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Post-translational modifications of Parkinson's disease-related proteins: Phosphorylation, SUMOylation and Ubiquitination☆

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ABSTRACT

Parkinson's disease (PD) is a neurodegenerative disorder characterized by loss of dopaminergic neurons in the nigrostriatal pathway. The etiology of PD remains unclear and most cases are sporadic, however genetic mutations in more than 20 proteins have been shown to cause inherited forms of PD. Many of these proteins are linked to mitochondrial function, defects in which are a central characteristic of PD. Post-translational modifications (PTMs) allow rapid and reversible control over protein function. Largely focussing on mitochondrial dysfunction in PD, here we review findings on the PTMs phosphorylation, SUMOylation and ubiquitination that have been shown to affect PD-related proteins.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder affecting around 1–3% of the elderly population over 65 years. The loss of dopaminergic neurons in the *susbstantia nigra* (SN) *pars compacta* and Lewy body (LB) inclusions are the main pathological hallmarks of PD. Currently, it is known that PD patients can present non-motor symptoms (olfactory dysfunction, dementia, cognitive decline) prior to developing the characteristic motor symptoms, rigidity, resting tremor and bradykinesia [1]. Most PD cases are sporadic but a number of genetic and environmental risk factors have been identified. Furthermore, mutations in more than 20 genes have been shown to cause autosomal dominant or recessive forms of PD [2]. Amongst these, autosomal dominant mutations in alpha-synuclein (α-syn), leucine-rich repeat kinase 2 (LRRK2), and recessive mutations in the mitochondria-associated proteins PTEN-induced putative kinase 1 (PINK1), Parkin and DJ-1 are amongst the most common (Fig. 1). Here, we briefly review how these proteins control neuronal and mitochondrial function, and discuss how PTMs of these proteins control their behavior, focusing on phosphorylation, SUMOylation and ubiquitination.

2. The PD-associated proteins, alpha-synuclein, PINK1, Parkin and DJ-1

α-Syn is a soluble protein highly expressed presynaptically in neurons and can be found as an α-helical structure associated with phospholipids or in an unfolded conformation in the cytosol [3,4]. Misfolded α-syn forms oligomers and fibrils that are highly toxic to cells, and is the main component of Lewy Bodies, intracellular inclusions characteristic of PD which may promote neuroprotection through sequestration of toxic α-syn fibrils, or directly contribute to neurotoxicity [4]. Although its physiological function remains not well understood, α-syn has been strongly implicated in synaptic plasticity and neurotransmitter release [5]. Mutations in α-syn were the first identified genetic cause of PD and subsequently a number of missense mutations, as well as gene duplications, have been observed in PD patients [2].

Mitochondria undergo constant rounds of fission (mitochondrial division), or fusion. These processes, termed mitochondrial dynamics, allow the cell to adapt to fluctuating energy demands, as well as maintaining mitochondrial quality through partitioning damaged mitochondria for subsequent degradation by mitophagy [6]. A large body of evidence implicates mitochondrial dysfunction in PD, and alterations in the balance between mitochondrial fusion and fission, and defects in

