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Lysosomes and α -synuclein form a dangerous duet leading to neuronal cell death

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Neurodegenerative diseases are (i) characterized by a selective neuronal vulnerability to degeneration in specific brain regions; and (ii) likely to be caused by disease-specific protein misfolding. Parkinson's disease (PD) is characterized by the presence of intraneuronal proteinaceous cytoplasmic inclusions, called Lewy Bodies (LB). α -Synuclein, an aggregation prone protein, has been identified as a major protein component of LB and the causative for autosomal dominant PD. Lysosomes are responsible for the clearance of long-lived proteins, such as α -synuclein, and for the removal of old or damaged organelles, such as mitochondria. Interestingly, PD-linked α -synuclein mutants and dopamine-modified wild-type α -synuclein block its own degradation, which result in insufficient clearance, leading to its aggregation and cell toxicity. Moreover, both lysosomes and lysosomal proteases have been found to be involved in the activation of certain cell death pathways. Interestingly, lysosomal alterations are observed in the brains of patients suffering from sporadic PD and also in toxic and genetic rodent models of PD-related neurodegeneration. All these events have unraveled a causal link between lysosomal impairment, α -synuclein accumulation, and neurotoxicity. In this review, we emphasize the pathophysiological mechanisms connecting α -synuclein and lysosomal dysfunction in neuronal cell death.

Keywords: α -synuclein, lysosome, Parkinson's disease, cell death

INTRODUCTION

Neurodegenerative diseases are (i) characterized by a selective neuronal vulnerability to degeneration in specific brain regions; and (ii) likely caused by disease-specific protein misfolding. Parkinson's disease (PD), the second most common neurodegenerative disorder after Alzheimer's disease, is notably characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc). Loss of dopamine perturbs the cortico-basal ganglia-cortical control of voluntary movements. Current treatments have no proven protective or restorative effect and are only symptomatic. Moreover, their long-term use is associated with the onset of dramatic side effects i.e., fluctuated responses and L-Dopa induced dyskinesia. The important of understanding the mechanisms of neuronal death underlying neurodegenerative diseases is crucial for identifying targets for disease-modifying/curative strategies. In addition to dopaminergic neuronal cell loss, the main pathological hallmark of PD is the presence of intraneuronal proteinaceous cytoplasmic inclusions, named Lewy bodies (LB). α -Synuclein (α -syn), a major protein component of LB, has been identified as autosomal dominant cause of PD, which is found increased in expression in patients (Goedert et al., 2013; Lashuel et al., 2013). The presence of LB in PD suggests that defective protein handling contributes to the pathogenesis of the disease. Proteasomal and autophagic proteolysis are the two major pathways for degradation of cellular constituents in

eukaryotic cells. Mounting evidence indicates that alterations in autophagy-lysosomal pathways (ALP) may be preferentially involved in PD. In this article, we review the close relationship between α -syn and the lysosome, two players involved in neuronal cell death in PD.

THE HARMFUL α -SYNUCLEIN

α -Syn has a central role in the pathogenesis of PD and other synucleinopathies, as dementia with Lewy bodies (DLB) and Multiple System Atrophy (MSA; Spillantini and Goedert, 2000). In 1997, the first link between PD and α -syn was described with the identification of point mutations -A53T- in the SNCA gene in autosomal-dominant forms of PD (Polymeropoulos et al., 1997; Athanassiadou et al., 1999; Spira et al., 2001; Ki et al., 2007; Choi et al., 2008; Puschmann et al., 2009). To date, the list of missense mutations continues to grow with A30P, E46K, H50Q, G51D, A53E (all classified as *PARK1* locus) (Krüger et al., 1998; Zarranz et al., 2004; Appel-Cresswell et al., 2013; Lesage et al., 2013; Proukakis et al., 2013; Pasanen et al., 2014). The subsequent identification of families with multiplication (duplication or triplication) of its allele (*PARK4* locus) strengthen the link between α -syn and PD (Singleton et al., 2003; Chartier-Harlin et al., 2004), suggesting that increased expression levels of the normal α -syn can be causal for PD and others synucleinopathies. Furthermore, genome-wide association studies (GWAS) have linked single nucleotide polymorphisms

