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Alpha-synuclein: Pathology, mitochondrial dysfunction and neuroinflammation in Parkinson's disease

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ABSTRACT

Parkinson's disease (PD) is a complex, chronic and progressive neurodegenerative disease. While the etiology of PD is likely multifactorial, the protein α-synuclein is a central component to the pathogenesis of the disease. However, the mechanism by which α-synuclein causes toxicity and contributes to neuronal death remains unclear. Mitochondrial dysfunction is also widely considered to play a major role in the underlying mechanisms contributing to neurodegeneration in PD. This review discusses evidence for the neuropathological role for α-synuclein in the dysfunction of dopamine neurons in PD. We also discuss insights into the structure, localization, and cellular roles for α-synuclein that may influence its aggregation properties, ultimately impacting its pathogenicity, role in lysosomal dysfunction and activation of the neuroimmune response. We further highlight recent evidence linking α-synuclein and mitochondrial dysfunction in neurodegeneration. Identifying the underlying mechanisms responsible for this bi-directional relationship between α-synuclein and mitochondrial dysfunction may provide new insights into the pathophysiology of PD.

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the loss of dopamine (DA) neurons in the substantia nigra pars compacta (SNc) and accumulation of insoluble cytoplasmic protein inclusions referred to as Lewy bodies and Lewy neurites. The precise mechanism underlying the pathogenesis of PD is not yet understood. Accumulating evidence suggests that soluble α-synuclein aggregates, known as oligomers, play a significant role in the PD neurodegenerative process by impairing many subcellular functions (Choi et al., 2013; Colla et al., 2012; Emmanouilidou et al., 2010; Winner et al., 2011).

In this review, we summarize the current data describing what is known about α-synuclein physiology and how changes in α-synuclein biology can contribute to PD. We further discuss a role for mitochondrial dysfunction and neuroinflammation in PD and how α-synuclein is intricately involved in many aspects of neuronal function including mitochondrial homeostasis. Understanding how the different structural forms of α-synuclein influence mitochondrial function (and *vice versa*), may ultimately help us better design PD therapeutics.

1.1. α-Synuclein in Lewy bodies and Lewy neurites: a histopathological signature of PD

Lewy bodies and Lewy neurites are abnormal inclusions that accumulate within neurons in PD. Lewy body and Lewy neurite pathology have been described in several other neurodegenerative diseases including Lewy body dementia (LBD) and multiple system atrophy (MSA), but the significance of these protein aggregates remains to be determined. Post-mortem analysis of PD brains has revealed that the majority of Lewy bodies and Lewy neurites occur within the pigmented neurons in the SNc, in addition to other central and peripheral neuronal populations (Dickson, 2012; Hughes et al., 1993; Jellinger, 1987; Takahashi and Wakabayashi, 2001). The major component of these Lewy bodies and Lewy neurites is insoluble α-synuclein fibrils (Spillantini et al., 1997).

Classical Lewy bodies are found in the remaining DA neurons of the SNc and are described as intraneuronal, round, eosinophilic inclusions with a hyaline core and a pale peripheral halo that are always positive for α-synuclein and ubiquitin (Takahashi and Wakabayashi, 2001). Lewy neurites refer to abnormal neurites containing granular material and α-synuclein filaments, similar to those found in Lewy bodies. Lewy neurites are more abundant than Lewy bodies and accumulate in the amygdala and striatum in most PD cases (Braak et al., 2003; Duda et al., 2002). Interestingly, Lewy neurites are detected prior to the appearance of Lewy bodies and therefore the impact of Lewy bodies on cellular physiology may have greater relevance for later stages of PD.

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Lewy neurites may disrupt axonal transport and other important cellular processes, thus compromising neuronal function and survival (Morfini et al., 2009; Perlson et al., 2010; Volpicelli-Daley et al., 2014). Substantial evidence from animal models, biochemical, and biophysical approaches suggest that the prefibrillar forms of α-synuclein, referred to as soluble oligomers are the early and toxic species that contribute to the neurodegenerative processes in PD (Choi et al., 2013; Colla et al., 2012; Emmanouilidou et al., 2010; Roberts et al., 2015; Winner et al., 2011). Investigating the role these early aggregates have in modulating mitochondrial function, mitophagy, transport, and other neuronal functions in the presynaptic terminals and axons may better help our understanding into the etiology of PD.

1.2. SNCA mutations in PD

The vast majority of PD cases are sporadic with an average age at onset of 60 years of age (Pankratz and Foroud, 2007). Approximately 5–10% of patients are diagnosed with a monogenic form of the disease, which typically has an earlier age at onset and is accompanied by more extensive neuropathology. Though in some genetic cases, the disease may manifest at a late-age and clinically resemble sporadic PD (Pankratz and Foroud, 2007). Current advancements in understanding sporadic PD have been mainly driven by studies focused on elucidating the functional roles of genes identified as monogenic forms of PD. Mutations in *SNCA, LRRK2*, and *VPS35* genes are highly penetrant and cause autosomal dominant forms of PD. The more rare autosomal recessive forms of PD, which include mutations in *PINK1*, *DJ-1*, *PARKIN*, and *ATP13A2* are less penetrant and cause a disease phenotype that has considerable overlap in the clinical and pathological features of sporadic PD, but is more consistent with parkinsonism, than true sporadic PD (Park et al., 2011; Ramirez et al., 2006). The topic of genetic causes of PD is beyond the scope of this review, but has been extensively examined and is discussed elsewhere (Houlden and Singleton, 2012).

