

## Review

# Parkinson's disease: a short story of 200 years

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**Summary.** After Alzheimer's disease, Parkinson's disease (PD) is the second most prevalent and incidental neurodegenerative disorder, affecting more than 2% of the population older than 65 years old. Since it was first described 200 years ago by Dr James Parkinson, great steps have been made in the understanding of the pathology. However, the cause(s) that initiates and perpetuates the neurodegenerative process is (are) still not clear. Thus, early diagnosis is not available, nor are there efficient therapies that can stop neurodegeneration. PD clinical features are defined by motor (like bradykinesia, resting tremor, gait impairment) and non-motor symptoms (like constipation, apathy, fatigue, olfactory dysfunction, depression and cognitive decline) that get more severe as the disease advances. Neuropathological hallmarks comprise selective loss of dopaminergic neurons in the Substantia Nigra *pars compacta* (SNpc) and Lewy bodies (LB) in different nuclei of the nervous system. Numerous studies have shown that these pathological features are aggravated by the confluence of other contributing factors, such as a genetic component, exposure to environmental toxins, mitochondrial dysfunction, increase of oxidative stress, calcium imbalance and chronic neuroinflammation, among others. Here, we provide a summary of the actual state of PD's pathology, the most studied molecular mechanisms, classic and novel therapeutic strategies and

diagnosis methods, especially highlighting recent advances in these 200 years.

**Key words:** Parkinson's disease, 200 years anniversary, Neurodegeneration, Dopamine, Lewy bodies

### Introduction

Parkinson's disease (PD) is a progressive, chronic, age-related disorder and the second most common neurodegenerative disease (Nagatsu et al., 2018). As the population increases the life expectancy, prevalence and incidence of PD are growing, and both are expected to be double by 2030 (Lee and Gilbert, 2016). The global prevalence is estimated to be 2% of the population in the

**Abbreviations:** asyn, alpha-synuclein; AADC, aromatic L-amino-acid decarboxylase; CMA, chaperone-mediated autophagy; CNS, central nervous system; CSF, cerebrospinal fluid; DA, dopamine; DAT, dopamine transporter; DBS, deep brain stimulation; ENS, enteric nervous system; GDNF, glial cell line-derived neurotrophic factor; GWAS, Genome-Wide Association Studies; HGNC, HUGO Gene Nomenclature Committee; hSC, human stem cells; HLA, human leukocyte antigen; IFN- $\gamma$ , interferon-gamma; IL, interleukin; LB, Lewy bodies; levodopa, L-DOPA; LPS, lipopolysaccharide; LRRK2, Leucine rich repeat kinase; MAO-B, monoamine oxidase B; MPTP, 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine; MRI, Magnetic resonance imaging; NO, nitric oxide; NSAIDs, non-steroidal anti-inflammatory drugs; PD, Parkinson's disease; PGE2, prostaglandin E2; PNS, peripheral nervous system; ROS, reactive oxygen species; SNpc, Substantia Nigra pars compacta; TH, tyrosine hydroxylase; TNF $\alpha$ , tumor necrosis factor; VMAT2, vesicular mono-amine transporter type 2

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sixth decade of life and >3% in those >80 years of age (Tysnes and Storstein, 2017). Regarding sex differences, epidemiological meta-analysis studies have demonstrated that the incidence and the prevalence of the disease are higher in women than in men (Goetz et al., 2016; Lee and Gilbert, 2016). PD is not a mortal disease, but after the first year of onset, PD patients' mortality duplicates compared to non-PD population (Espay et al., 2017). The incidence varies depending on geographical location, race, ethnicity, genetic interaction and exposure to different environmental factors (Goetz et al., 2016; Tysnes and Storstein, 2017). Then, as there is a large variability in individual onset and individual course of the disease, with a wide clinical picture, it has been suggested that PD is not a single disease but a heterogeneous neurodegenerative disorder (Lang and Espay, 2018). Different methods have been applied to classify PD in different subtypes and some authors claim that this diversity is the result of different disease stages, while others defend the existence of different pathological subtypes of PD and define the disease as a complex syndrome (Linazasoro, 2007). PD has largely been considered to be a movement disorder affecting the central nervous system (CNS), but after years of research today we know that several brain areas are affected in addition to the Substantia Nigra *pars compacta* (SNpc) or the striatum, such as the pedunculopontine nucleus, the locus coeruleus and/or the cerebellum (Rolland et al., 2007, 2009; Heman et al., 2012; Gallea et al., 2017). For this, PD is considered a multisystemic syndrome, in which the nervous system is not only affected but also the autonomic system (Kalia and Lang, 2015; Braak and Del Tredici, 2017; Obeso et al., 2017).

PD neuropathological hallmarks are the reduction of dopamine (DA) levels in the basal ganglia due to neuronal death specifically in the SNpc, and the presence of abnormal intra-cytoplasmic deposits called Lewy bodies (LB) (Graybiel, 2005; Kalia and Kalia, 2015).

PD was first named as "shaking palsy" by Dr James Parkinson in 1817 based on his observations to describe a group of clinical manifestations in 6 people that he compiled in his publication "An Essay on the Shaking Palsy" (Kempster et al., 2007). In his manuscript, he stated the progressive and disabling nature of the disease and some key motor symptoms: resting tremor, postural instability and gait festination (Kempster et al., 2007). The relevance of his findings was not considered until more than one hundred years later, when the French neurologist Jean-Martin Charcot who was particularly interested in Dr Parkinson's work, talked about the shaking palsy during his lecture on the 12<sup>th</sup> of June of 1888, catching the attention of the scientific community (Goedert et al., 2013). Charcot re-named the disorder as Parkinson's disease and made some important contributions, such as describing bradykinesia and rigidity as central characteristics (Obeso et al., 2017). The SNpc implication in PD was set in 1919 by

Tretiakoff (Arai et al., 1989). He analyzed 9 PD cases and he found a depigmentation in the nucleus, accompanied by a neuronal loss and increased gliosis (Goedert et al., 2013). Tretiakoff also studied the SNpc in hemi-Parkinsonian subjects reaching the conclusion that the lesions observed in this area were responsible for the motor alterations in the contralateral side of the body (Arai et al., 1989). Additionally, he observed the cytoplasmic inclusions in the neuronal population that were described years before by Lewy (Arai et al., 1989), so he gave them the name of LB and "grumose degeneration" to the pathology (Fahn, 2018).