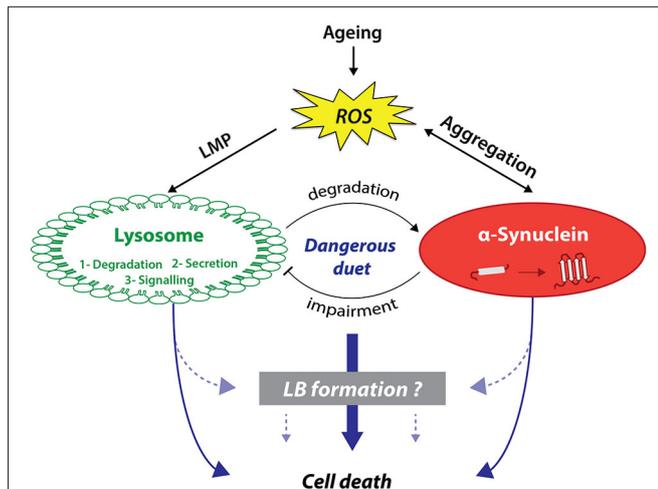


FIGURE 1 | Lysosomes and α -synuclein are involved in a vicious pathogenic loop eventually leading to cell death and LB formation. On the one hand, lysosomes have been shown to be involved in cell death activation through canonical or non-canonical pathways. On the other hand, α -synuclein (α -syn) can also trigger cell death through several distinct pathways including membranes permeabilization. Lysosomes and α -syn display a bidirectional relationship. While lysosomes predominantly degrade α -syn, α -syn aggregation can lead to lysosomal dysfunction in return. α -Syn-mediated lysosome impairment can lead to alterations of one of lysosomal main function: protein degradation, lysosome-to-nucleus signaling, and secretion. This pathogenic loop can be worsened with age and in particular ROS production, which can induce both LMP and α -syn aggregation. Interestingly, α -syn aggregation, especially specific oligomeric species, can increase ROS production. We previously suggested that this loop might be the template for the formation of LB, which remains currently unknown.

(SNPs) in the *SNCA* gene with increased susceptibility of developing PD (Simón-Sánchez et al., 2009; Edwards et al., 2010; International Parkinson Disease Genomics et al., 2011). α -Syn is a 14 kDa neuronal protein consisting of 140 amino acids mainly localized to presynaptic terminals. While the exact physiological function of α -syn remains to be fully understood, several studies have implicated its capacity to interact directly with cellular membranes, such as vesicles (Auluck et al., 2010) or mitochondria-associated membrane, which is an endoplasmic reticulum subdomain involved in lipid and calcium homeostasis (Guardia-Laguarta et al., 2014). Nevertheless, substantial evidence suggests that α -syn function is related to vesicle dynamics, neurotransmission and synaptic plasticity, the mechanisms of which have been reviewed elsewhere (Bellani et al., 2010). In its native state, the previous paradigm was that α -syn behaves as an unfolded monomer. However, a recent report now hints at a more complex picture as the predominant physiological species of α -syn is a helically folded tetramer (Bartels et al., 2011). α -Syn is, however, intrinsically defined as an aggregation-prone protein. In PD brains, α -syn antibodies strongly react in LB (Spillantini et al., 1997) and Lewy neurites (Takeda et al., 1998). Biochemical analyses have shown that α -syn is a major protein component of LB and may be part of the β -sheet enriched fibrillar structure of these inclusions (Crowther et al., 2000).