The NG_011851 (*SNCA*) gene encodes the human α-synuclein protein. The presence of either a point mutation (e.g. p.A53T; p.A30P and p.E46K) in the *SNCA* gene or a whole locus multiplication will result in an autosomal dominant form of PD (Singleton et al., 2003). Almost twenty years ago, the first *SNCA* mutation was identified as a p.A53T substitution (Polymeropoulos et al., 1997). It is important to mention that additional *SNCA* missense mutations have been identified in different populations, but are more rare, and thus little data is available on these monogenic forms of PD (Appel-Cresswell et al., 2013; Kiely et al., 2015; Porcari et al., 2015). The average age at onset for an individual with a missense *SNCA* mutation is between 50 and 65 years of age – with rapid disease progression and is associated with cognitive decline and Lewy body pathology (Houlden and Singleton, 2012). Overproduction of α-synuclein through a *SNCA* gene duplication or triplication is even more aggressive, resembling LBD or MSA (Konno et al., 2016; Ross et al., 2008; Singleton et al., 2003).

1.3. Structure of α-synuclein

There are conflicting reports on the native state of α-synuclein. α-Synuclein is a small 140 amino acid protein and is divided into three distinct regions: a positively charged N-terminal region, a central hydrophobic region that has a high propensity to aggregate (Giasson et al., 2001), and a highly acidic C-terminal domain (Bayer et al., 1999; Guardia-Laguarta et al., 2014). One hypothesis suggests α-synuclein exists as an intrinsically disordered protein or unstructured monomer (Binolfi et al., 2012; Burre et al., 2013; Fauvet et al., 2012). Theillet et al., (2016) demonstrated that monomeric α-synuclein is the predominant species in the cytoplasm in the absence of chemical cross-linking and oligomer promoting agents such as dimethyl sulfoxide (Theillet et al., 2016). Alternatively, α-synuclein may exist as a tetramer and the use of denaturing detergents and cell lysis approaches may destabilize the tetramer resulting in a monomer (Bartels et al., 2011; Dettmer et al., 2013; Dettmer et al., 2015; Wang et al., 2011). It is likely that both unstructured monomers and tetrameric α-helical oligomers resistant to fibrillization are present in equilibrium within healthy neurons (Bartels et al., 2011; Wang et al., 2011). Missense mutations in α-synuclein gene can decrease the tetramer:monomer ratio causing a shift favoring a pathogenic state (Dettmer et al., 2015). High levels of the soluble oligomeric form, rather than the insoluble fibril form of α-synuclein is now proposed to be pathogenic species in PD (Lashuel et al., 2013). Soluble α-synuclein oligomers can disrupt membranes (van Rooijen et al., 2008; Volles et al., 2001) and cause cell death both *in vitro* (Danzer et al., 2007; Kayed et al., 2003) and in animal models (Karpinar et al., 2009; Winner et al., 2011).

1.4. Clues from α-synuclein localization and putative physiological function

Despite the general consensus that α-synuclein accumulation is pathogenic in PD, its physiological role is widely debated. α-Synuclein is predominantly located in the presynaptic terminals of neurons and is thought to be important for synaptic plasticity and vesicular packaging and trafficking (Fortin et al., 2004; Kahle et al., 2000; Ross et al., 2008). There is overwhelming support for the involvement of α-synuclein in the dynamics of synaptic vesicle trafficking, where it is believed to regulate the amount of synaptic vesicles docked at the synapse during neurotransmitter release (Wislet-Gendebien et al., 2006). This is supported by *in vitro* and *in vivo* evidence demonstrating that α-synuclein can facilitate an interaction between synaptic vesicles and regulate their assembly (Bodner et al., 2009; Diao et al., 2013; Soper et al., 2008).

While α-synuclein may interact with histones and nuclear DNA (Goers et al., 2003; Goncalves and Outeiro, 2013; Guerrero et al., 2013; McLean et al., 2000), the localization of α-synuclein in the nucleus remains contentious. Using subcellular fractionation methods and histological techniques, phosphorylated α-synuclein was reported to be highly enriched in the nucleus of cultured neurons, as well as in cortical neurons of aged transgenic mice that overexpress α-synuclein (Mbefo et al., 2010; Schell et al., 2009). Further investigation is required to elucidate the role that α-synuclein plays in the nucleus under both physiological and pathological conditions.

