

Review Article

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The function of lysosomes and their role in Parkinson's disease

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Abstract: Lysosomes are cellular organelles that are important for the degradation and recycling of various biomolecules. Specialized lysosomal membrane proteins, as well as soluble enzymes, are important for the efficient turn-over of lysosomal substrates. A deficiency in the degradative capacity of lysosomes leads to severe pathologies referred to as lysosomal storage disorders. There is increasing evidence for the importance of lysosomal function in neurodegenerative disorders, including Parkinson's disease. One reason for this might be the vulnerability of neuronal cells. Since neurons do not undergo further cell division, non-degraded substrates accumulate in aging cells, causing a buildup of toxicity. Recent genomic screenings identified a number of lysosome-associated genes as potential risk factors for Parkinson's disease, which are discussed in this review. Moreover, it is outlined how targeting lysosomal function might help in developing novel therapeutic strategies.

Keywords: α -synuclein, lysosomes, lysosomal enzymes, lysosomal storage disorders (LSD), Parkinson's disease

Zusammenfassung: Lysosomen sind membranumschlossene Zellorganelle, in denen lösliche Enzyme für den Abbau sowie das Recycling intrazellulärer als auch extrazellulärer Biomoleküle sorgen. Kommt es dagegen zu einer unvollständigen Degradation hat das schwerwiegende pathologische Konsequenzen und führt zu sogenannten lysosomalen Speichererkrankungen. Forschungsergebnisse der letzten Jahre deuten auf einen Zusammenhang zwischen lysosomaler Dysfunktion und dem Krankheitsverlauf neurodegenerativen Erkrankungen hin – so wie zum Beispiel beim Morbus Parkinson. Eine mögliche Erklärung hierfür ist, dass neuronale Zellen keine Zellteilung mehr durchlaufen und sich so über die Zeit lysosomale Substrate anhäufen. Interessanterweise zeigen

genetische Untersuchungen von Parkinson Patienten eine Anhäufung lysosomaler Gene, welche als Risikofaktoren für die Erkrankung beschrieben und in diesem Review behandelt werden. Des Weiteren wird diskutiert, welche Rolle Lysosomen bei der Entwicklung neuartiger Therapien zur Behandlung der Parkinson Erkrankung spielen können.

Schlüsselwörter: Lysosomen, Lysosomale Speichererkrankungen, lysosomale Enzyme, Morbus Parkinson, α -Synuclein

Introduction

Recent studies have shown that lysosomal dysfunction is not only linked to rare lysosomal storage disorders, but also to age-dependent neurodegenerative diseases, such as Parkinson's disease (Fraldi et al., 2016). Whereas most cases of Parkinson's disease are idiopathic (~90 %), meaning they do not have a clear heritable genetic link, the remaining ~10 % of Parkinson's disease cases are familial and show Mendelian inheritance of affected genetic variants (Kalia and Lang, 2015). In order to understand the underlying molecular disease pathways, single genetic variants are of particular value for scientific studies. Recent genetic meta-analyses of Parkinson's patients (both familial and idiopathic) reveal enrichment in genetic risk loci related to lysosomal homeostasis (Chang et al., 2017; Robak et al., 2017). Hence, the majority of Parkinson's disease-associated genes are linked to lysosomal protein trafficking or lysosomal function (Klein and Mazzulli, 2018). The following review will give an overview of the composition and function of lysosomes in general, their role in neurodegeneration with focus on Parkinson's disease, and discuss potential new treatment strategies targeting lysosomal proteins or pathways.

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The composition and function of lysosomes

Lysosomes were first described in the 1950s by Christian DeDuve, and are membrane-surrounded cellular organelles ubiquitously found within the cytosol of mammalian cells (DeDuve et al., 1955). Lysosomes contain specialized membrane proteins, as well as luminal hydrolytic enzymes, that can break down many kinds of biomolecules, including intracellular and extracellular substrates. The importance of lysosomal function is highlighted by a number of diseases called lysosomal storage disorders (LSDs), that result from defects in soluble lysosomal proteins and proteins of the lysosomal membrane (Eskelinen et al., 2003).