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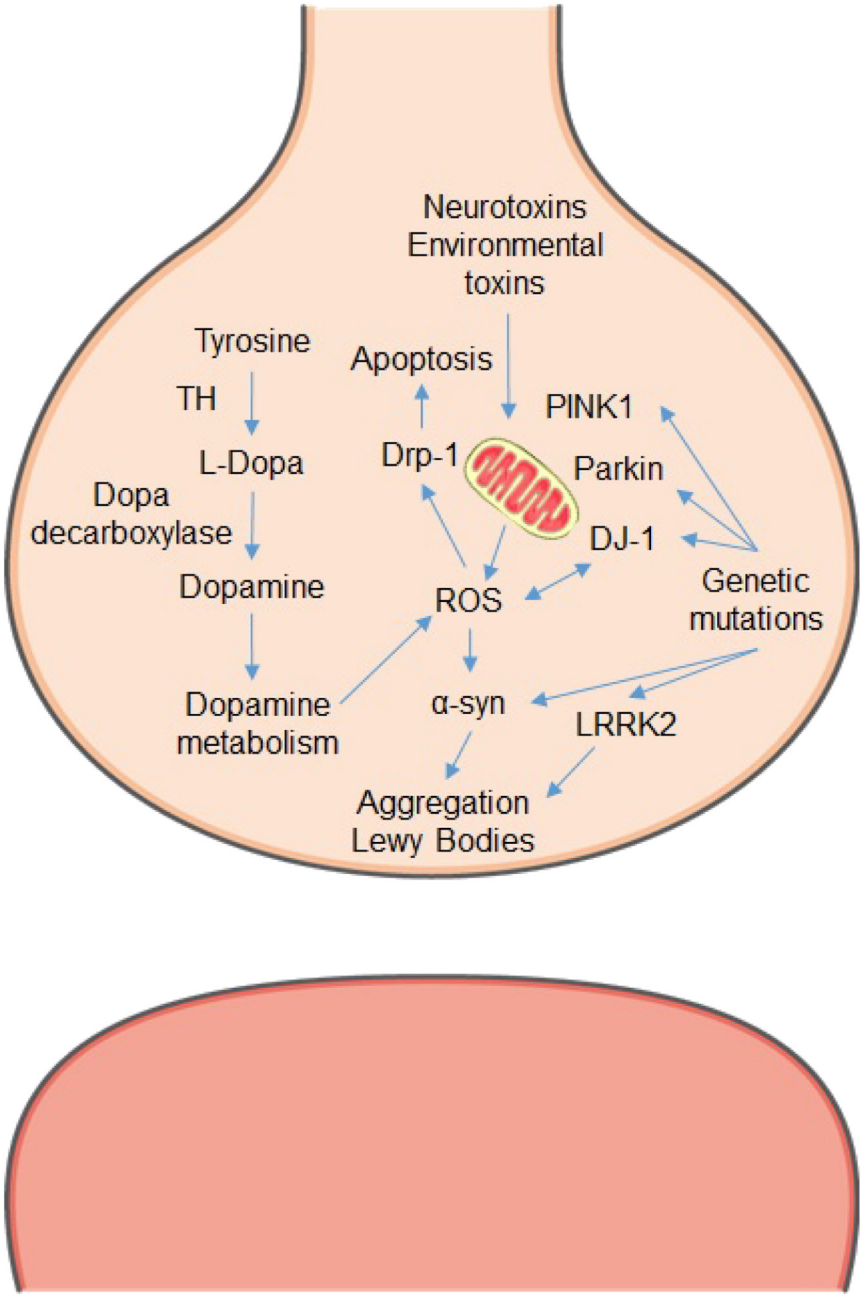

Fig. 1. Dopaminergic signaling and Parkinson's disease (PD)-associated proteins. The synthesis pathway of dopamine can be found on the left hand side of the synaptic terminal. Genetic and risk factors, like neurotoxins and environmental toxins, can alter proteins associated with PD pathogenesis and also induce stress conditions inside the cell stimulating the formation of Lewy bodies inclusions and ultimately cell death.

mitochondrial quality control, are observed in both human patients and animal and cell culture models [6,7]. At the molecular level, mitochondrial fusion and fission are controlled by distinct GTPases – Mfn1 and 2 and OPA1 for fusion, and Drp1 for fission [8]. The balance of activity of these GTPases ultimately determines the balance between fission and fusion, and the morphology of the mitochondrial network. For example, under stress conditions, an imbalance in mitochondrial Drp1 leads to apoptosis [9], and in sporadic PD, aberrant mitochondrial dynamics and the consequent cellular dysfunction have been attributed to Drp1-dependent mitochondrial fragmentation [10,11]. Thus, factors that control the localization and activity of Drp-1 are highly relevant to the pathology of PD.

Both PINK1 and Parkin are required in order to maintain mitochondrial quality control. PINK1 is a Ser-Thr kinase with a mitochondrial targeting sequence. In healthy conditions, PINK1 is imported to mitochondria, cleaved and degraded. When there is mitochondrial damage, it accumulates on the cytosolic face of the outer membrane and initiates a quality control pathway involving Parkin [6]. Parkin is a cytosolic E3 ubiquitin ligase recruited to damaged mitochondria by PINK1. PINK1 activates Parkin directly *via* phosphorylation and indirectly through phosphorylation of ubiquitin, leading to maximal Parkin E3 ligase activity [12]. Parkin can also be found in synaptic vesicles and LB inclusions [10,13], facilitating autophagic degradation of intracellular protein aggregates (aggrephagy) [14]. Nonetheless, it is most well characterized for its role in ubiquitinating mitochondrial target proteins, either to restore mitochondrial proteostasis by targeting misfolded proteins for degradation, or to target the whole organelle for removal by mitophagy. Importantly, amongst the