Since then, a large number of different alterations involving other cell types and molecular mechanisms have shown a complex neurodegenerative process with motor and non-motor manifestations. Motor symptoms include the classic tetrad of resting tremor, postural instability, rigidity and bradykinesia. Non-motor symptoms may (and usually) appear before motor symptoms as a prodromic syndrome which worsens as the disease progresses. The first non-motor signs are slight depression, constipation, fatigue, sleep disturbance and hyposmia (Almirall et al., 1999; Blanco et al., 2013; Zhang et al., 2016; Poewe et al., 2017); but the most undesirable non-motor alteration is cognitive impairment which appears in the late stages of the disease (Foo et al., 2016; Zhang et al., 2016).

Since it was first described, the cause that initiates the uncontrolled and progressive neurodegenerative process still remains unknown. In this line, clinical and experimental research together with technological advances have allowed an increasing knowledge of the disease and its underlying pathological mechanisms, as well as diagnostic methods and treatments.

The aim of this review is to give a brief summary of the actual state of PD's underlying pathology and the most studied molecular mechanisms today, especially highlighting recent advances, classic and novel therapeutic strategies, as well as current diagnostic methods.

## Etiology

Despite all the efforts that have been directed to uncover what is the cause of progressive and chronic neurodegeneration in PD, 200 years after the disease was described, its origin remains unknown (Obeso et al., 2017). According to its first cause, PD has been strictly classified into idiopathic PD and genetic/hereditary PD. In practice, most PD cases have a multifactorial etiology, resulting from the confluence of genetic factors together with environmental exposure (Tanner et al., 2014; Poewe et al., 2017).

## Genetics

Genetic PD is the less frequent form as only 15% of cases have a clinical family history, but these are of high relevance since they have provided extended information

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about pathways that could have a key role in the development of the disease, not only in the genetic PD cases but also in the sporadic ones (Deng et al., 2018; Nagatsu et al., 2018). The first PD-associated mutation, substitution of alanine in position 53 for threonine (A53T) in  $\alpha$ -synuclein ( $\alpha$ syn), was identified by Polymeropoulos and colleagues more than 20 years ago (Polymeropoulos et al., 1997). Since then, the number of PD-related genes as risk factors has exponentially increased, suggesting that the product of these genes

may have an important role in the etiology of the disease. Twenty-three loci and nineteen genes have been directly linked to the cause of genetic PD by the HUGO Gene Nomenclature Committee (HGNC) (Deng et al., 2018) (Table 1). Also, Genome-Wide Association Studies (GWAS) have led to the discovery of additional risk genes and loci in PD sporadic cases (Hamza et al., 2010; Deng et al., 2018). Thus, some PD-associated genes have been established, whose alteration has turned out to be a condition of predisposition. Among the genes

**Table 1.** PD-causing locus and genes.

Inheritance	Locus name (OMIM)	Locus location	Gene name (Symbol)	Clinical features	Lewy bodies
	PARK1 (168601) <sup>1a</sup> PARK4 (605543) <sup>1b</sup>	4q22.1	$\alpha$ -synuclein (SNCA)	Early-onset, late-onset* Classic PD phenotype caused by PARK1 missense mutations. Duplication/triplications of PARK4 produce early-onset PD. SNCA described alterations include point mutations and duplications/triplications of the gene.	C
	PARK3 (602404) <sup>2</sup>	2p13	PD 3 (unclear)	Late-onset	NC
	PARK5 (613643) <sup>3</sup>	4p13	Ubiquitin C-terminal hydrolase L1 gene (NCHL1)	Early-onset, late-onset	NC
Autosomal dominant	PARK8 (607060) <sup>4</sup>	12q12	Leucine rich repeat kinase 2 gene (LRRK2)	Late-onset. Classic PD phenotype. Variations in PARK8 can be disease-causing mutations or risk-factor variations	C
	PARK11 (607688) <sup>5</sup>	2q37.1	GRB10 interacting GYF protein 2 gene (GIGYF2)	Late-onset	NC
	PARK13 (610297) <sup>6</sup>	2p13.1	Htra serine peptidase 2 gene (HTRA2)	Early-onset*, late-onset	NC
	PARK17 (614203) <sup>7</sup>	16q11.2	VPS35, retromer complex component gene (VPS35)	Late-onset. Classic PD phenotype	NC
	PARK18 (614251) <sup>8</sup>	3q27.1	Eukaryotic translation initiation factor 4 gamma 1 gene (EIF4G1)	Late-onset	NC
	PARK21 (616361) <sup>9</sup>	20p13	Transmembrane protein 230 gene (TMEM230)	Early-onset*, late-onset	C
	PARK22 (616710) <sup>10</sup>	7p11.2	Coiled-coil-helix-coiled-coil-helix domain containing 2 gene (CHCHD2)	Early-onset*, late-onset	NC
	PARK23 (616840) <sup>11</sup>	11p15.4	RIC3 acetylcholine receptor chaperone gene (RIC3)	Early-onset*, late-onset	NC
	PARK2 (600116) <sup>12</sup>	6q26	Parkin RBR E3 ubiquitin protein ligase gene (PRKN)	Early-onset	NC
	PARK6 (605909) <sup>13</sup>	1p36	PTEN indNCed putative kinase 1 gene (PINK1)	Early-onset. Patients usually present psychiatric alterations	NC
	PARK7 (606324) <sup>14</sup>	1p36.23	Parkinsonism associated deglycase gene (DJ-1)	Early-onset	NC
	PARK9 (606693) <sup>15</sup>	1p36.13	ATPase 13A2 gene (ATP13A2)	Early-onset. Complex phenotypic alterations including motor (like dystonia) and non-motor (cognitive impairment).	NC
Autosomal recessive	PARK14 (612593) <sup>16</sup>	22q13.1	Phospholipase A2 group VI gene (PLA2G6)	Early-onset. Complex phenotypic alterations, normally excluding parkinsonism	NC
	PARK15 (260300) <sup>17</sup>	22q12.3	F-box protein 7 gene (FBXO7)	Early-onset	NC
	PARK19 (615528) <sup>18</sup>	1p31.3	DnaJ heat shock protein family (Hsp40) member C6 gene (DNAJC6)	Early-onset, between 30-50 years old	NC
	PARK20 (615530) <sup>19</sup>	21q22.1	Synaptojanin 1 gene (SYNJ1)	Early-onset	NC
	PARK23 (616840) <sup>20</sup>	15q22.2	Vacuolar protein sorting 13 homolog C gene (VPS13C)	Early-onset	NC
X-linked	PARK12 (300557) <sup>21</sup>	Xq21-q25	PD 12 (unclear)	Late-onset	NC
Unclear	PARK10 (606852) <sup>22</sup>	1p32	PD 10 (unclear)	Late-onset	NC
	PARK16 (613164) <sup>23</sup>	1q32	PD 16 (unclear)	Late-onset	NC