1.5. Post-translational modifications and α-synuclein aggregation

The α-synuclein protein undergoes extensive post-translational modifications (PTMs), including phosphorylation, nitration, and DA modification, that all seem to favor oligomerization (Barrett and Greenamyre, 2015). Interestingly, both nitrated and phosphorylated forms of α-synuclein are present in the brains of PD patients, suggesting that these modifications may contribute to PD pathology. In the brains of healthy individuals only a small fraction (~4%) of total α-synuclein is phosphorylated at residue Serine-129 (Ser-129). In contrast, phosphorylation at Ser-129 is the most prevalent (~90%) PTM form of α-synuclein detected in PD brains containing Lewy bodies (Fujiwara et al., 2002; Neumann et al., 2002). Phosphorylation of α-synuclein at Ser-129 can promote the accumulation of oligomeric α-synuclein *in vitro* (Anderson et al., 2006) and accelerate the formation of α-synuclein inclusions (Smith et al., 2005; Sugeno et al., 2008). Moreover, phosphorylation at Ser-129 accelerated neuronal loss in transgenic mice overexpressing α-synuclein in comparison to those expressing wildtype (WT) or phosphorylation-deficient (S129A) forms (Chen and Feany, 2005; Neumann et al., 2002; Rieker et al., 2011; Schell et al., 2009; Wakamatsu et al., 2007). Further studies show that hyper-phosphorylation of α-synuclein may affect its solubility, membrane-binding properties and subcellular distribution, thus favoring a pathogenic state (Visanji et al., 2011; Zhou et al., 2011). While the function of phosphorylated Ser-129 α-synuclein is unclear, substantial evidence indicates that phosphorylation at Ser-129 is implicated in the disease process (Oueslati et al., 2010; Sato et al., 2013).

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The phosphorylation and dephosphorylation of α-synuclein is regulated by protein kinases and phosphoprotein phosphatases, respectively. It is still unclear which kinase(s) phosphorylate α-synuclein at Ser-129 under pathogenic circumstances. Phosphorylation at Ser-129 is mediated by casein kinases (Inglis et al., 2009; Pronin et al., 2000), LRRK2 (Qing et al., 2009) and Polo-like kinases (Inglis et al., 2009; Mbefo et al., 2010). Unlike the other kinases, Polo-like kinase 2 (PLK2), a serine/threonine kinase strictly phosphorylates α-synuclein at Ser-129 and not β- or γ-synuclein (Inglis et al., 2009; Mbefo et al., 2010; Oueslati et al., 2013; Salvi et al., 2012). Neuropathological analysis of aged non-human primate brains shows that PLK2 expression levels were elevated and correlated with increased phosphorylated Ser-129 α-synuclein (McCormack et al., 2012). Transgenic mice that overexpress WT α-synuclein show significantly higher levels of PLK2 in comparison to controls; furthermore, PLK2 colocalized with phosphorylated Ser-129 α-synuclein (Mbefo et al., 2010). Sato et al. (2011) overexpressed G-protein-coupled receptor kinase 6 to increase phosphorylated Ser-129 α-synuclein in DA neurons of the SN and caused robust neurodegeneration and α-synuclein inclusions (Sato et al., 2011). On the other hand, Oueslati et al. (2013) demonstrated that overexpression of PLK2 reduced α-synuclein load in the SN and prevented degeneration by promoting autophagy clearance of α-synuclein (Oueslati et al., 2013). Given the pleiotropic nature of this kinase, further investigation regarding its role in the phosphorylation of α-synuclein at Ser-129 needs to be completed in the future.

Phosphoprotein phosphatase 2A (PP2A) is a ubiquitous cytoplasmic serine/threonine phosphatase and accounts for over 50% of total brain serine/threonine phosphatase activity (Strack et al., 1997). PP2A is important for dephosphorylating α-synuclein at Ser-129. In fact, PP2A and not PP1 can dephosphorylate α-synuclein at Ser-129 *in vitro* (Lee et al., 2011). Both treatments with okadaic acid (OA), a PP2A inhibitor, and knockdown of the PP2A catalytic subunit can promote α-synuclein phosphorylation at Ser-129 (Lee et al., 2011). Furthermore, insoluble α-synuclein can reduce the activity of PP2A and overexpression of PP2A can prevent neuropathology changes caused by overexpression of α-synuclein in mice (Wu et al., 2012).

More recently, evidence suggests that alterations in PP2A activity may be linked to age and neurodegenerative processes. PLK2 levels were increased and PP2A activity decreased in an age- and brain region-dependent manner in monkey brains, which correlated with increased levels of phosphorylated Ser-129 and oligomeric α-synuclein (Chen et al., 2016; Liu et al., 2015). Neuropathological analysis of brains from PD patients with a triplication of α-synuclein revealed high levels of phosphorylated Ser-129 α-synuclein as well as reduced PP2A activity (Wu et al., 2012). Along these lines, it was found in post-mortem tissue from PD and DLB patients that while total PP2A levels were unchanged, there was an increase in protein phosphatase methylesterase (PME-1), which regulates PP2A activity and, therefore altered the methylation state of PP2A (Park et al., 2016). Environmental toxicity could also play a role in PP2A regulation. Rotenone, a pesticide associated with an increased risk of PD (Sanders and Greenamyre, 2013; Tanner et al., 2011) caused down regulation of PP2A activity *in vitro* (Wang et al., 2016b). Collectively these data suggest that modulating PP2A activity and evaluating its effects on α-synuclein phosphorylation will be an interesting avenue to pursue.