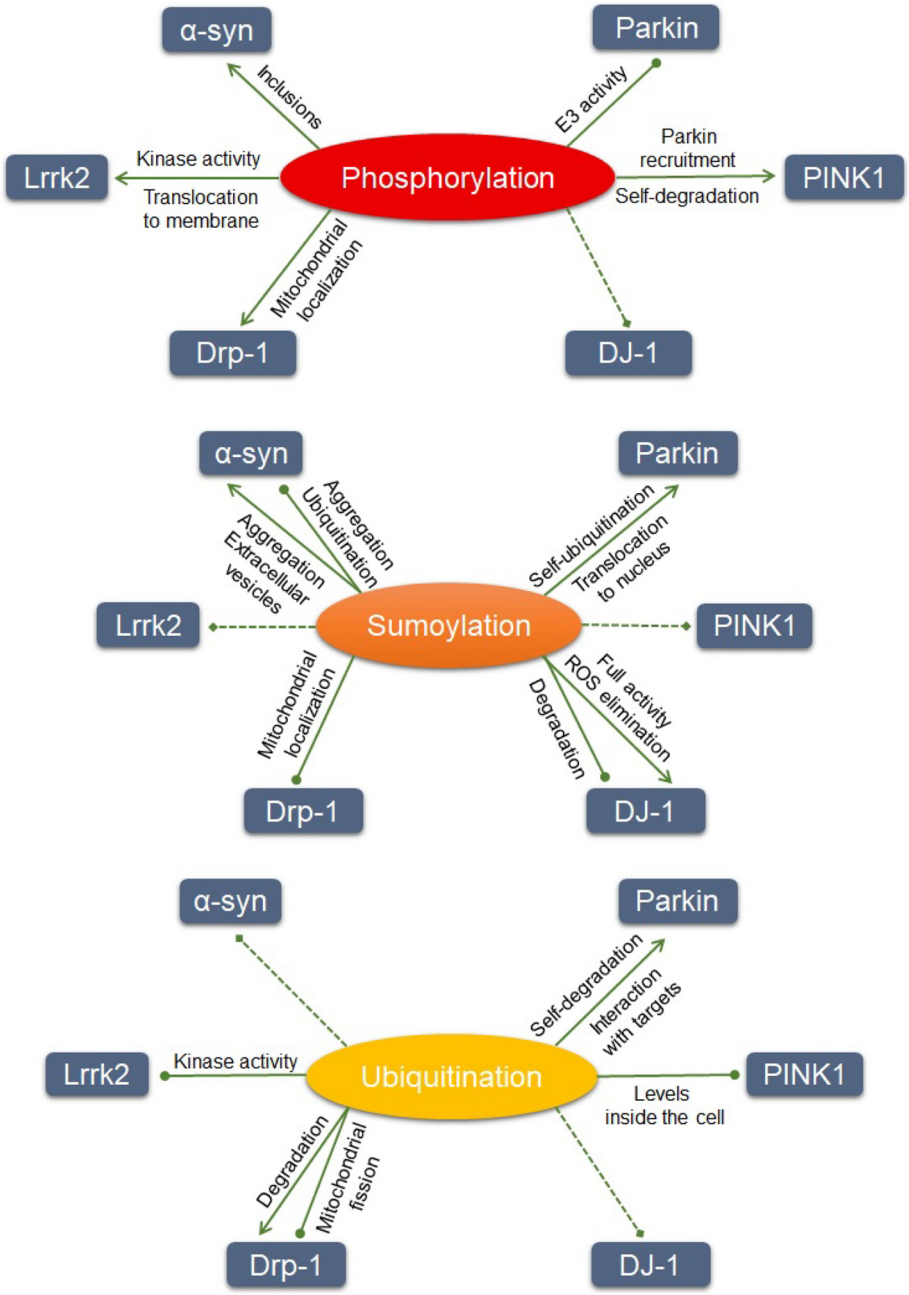

Fig. 2. Summary of the effects of Phosphorylation, SUMOylation and Ubiquitination on PD-associated proteins. Stimulation (→), inhibition (—●) and unknown or not investigated (—♦) are depicted by arrows.

identified targets for Parkin-mediated ubiquitination, are the fusion GTPases Mfn1 and 2 [15] and the fission GTPase Drp1 [8] highlighting Parkin as a central determinant of mitochondrial morphology and quality control.