α -Syn can undergo several post-translational modification such as truncation, nitration, oxidation, sumoylation, ubiquitinylation and phosphorylation (Giasson et al., 2000; Fujiwara et al., 2002; Tofaris et al., 2003; Anderson et al., 2006; Dorval and Fraser, 2006; Krumova et al., 2011). Interestingly, post-translationally modified α -syn has been found in LB and some post-translational modifications, such as oxidation or nitration, have been shown to impact its aggregation process in favor to oligomeric species (Fujiwara et al., 2002; Norris et al., 2003; Yamin et al., 2003). In the past few years, substantial progress has been made not only at elucidating how α -syn undergoes spontaneous self-aggregation, but also in its highly heterogeneous aggregation process that turns its monomers into multiple oligomeric forms, then protofibrils, fibrils and aggregates. The identification of pathological species of α -syn involved in the perturbation of cellular function is an expanding area of research. Recent studies support the concept of soluble oligomers as the prominent toxic α -syn species in *in vitro* and *in vivo* settings, although the precise size and type of the toxic oligomeric species remains to be determined (Auluck et al., 2010; Winner et al., 2011; Cremades et al., 2012). Recent evidence piles up for prion-like propagation mechanisms in synucleinopathies, including PD. Indeed, α -syn might behave as a prion, responsible for initiating and spreading the pathological process in PD. Supporting this concept, α -syn can be transmitted to neighboring neurons and neuronal precursor cells (Puschmann et al., 2009; Hansen et al., 2011). *In vivo* studies have added a further piece to the puzzle with the observation that intracerebral inoculation of synthetic recombinant α -syn fibrils (Pffs) can mimic α -syn pathology in mice (Luk et al., 2012). More recently, through an innovative strategy based on the purification of aggregated α -syn from the SNpc of PD patients, intranigral or intrastriatal inoculations of PD-derived LB extracts resulted in progressive nigrostriatal neurodegeneration in both mice and monkeys (Recasens et al., 2014), which were found to originate at striatal dopaminergic terminals. Overall, these results demonstrated that human α -syn species contained in PD-derived LB are pathogenic and have the capacity to initiate a PD-like pathological process, not only in rodents but also in non-human primates (Recasens et al., 2014). Taken together, α -syn has multiple ways to cause cellular perturbations and lead to cell death. The presence of undegraded proteinaceous inclusions led the research community to wonder how is handled α -syn degradation? It is now understood that this involves both the ubiquitin-proteasome system (UPS) and the ALP. α -Syn is, however, predominantly degraded inside lysosomes, through chaperone-mediated autophagy (CMA) or endocytosis (Webb et al., 2003; Cuervo et al., 2004; Martinez-Vicente and Vila, 2013). The signals responsible for targeting α -syn (although it contains a KFERQ-like sequence, i.e., a motif recognized by heat shock cognate70 (hsc70) allowing direct lysosomal import) to a given degradation pathway are not yet fully understood, but may heavily depend on its folding state. Aggregated proteins will be preferentially routed for degradation to the lysosome through macroautophagy, whereas soluble forms would be both targeted to the proteasome or to the CMA. Overall, defective α -syn protein degradation can be recognized as an important pathogenic factor.

LYSOSOME: WHITE KNIGHT OR TWO-FACE

Lysosomes are dynamic acidic organelles that contain hydrolytic enzyme capable of degrading intracellular components, which were discovered by Christian de Duve more than 50 years ago (De Duve et al., 1955; Luzio et al., 2007). Acidic pH (around 4.6) is maintained in the lumen by proton-pumping vacuolar ATPases. Around 200 proteins have been reported as lysosomal membrane proteins such as proton pumps, secretory, plasma membrane, signaling or transport proteins (Schröder et al., 2007). The most abundant proteins are the lysosomal-associated membrane protein (LAMP)-1 and LAMP-2 as well as the lysosomal integral membrane protein (LIMP)-2 and CD63 (Saftig et al., 2010). Interestingly, lysosomes have a high intravesicular Ca^{2+} concentration (around 500–600 μM). Defective lysosomal Ca^{2+} uptake has been associated with human diseases, such as Niemann-Pick type C (Lloyd-Evans and Platt, 2011). Several lysosomal storage disorders are caused by lysosomal membrane dysfunctions (Ruivo et al., 2009). These defects are mostly due to non-enzymatic transport defects, highlighting the importance of transport and channel proteins in lysosome physiology (Ruivo et al., 2009). As mitochondrial outer membrane permeabilization (MOMP) is a major checkpoint of apoptosis pathway, lysosomal membrane permeabilization (LMP) has also been shown to induce cell death (Boya and Kroemer, 2008). Following LMP, cell death can occur through several pathway including canonical MOMP/caspase pathway but also MOMP- and caspase-independent pathways (Boya and Kroemer, 2008). The two main effects of LMP are the release of lysosomal proteases, such as cathepsins B or D (CSTB/CTSD), and cytosolic acidification. CTSD or CTSB could then directly or indirectly promote cytochrome C release from mitochondria (Boya and Kroemer, 2008). Currently, the principal inducer of LMP remains to be reactive oxygen species (ROS), although Bcl-2-associated X protein (Bax) has also shown to initiate this process (Kågedal et al., 2005).

