMP2A to leave these domains.[191] Retention of LAMP2A within the lipid microdomains may not allow protein-complex formation, which in turn will prevent the autophagy of SNCA, resulting in SNCA accumulation.

GBA is located on the surface of the inner membrane of the lysosome, where it cleaves membrane glucocerebrosides into ceramide and glucose. In a cellular model of Gaucher disease, when GBA is inhibited, the composition of the lysosomal membrane changes, including increased concentration of glucocerebrosides.[192] Similar results were observed in a mouse model of Gaucher disease, demonstrating highly increased concentrations of glucocerebrosides in lipid rafts.[193] This process may prevent or reduce the formation of LAMP2A protein-complexes, which will then reduce the autophagy of SNCA, and result in its accumulation. It is possible that alterations in the composition of the lysosomal membrane may affect other forms of autophagy, such as microautophagy, macroautophagy and mitophagy, contributing to PD development. It was already demonstrated, for example, that GBA deficiency may lead to defective mitophagy and mitochondrial damage.[194,195]

Is it possible that this model can be relevant not only for *GBA*-associated PD, but for other forms of PD as well? Is it possible that other events, such as oxidative stress or aging affect the composition of the lysosomal membrane and therefore affect its ability to internalize SNCA for degradation? It seems that the answer for both questions may be yes. There is a growing body of evidence that GBA activity is reduced not only in *GBA*-associated PD, but in sporadic PD as well,[74,196,197] suggesting that other genetic or environmental factors may lead to GBA impairment and to the subsequent pathological effect. One possible factor is SNCA itself, which may interact with and inhibit wild-type GBA.[71,198] An interesting observation suggests that in the normal process of aging, the mobilization of LAMP2A to the lysosome membrane is altered.[199] More research is needed to answer these questions and to determine the exact mechanisms by which dysfunction of the ALP affects SNCA accumulation and increases the risk for PD.