The small protein deglycase DJ-1, ubiquitously expressed in almost all cells and tissues, is present in the brain in the cytoplasm, nucleus and to a lesser extension at mitochondria. DJ-1, amongst other things, is implicated in cellular redox homeostasis, mitochondrial protection, inhibition of α-syn aggregation, neuroprotection from dopamine toxicity and transcription of tyrosine hydroxylase (TH) [16], however its specific role in PD still remains unclear.

The kinase LRRK2 is expressed throughout the brain, in some peripheral organs and immune cells. It is involved in pathways including regulation of protein synthesis, neural cell morphology and mitochondrial function. Moreover, inclusion body formation and nigrostriatal dopaminergic neurodegeneration have been attributed to site-specific LRRK2-kinase activity [17,18]. Interestingly, similar to PINK1/Parkin, LRRK2 has been linked to mitochondrial quality control, and has been shown to interact with Drp1 [18]. Moreover, expression of pathogenic LRRK2 mutants in neurons induces mitochondrial fragmentation through Drp1 [19], further highlighting the balance of mitochondrial fusion and fission as a central factor in PD pathogenesis. Nonetheless, although the exact function and targets of LRRK2 kinase activity are still unclear, mutations in LRRK2 represent the most common in PD [20], the most frequent of which is a point mutation, G2019S [2].

3. Phosphorylation, ubiquitination and SUMOylation

PTMs play crucial roles in almost every biological process. They consist of alterations that occur on a protein after it is translated by the

ribosome, affecting its function, stability, localization, interaction with other proteins and degradation [10,21–24]. The ability to modify existing proteins allows the cell to respond rapidly to stimuli, and this is particularly important in neurons, where neurotransmission typically occurs on the millisecond timescale.

Phosphorylation is the addition of a phosphate group on Ser (86.4% of cases), Thr (11.8% of cases) or Tyr (1.8% of cases) residues of substrate proteins by a protein kinase, while dephosphorylation is performed by a protein phosphatase [25]. This process of phosphorylation and dephosphorylation orchestrates a vast array of cellular processes, regulating protein functions in response to external stimuli and allowing cells to sense and actively respond to changes in their environment [24–27].

SUMOylation consists of the conjugation of different isoforms of the small ubiquitin like modifier protein (SUMO) to target proteins. SUMO is a ~11 kDa protein that is covalently conjugated to Lys residues in target proteins, usually within a consensus motif, altering their function, stability, or subcellular localization. So far, three validated SUMO isoforms (SUMO1-3) have been identified in vertebrates, but since SUMO2 and 3 differ by only four amino acids, they are usually collectively referred to as SUMO2/3. SUMOylation occurs *via* the action of a 3-step enzymatic cascade involving an E1 enzyme, a sole E2 conjugating enzyme, Ubc9, and a number of E3 ligase enzymes Furthermore, SUMOylation can be reversed *via* the action of SUMO-specific proteases, the most well-characterized of which are the sentrin-specific proteases (SENPs) [28].

Ubiquitination is also a key process for cell survival and maintenance. The protein ubiquitin (Ub) is responsible for marking proteins for degradation by being covalently conjugated to Lys residues, either as a monomer, or as an array of complex ubiquitin chains resulting from the conjugation of ubiquitin molecules to one another, *via* several internal lysine residues [29]. It is known that the deregulation of ubiquitination can lead to cellular pathology, including the accumulation of misfolded proteins during neurodegenerative diseases [30]. In addition to this function, ubiquitin can be attached to proteins to control their protein-protein interactions, protein subcellular localization and protein activity, depending on the type of ubiquitin chain attached to the target [24].