Several pathways converge to the lysosome: phagocytosis, endocytosis, and autophagy through three different means respectively named microautophagy, CMA and macroautophagy. Autophagy (which comes from the Greek: “self-eating”) is an evolutionary conserved mechanism that allows cells to degrade their own components and recycle important molecules (Wong and Cuervo, 2010; Cuervo, 2011; Boya et al., 2013). Briefly, CMA involves selective recognition by a chaperone and import through LAMP-2a, while microautophagy and macroautophagy involve direct sequestration of a portion of the cytosol (including proteins and organelles). While microautophagy requires the direct invagination of lysosomal membrane, macroautophagy involves the formation of a vesicle named autophagosome that will then fused with lysosomes to allow degradation of the sequestered material. In regards to protein aggregation, macroautophagy has been suggested to be the mammalian counterpart of the cytosolic-to-vacuole (Cvt)-pathway in yeast responsible for cargo-selective degradation (Yamamoto and Simonsen, 2011). Selective degradation of protein aggregates, named aggrephagy, has been characterized based on the observation of autophagosomes specifically containing aggregates (Filimonenko et al., 2010). Moreover, a phosphatidylinositol 3-phosphate-binding protein, Alf γ , has been shown to specifically

recognize and promote degradation of huntingtin aggregates (Filimonenko et al., 2010). For several decades, lysosomes have been only considered as terminal degradative compartments. However, recent studies suggest that lysosomes are involved in a vast number of cellular functions including lysosome-to-nucleus signaling, secretion, energy metabolism and cell death pathways (Rodriguez et al., 1997; Settembre et al., 2012, 2013).

Impairment of ALP, which is essential to maintain proper protein and organelle quantity and quality within cells, is increasingly regarded as a major pathogenic event in neurodegenerative diseases, including PD. The presence of LB in brains of PD patients made the first connection with ALP and led to the hypothesis that defective protein handling system might contribute to the pathogenesis of the disease. Several studies from independent groups reported ALP impairment associated with lysosomal depletion in brain tissue from idiopathic PD patients (Chu et al., 2009; Alvarez-Erviti et al., 2010; Dehay et al., 2010). More precisely, accumulation of undegraded microtubule-associated protein light chain 3 (LC3)-positive vesicles, decreased cytosolic hsc70, LAMP-1 and LAMP-2a have been reported (Chu et al., 2009; Alvarez-Erviti et al., 2010; Dehay et al., 2010). Genetic studies further strengthen the connection between PD and ALP dysfunction, which have indicated that lysosomal impairments may play a primary pathogenic role in the disease process. Interestingly, both CMA and proteasome can degrade the two proteins associated with autosomal dominant inheritance of PD, i.e., α -syn (*PARK1/PARK4* locus) and Leucine-rich repeat kinase 2 (*LRRK2-PARK8* locus) (Webb et al., 2003; Cuervo et al., 2004; Orenstein et al., 2013). However, PD-linked α -syn mutants (as well as post-translationally dopamine-modified wild-type α -syn) and mutant forms of LRRK2 block CMA activity, resulting in insufficient clearance and subsequent accumulation and aggregation of α -syn (Cuervo et al., 2004; Martinez-Vicente et al., 2008; Mak et al., 2010; Orenstein et al., 2013). Notably, two other genes encoding for lysosomal proteins have been linked to PD: the lysosomal type 5 P-type ATPase (*ATP13A2-PARK9* locus) (Ramirez et al., 2006) and the enzyme glucocerebrosidase (GBA; Aharon-Peretz et al., 2004; Di Fonzo et al., 2007; Sidransky et al., 2009). While the former has been characterized in rare families with prominent parkinsonism (Ramirez et al., 2006; Di Fonzo et al., 2007), the latter has been identified as risk factor in multicenter genetic analysis of patients (Sidransky et al., 2009). Recently, genetic analysis suggested that lysosomal dysfunction may play an important role in the etiology of DLB (Bras et al., 2014). Relevant to PD, these two proteins have been reported to be components of LB (Goker-Alpan et al., 2010; Dehay et al., 2012). Defects in one of these two proteins may result in insufficient clearance of α -syn through lysosomes, hence leading to the accumulation of this protein in both cytosol and lysosome lumen (Dehay et al., 2012). Such vicious pathogenic loop has been reported between GBA and α -syn (Mazzulli et al., 2011). One can thus imagine a similar scenario in which toxic species of α -syn “damage” lysosomes, hence leading to an impairment of α -syn clearance that subsequently favor α -syn-aggregation. Such aggregates then cause, in return, other damages, while concomitantly accumulating in lysosomes/autolysosomes to form LB (Dehay et al., 2012).