1.6. Lysosomal dysfunction and α-synuclein aggregation

Dysfunctional lysosomal clearance mechanisms can also promote accumulation of soluble α-synuclein oligomers and may be central to PD progression (Lee et al., 2004; Mak et al., 2010; Rideout et al., 2004). Individuals with a heterozygous mutation in the lysosomal hydrolase *GBA1* have approximately a 7% probability of developing sporadic PD (Sidransky et al., 2009). It is unclear how a modest 30-50% reduction in glucocerebrosidase (GCase) caused by a mutation in *GBA1* can promote the onset and/or progression of PD. However, in light of this genetic association, several independent groups have demonstrated a link between α-synuclein aggregation and functional GCase. Pharmacological inhibition or genetic knockdown of GCase can promote accumulation of insoluble α-synuclein aggregates (Manning-Bog et al., 2009; Rocha et al., 2015). This inverse relationship between GCase and α-synuclein may be the result of the accumulation of the main substrate for GCase, glucosylceramide (GluCer). GluCer can directly interact with α-synuclein and can promote conformational conversion into toxic oligomeric species and amyloidogenic fibrils when GCase is reduced (Mazzulli et al., 2011).

Accumulation of oligomeric and phosphorylated Ser-129 α-synuclein in aged non-human primate brains is associated with a reduction in both GCase and PP2A in brain regions susceptible to neurodegeneration in PD (Chen et al., 2016; Liu et al., 2015). Several lines of evidence indicate that there is an inverse relationship between GCase and PP2A activity and α-synuclein phosphorylation. As such, inhibition of GCase activity can promote high levels of phosphorylated Ser-129 α-synuclein and a reduction in PP2A activity (Chen et al., 2016; Du et al., 2015; Liu et al., 2015; Volpicelli-Daley et al., 2014). Inhibition of autophagy-related proteins caused by GCase knockdown resulted in inactivation of PP2A (Du et al., 2015). Moreover, pharmacological induction of autophagy using either rapamycin or metformin-stimulated PP2A can reduce levels of phosphorylated Ser-129 α-synuclein (Perez-Revuelta et al., 2014; Peterson et al., 1999). It is possible that diminished GCase activity impacts PP2A activity through overall lysosomal dysfunction, thereby promoting α-synuclein accumulation. It is also plausible that GCase modulates PP2A through ceramide, which has been shown to be an activator of both autophagy and PP2A (Chalfant et al., 1999; Dobrowsky et al., 1993). Increasing ceramide levels can diminish α-synuclein load in GCase mutant mice (Du et al., 2015). PP2A may be an upstream mediator regulating the relationship between GCase and α-synuclein or PP2A may be directly regulated by GCase activity. Currently, the mechanism that links GBA and PP2A with α-synuclein levels is unknown.

1.7. Dysfunctional degradation pathways and α-synuclein aggregation

Several proteolytic systems, including the ubiquitin-proteasome system (UPS) and autophagy-lysosomal pathway (ALP) participate in the degradation of α-synuclein (Tofaris et al., 2011). The UPS is mainly responsible for the degradation of short-lived soluble proteins (Goldberg, 2003), while the autophagy-lysosome pathway degrades long-lived macromolecules, cytosolic components and dysfunctional organelles (Klionsky and Emr, 2000). Failure of these functionally interconnected proteolytic systems can be accompanied by an accumulation of aggregated α-synuclein, that ultimately interferes with proper cellular function and contributes to PD pathogenesis (Xilouri et al., 2013b). In particular, (but not at the exclusion of other ALP pathways) chaperone-mediated autophagy (CMA) has been proposed to effect α-synuclein turnover and metabolism.

CMA is a selective form of autophagy that is often up-regulated in response to cellular stress (Cuervo and Dice, 2000a; Cuervo and Dice, 2000b). Substrates with a KFERQ motif are recognized by a complex of chaperones, which then bind to the lysosome-associated membrane protein type 2A (LAMP-2A), acting as the receptor for this pathway (Cuervo et al., 2000). CMA activity is directly correlated with levels of LAMP-2A (Cuervo and Dice, 2000b), and importantly LAMP-2A expression is decreased in the SN of PD brains (Alvarez-Erviti et al., 2010). Reduction in LAMP-2A levels has been reported to result in the accumulation of α-synuclein and nigral cell death (Vogiatzi et al., 2008; Xilouri et al., 2016). While on the other hand, overexpression of LAMP-2A protected rodents against α-synuclein-induced neuronal cell death (Xilouri et al., 2013a). Moreover, pathogenic α-synuclein mutants (i.e., A30P, A53T) can block CMA (Cuervo et al., 2004).

1.8. Mitochondrial dysfunction in Parkinson's disease

Mitochondrial dysfunction is proposed to be central to the pathogenesis of both sporadic and familial PD. Observations from experimental models and human PD provide strong evidence for disruptions in

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mitochondrial dynamics, bioenergetics defects, complex I inhibition of the electron transport chain (ETC), and increased reactive oxygen species (ROS) (Ryan et al., 2015; Winklhofer and Haass, 2010). The majority of PD-associated genes play a role in mitochondrial homeostasis. The genetic mutations that cause familial PD and their functional relationship to mitochondrial dysfunction have recently been described elsewhere (Ryan et al., 2015). New data indicates that α-synuclein can interact with mitochondria by binding to the outer mitochondrial membrane and can be imported under certain conditions, as well as interact with the F-type ATPase (Di Maio et al., 2016; Ludtmann et al., 2016). This raises the possibility that there is a salient relationship between α-synuclein and mitochondria under normal physiological and/or pathological conditions.