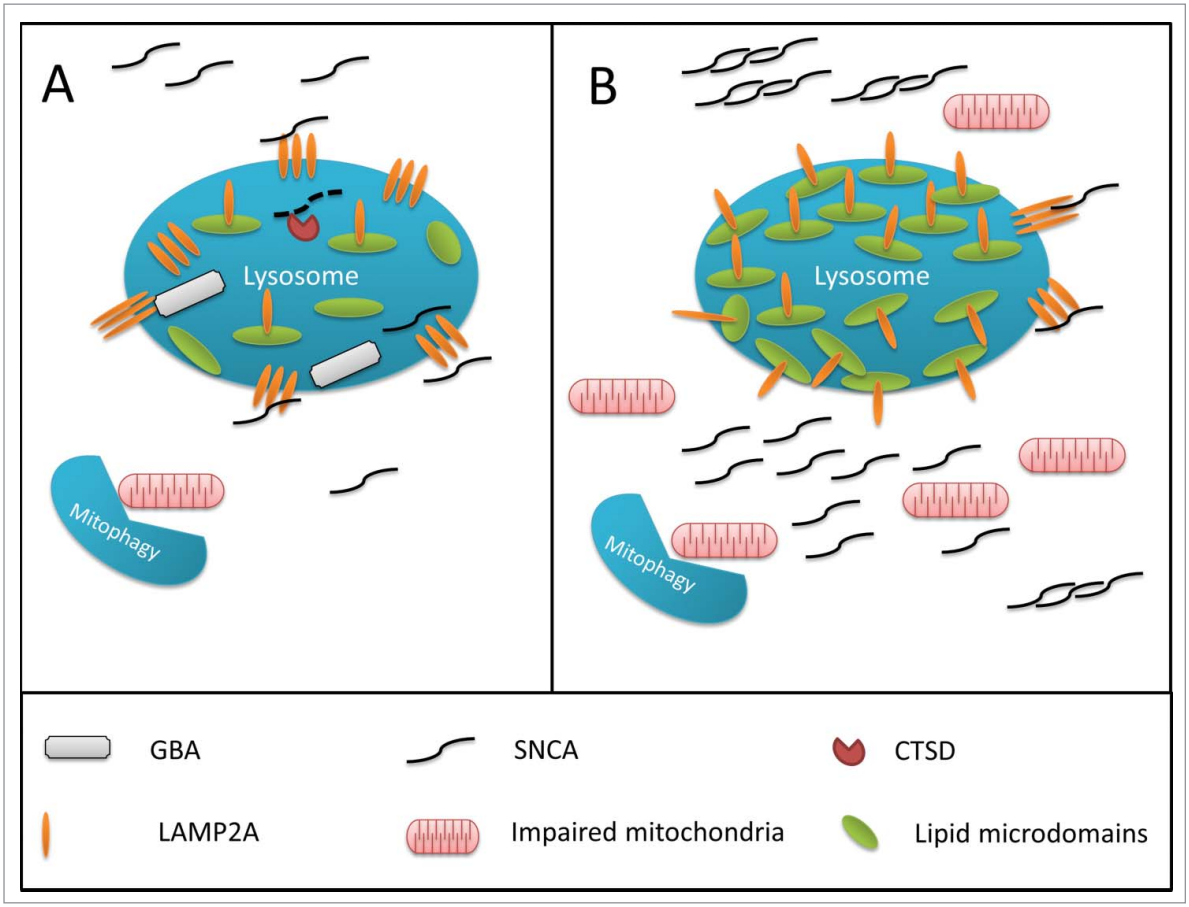

Figure 2. Hypothesized mechanism for *GBA*-associated lysosomal dysfunction in Parkinson disease. (**A**) In a normally functioning lysosome, GBA is associated with the inner part of the lysosomal membrane, and degrades glucocerebrosides to glucose and ceramide, thus controlling the proper composition of the membrane. The chaperone-mediated autophagy receptor, LAMP2A, is able to freely move out of lipid rafts, create complexes, and internalize SNCA into the lysosome for degradation. (**B**) Impaired GBA activity can affect the composition of the membrane, leading to an increased density of lipid rafts on the lysosomal membrane. In this scenario, it is more difficult for LAMP2A to create the complexes required for the internalization of SNCA into the lysosome, leading to SNCA accumulation. This effect of GBA impairment on the lysosomal membrane may interrupt other pathways, and affect macroautophagy and mitophagy, which will lead to the accumulation of damaged mitochondria and increased oxidative stress.

Therefore, this hypothesis may be valid mainly to *GBA*-associated PD and to other forms of PD in which GBA activity is reduced, or to late onset PD in which aging has a similar effect on the lysosomal membrane. While these patients could be the majority of patients, it is possible that different ALP subpathways are involved in other forms of PD. Furthermore, it is possible that what we call PD, is a group of phenotypically similar yet pathogenically somewhat different diseases. In *PARK2*-associated PD, in which the pathology is limited in most cases to nigral degeneration only, and in *LRRK2*-associated PD in which there is no SNCA accumulation in some cases, a different ALP dysfunctional mechanism may be involved. This could be true as well for *PINK1*- and *PARK7*-associated PD, in which mitophagy is impaired in a similar way to *PARK2*-associated PD. Accordingly, future treatment of these forms of PD could be different, and it is already hypothesized that *LRRK2*-associated PD may benefit from kinase inhibitors [200,201] whereas *GBA*-associated PD may benefit from enzymatic therapy, once it can cross the blood-brain barrier.

Conclusion

This review summarizes the knowledge arising from genetic studies, emphasizing the central role of the ALP and endolysosomal trafficking in PD. Given the presented evidence, it is likely that lysosomal dysfunction results in a reduced ability to degrade SNCA and/or defective mitochondria, leading to the loss of dopaminergic neurons seen in PD. The exact mechanism and why it happens in dopaminergic neurons rather than others is still to be explained, and several hypotheses have been raised, such as specific calcium-related properties of dopaminergic neurons,[202] or blockage of CMA by modified dopamine.[122] Whether the ALP can serve as a cell death-signaling pathway, or whether it is a more pro-survival mechanism, is still under debate.[203-205] Nevertheless, the contribution of the ALP to the normal function of cells is clear, and therefore impairment of the ALP may lead to reduced ability of cells to survive. It is also likely, however, that the ALP participates in the cell death that occurs in PD.

It is important to note that although this review focuses on the ALP, it is clear that other pathways and mechanisms are also involved in PD pathogenesis. Such mechanisms include, for example, prion-like propagation of SNCA,[206] mitochondrial dysfunction, neuro-inflammation,[207] and calcium regulation,[208] and efforts to find therapeutic interventions targeting these and other pathways are of great importance as well.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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