Importantly, it has been realized that lysosomes are not only degradative organelles, but also play a pivotal role in cell metabolism. Hence, they are involved in processes of cell signaling, repair of the plasma membrane, defense against pathogens, cholesterol metabolism, cell death, and energy metabolism (Schulze and Sandhoff, 2011; Settembre et al., 2013). Lysosomes emerge from the fusion of endosomes, which are specialized vesicles with an acidic pH. The pH within the lysosomes reaches as low as pH 4.5–5.0, and is mainly mediated by the ATP-dependent vacuolar(v)-type H⁺ ATPase (Ohkuma et al., 1982) (Figure 1).

Lysosomal enzymes reach lysosomes via the secretory pathway, which means that they are synthesized in the endoplasmic reticulum (ER) as membrane-integrated or soluble glycoproteins and pass through the Golgi apparatus. Since the majority of lysosomal proteins are transported to lysosomes by the mannose-6-phosphate (M6P)-dependent pathway, proteins are tagged with an M6P recognition marker. This terminal residue is then recognized by M6P-receptors, which mediate protein delivery to lysosomes via clathrin coated vesicles (Kornfeld, 1992). It must be noted that M6P-independent lysosomal transport mechanisms also exist. Moreover, some lysosomal proteins can escape the lysosomal targeting pathways. They can be transported to the plasma membrane or outside the cell, where they are taken up and transported back to lysosomes by a process called endocytosis (Janvier and Bonifacino, 2005).

To date, 60 different lysosomal enzymes have been found to be responsible for the degradation of various substrates (Settembre et al., 2013). Depending on their degradation products, lysosomal enzymes are classified as proteases, nucleases, glucosidases, phosphatases, polysaccharide hydrolyzing enzymes or lipid degrading enzymes (Bainton, 1981). All require an acidic envi-

ronment for optimal enzymatic function (De Duve and Beaufay, 1959).

The lysosomal membrane contains highly glycosylated membrane proteins, which contribute to the stability of the membrane, as well as the luminal glycocalyx (Schwake et al., 2013). Most abundant in the lysosomal membrane, and thus important for its integrity, are the lysosomal associated membrane proteins type-1 and -2 (LAMP-1, LAMP-2), and the lysosomal integral membrane proteins type-1 and -2 (LIMP-1, LIMP-2/SCARB2). Interestingly, the LIMP-2 protein has not only been shown to be important for the integrity of the lysosomal membrane, but also for the M6P-independent lysosomal transport of the lysosomal enzyme β -glucocerebrosidase (GCase) (Blanz et al., 2015; Reczek et al., 2007; Zunke et al., 2016).

Furthermore, various channel proteins and small molecule transporters, like the transmembrane protein 175 (TMEM175), a potassium channel, or the sialic acid transporter, Sialin, are major integral components of the lysosomal membrane (Eskelinen et al., 2003). Additionally, transporter proteins, like the lysosomal cholesterol transporter Niemann-Pick Type C1 (NPC1), are found in the lysosomal membrane and play an important role in cellular cholesterol homeostasis (Infante et al., 2008) (Figure 1).

Lysosomal dysfunction and neurodegenerative diseases

Genetic variants within genes encoding for lysosomal proteins resulting in less or non-functional protein (loss-of-function mutation) lead to lysosomal dysfunction and buildup of lysosomal substrates. This disease family is called lysosomal storage disorders (LSDs) and comprises over 70 distinct diseases, which in total have an incidence of ~1:7,000 live births (Gieselmann, 1995). The majority of LSDs are autosomal recessive and are caused by severe loss-of-function mutations within lysosomal trafficking components, lysosomal enzymes or membrane proteins (Platt et al., 2018). For instance, the most common LSD – Gaucher disease – is caused by mutations within the lysosomal enzyme GCase (gene name: *GBA1*). The resulting enzymatic dysfunction leads to the lysosomal accumulation of the non-degraded substrate glucosylceramide (a glycolipid), causing an enlargement of organs (organomegaly), anemia and bone malformation as well as, in some cases, neurological dysfunction (Pastores, 1997).