It is becoming increasingly apparent that PTMs are involved in diverse cellular processes by acting directly on a target protein or by complex cross-regulation between modifications, and alterations in phosphorylation, SUMOylation and ubiquitination have been observed in a number of disease states [31], suggesting that perturbations in these pathways may influence disease progression and pathology. In PD it has been shown that all three PTMs play a role in protein aggregation, exocytosis, and degradation [5,21–23,27,32–34]. Therefore, comprehending how these modifications control the function of PD-related proteins, and how these PTMs are altered in disease, could bring new insights into the etiology of the disease, as well as identify potential targets for therapeutic intervention. Thus, our aim in this mini-review is to summarize what we know so far about how these three PTMs can affect the PD-related proteins α-syn, Parkin, PINK1, DJ-1, LRRK2 and Drp1 (Fig. 2).

3.1. PTMs of α-syn

α-Syn is considered to be a key protein in PD pathogenesis in both familial and sporadic forms. In humans, it is encoded by the *SCNA* gene, and mutations in this gene were the first genetic alterations to be associated with the etiology of PD [35]. To date a total of six PD-related point mutations (A53T, A30P, E64K, H50Q, G51D, and A53E) have been identified [35]. Recent insights have shown that this protein may also act like a prion, propagating from one neuron to another, therefore enhancing brain degeneration [33,35,36]. Phosphorylation of α-syn at Ser-129 exacerbates the formation of α-syn inclusions, with over 90% of α-syn in LBs being phosphorylated at this residue, resulting in increased toxicity and neuronal death [5,23,27,34]. In a study by Karampetsou and colleagues (2017), α-syn was injected into mouse striatum in its wild type form *versus* its phosphorylated form, and they observed that phosphorylated α-syn demonstrated enhanced pathology in the SN compared to WT α-syn, increasing dopaminergic neuronal loss [27]. It is known that various kinases can contribute to this over-phosphorylation at Ser-129, and one example is the inflammation kinase PKR, highlighting how neuroinflammation can play a role in PD progression through α-syn dysfunction [5,23].

SUMOylation also plays a role in α-syn fate, influencing its aggregation, exocytosis and degradation [21,22,32,33]. Potentially supporting the idea that α-syn may act as a prion, spreading degeneration, Kunadt and colleagues (2015) have shown that α-syn is present in extracellular vesicles from human cerebrospinal fluid and that sorting of α-syn in extracellular vesicles is mediated by SUMOylation [33]. Furthermore, Abeywardana and colleagues (2015) have shown that SUMOylation can inhibit α-syn aggregation in a site and isoform-specific manner. Their results showed that SUMO1 is a more potent blocker of aggregation than SUMO3 and that SUMOylation at the acceptor site Lys-102 of α-syn leads to a more pronounced inhibition of aggregation than the corresponding modification at Lys-96 [32]. However, the exact role of SUMOylation in α-syn aggregation is still unclear. It is possible that this divergence occurs due to different outcomes for each specific site that can be affected, as well as because of the specific actions of each isoform.

Ubiquitination is also a key process in cell survival, and Rott and colleagues (2017) have shown that there may be a cross-regulation between this modification and SUMOylation, in which the conjugation of SUMO proteins to α-syn decreases its ubiquitination, causing its accumulation and aggregation into inclusions [22].

These interactions between PTMs in regulating α-syn accumulation create a very complex panel to be clarified. Currently, the exact function of α-syn is still poorly understood, which makes this investigation even more challenging. Nonetheless, understanding the influence of PTMs on this protein will provide important insights into both its normal and pathological roles, potentially opening new avenues for the design of therapeutic interventions aimed at targeting PTMs of α-syn.

3.2. PTMs of PINK1, Parkin, DJ-1 and Drp1

The mitochondrial Ser/Thr kinase PINK1, the cytosolic E3-ubiquitin ligase Parkin, the protein DJ-1 and the GTPase Drp1 share overlapping roles in determining mitochondrial dynamics and quality control through regulation of mitophagy, fusion and fission, and oxidative stress responses [10,16]. Cellular control over the activity of these proteins is thus tightly regulated, and each of them has been reported to be targeted by several PTMs.