Adapted from (Deng et al., 2018). \*Minority cases. C: Confirmed; NC: not confirmed. OMIM (Online Mendelian Inheritance in Man): <https://omim.org>.  
<sup>1a</sup>: Polymeropoulos et al., 1997; <sup>1b</sup>: Farrer et al., 1999; <sup>2</sup>: Gasser et al., 1998; <sup>3</sup>: Leroy et al., 1998; <sup>4</sup>: Strauss et al., 2005; <sup>5</sup>: Lautier et al., 2008; <sup>6</sup>: Strauss et al., 2005; <sup>7</sup>: Vilarinho-Guell et al., 2011; <sup>8</sup>: Chartier-Harlin et al., 2011; <sup>9</sup>: Vilarinho-Guell et al., 2014; <sup>10</sup>: Funayama et al., 2002; <sup>11</sup>: Lesage et al., 2016; <sup>12</sup>: Kitada et al., 1998; <sup>13</sup>: Valente et al., 2001; <sup>14</sup>: van Duijn et al., 2001; <sup>15</sup>: Ramirez et al., 2006; <sup>16</sup>: Paisan-Ruiz et al., 2009; <sup>17</sup>: Shojaaee et al., 2008; <sup>18</sup>: Edvardson et al., 2012; <sup>19</sup>: Krebs et al., 2010; Quadri et al., 2013; <sup>20</sup>: Lesage et al., 2016; <sup>21</sup>: Pankratz et al., 2003; <sup>22</sup>: Hicks et al., 2002; <sup>23</sup>: Satake et al., 2009.

that have been strongly associated, we can distinguish those that cause PD forms: i) autosomal dominant; ii) autosomal recessive; iii) X-linked inheritance; and iv) unclear inheritance form (Beilina and Cookson, 2016; Poewe et al., 2017; Deng et al., 2018) (Table 1). The list of loci that cause autosomal dominant inherited PD to have a variable time of onset (from early to late) and include PARK1/4, PARK3, PARK5, PARK8, PARK11, PARK13, PARK17, PARK18, PARK21, PARK22 and PARK 23 (Table 1). LB pathology has been confirmed in PD patients with mutations in the loci: PARK1/4 (encoding for  $\alpha$ syn, SNCA), PARK8 (that encodes leucine-rich repeat kinase 2, LRRK2) and PARK21 (transmembrane protein 230 gene, TMEM230) (Deng et al., 2018; Karimi-Moghadam et al., 2018). Mutations in PARK2, PARK6, PARK7, PARK9, PARK14, PARK15, PARK19, PARK20 and PARK23 have been linked to autosomal recessive inheritance forms, all of them causing early-onset PD (Table 1). PARK12 is the only PD-causing gene that has been found to have X-linked inheritance. The loci that have been described to be implicated in hereditary PD with an unclear inheritance are PARK10 and PARK16. Together with the list of loci that have been described to cause familial PD, some loci variants of the genes SNCA, LRRK2, GBA and MAPT have been identified to increase the risk of sporadic PD (Deng et al., 2018).

#### *Environmental risk factors*

In 1983, Langston and co-workers discovered that intravenous injection of the toxin 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP) from failed drug synthesis was able to induce Parkinsonian syndrome (Langston et al., 1983; Tanner, 1989; Halliday et al., 2009). Since then, epidemiological research has revealed several environmental and lifestyle-linked factors that are key elements underlying the pathogenesis of idiopathic PD and contribute to genetic predisposition (Tanner, 1989, 2010; Tysnes and Storstein, 2017). This evidence is in concordance with the fact that more than 90% of PD cases do not have a clear genetic cause and some risk factors can be modulated in experimental models of the disease, promoting a neuroprotective or neurotoxic effect (Ascherio and Schwarzschild, 2016). Some people are exposed to environmental toxins during their lives that, together with genetic predisposition, would cause PD. In the beginning, these sporadic cases manifest no clinical signs, even though the disease has already developed, and neurodegeneration is progressing (Fereshtehnejad et al., 2017). Aging is an important contributing factor that accelerates the neurodegenerative process to reach the clinical threshold to be detected (Rodriguez et al., 2015; Fereshtehnejad et al., 2017). In this sense, early markers of the disease are needed to be able to start treating even when clinical features are not manifested.

Excluding those PD cases that develop in people aged less than 45 years old, who have a strong genetic

component, advanced age is considered the main risk factor that contributes to PD (Collier et al., 2017). Several epidemiologic studies have made clear that as age increases, so does PD prevalence (Collier et al., 2017). It is also known that age of onset also determines phenotype and evolution of the disease as early-onset and late-onset cases show significantly different clinical pictures (Rodriguez et al., 2015; Collier et al., 2017). Also, extensive evidence shows that the progressive decline that characterizes aging is strongly associated with many PD pathological markers such as mitochondrial impairment, increased oxidative stress or protein homeostasis dysregulation (Kaushik and Cuervo, 2015; Rodriguez et al., 2015; Rango and Bresolin, 2018). Additionally, the aging process may also affect the SNpc DA neurons vulnerability to degenerate in PD (Rodriguez et al., 2015; Surmeier et al., 2017a).