In a group of LSDs called neuronal ceroid lipofuscinosis (NCL), a lipopigment (lipofuscin) aggregates within lysosomal structures, resulting in a progressive loss of

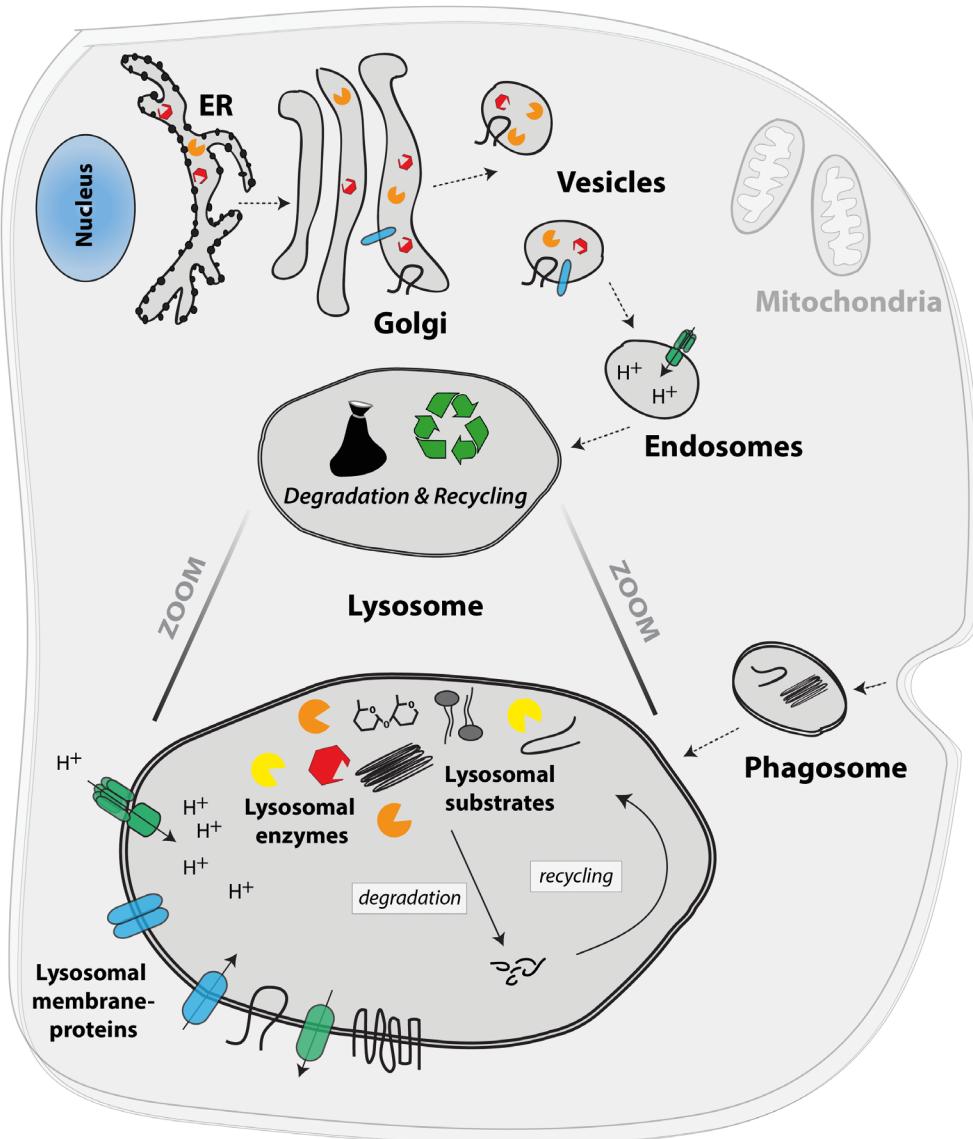


Fig. 1: The eukaryotic cell and its organelles, highlighting the lysosome and its components.