When mitochondria undergo damage, PINK1 stabilizes at the mitochondrial outer membrane (MOM) and phosphorylates Ub and Parkin, both at Ser-65. Phosphorylated Ub (p-Ub) then binds and activates Parkin which, in turn, then ubiquitinates other MOM proteins [37]. Interestingly, studies have suggested that p-Ub at Ser-65 could be a biomarker for PD diagnosis since it is found in cytoplasmic granules near LBs and it appears to increase with aging and in sporadic PD [38]. Several PD-linked mutations occur at kinase domain of PINK1, abolishing its catalytic activity and the consequent recruitment of Parkin [6] Furthermore, mutations in Parkin represent the most common autosomal recessive causes of PD [2] highlighting dysfunction in the PINK1-Parkin pathway as a recurring feature of PD pathology.

It has been shown that PINK1 autophosphorylation on Ser-228, Ser-402 and Ser-465 increase its ability to phosphorylate and recruit Parkin, induce mitophagy and initiate substrate clearance [39–41]. In particular, phosphorylation on Ser-465 has been linked to PINK1 degradation, being important to maintain cellular levels of PINK1 and mediate Parkin translocation [40], but phosphorylation of Thr-175 and Thr-217 in PINK1 have been reported to be crucial for Parkin

translocation [24]. Ubiquitination has also been shown to have an important role in regulating PINK1 levels inside the cell, maintaining it at low levels under basal conditions as a result of poly-ubquitination, which has been reported to occur primarily at Lys-137 [13].

Parkin functions as an E3-Ub ligase, ubiquitinating a wide variety of substrates *via* Ub chain formation at Lys-48 leading to proteasomal degradation and at Lys-63 to recruit autophagy adaptors, although this latter role remains controversial [24,42]. It has been suggested that Ub-Parkin is its inactive form, since Ub-Parkin was found in LBs in PD patient brains [24]. However, mono-ubiquitination at different sites is thought to activate Parkin, and to be involved in the regulation of its subcellular localization [24]. Furthermore Parkin ubiquitination at Lys-27, Lys-48, and Lys-76 in its N-terminal Ubl domain can regulate Parkin interaction with its targets [42] and the inhibition of deubiquitinating enzymes that act on Parkin have been shown to improve motor behavior and mediate neuroprotection in *in vivo* PD models [38]. Parkin E3-Ub activity can be lost when phosphorylated at Tyr-143 by c-Abl in an *in vivo* PD model, which is consistent with increased levels of c-Abl and p-Tyr-143 Parkin observed in *post mortem* brains from PD patients [24]. In addition, phosphorylation of Parkin at Ser-94 is involved in regulation of spontaneous dopamine release from neuron terminals and survival rates [24].

Another PTM that seems to play a role on in the PINK1/Parkin pathway is SUMOylation. While not reported to be directly covalently modified by SUMO, Parkin has been shown to bind SUMO non-covalently, increasing its self-ubiquitination, and altering Parkin cellular localization by translocating it into the nucleus, which decreases the amount of Parkin available for mitochondrial recruitment by PINK1 [10].

It has been reported that, under oxidative stress conditions, Parkin interacts with DJ-1 without promoting its ubiquitination [16]. In contrast, the PD-linked DJ-1 mutant, L166P, can be ubiquitinated by Parkin but, somewhat counter-intuitively, this does not lead to its degradation, but instead promotes its cellular stability [16]. DJ-1 has also been reported to be SUMOylated, with this modification appearing essential for its full activity and reducing its degradation. In addition, the SUMOylated form of DJ-1 also seems to support the elimination of reactive oxidative species during oxidative stress [10].

The GTPase Drp1 is a central determinant of mitochondrial function and dynamics through mediating fission. Drp1 function is very tightly regulated by multiple PTMs, including phosphorylation, ubiquitination and SUMOylation [10]. Drp1 can be phosphorylated at different Ser residues and its mitochondrial recruitment is phosphorylation site-dependent to either enhance or reduce mitochondrial fission [9]. Previous studies have reported that PD toxin-based cell models increase Drp1 phosphorylation at Ser-616 and enhance Drp1 mitochondrial recruitment and consequent mitochondrial fission [8,11]. Furthermore, Drp1 can be ubiquitinated by Parkin, promoting its degradation and counteracting mitochondrial fission. However, Zang and colleagues (2016) have shown that Parkin binding to Drp1 is decreased in a 1-methyl-4-phenylpyridinium (MPP^+) PD cell model, leading to an increase in Drp1 levels. Furthermore, in the same study it was shown that Parkin attenuates the toxicity of excessive Drp1 activity in MPP^+-treated cells [8]. Drp1 is a direct target of both SUMO1 and SUMO2/3 and can be SUMOylated at one or more Lys residues. Whereas SUMOylation of Drp1 by SUMO1 enhances its mitochondrial recruitment and promotes fragmentation and apoptosis, SUMOylation by SUMO2/3 decreases mitochondrial localization and prevents cell death [9,10]. Although it is well established that disruption of mitochondrial dynamics is a central feature of PD pathogenesis, the roles of Drp1 SUMOylation in PD remain to be defined.