Other circumstances that have been demonstrated to be capable to increase PD risk are high consumption of dairy products (Saaksjarvi et al., 2013; Ascherio and Schwarzschild, 2016), exposure to pesticides and other environmental chemicals (Petrovitch et al., 2002; Kamel et al., 2007; Ascherio and Schwarzschild, 2016), use of amphetamine and methamphetamine (Callaghan et al., 2010; Ascherio and Schwarzschild, 2016), suffering from melanoma (Wirdefeldt et al., 2014) and traumatic brain injury (Gardner et al., 2015). Controversial results have been found in the link between high PD risk and body-mass index, diabetes, blood cholesterol, reproductive hormones or vitamins and other micronutrients (Ascherio and Schwarzschild, 2016).

#### **Neuropathology**

The two key pathological hallmarks of PD are the progressive loss of dopaminergic neurons in the SNpc and the LB. Increasing evidence supports that other areas and nuclei of the CNS and peripheral system are also affected.

#### *Parkinson's disease and dopamine depletion*

Although toxic accumulation of  $\alpha$ syn oligomers is assumed to be the biggest contributing factor to the pathogenesis of PD, motor symptoms are still the basis for clinical diagnosis (Spillantini et al., 1998) and they are caused by the decrease in striatal DA levels due to the loss of the projecting dopaminergic neurons of the SNpc (O'Keefe and Sullivan, 2018).

The role of DA in PD was mainly established thanks to Arvid Carlsson and Oleh Hornykiewicz works. In 1957, Carlsson and collaborators carried out a key experiment with rabbits that were Parkinsonized with reserpine and whose motor symptoms were restituted by the administration of the DA precursor levodopa (L-DOPA, L-3,4 dihydroxyphenylalanine) (Carlsson et al., 1957; Lees et al., 2015). His contributions to the role of DA in the brain and motor function led him to win the Nobel Prize for Medicine in 2000 and also inspired other

investigators such as Hornykiewicz. In 1960, Hornykiewicz performed DA level measurements in the striatum of *post-mortem* brain belonging to PD patients and he found that there was huge striatal DA depletion compared to the control subjects (Fahn, 2018). He established that the bigger the DA depletion was, the more severe the motor symptoms were. Hornykiewicz was also the first scientist to administer L-DOPA to PD patients and found that the amount of DA in the SNpc was diminished in PD patients, probably due to the neuronal loss. The decrease in DA levels in the basal ganglia is due to the specific death of the neuronal population in the SNpc, as first suggested by Ungerstedt (Hokfelt and Ungerstedt, 1973).

“Why are the DA neurons lost in PD?” may be one of the most formulated questions in this field. To answer this, two hypotheses (which are compatible with each other) have been widely recognized. One of them considers mitochondrial dysfunction (and thus oxidant stress) as the main culprit of DA neuronal death (Haelterman et al., 2014). The other theory holds that DA neurons are more susceptible to  $\alpha$ syn oligomers' toxicity, as they have been found in different brain areas at early stages of the disease without causing neurodegeneration or cell death (Osterberg et al., 2015; Brundin and Melki, 2017). Some evidence points out that the selective vulnerability of these neurons to both mitochondrial dysfunction and  $\alpha$ syn toxicity relies on several features of the SNpc DA neurons: they possess long unmyelinated axons with large numbers of neurotransmitter release sites (Poewe et al., 2017; Surmeier et al., 2017a), cytosolic calcium regulation is energy-dependent (Surmeier et al., 2017b), and dopamine metabolism is associated with oxidative stress (Surmeier et al., 2017a; Surmeier, 2018).

It is clear that dopaminergic cell death in the SNpc is a key element for motor deficits. However, accumulating evidence suggests that, in the dopaminergic system, the neurodegenerative process starts in the nigrostriatal terminals of the midbrain neurons at early stages of the disease, as some studies have shown that there is a greater reduction of the dopaminergic markers such as the aromatic L-amino-acid decarboxylase (AADC), the dopamine transporter (DAT), the activity of vesicular monoamine transporter type 2 (VMAT2) or tyrosine hydroxylase (TH) immunoreactivity in the striatum than in the SNpc at different disease stages (Matsuda et al., 2009; Caminiti et al., 2017). These results are supported by neuroimaging studies that have also found that the reduction of dopaminergic signals is greater in the putamen than in the SNpc (Hsiao et al., 2014; Kaasinen and Vahlberg, 2017). These results have a wide list of implications, which range from early diagnosis to therapies focused on axonal regeneration from residual DA neurons (O'Keefe and Sullivan, 2018).

### Lewy bodies

Protein inclusions are key players in many

neurodegenerative disorders, like PD, Alzheimer's disease and some types of dementia (Kalia and Kalia, 2015). One of the most studied protein aggregates are the Lewy bodies, named in honour of their discoverer Fritz Heinrich Lewy who found them in brains of PD patients (Goedert et al., 2013; Kalia and Kalia, 2015). The LB are fibrillary inclusions that can be found in cell bodies and neurites and, since they were described in 1912, almost 100 molecules have been discovered as LB components, including  $\alpha$ syn, LRRK2, PINK-1, parkin and DJ-1 (Spillantini et al., 1998; Wakabayashi et al., 2012; Toulorge et al., 2016). For a detailed review of LB composition see Wakabayashi et al., 2012. The largest contributing component is the presynaptic protein  $\alpha$ syn, both in sporadic PD and hereditary PD (Spillantini et al., 1997, 1998). The main physiological functions of  $\alpha$ syn are neuronal membrane stabilization, regulation of vesicular transport and pre-synaptic signalling (Lashuel et al., 2002; Brundin and Melki, 2017), and this protein is not found in the neuronal cytoplasm (Wakabayashi et al., 2012). Point mutations in the  $\alpha$ syn gene (SNCA) together with environmental factors provoke changes in its synthesis, maturation and post-translational processing, finally promoting the protein oligomerization to a toxic form (Wakabayashi et al., 2012; Osterberg et al., 2015; Brundin and Melki, 2017). In PD and dementia with Lewy bodies, these inclusions are found in cell bodies and in the processes of neurons and glial cells, presented as two morphologically distinct entities: Lewy bodies and Lewy neurites (Malek et al., 2014; Osterberg et al., 2015). LB have also been found in peripheral tissues of PD patients (Htike et al., 2019; Brundin and Melki, 2017), giving the opportunity to use it as an early marker, allowing to early detection the disease with the possibility to treat the patient and try to establish disease-modifying treatments.