The nucleus contains the majority of the cell's genetic material and is the location of the DNA transcription process (DNA → RNA). Further protein translation (RNA → protein) is mediated at free ribosomes within the cytosol (not shown) or at ribosomes located at membranes of the endoplasmic reticulum (ER; indicated as black dots on ER membrane). The Golgi apparatus (Golgi) is important for further protein modification and sorting. Vesicles originating from the Golgi compartment can fuse with intracellular organelles, like the lysosome, or with the cell membrane. Mitochondria are the 'powerhouse' of the cell, generating energy by performing cellular respiration and producing ATP. The lysosome is the cell's degradative organelle and arises from the fusion of Golgi-derived vesicles with endosomes, as indicated by dotted arrows. Lysosomes are not only responsible for degradation and recycling, but are also involved in pathogen defense, cell death, and energy metabolism. Their acidic pH (pH 4.5–5.0) is mainly maintained by the vacuolar-type H⁺ ATPase, which pumps H⁺ ions via the lysosomal membrane. A total of around 50 specialized lysosomal membrane proteins (blue and green molecules) are not only important for the maintenance and stability of the organelle, but also for the formation of the lysosomal glycocalyx at the inside of lysosomes, lysosomal protein transport, and the transport and exchange of biomolecules through the lysosomal membrane (mediated by a variety of channel and transporter proteins). Lysosomal substrates comprise a variety of intra-cellular as well as extracellular biomolecules including proteins, peptides, lipids, nucleic acids and carbohydrates. Substrates enter the lysosome via macro-, micro- and chaperone-mediated autophagy, as well as by fusion of lysosomes with phagosomes, which comprise extracellular material (indicated by dotted arrows). Around 60 different lysosomal enzymes (yellow, orange and red symbols) are responsible for the breakdown and recycling of specific substrates (shown in black and gray within the lysosome). These enzymes require an acidic pH and include proteases, nucleases, glucosidases, phosphatases, polysaccharide hydrolyzing enzymes, and lipid degrading enzymes.

motor and cognitive abilities. NCLs are classified into ten different types caused by mutations within lysosomal enzymes – such as cathepsin D – but also membrane proteins (Bennett and Rakheja, 2013).

Interestingly, neurodegeneration is observed in nearly all LSDs, which emphasizes the importance of lysosomal degradation within neuronal cell homeostasis (Fraldi et al., 2016). There is increasing evidence for the contribution of lysosomal dysfunction in age-related neurodegenerative diseases, such as Huntington's, Alzheimer's and Parkinson's diseases (Klein and Mazzulli, 2018; Pitcairn et al., 2019). The efficient degradation of lysosomal substrates (proteins, lipids, carbohydrates, etc.) is essential for neuronal survival, since neurons are particularly sensitive to alterations in the lysosomal degradation pathway. This is probably due to their post-mitotic state, since non-degraded lysosomal substrates will not be diluted by cell division, but accumulate over time until they reach critical concentrations. Studies have shown that abnormal protein accumulation can cause neurotoxicity and induce neuronal cell death (Hara et al., 2006; Komatsu et al., 2006). Since our brain cannot regenerate this cell type, the progressive loss of neurons results in neuropathology. Interestingly, a decrease in lysosomal activity could also be measured in postmortem brain samples derived from Parkinson's disease patients (Dehay et al., 2010).