1.9. α-Synuclein and mitochondrial protein import mechanisms

Whether α-synuclein is localized in the mitochondria is controversial (Guardia-Laguarta et al., 2014). Recent studies demonstrate that α-synuclein can disrupt mitochondrial protein import mechanisms in PD. α-Synuclein is reported to have a mitochondrial targeting sequence (MTS) at its N-terminus (Devi et al., 2008). A MTS is a short peptide sequence that directs the transport of nuclear-encoded mitochondrial proteins into the mitochondria. The MTS is recognized by the translocase of the outer membrane (TOM) receptors, which is located on the outer membrane of the mitochondria. These matrix-targeted proteins are then translocated through the TOM complex to the translocase inner membrane (TIM) and finally into the matrix. α-Synuclein can localize to the outer mitochondrial membrane and interact with members of the TOM complex in models of PD and post-mortem PD brain tissue (Bender et al., 2013; Devi et al., 2008; Di Maio et al., 2016). Likewise, select α-synuclein species (e.g. oligomeric, DA-modified and Ser-129E phosphomimetic) can bind to the TOM20 receptor and prevent its interaction with its co-receptor TOM22, and inhibit mitochondrial protein import *in vitro* (Di Maio et al., 2016). The interaction between α-synuclein and TOM20 was associated with mitochondrial impairment and excessive ROS production (Di Maio et al., 2016). Whether blockade of mitochondrial protein import is sufficient to drive nigrostriatal degeneration is unclear. In a Huntington's disease model, deficient mitochondrial protein import caused neuronal death (Yano et al., 2014). Collectively, these findings suggest potential converging mechanisms in neurodegenerative diseases and highlight a new potential therapeutic avenue of mitochondrial protein import-based therapies.

Perhaps it is not surprising that α-synuclein was found to have a role at the mitochondrial membrane, given the affinity of α-synuclein for high-curvature, detergent-resistant membranes enriched in cholesterol, sphingolipids, and acidic phospholipids such as cardiolipin (Jensen et al., 2011; Middleton and Rhoades, 2010). Upon binding to lipid membranes and vesicles, α-synuclein will adopt an amphipathic α-helical structure, which can favor fibril formation, and is thought to be an important step in the initial process of oligomerization (Beyer, 2007; Lee et al., 2002; Tsigelny et al., 2012). The accumulation of α-synuclein at the outer membrane may interfere with protein import mechanisms but also other mitochondrial homeostasis pathways.

1.10. Mitochondrial dynamics

Mitochondrial dynamics, which include mitochondrial fission, fusion, transport, autophagic degradation (mitophagy), and biogenesis, are essential for cellular health. Dysregulation of mitochondrial dynamics has been linked to neuronal dysfunction and PD (Van Laar and Berman, 2013). There is growing evidence to suggest α-synuclein can affect mitochondrial dynamics, with particular disruption of the fusion process. Overexpression of α-synuclein in a *Caenorhabditis elegans* model resulted in disruptions in mitochondrial fusion, leading to mitochondrial fragmentation (Kamp et al., 2010). Interestingly, while these fusion deficits can be rescued by overexpressing several PD-related proteins (e.g. PINK1, Parkin and DJ-1), re-introduction of known mitochondrial fusion proteins such as mitofusion (Mfn) 1 and 2 and Opa1, failed to rescue the fusion deficit (Kamp et al., 2010). Studies of mammalian cell lines and neuronal cells, both *in vitro* and *in vivo*, further demonstrated that α-synuclein associates with mitochondrial membranes, and that α-synuclein overexpression and mutants induce mitochondrial fragmentation independent of Mfn2 or the fission protein Drp1 (Guardia-Laguarta et al., 2014; Kamp et al., 2010; Nakamura et al., 2011). In addition, mutant A53T α-synuclein was shown to modulate mitochondrial morphology in central nervous system neurons *in vivo* in an age-dependent fashion, as well as impair mitochondrial transport *in vitro* (Xie and Chung, 2012). These data suggest that altered α-synuclein can impair proper mitochondrial fusion/fission dynamics, possibly by acting independently and/or downstream of fusion/fission machinery, as well as affect transport dynamics. The precise mechanisms of α-synuclein effects on mitochondrial dynamics require further characterization.

Clearance of dysfunctional mitochondria may also be affected by α-synuclein. Transgenic mice expressing A53T α-synuclein in dopaminergic neurons exhibited mitochondrial accumulation of α-synuclein, associated with respiratory dysfunction and increased lysosome-mediated mitophagy *in vivo* (Chinta et al., 2010). Notably, the prolonged retention of Miro (an outer mitochondrial membrane protein crucial to mitochondrial transport), which delays the clearance of dysfunctional mitochondria, appears to be a common characteristic of familial and sporadic PD (Hsieh et al., 2016). It will be of great interest to determine the role of α-synuclein in mitochondrial turnover.