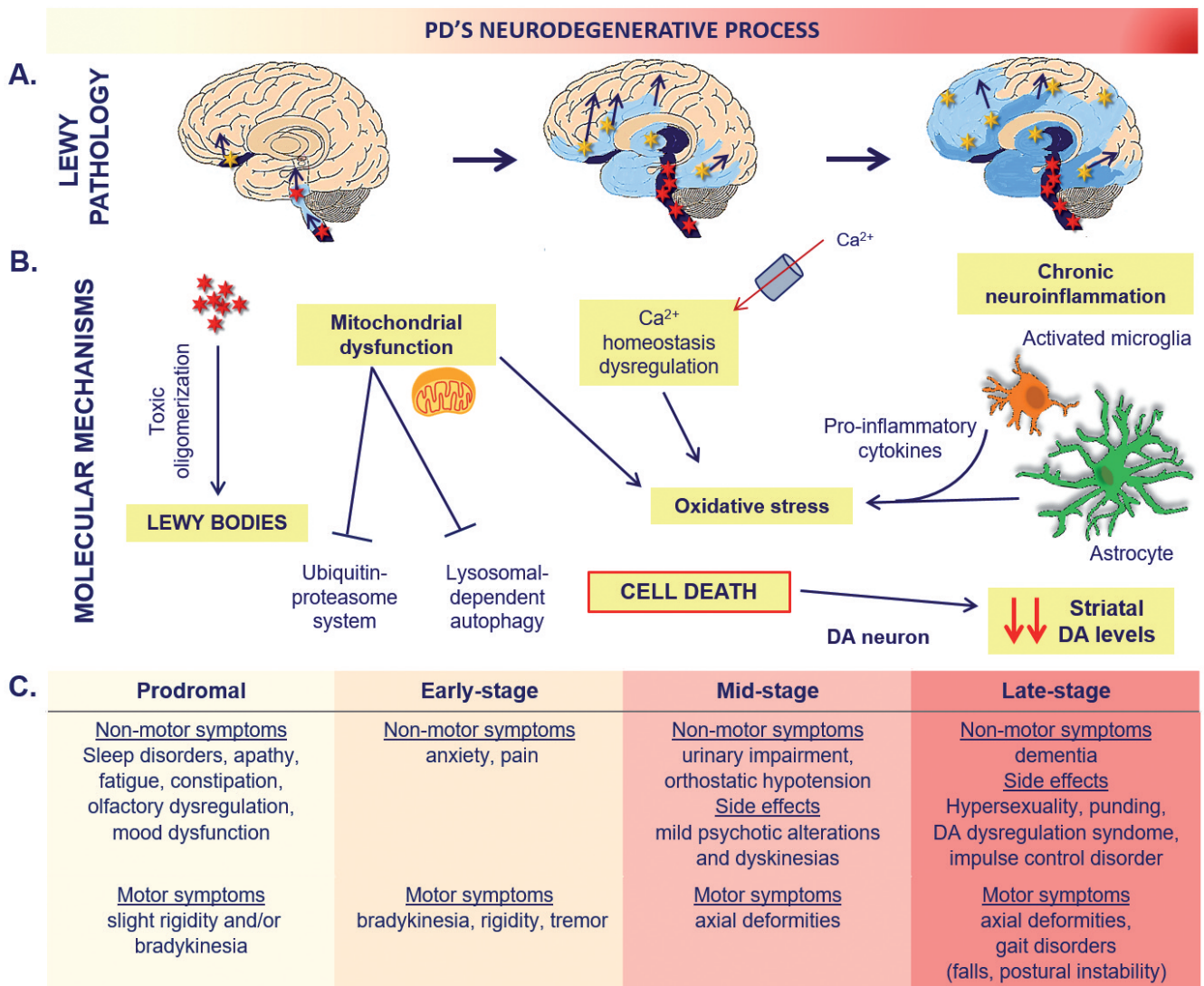
A large piece of evidence has demonstrated the direct pathogenic role of  $\alpha$ syn in PD, other Lewy body pathologies and lysosomal disorders, both by genetic and histopathological studies (Wakabayashi et al., 2012). A broad spectrum of pathogenic mechanisms of the  $\alpha$ syn aggregates have been proposed, among them: i) impairment of the normal organelle's function, giving rise to a vicious cycle of toxicity (Lang and Espay, 2018; Surmeier, 2018); ii) dopamine interaction, making DA neurons more susceptible (Surmeier et al., 2017a; Surmeier, 2018); iii) activation of inflammatory processes (Ferreira and Romero-Ramos, 2018); iv) its ability to act as a prion-like protein, transmitting from one cell to another (Osterberg et al., 2015; Brundin and Melki, 2017). Contrary to what has been assumed, some authors have placed  $\alpha$ syn aggregation as a neuroprotective mechanism in PD (Ding et al., 2002; Lashuel et al., 2002).