Parkinson's disease is a progressive neurodegenerative disorder that affects about 1–2 % of the population above the age of 65. Parkinson's disease symptoms comprise movement abnormalities, including tremor, bradykinesia (slowness of movement), and muscle rigidity (Kalia and Lang, 2015). During the course of the disease, non-motor symptoms may also arise, consisting of dementia, behavioral and digestive problems, as well as depression (Chaudhuri et al., 2006). These clinical manifestations result from the specific loss of neurons that produce the neurotransmitter dopamine. These so-called dopaminergic neurons are located within the substantia nigra, an area of the midbrain (Davie, 2008). Moreover, a histological hallmark of Parkinson's disease is the intracellular aggregation of the cytosolic protein α -synuclein, which is a major component of Lewy body inclusions found in post-mortem brains of Parkinson's disease patients (Baba et al., 1998; Braak and Del Tredici, 2017; Xia et al., 2008). It has been shown that intracellular α -synuclein aggregation leads to pathological manifestations and conveys cell toxicity (Lashuel and Lansbury, 2006; Lashuel et al., 2002). Importantly, accumulation of α -synuclein is a common feature observed in many LSDs (Shachar et al., 2011), further emphasizing the strong interplay between lysosomal function and α -synuclein aggregation.

The effect of lysosomal dysfunction on α -synuclein aggregation

α -Synuclein is a small cytosolic protein consisting of 140 amino acids encoded by the SNCA gene, and is (under physiological conditions) mainly found in the pre-synaptic terminals of neurons, where it is involved in synaptic neurotransmitter release and synaptic plasticity (George, 2002; Sulzer and Edwards, 2019). Recent studies further illuminate the relationship between lysosomal dysfunction and α -synuclein aggregation. Physiological α -synuclein can be degraded within lysosomes, where lysosomal cathepsins (CTSD and CTSB) are most likely involved in its degradation (Cuervo et al., 2004; Cullen et al., 2009; McGlinchey and Lee, 2015). Since α -synuclein is a very abundant and aggregation-prone protein, even subtle elevations in its concentration within the cell may drive the protein into pathological aggregates (Giasson et al., 1999). Hence, impairments in the lysosomal system have been shown to affect α -synuclein levels and aggregation. Moreover, multiple studies have demonstrated that metabolites like glycolipids that accumulate under lysosomal impairment can specifically interact with α -synuclein and further induce its aggregation (Mazzulli et al., 2011; Suzuki et al., 2015; Taguchi et al., 2017) (Figure 2). This process is thought to be mediated through a toxic structural conversion of α -synuclein oligomers resulting in amyloid fibril formation (Zunke et al., 2018) (Figure 2). Likewise, intra-lysosomal cholesterol may be an important modulator in Parkinson's disease, as it has been shown to directly induce α -synuclein fibrilization (Bosco et al., 2006). Taken together, molecular data indicate that lysosomal storage of certain metabolites influences α -synuclein structure and aggregation capacity. This gives rise to the selective relationship between lysosomal dysfunction and α -synuclein aggregation, similar to that observed in Parkinson's disease.

Lysosomal risk factors in Parkinson's disease

Over the years, numerous molecular, clinical and genetic studies have emphasized a central role for lysosomal pathways and proteins in the pathogenesis of Parkinson's disease (Kalia and Lang, 2015; Klein and Mazzulli, 2018; Mazzulli et al., 2011; Pitcairn et al., 2019). Importantly, genetic meta-analyses of Parkinson's disease patients