1.11. Tubulin and α-synuclein interaction: implications for transport

Cellular processes such as intracellular transport and metabolism depend on microtubule dynamics of the cytoskeleton, the major constituent of which is tubulin. Zhou and colleagues originally reported that α-synuclein interacts with tubulin (Zhou et al., 2010). This group also showed that exposure to exogenous α-synuclein inhibited microtubule formation, suggesting a role in regulating microtubule dynamics (Zhou et al., 2010). In support of these findings, it was also shown that α-synuclein missense mutations impair microtubule-kinesin interactions, altering cytoskeletal motility (Prots et al., 2013). Interestingly, it has been reported that tubulin can promote α-synuclein fibril formation (Alim et al., 2002), but these results await confirmation *in vivo*. Recently, WT α-synuclein is proposed to act as a microtubule "dynamase," capable of regulating both microtubule nucleation and catastrophe, which is defined as the process of switching from microtubule growth to shrinkage (Cartelli et al., 2016; Erent et al., 2012). PD-linked α-synuclein missense variants also had different effects on tubulin, tilting more towards aggregation than polymerization (Cartelli et al., 2016). Though not directly tested, the effect of α-synuclein on the microtubule network could impact the transport and distribution of mitochondria (and *vice versa*). For a recent full review of α-synuclein effects on axonal transport, see (Volpicelli-Daley, 2016).

1.12. Mitochondrial bioenergetics defects and α-synuclein

The complex interplay between mitochondrial dynamics and bioenergetics is especially important for neuronal function. In general, neurons have high-energy demands that require large numbers of functional mitochondria. Most of the ATP demands in neurons are derived from oxidative phosphorylation. Mitochondrial respiration can be assessed in various ways and one such indicator is directly measuring oxygen consumption rate (OCR), however, there are relatively few studies that measure the impact of WT or mutant α-synuclein on OCR. A recent study showed that exposure to either oligomeric or DA-modified α-synuclein decreased mitochondrial basal OCR and respiratory capacity *in vitro* (Di Maio et al., 2016). In a different study, cortical neurons

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that overexpress the A53T mutation had mitochondrial respiratory impairments relative to WT littermates (Li et al., 2013). Given these findings, it would be interesting to investigate whether overexpression of WT and other α-synuclein variants in cortical and ventral midbrain neurons also cause mitochondrial impairment, since there are intrinsic differences in how these neuronal subpopulations respond to complex I defects (Sanders et al., 2014).

In an elegant *in vivo* study, OCR was measured in different brain regions from α-synuclein overexpressing mice using a seahorse extracellular flux analyzer (Subramaniam et al., 2014). Despite similar levels of α-synuclein in mitochondria from each brain region, bioenergetics defects were found specifically in the nigrostriatal pathway and preceded striatal DA loss (Subramaniam et al., 2014). Future studies may investigate how different structural states and PTMs of α-synuclein influence mitochondrial bioenergetics. On the other hand, the effect of the mitochondrial impairment on oligomerization, conformational states, and PTMs of α-synuclein will be equally informative.

1.13. Complex I inhibition by α-synuclein

There is compelling evidence for mitochondrial complex I inhibition in PD (De Miranda, 2016). The specific role α-synuclein might play in modulating complex I activity is an important field of investigation. Some studies suggest that α-synuclein is transported inside mitochondria and inhibits complex I activity in a dose-dependent fashion (Liu et al., 2009). Using isolated mitochondria, the prefibrillar oligomeric form of α-synuclein is capable of causing complex I dysfunction (Luth et al., 2014). This inhibition is postulated to be through direct association with complex I (Devi et al., 2008). In transgenic mice that overexpress the A53T mutation in DA neurons, α-synuclein inhibited complex I function (Chinta et al., 2010). Interestingly, using a different strain of mice that overexpress either WT or mutant A53T α-synuclein, it was concluded that α-synuclein has a physiological role regulating complex I activity (Loeb et al., 2010). In contrast, Banerjee and colleagues found that neither WT nor mutant forms of α-synuclein influence complex I activity (or the other respiratory chain complexes). Instead, it was suggested that WT and mutant forms of α-synuclein lead to a loss of mitochondrial transmembrane potential (Banerjee et al., 2010). A study by Reeve et al. (2015) may explain these confounding results, however, by showing that α-synuclein reduces mitochondrial membrane potential and inhibits complex I activity except in cells already expressing a complex I deficit (Reeve et al., 2015).

α-Synuclein may also play an indirect role in modulating complex I activity through interaction with cardiolipin, a protein necessary for complex I function (Fry and Green, 1981; Zhang et al., 2002). Cardiolipin is an anionic phospholipid that is almost exclusively found in the inner mitochondrial membrane (Kubo et al., 2005). Cardiolipin appears to be required for the formation of the mitochondrial supercomplex, which involves complex I, III, and IV. Therefore, a physical interaction between cardiolipin and α-synuclein could disrupt electron transfer (Mileykovskaya and Dowhan, 2014). Monomeric and oligomeric forms of WT α-synuclein display a preference for the cardiolipin-enriched inner mitochondrial membrane over the outer mitochondrial membrane (Camilleri et al., 2013; Zigoneanu et al., 2012). Interestingly, cardiolipin is externalized in response to mitochondrial damage and will interact with the autophagy protein LC3-II to mediate mitophagy in neuronal cells (Chu et al., 2013). Moreover, α-synuclein oligomers that bind to cardiolipin can form a complex and act as a substrate for cytochrome c peroxidase activity, which can induce mitochondrial permeabilization (Bayir et al., 2009). Furthermore, α-synuclein knockout mice have decreased cardiolipin content, which was associated with a reduction in complex I/III activity (Ellis et al., 2005). In total, these data support a role for α-synuclein in regulating mitochondrial complex I activity, though it remains controversial through which mechanism or combination of events this occurs. In addition, it is unclear which forms of α-synuclein (i.e. oligomeric, monomeric, PTM) may instigate the most damage in this regard.