### PD evolution: Braak's theory

Since the discovery of LB, it has been very well established that these proteinaceous inclusions not only

affect the population of neurons in the SNpc. The studies conducted by Braak and colleagues in 2003 found that actually, the SNpc was not the first structure where PD-related lesions could be found (Braak et al., 2003). The presence of lesions in other brain areas in the early stages of the disease such as the olfactory bulb or the gut myenteric plexus (prior neurodegeneration of the nigrostriatal pathway and motor symptoms appear), could explain the development of non-motor symptoms, like smell impairment, sleep alterations, constipation or depression (Braak et al., 2003; Braak and Del Tredici, 2017). According to their results, they postulated a six-stage theory for the development of Lewy's pathology in sporadic PD (Braak et al., 2003). This theory considers

that Lewy deposits sequentially invade neuro-anatomically interconnected pathways until they reach the neurons of the SNpc and *locus coeruleus* (Fig. 1A) (Braak et al., 2003). The first affected structures would be non-dopaminergic areas with vulnerable environmental cellular conditions, such as the olfactory bulb or the enteric nervous system (ENS) (Braak et al., 2003; Brundin and Melki, 2017). The areas affected in the first stages (stage 1 and 2) include the olfactory bulb, the dorsal nucleus of the vagal nerve, locus coeruleus and caudal raphe nuclei. Then, the LB lesions extend to the amygdala, the pedunculopontine nuclei, and the SNpc (stages 3 and 4). Finally, in stages 5 and 6 a large part of the brain is affected, including neocortical areas,



**Fig. 1.** Graphic summary of the components, factors and steps in PD neurodegeneration. **A.** Sequential invasion of LB in the different brain areas as the disease progresses, as described by Braak et al., 2003. **B.** Scheme of the main contributing factors to DA neuronal death in the SNpc that leads to dopamine level depletion in the striatum. **C.** PD stages and the associated non-motor and motor symptoms. (Illustration inspired by and adapted from Halliday and McCann, 2010; Obeso et al., 2017; Poewe et al., 2017).

temporal lobe and limbic structures like the hippocampal formation or the anteromedial temporal mesocortex, which directly correlate with cognitive impairment (Braak et al., 2003).

The way that aggregates of misfolded  $\alpha$ syn go from the initially affected regions to the SNpc is still unclear and many hypotheses have been proposed. However, the repercussions of this staging theory are notable. On the one hand, it allows the study of the disease in the peripheral nervous system (PNS), ENS and spinal cord, and the possibility to establish diagnostic markers and risk factors (Halliday and McCann, 2008; Braak and Del Tredici, 2017). On the other hand, including this perspective in experimental studies of the disease will provide a wide range of information in order to better understand the development and evolution of the disease (Brundin and Melki, 2017). Additionally, strategies for therapy may emerge before the nigrostriatal pathway is affected (Braak and Del Tredici, 2017; Aaseth et al., 2018).

### **Etiopathogenesis**

Some authors still simply ascribe PD to dopaminergic neuronal death and the presence of Lewy bodies. However, PD is more complex as a large number of cellular and molecular mechanisms have been described to contribute to its pathogenesis, both in the CNS and in the peripheral tissues. Examples of these additional alterations are calcium homeostasis, mitochondrial dysfunction and oxidant stress, protein homeostasis and neuro-inflammation (Fig. 1B).

#### *Mitochondrial dysfunction*

The mitochondria is a key multifunctional component in the cell for energetic metabolism, thermogenesis, calcium maintenance and regulation of redox signalling (Zhang et al., 2018). Numerous works have shown a direct implication of mitochondrial dysfunction in the pathogenesis of PD. The first line of evidence was documented in 1989 by Schapira and co-workers as they found a decrease in the Complex I of the Electron Transport Chain (ETC) in the SNpc of PD patients (Schapira et al., 1990), which have been further confirmed (Bose and Beal, 2016). Since then, a growing number of changes in mitochondrial protein expression have been described, e.g. the molecular chaperones (Ferrer et al., 2007), the protease HtrA2 (Vande Walle et al., 2008), a and b hemoglobins (Freed and Chakrabarti, 2016) or the outer mitochondrial membrane VDAC1 (Chaudhuri et al., 2016).

Another piece of evidence that shows a relationship between mitochondrial impairment and the loss of DA neurons in the SNpc is that, as already mentioned, described alterations in PD-related genes that cause direct and indirect mitochondrial function failure (Surmeier, 2018; Zhang et al., 2018). On the other hand, recent studies showed that a vicious cycle between  $\alpha$ syn

aggregation and mitochondrial impairment may exist in DA neurons (Poewe et al., 2017). Interestingly, many animal models of the disease are based on neurotoxins that produce impairment in the mitochondrial function, such as rotenone and MPTP (Perez-Otaño et al., 1994; Bezard and Przedborski, 2011; Bose and Beal, 2016).

#### *Oxidative stress*

Reactive oxygen species (ROS) and other reactive species are necessary components in the maintenance of cellular homeostasis and they are strictly regulated by the action of anti-oxidant proteins and systems (Puspita, et al., 2017). In pathological conditions, a failure in the regulation of this reactive species may lead to an increase in oxidative stress that will produce metabolic dysfunction and finally will induce cell death (Kim et al., 2015; Puspita et al., 2017). Accumulating evidence shows that oxidative stress is elevated in the brains of PD patients of both genetic and sporadic cases, and oxidative stress markers can be found in the SNpc DA neurons and their striatal axons (Surmeier, 2018; Zhou et al., 2008).

DA metabolism, mitochondrial dysfunction and neuroinflammatory processes are the main contributors to oxidative stress augmentation in PD (Blesa et al., 2015). Following DA synthesis in DA neurons, it is stored in synaptic vesicles. However, an excess of DA levels in the cytosol lead to its oxidation and accumulation of toxic metabolites, increasing oxidative stress in DA SNpc neurons. This harmful condition provokes lysosomal impairment, a decrease in glucocerebrosidase activity and facilitates  $\alpha$ syn aggregation in the parkinsonian brain (Blesa et al., 2015; Puspita et al., 2017; Zeng et al., 2018). As mentioned previously, mitochondrial impairment is well established in PD: failures in the mitochondrial function are an emerging point for oxidative stress molecules production (Zeng et al., 2018). Furthermore, progressive neuronal death in the SNpc is associated with a chronic inflammatory response in the PD brain (reviewed above). Uncontrolled neuroinflammatory response leads to abnormal production of cytokines and other immune-related molecules (like nitric oxide and ROS) which also contribute to increase oxidative stress (Miller et al., 2009; Puspita et al., 2017).