In addition to the aforementioned genes, hereditary parkinsonism has been identified in families carrying mutations for ALP-related pathways. For instance, mutations in parkin (*PARK2* locus), in the phosphatase and tensin homolog (PTEN)-induced putative kinase 1 (PINK1) (*PARK6* locus) or in DJ-1 (*PARK7* locus), which are all involved in mitophagy, lead to autosomal recessive forms of PD (Corti et al., 2011). While PINK1 and parkin belong to the same pathway, DJ-1 has been shown to be involved in an independent parallel pathway, which can rescue a loss of function of PINK1 (Hao et al., 2010; Thomas et al., 2011). A defective degradation of dysfunctional mitochondria leads to maintaining those in the neuron and hence promotes the mitochondrial dysfunctions that have been characterized in PD patients (i.e., decrease in complex I activity and accumulation of large-scale mitochondrial DNA mutations) (Schapira et al., 1989; Bender et al., 2006). Mutations in the PD-associated gene *UCH-L1* (*PARK5*) abnormally interact with LAMP-2A, also causing an increase amount of α -syn (Kabuta et al., 2008). From a genetic point of view, all genes that have been positively associated with PD (Corti et al., 2011) are also connected to ALP, which shed light on the lysosome as an important player in PD-induced cell death.

NEURONAL CELL DEATH: THE THIRD PARTNER

Lysosomal function impairment and α -syn aggregation can both induce cell death either on their own or through a dramatic additive effect. Of importance, α -syn seems to induce cell toxicity through its different pathological α -syn species, which include post-translationally modified, mutant, oligomeric and aggregated forms. These can (i) disrupt its typical function in neurotransmission release (Abeliovich et al., 2000; Jenco et al., 1998); (ii) impair mitochondrial dynamics, structure and function (Martin et al., 2006; Nakamura et al., 2011; Stefanovic et al., 2014); and (iii) disrupt ER-Golgi vesicle trafficking (Cooper et al., 2006; Gitler et al., 2008) and mitochondria-associated ER membrane (Mercado et al., 2013; Guardia-Laguarta et al., 2014), which results in ER stress. Further supporting the α -syn species toxicity, CMA inhibition by either PD-linked α -syn mutants or dopamine-modified wild-type α -syn results in an accumulation of α -syn, but also of undegraded CMA-substrates, involved for instance in the regulation of neuronal survival through the degradation of the neuronal survival factor myocyte enhancer factor 2D (MEF2D; Yang et al., 2009).