1.14. α-Synuclein modulates complex I toxin susceptibility

There are several toxins that selectively target mitochondrial complex I, many of which produce a parkinsonian-like phenotype (De Miranda et al., 2016). Complex I inhibitors 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydrodropyridine (MPTP) and rotenone, are commonly used to model PD in both rodents and cell culture systems. MPTP selectively kills dopaminergic neurons of the SN in both nonhuman primates and mice (Ovadia et al., 1995; Rose et al., 1993). Mice that overexpress α-synuclein are more susceptible to MPTP toxicity and demonstrate extensive mitochondrial alterations in the SN and not in other brain regions (Song et al., 2004). Similarly, overexpression of α-synuclein in the SN in mice using viral-mediated gene transfer increased the susceptibility to MPTP (Song et al., 2015), and conversely, α-synuclein knockout mice are resistant to MPTP (Dauer et al., 2002). Paradoxically, while acute MPTP administration to mice does not cause α-synuclein positive aggregates (Meredith and Rademacher, 2011), chronic and continuous MPTP infusion via osmotic minipumps has been shown to produce ubiquitin and α-synuclein-positive inclusions in the remaining neurons in the SN (Fornai et al., 2005).

Rotenone is an organic pesticide that acts as a prototypical complex I inhibitor (Sanders and Greenamyre, 2013). Unlike MPTP, rotenone can freely diffuse across cell membranes, though it is selectively toxic to DA neurons in the SN, and leads to the accumulation of α-synuclein positive Lewy bodies and Lewy neurites in the ventral midbrain of rats (Betarbet et al., 2000; Cannon et al., 2009). Similar to MPTP, overexpression of α-synuclein *in vitro* enhanced rotenone toxicity (Shavali et al., 2008). Moreover, rats that overexpress the E46K α-synuclein mutation are more sensitive to rotenone (Cannon et al., 2013). Lastly, α-synuclein knockdown is neuroprotective against rotenone-induced neuropathological changes (Zharikov et al., 2015). Overall, there is a strong indication that α-synuclein levels contribute to the specific vulnerability of DA neurons and modulate susceptibility to environmental exposures.

1.15. Activation of microglia by α-synuclein

The brain is exceedingly vulnerable to oxidative stress in comparison to peripheral organs due to high levels of polyunsaturated fats and relatively low antioxidant activity (Sanders and Greenamyre, 2013). Substantial evidence suggests there is a bi-directional relationship between α-synuclein oligomerization and the generation of ROS (Wang et al., 2016a; Zhang et al., 2007; Zhang et al., 2005). One pathway for the generation of oxidative stress from α-synuclein accumulation is via the activation of microglial cells. As the resident macrophages within the brain, microglia are exceptionally sensitive to cellular damage signals produced by dysfunctional neurons, including changes in the extracellular matrix. These signals will result in their activation and produce phagocytic activity capable of clearing debris (Milner and Campbell, 2003). There are now several lines of evidence suggesting that activated microglial cells directly engulf α-synuclein in an attempt to clear it from the extracellular space; either as a result of apoptotic neuron death, or from mechanisms of cellular release (Goedert et al., 2014; Hoffmann et al., 2016; Jiang et al., 2015; Su et al., 2008). While microglial activation for cellular damage resolution is a key player in brain homeostasis, it is clear that α-synuclein-induced activation of microglia leads to multiple proinflammatory changes that ultimately are neurotoxic, including increased production of ROS (Hoenen et al., 2016; Su et al., 2008; Zhang et al., 2005).

Microglia are primed for detecting pathogenic antigens within the CNS, and express a multitude of cell surface receptors, including toll-like receptors (TLRs), that when bound induce inflammatory signaling cascades necessary for their oxidative burst action within phagosomes (Quinn and Gauss, 2004). Generation of the superoxide anion (O_2^-)

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from microglial nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) is essential for this anti-microbial action and is dynamically regulated via protein assembly of six subunits within the membrane-bound enzyme (Quinn and Gauss, 2004; Wilkinson and Landreth, 2006). Zhang et al. (2005) first reported that microglial ROS production was directly augmented by α-synuclein within primary mesencephalic neuron-glia culture systems (Zhang et al., 2005). Human aggregated α-synuclein induced significant activation of NOX activity, which was dependent on the phagocytosis of α-synuclein (Zhang et al., 2005). More recently, it has been shown that mutated forms of α-synuclein (A30P, A53T) create greater NOX activation in microglia than WT synuclein, leading to elevated ROS production (Wang et al., 2016a; Zhang et al., 2007). Peptide sequences synthesized within the A30P mutation of α-synuclein were found to bind directly to $gp91^{phox}$, the catalytic subunit of the NOX complex and generated abundant levels of extracellular superoxide (Wang et al., 2016a).