Additionally, the underlying condition of the aged brain is also a major source of oxidative stress. Extended evidence has shown that the aging cells lose their ability to maintain physiological balance and, in consequence, progressive oxidative damage can be found (Kong et al., 2014). The use of anti-inflammatory therapies is of increasing interest in the last years because they have shown promising results in terms of neuroprotection in PD (Gil-Martinez et al., 2018a).

#### *Calcium homeostasis*

Substantial data have demonstrated the key role of

calcium homeostasis dysregulation and the degenerative process in several neurodegenerative disorders. Regulation of calcium levels is crucial for maintaining neuronal function (Wegierski and Kuznicki, 2018). Cytoplasmatic calcium low levels are finely controlled and an increase in its level exerts cellular excitotoxicity (Wegierski and Kuznicki, 2018). Mutations in PD-associated genes, such as SNCA, LRRK2 and PINK1, have been correlated with dysregulation of intracellular calcium homeostasis (Verma et al., 2018). Importantly, uncontrolled changes in intracellular calcium levels are responsible for mitochondrial impairment, thus triggering an increase in oxidant stress and apoptosis (Verma et al., 2018). Interestingly, calcium channel inhibitors (i.e. isradipine) are considered a promising therapeutic strategy as they have been shown to have a neuroprotective effect in PD (Surmeier et al., 2017b).

### Protein homeostasis

Since PD is characterized by the accumulation of protein aggregates and damaged organelles (mainly mitochondria), there is consistent literature that suggests a crucial role of impaired protein turnover, especially in the degradation of misfolded proteins or damaged and dysfunctional organelles in the pathogenesis of PD (Bandhyopadhyay and Cuervo, 2007; Zhang et al., 2018). Together with LB deposits, several studies have found the co-presence of  $\beta$ -amyloid plaques (typical of Alzheimer's disease) in the brains of PD patients (Obeso et al., 2017). The two main mechanisms to carry out the clearance are the ubiquitin-proteasome system and autophagy-lysosome pathway. Importantly, point mutations affecting the genes involved in both mechanisms have been described in family cases of PD, thus causing abnormal removal and degradation of proteins (Yang et al., 2009; Zhang et al., 2018).

### Ubiquitin-proteasome system

The ubiquitin-proteasome system is the main process for little protein degradation in mammals consisting of two stages: conjugation of the protein to ubiquitin molecules to be subsequently degraded in the proteasome (Toulogre et al., 2016). Evidence obtained from *postmortem* analysis of PD brains suggests that the ubiquitin-proteasome system is altered, as an increase in the total levels of ubiquitinated proteins in the striatum has been reported (Lonskaya et al., 2013) and under-expression of the 20S and 19S subunit of the proteasome in the SNpc, defective expression of ubiquitin ligase and deubiquitinase, among others (Toulogre et al., 2016). Also, mutations in parkin, an important element for the ubiquitin ligase activity, have been linked to hereditary PD (Seirafi et al., 2015).

### Lysosomal-mediated autophagy

### Protein clearance of cellular substrates by autophagy

consists of lysosomal degradation and it is the key process to maintain protein homeostasis. Different to the ubiquitin-proteasome system, lysosomal-mediated autophagy can promote the elimination of bigger proteins and even organelles (Chu, 2018). There are different types of autophagy: chaperone-mediated autophagy, macroautophagy and microautophagy. Several studies have demonstrated that chaperone-mediated autophagy (CMA), macroautophagy and lysosomal degradation are altered in sporadic and genetic PD brains (Koga and Cuervo, 2011; Toulogre et al., 2016). Two important proteins for CMA, the heat-shock cognate 70 and its lysosomal surface receptor lysosomal-associated membrane protein 2, are decreased in PD brain, suggesting an impaired CMA function in PD (Cuervo and Wong, 2014). An increase in macroautophagy's markers has been described in the SNpc of PD patients, as LC3II (Dehay et al., 2010) and Beclin-1 (Miki et al., 2018). Some studies also found changes in lysosomal degradation, like a dramatic reduction of autophagic vacuoles in SNpc DA neurons of PD brains and some key lysosomal proteins (Chu, 2018; Zhang et al., 2018). An extended list of these markers can be seen in Toulogre et al. (2016). A recent analysis conducted by Miki and colleagues in the peripheral blood mononuclear cells of PD patients found a decrease in mRNA levels of crucial autophagy-related genes (Miki et al., 2018).

Additionally, LRRK2 has a key role in autophagy regulation and it has been demonstrated that the presence of the mutated protein leads to dysregulation of autophagy (Beilina and Cookson, 2016; Zhang et al., 2018).

### Parkinson's disease as a prion-like disorder

The crucial fact that led to consider PD as a prion-like disorder was the simultaneous findings of three studies carried out by different groups in the world in 2008: PD patients who had been transplanted more than a decade before with fetal cells in the midbrain and striatum were found to be  $\alpha$ syn immunoreactive in these grafted cells, thus suggesting that the  $\alpha$ syn was able to propagate from cell to cell and invade healthy neurons (Kordower et al., 2008; Li et al., 2008; Mendez et al., 2009). Since then, a great number of studies have proposed the key involvement of the  $\alpha$ syn propagation from cell to cell and from one brain region to another in the progression of PD and the worsening of the symptoms as the disease goes on (Braak and Del Tredici, 2017; Brundin and Melki, 2017). In addition, immunohistochemistry of  $\alpha$ syn has revealed the presence of the misfolded protein in peripheral nerves of the autonomic nervous system (Braak et al., 2003; Brundin and Melki, 2017). Taking into consideration that as the disease advances an increasing number of brain regions are affected by  $\alpha$ syn aggregation and that they are connected by a neural system, the prion-like hypothesis was proposed and the idea that PD may be a



prion-like disorder has emerged since both *in vivo* and cell culture studies have demonstrated the ability of misfolded  $\alpha$ syn to transfer from cell to cell (Dunning et al., 2012; Goedert et al., 2013; Kalia and Kalia, 2015). Interestingly,  $\alpha$ syn aggregates can move via anterograde or retrograde transport (Brahic et al., 2016) and failures of the lysosomal or proteasome system increase the excretion of  $\alpha$ syn (Bandhyopadhyay and Cuervo, 2007; Fernandes et al., 2016). An important point in the prion-like hypothesis is that once the  $\alpha$ syn inclusions are released to the extracellular space, they can be up-taken by neighbouring neurons (Reyes et al., 2015), microglia or astrocytes (Lim et al., 2018) due to the different  $\alpha$ syn aggregates ability to bind cell membranes (Grey et al., 2011).