3.3. PTMs of LRRK2

LRRK2 is a large protein kinase characterized by several domains, including various protein-protein interaction regions, a GTPase domain and a kinase domain. This protein localizes to the cytosol in a monomeric and inactive form and in the membrane predominantly as active dimers. LRRK2 exhibits both kinase and GTPase activity, and there is evidence to suggest that both of these activities contribute to the pathogenicity of LRRK2 mutants in PD. LRRK2 exhibits autophosphorylation activity on Ser-910, Ser-935 and Ser-1292 linked to regulation of its kinase activity while phosphorylation of LRRK2 GTPase domain can stimulate GTP hydrolysis [17]. Amongst the seven pathogenic mutations reported in LRRK2, the most common, G2019S (substitution of Gly 2019 with a Ser), occurs in the kinase domain and increases its phosphorylation activity [18]. Interestingly, increased levels of phosphorylated Ser-1292 were found in the urine of idiopathic PD patients with the LRRK2 G2019S mutation and this also correlated with the severity of cognitive impairment and difficulty in performing daily activities, suggesting it may be a useful early detection marker [17]. Some evidence points to an indirect involvement of phosphorylation on Ser-910 and Ser-935 in the reduction in neurite length observed in G2019S neuronal cultures [26]. Ser-935 phosphorylation precedes LRRK2 translocation from the cytosol to cellular membrane [43]. On the other hand, wild type LRRK2 and some PD-related LRRK2 mutants accumulate in cytosolic inclusions when Ser-910 and Ser-935 phosphorylation are inhibited [17,18]. Interestingly, a 36% reduction in LRRK2 phosphorylation, particularly at Ser-935, has been observed in SN of clinical PD patients [43]. The potential relevance of this site to PD pathogenesis has been demonstrated by examining the E193K LRRK2 mutant, a recent variant identified in an Italian family that influences LRRK2 biochemical properties. Fibroblast cells carrying this variant exhibit impaired p-Ser-935 levels and upon MPP^+ treatment they demonstrated increased cellular toxicity and abnormal mitochondrial fission [19]. Furthermore, Stanic and colleagues (2016) proposed that LRRK2 phosphorylation at Ser-935 is involved in L-DOPA-induced dyskinesias (LIDs), the major side effect in PD therapy. Data obtained from an *in vivo* PD model showed a significant p-Ser-935 decrease in dyskinetic rats compared to non-dyskinetic rats, making this site-specific LRRK2 phosphorylation a potential therapeutic target for LIDs prevention [44]. Phosphorylation of another LRRK2 site, Ser-1627, is increased in the PD LRRK2 mutation R1628P in an indirect way that upregulates the kinase activity of LRRK2. In the MPP^+ *in vitro* PD model, this increased p-Ser-1627 LRRK2 leads to a higher toxicity and consequently neuronal death [45].

A previous study has shown a link between increased LRRK2 ubiquitination and the inhibition of its kinase activity [46]. After dephosphorylation of Ser-935 as a result of inhibition of the kinase domain, a considerable amount of LRRK2 is ubiquitinated, mainly through Lys-48 and Lys-63 ubiquitin chains, and then degraded [46]. Nucifora and colleagues (2016) have shown in *in vivo* and *in vitro* models with G2019S LRRK2 that the E3 ligase WD repeat and SOCS box-containing protein 1 (WSB1) ubiquitinates LRRK2 through Lys-27 and Lys-29 linkage chains, leading to LRRK2 aggregation and neuronal protection, while knocking down endogenous WSB1 exacerbates neuronal toxicity [30]. Curiously, WSB1 was found in LBs of human PD *post mortem* tissue suggesting LRRK2 ubiquitination may be a signal for aggregation and neuronal protection in PD [30]. There is also evidence to suggest that the G2385R LRRK2 variant exhibits higher levels of proteasomal degradation, leading to lower steady state intracellular protein levels compared to wild type LRRK2, suggesting G2385R may be a risk factor instead of a variant for inherited PD [47].