In addition to direct superoxide production, soluble α-synuclein may indirectly cause an increase in oxidative stress when it binds to microglial cell surface receptors TLR2, TLR4, and CD11b, resulting in activation of inflammatory pathways including nuclear factor kappa-B (NF-kB) and mitogen-activated protein kinase (Kim et al., 2016; Wang et al., 2015; Zhang et al., 2017). Induction of NF-kB and other classical inflammatory pathways within microglia are also responsible for activating astrocytes, which rapidly upregulate inflammatory signaling molecules, including inducible nitric oxide synthase (iNOS) responsible for producing nitric oxide (NO; (Hewett et al., 1993). In addition to its contribution to oxidative burden, high levels of intracellular NO have been reported to induce α-synuclein aggregation (Paxinou et al., 2001). Additionally, the interaction of NO with superoxide produces the peroxynitrite anion ($ONOO^-$), which can directly bind nucleophilic protein residues (Pacher et al., 2007). Moreover, nitrosative modification to α-synuclein within Lewy bodies has been observed in post-mortem tissue of individuals with PD (Giasson et al., 2000). While this nitrosative stress is, in part, the result of ongoing inflammatory changes produced by α-synuclein, there is also evidence that NO causes abnormal protein accumulation by impairing the ubiquitin-proteasome system (Gu et al., 2005). Thus, the cycle of protein accumulation, inflammatory microglia, and neuronal damage contribute to the progressive nature of PD.

It is clear that microglial activation plays a central role in neuroinflammatory changes and ROS production within the SN. While microglial and subsequent astrocyte activation is typically viewed as a secondary response to neuron damage, evidence of proinflammatory changes within microglia leading to dopamine neuron damage has been observed in animal models of PD. For example, microglial cells treated with exogenous A53T mutant α-synuclein protein results in a stronger inflammatory activation to lipopolysaccharide than treatments with WT α-synuclein or other point mutations, such as E46K and A30P (Hoenen et al., 2016). In addition, treatment with the A53T mutant α-synuclein in BV-2 cells has been shown to produce stronger NOX activation than WT α-synuclein alone, an effect that was shown to be dependent on the purinergic cell surface receptor P2X7 (Jiang et al., 2015).

Induction of neurodegeneration by α-synuclein in animal models is not limited to microglia alone. Astrocytes overexpressing the A53T mutant form of α-synuclein cause significant activation of microglia as well as loss of dopamine neurons within the SN (Gu et al., 2010). Astrocytic α-synuclein accumulation has also been observed within the neocortex and striatum of post-mortem PD tissue (Braak et al., 2007). Evidence of astrocytic activation by α-synuclein has also been shown in other neurodegenerative diseases where protein accumulation is a key pathological hallmark. For example, in a model of MSA, astrocyte activation was directly related to the proximity of α-synuclein inclusions within oligodendrocytes, called glial cytoplasmic inclusions (Radford et al., 2015). Taken together, these data suggest that the glial response to α-synuclein accumulation within both sporadic and inherited forms of PD is a mitigating factor in the pathogenesis of the disease.

Microglial activation is often discussed as a double-edged sword of tissue homeostasis. On the one hand, microglial activation is necessary to clear debris from apoptotic dopamine neurons, but on the other, contributes to an increased amount of ROS, cytokine, and chemokine production due to both direct α-synuclein stimulation and indirect inflammatory signaling. The burden of ROS emanating from α-synuclein-induced microglial activation is especially detrimental to dopamine neurons already exhibiting mitochondrial dysfunction, and may tip the scales in favor of dopamine neuron dysfunction or cell death. Many PD therapeutic trials have targeted microglia to limit inflammation and block the self-perpetuating ROS production cycle, however there has yet to be success in clinical trials using anti-inflammatories to slow PD progression (Glass et al., 2010). Perhaps understanding α-synuclein accumulation in early stages of microglial activation will better predict therapeutics able to mitigate inflammatory gliosis and ROS within the PD brain.

2. Conclusions

The precise role of the various forms of α-synuclein in the etiology of PD are unclear; however data generated from numerous cell culture models, animal studies as well as from samples derived from human PD subjects, suggest that α-synuclein plays a significant role in the pathogenesis of this disease. Based on the unique structure of α-synuclein, it can readily interact with anionic lipids, which can cause conformational changes that favor aggregation. In turn, these aggregate-prone soluble forms of α-synuclein can interfere with lysosomal and mitochondrial function, autophagy, vesicular homeostasis and microtubule transport. Disruption of tubulins, kinesin- and dynein-containing complexes will interfere with anterograde and retrograde transport, respectively. In addition, cellular processes such as mitochondrial dysfunction, may initiate the accumulation of α-synuclein. Any of these intracellular changes can be devastating for neuronal survival. Many questions still remain, and hopefully new treatments will be uncovered by understanding the underlying molecular mechanisms of α-synuclein toxicity in PD.

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