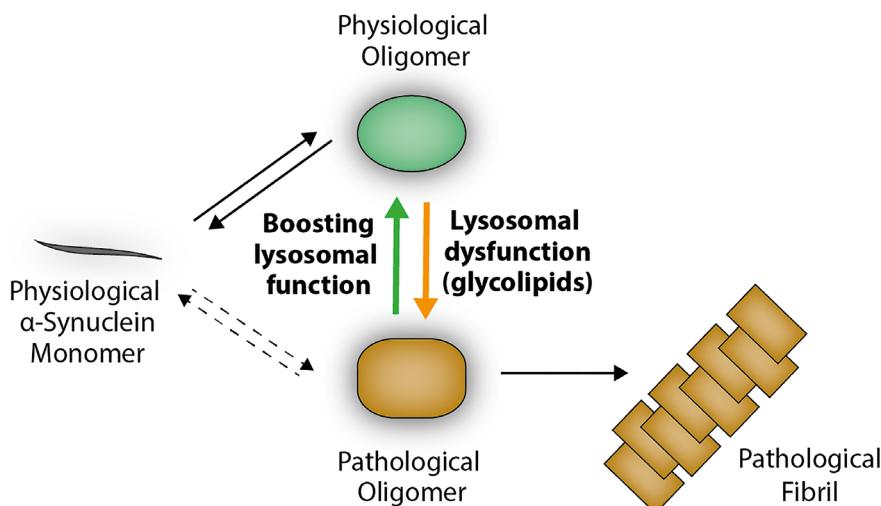


Fig. 2: Schematic overview of α -synuclein aggregation.

Under physiological conditions, α -synuclein mainly exists as a monomer (gray), but can also form physiological oligomers (green) within the cytosol. Lysosomal dysfunction and aggregation of substrates like the GCase-substrate glucosylceramide (a glycolipid) have been shown to interfere with α -synuclein within lysosomes. This interaction of the protein with lysosomal glycolipids results in a structural change in the protein oligomer (orange). These pathological oligomers (orange) have been shown to be neurotoxic and induce pathological fibril formation (orange fibril), which is enhanced by the acidic pH within lysosomes. Interestingly, boosting lysosomal function or decreasing glycolipid levels has been shown to reverse pathological oligomers (orange) back to their physiological state (green). This molecular mechanism is utilized in substrate reduction therapy or by application of small compounds activating substrate-degrading enzymes (e.g. GCase) (modified from Riederer et al., 2019; Zunke et al., 2018).

reveal enrichment in genetic risk loci related to lysosomal function (Chang et al., 2017; Robak et al., 2017; Sidransky et al., 2009). Among these genetic risk factors are lysosomal hydrolases, such as GCase (*GBA1*), galactosylceramidase (*GALC*), sphingomyelin phosphodiesterase 1 (*SMPD1*), N-acylsphingosine Amidohydrolase 1 (*ASAH1*), and N-acetyl-glucosaminidase (*NAGLU*), as well as the two cathepsins B and D (*CTSB*, *CTSD*), which have been shown to degrade α -synuclein (Table 1). All enzymes degrade different lysosomal substrates comprised of various lipids (glycolipids, sphingomyelin, sphingosine) and proteins. Additionally, lysosomal membrane proteins have been added to the list of Parkinson's disease risk genes, including the lysosomal integral membrane protein type-2 (*LIMP-2*), which is the lysosomal transport receptor of GCase, the transmembrane protein 175 (*TMEM175*) and the lysosome-associated membrane protein 3 (*LAMP3*). Furthermore, lysosomal transporter and channel proteins have been identified as risk genes and comprise cation-transporting ATPase 13A2 (*ATP13A2*), the proton pump ATPase H⁺ transporting V0 subunit A1 (*ATP6VOA1*), which is important for the regulation of lysosomal pH, the sialic acid exporter Sialin (*SLC17A5*), and the cholesterol transporter Niemann-Pick C protein (*NPC1*) (Table 1). Moreover, it is no surprise that two vacuolar protein sorting-associated proteins (VPS35/13C), that play an important role in

vesicle-mediated protein trafficking, as well as two ras-related proteins (Rab7L1/39) crucial for vesicle fusion, are found on the list of lysosome-associated risk factors for Parkinson's disease.

Of the lysosomal risk genes, *GBA1* (GCase) has the highest prevalence and thus has been most intensively studied to date. The general mechanistic understanding is that slowed lysosomal digestion of GCase-substrates, including the glycolipid glucosylceramide, interferes with α -synuclein and accelerates its accumulation (Mazzulli et al., 2011; Zunke et al., 2018) (Figure 2). Data from genome studies indicate that mutations in *GBA1* are linked to a ~20-fold increase in the risk of developing Parkinson's disease (Beavan and Schapira, 2013). Additionally, genetic studies show that 5–10 % of Parkinson's disease patients carry mutations in *GBA1* (Lesage et al., 2011; McNeill et al., 2012; Sidransky et al., 2009).