Regarding the lysosome, LMP is one mechanism for the induction of certain cell death pathways. As mentioned above, disruption of lysosomal membrane provokes cell death through release of CTs and other hydrolases from the lysosomal lumen to the cytosol. These lysosomal proteases can remain active at cytosolic pH and induce cellular damages by degradation of vital proteins or activation of caspases. In relation to PD pathophysiology, mechanistic studies using the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model of PD have reported a lysosomal dysfunction, characterized by lysosomal depletion and autophagosome accumulation. Such lysosomal deficiency was secondary to abnormal LMP induced by Complex I inhibition-mediated ROS production (Dehay et al., 2010; Vila et al., 2011). Recent studies reported that the pro-apoptotic Bax

protein, which mediates MOMP, is activated in PD patients (Bové et al., 2014). In experimental PD mouse model, Bax translocates to the lysosome and mediates LMP before MOMP (Bové et al., 2014). Interestingly, pharmacological inhibition of Bax-mediated LMP and MOMP results in an overall attenuation of MPTP-mediated cell death, even if the treatment is administered once pathogenic neuronal changes are already in motion (Bové et al., 2014), suggesting that the phenomenon at work is reversible.

One of the meeting points between α -syn and lysosome involves ROS. Recent reports suggest that α -syn oligomers can induce both MOMP and in particular LMP (Freeman et al., 2013; Stefanovic et al., 2014). α -Syn aggregation underlies a bidirectional relationship with ROS production. Specific α -syn oligomers increase ROS production, whereas oxidized α -syn inhibits fibril formation in favor to toxic species (Norris et al., 2003; Cremades et al., 2012). Hence, α -syn-mediated ROS production can lead to LMP, as previously characterized in PD, and subsequently to cell death. All these studies suggest that oxidative stress impact both lysosomes and α -syn aggregation. In the past few years, another piece has been added to the puzzle, suggesting that α -syn might potentially spread in a prion-like manner, from cell to cell and region to region. Although mechanisms of α -syn release are not yet elucidated, α -syn may be released by exocytosis in a calcium-dependent manner (Lee et al., 2005; Emmanouilidou et al., 2010), a phenomenon exacerbated after lysosomal inhibition (Alvarez-Erviti et al., 2011), subsequently enhancing disease progression and the lysosomal contribution to the pathology. Non-genetic factors, however, cannot be excluded as important risks to PD. This includes ageing for instance which remains the most compelling risk factor for PD. Ageing is also associated with mitochondrial and lysosomal impairments as well as ROS production (Dufour and Larsson, 2004; Mattson and Magnus, 2006), linking the several key events that occur in neuronal cell death in PD.

Of interest, pharmacological or genetic enhancement of autophagy has been shown to be beneficial in PD models. For example, in the MPTP-treated mouse model, pharmacological activation of ALP with the mammalian target of rapamycin (mTOR) inhibitor, rapamycin, attenuates neurodegeneration and lysosomal dysfunction (Dehay et al., 2010; Malagelada et al., 2010). Consistent with this approach, viral-mediated overexpression of ALP components, such as transcription factor EB (TFEB), LAMP2a or Beclin-1, provided neuroprotection in viral-mediated α -syn-overexpressing rodent models of PD (Spencer et al., 2009; Decressac et al., 2013; Xilouri et al., 2013). With regards to the development of therapeutic approaches, we must keep in mind that a balance needs to be maintained between boosting and inhibiting processes of autophagy. Indeed, autophagy has been shown to have both survival promoting and death promoting roles (Eskelinen, 2005). Hence, enhancement of lysosomal biogenesis or specific activation of late steps of the autophagy machinery might provide more successful approach compared to a broad activation of the whole autophagy machinery, potentially leading to a deleterious effect and eventually cell death. Increasing the ability of neurons under attack to degrade protein aggregates remains a promising strategy for PD.

CONCLUDING REMARKS

Seventeen years after its association with PD, α -syn is now considered as a central player in PD pathogenesis, linking genetic and idiopathic forms of parkinsonism. Two key elements strongly associate α -syn aggregation and lysosomal dysfunction: (i) aggregated or post-translationally modified forms of α -syn can directly or indirectly inhibit lysosomal function; and (ii) the occurrence of a lysosomal depletion in brains from PD patients as well as in several experimental models of PD. Consistent with these evidences, LB formation might be the result of the combination of both α -syn aggregation and lysosomal failure, as key components of autophagy and α -syn have been localized in LB. Altogether, this suggests that α -syn aggregation and lysosomal impairment, enhanced with ageing, could play a deleterious duet leading to dopaminergic cell death (Figure 1).

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