4. Perspectives

Understanding the function and regulation of proteins known to be central to PD pathogenesis is a key research question. The investment of research to discover the specific sites of PTMs of PD-related proteins and their physiological consequences will undoubtedly contribute to our understanding of how these proteins work, and how this complex array of modifications control their function. Furthermore, determining

Table 1
Summary of site-specific modifications. Abbreviations: α-Syn - alpha-synuclein; Drp1 - dynamin related protein-1; Lys - lysine; LRRK2 - leucine-rich repeat kinase 2; PINK1 - PTEN-induced putative kinase 1; Ser - serine; Thr - threonine.

Protein	PTM	Site	Main findings	Study
α-Syn	Phosphorylation	Ser-129	Exacerbates the formation of α-syn inclusions, increasing toxicity and neuronal death	5,23,27,34
	SUMOylation	Lys-102	Pronounced inhibition of aggregation	32
	SUMOylation	Not specified	Sorting of α-syn into extracellular vesicles	33
	SUMOylation	Not specified	Decreases its ubiquitination, causing its accumulation and aggregation	22
PINK1	Phosphorylation	Ser-228, Ser-402 and Ser-465	Increases its ability to phosphorylate and recruit Parkin	39–41
	Phosphorylation	Ser-465	PINK1 degradation	30
	Phosphorylation	Thr-175 and Thr-217	Parkin translocation	24
	Ubiquitination	Lys-137	Decreases PINK1 levels inside the cell	13
Parkin	Phosphorylation	Tyr-143	Reduces E3-ligase activity	24
	Non-covalent binding to SUMO	Not specified	Increases Parkin self-ubiquitination, changing its cellular localization by translocating it into the nucleus	10
	Ubiquitination	Lys-48	Self-degradation	24,42
	Ubiquitination	Lys-27, Lys-48, and Lys-76	Regulates interaction with target proteins	42
DJ-1	SUMOylation	Not specified	Required for full activity potential, reduces its degradation, contributes to elimination of reactive oxidative species	10
Drp1	Phosphorylation	Ser-616	Promotes mitochondrial recruitment	8,11
	Ubiquitination	Not specified	Promotes its degradation and counteracts mitochondrial fission	8
	SUMOylation	Not specified	SUMO1 enhances its mitochondrial recruitment and promotes fragmentation and apoptosis while SUMO2/3 decreases mitochondrial localization and prevents cell death	9,10
LRRK2	Phosphorylation	Ser-910, Ser-935 and Ser-1292	Linked to its kinase activity; LRRK2 translocation from cytosol to cellular membrane	17,5
	Ubiquitination	Not specified	Inhibition of its kinase activity	17

how these modifications are perturbed in PD will highlight how targeting these pathways may be of therapeutic benefit.

While a great deal of progress has been made in identifying sites of modification of PD-related proteins, many outstanding questions remain. Indeed, reports of the functional consequences of many of these modifications have been contradictory, possibly in part due to the different experimental models used (Table 1). Moreover, we are only just beginning to understand how crosstalk between multiple modifications can orchestrate target protein function. Nonetheless, targeting these pathways is likely to ultimately be of therapeutic benefit, and some compounds, like rifampicin and metformin, which are already on the market to treat other diseases, have, for example, been shown to affect α-syn SUMOylation and phosphorylation, respectively, promoting cellular survival [48,49]. Another study focusing on mitochondrial quality control has reported a compound that enhanced PINK1 activity and, consequently, Parkin recruitment, promoting cellular survival [38]. These findings encourage new research into the PTMs of PD-related proteins since these modifications can potentially be targeted for disease-modifying strategies which aim to prevent or slow the progression of PD and, potentially, other neurodegenerative diseases characterized by mitochondrial dysfunction and neuronal cell death. In addition, through identification of specific protein PTMs that are altered in PD, it may be possible to use these modifications as a peripheral biomarker to allow early diagnosis [50], to facilitate interventions aimed at slowing or reversing the symptoms of PD.

Transparency document

The Transparency document associated with this article can be found, in online version.

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