For most other identified genetic risk factors shown in Table 1 there is still a lack of knowledge about their contribution to molecular disease mechanisms and disease progression. Future studies, for instance in induced-pluripotent stem cell (iPSC) derived patient neurons (Zunke and Mazzulli, 2019), will shed light on the impact of some of these pathology-associated genes. This will help further our understanding of Parkinson's disease pathology and give rise to novel therapeutic approaches.

Tab. 1: Lysosomal genes associated with Parkinson's disease.

Gene name	Protein name	Function	Reference
Lysosomal enzymes			
<i>GBA1</i>	β -Glucocerebrosidase (GCase)	Degradation of lysosomal sphingolipids, mainly glucosylceramide	(Chang et al., 2017; Nalls et al., 2014; Robak et al., 2017; Sidransky et al., 2009)
<i>GALC</i>	Galactocerebrosidase	Degradation of lysosomal sphingolipids, mainly galactosylceramide	(Chang et al., 2017)
<i>SMPD1</i>	Sphingomyelin phosphodiesterase 1	Degradation of sphingomyelin	(Gan-Or et al., 2015; Gan-Or et al., 2013; Robak et al., 2017)
<i>ASAH1</i>	N-Acylsphingosine Amidohydrolase 1	Degradation of ceramide into sphingosine and free fatty acid	(Robak et al., 2017)
<i>CTSB</i>	Cathepsin B	Cysteine protease, involved in degradation of various substrates including α -synuclein	(Chang et al., 2017)
<i>CTSD</i>	Cathepsin D	Aspartyl protease, involved in degradation of various substrates including α -synuclein	(Robak et al., 2017)
<i>NAGLU</i>	N-Acetylglucosaminidase	Hydrolysis of terminal non-reducing N-acetyl-D-glucosamine	(Winder-Rhodes et al., 2012)
Lysosomal membrane proteins			
<i>TMEM175</i>	Transmembrane protein 175	Potassium channel	(Chang et al., 2017; Nalls et al., 2014)
<i>ATP13A2</i>	Cation-transporting ATPase 13A2	Cation transporter	(Ramirez et al., 2006)
<i>ATP6VOA1</i>	ATPase H ⁺ transporting V0 subunit A1	Component of the V-ATPase, acidification of lysosomes	(Chang et al., 2017)
<i>LAMP3</i>	Lysosome-associated membrane protein 3	Type I transmembrane glycoprotein, lysosomal glycocalyx	(Pihlstrom et al., 2013; Simon-Sanchez et al., 2009)
<i>SCARB2</i>	Lysosomal integral membrane protein type-2 (LIMP2)	Type III transmembrane glycoprotein, lysosomal glycocalyx, lysosomal transport of GCase	(Hopfner et al., 2011)
<i>SLC17A5</i>	Sialin	H ⁺ -coupled sialic acid exporter	(Robak et al., 2017)
<i>NPC1</i>	Niemann-Pick C1 protein	Lysosomal cholesterol transporter	(Kluenemann et al., 2013)
Proteins involved in lysosomal trafficking/autophagy			
<i>VPS35</i>	Vacuolar protein sorting-associated protein 35	Trafficking machinery, retromer complex component	(Vilarino-Guell et al., 2011; Zimprich et al., 2011)
<i>VPS13C</i>	Vacuolar protein sorting-associated protein 13C	Trafficking machinery, mitophagy, mitochondrial depolarization	(Lesage et al., 2015)
<i>Rab7L1</i>	Ras-related protein Rab-7L1	Retrograde trafficking pathway for recycling proteins	(MacLeod et al., 2013; Nalls et al., 2014)
<i>Rab39B</i>	Ras-related protein Rab-39B	Trafficking machinery, autophagy	(Lesage et al., 2015; Mata et al., 2015)
<i>GAK</i>	Cyclin G-associated kinase	Involved in the uncoating of clathrin-coated vesicles	(Dumitriu et al., 2011)
<i>KAT8</i>	Lysine acetyltransferase 8	Modulator of autophagic flux	(Chang et al., 2017)

Therapeutic approaches targeting lysosomes

As highlighted above, dysfunction in lysosomal pathways not only causes LSDs, but also plays a central role in neurodegenerative disorders, like Parkinson's disease. A number of treatment strategies aiming to boost lysosomal function have been identified or are under development for LSDs, and may also provide novel opportunities for treating Parkinson's disease. Considering the importance of cellular degradation in Parkinson's disease etiology, strategies to enhance lysosomal function involve: (a) enzyme replacement to substitute dysfunctional enzymes; (b) chaperones to stabilize unstable or misfolded enzymes in order to increase their lysosomal activity; (c) small molecules that act as direct allosteric activators on lysosomal enzymes; (d) substrate reduction therapies in order to decrease lysosomal load; (e) cell therapies to replace injured cells; (f) gene therapy (Klein and Futterman, 2013).

The most common treatment strategy for certain LSDs is the administration of functional recombinant enzymes by repetitive infusions (enzyme replacement therapy) (Beck, 2018). Although this treatment has been shown to be effective in patients, enzyme replacement therapy has several disadvantages. First of all, the production of enzymes is very expensive and, secondly, recombinant enzymes are usually large proteins and thus difficult to transport across the blood-brain barrier. Hence, most enzyme replacement therapies are able to improve non-neuronopathic, but not neurological pathologies. Compared to enzyme replacement therapy, small activators of lysosomal enzymes have the potential to cross the blood-brain barrier and thus are able to treat neurological symptoms. Various small activators of lysosomal enzymes, including chaperones for GCase, are under development or already approved as drugs for the treatment of LSDs (Beck, 2018).

Interestingly, some of the compounds applied for LSDs are now tested for their effectiveness in neurodegenerative disorders, including Parkinson's disease. Recent studies utilizing small activators/chaperones of the lysosomal enzyme GCase have been shown to improve Parkinson's disease pathology by reducing α -synuclein aggregation in iPSC-derived neurons of Parkinson's patients (Mazzulli et al., 2016), as well as in a transgenic Parkinson's disease mouse model (Mgdalska-Richards et al., 2016). The effect of GCase activators is due to increased enzymatic turnover and a reduction in glucosylceramide, which has been shown to interfere with α -synuclein, resulting in neurotoxic oligomeric conformers (Zunke et al., 2018) (Figure 2: conversion from physiological (green) to pathological

(orange) oligomer). Hence, a reduction in the glycolipid decreases the amount of toxic α -synuclein forms and thus α -synuclein-induced pathology (Figure 2: reversal of toxic form (orange) to physiological form (green)).

A similar reduction in α -synuclein aggregation could be observed after substrate reduction therapy. A small blood-brain-barrier-permeable molecule reducing the synthesis of the GCase-substrate glucosylceramide has been shown to reduce α -synuclein levels in Parkinson's iPSC neurons (Zunke et al., 2018), as well as to improve cognitive symptoms in Parkinson's disease mice (Sardi et al., 2017). Although substrate reduction is already in clinical use for some LSDs (e.g. Gaucher disease), this treatment option is still under investigation in clinical phases for Parkinson's disease patients.

Likewise, therapies aiming to lower levels of other lysosomal molecules that might interfere with protein aggregation have shown to be beneficial for neurodegenerative disorders. Accordingly, reducing cholesterol levels in a mouse model of Parkinson's disease also revealed a decrease in α -synuclein aggregation (Bar-On et al., 2006).

In summary, targeting lysosomal pathways in Parkinson's disease pathology provides new possibilities to treat this progressive neurological disorder, for which no curative treatment strategy currently exists. The molecular and genetic evidence reviewed here will help us to further understand cellular disease mechanisms and direct future drug development.

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