### Neuroinflammation

A large number of works have shown that neuroinflammation is a key feature in PD, as inflammatory markers have been found to be increased in brain *postmortem* studies, in brain imaging and cerebrospinal fluid. Briefly, the immune response in the CNS is initiated by resident microglia and is perpetuated by the recruitment of peripheral, and then amplified by astrocytes (Halliday and Stevens, 2011; Ferreira and Romero-Ramos, 2018). In order to maintain tissue homeostasis, after the insult resolution the inflammatory responses must be terminated to restore the physiological condition. However, several studies point out that there is an inflammatory response ongoing in the Parkinsonian brain, causing uncontrolled glial cell activation and collateral damage to healthy tissue and neurons and initiating a neurodegenerative vicious cycle (Dzamko et al., 2015; Deczkowska et al., 2018). In the brains of PD patients and experimental models of the disease, the number of microglial cells is elevated (Wang et al., 2015; Tang and Le, 2016). In addition, these cells seem to be in an activated state since there is an increased expression of the microglial activation markers like the Human leukocyte antigen (HLA)-DR, ICAM-1, CD68, lymphocyte function-associated antigen 1, activated caspase-3/8, CD23, CD163 (Tang and Le, 2016; Toulorge et al., 2016; Plaza-Zabala et al., 2017). Several pro-inflammatory cytokines have also been described to be increased in PD brains and experimental models of the disease: interleukin 1b (IL1b), IL-2, IL-6, tumor necrosis factor  $\alpha$  (TNF $\alpha$ ), S100B, interferon-gamma (IFN- $\gamma$ ) and its receptor (Barcia et al., 2005, 2011; Tang and Le, 2016; Toulorge et al., 2016; Plaza-Zabala et al., 2017). Additionally, metalloproteinases have been receiving special attention in the last decade because they have been shown to be implicated in the inflammatory response induced by dopaminergic neuronal death (Annese et al., 2015; De Stefano and Herrero, 2017). Although astrocytes' activation is still a controversial topic, some molecules associated with astrocytes-inflammatory response have been described in the Parkinsonian brain: elevated levels of

myeloperoxidase, milk fat globule-EGF factor 8 and heme-oxygenase-1 (Lin and Scott, 2012; Jyothi et al., 2015; Toulorge et al., 2016; Joe et al., 2018). Inflammatory markers have also been found in the neuronal population, like elevated levels of cyclooxygenase-2 and the nuclear fraction of nuclear factor-kappa B (Toulorge et al., 2016). In 2013, Annese and collaborators described a third nervous cell type implicated in Parkinsonism: the oligodendrocytes. In their work, they found an increase in the cell number and evident morphological changes in oligodendrocytes that correlated with the decrease in DA levels produced by MPTP administration (Annese et al., 2013).

Importantly, some studies have found alterations in the peripheral immune system, like an increase in pro-inflammatory parameters in PD patients serum (Bessler et al., 1999; Perry, 2004; Scalzo et al., 2010; Dzamko et al., 2016). Interestingly, some models of the disease are based on the fact that inflammatory agents such as bacterial lipopolysaccharide (LPS) or viral antigens can induce the neuronal death observed in PD (Jang et al., 2009; Qin et al., 2007). In this line, cell markers in the SNpc of PD patients like CD8 and CD4 have been detected, thus indicating a possible role of the lymphocytic infiltration (Lin and Scott, 2012).

The link between inflammation and PD is even stronger in elderly patients, who suffer a basal inflammatory condition recently entitled neuro-inflammaging, in which there is an increase in the inflammatory detrimental effect of the microglial cells and a loss of physiological regulatory function as a consequence of the aging process (Collier et al., 2017; Lecours et al., 2018).

The close relationship between inflammation and PD is reinforced with genetic studies and GWAS analysis, in which the list of genes that are responsible for the immune homeostasis is continuously expanding (Dzamko et al., 2015). One of the most evident contributing inflammatory markers is the HLA since it has been discovered in GWAS studies that there are several genetic variations (including single nucleotide polymorphisms) in the HLA coding region that are associated with a higher risk of developing late-onset PD and other neurodegenerative disorders (Pankratz et al., 2009; Hill-Burns et al., 2011). Among HLA variants, the HLA-DRA is the one with the highest link to PD (Hamza et al., 2010). Late-onset PD was classically considered to be more environmentally caused and that no genetic component was involved; however, the finding that there is an association between HLA-DR variations and PD has led to consider a new role for the genetic component also in sporadic late-onset PD (Hamza et al., 2010). Other loci have also been implicated in PD by GWAS studies such as the ones encoding the SPAK protein (Yan et al., 2012), the surface molecule CD157 (Quarona et al., 2013) the SCARB2 receptor (Yamayoshi et al., 2009), the microglial glycoprotein non-metastatic melanoma B (Shi et al., 2014) and the fibroblast growth factor 20 (Jeffers

et al., 2002). Interestingly, the kynurenine pathway (responsible for the catabolism of the tryptophan) has been found to exert a beneficial effect when it is activated in astrocytes, but appears to be detrimental when activated in microglia (Lim et al., 2017).

It is clear that inflammatory processes are involved in the pathogenesis of PD but their exact role has not been resolved yet (Deczkowska et al., 2018). While some authors claim that the inflammatory response appears as a consequence of dopaminergic neuronal death, others support the idea that neuroinflammation is the one that precedes neurodegeneration as inflammatory-related markers have been detected in asymptomatic genetic-PD patients and PNS's immune cells are recruited prior to neurodegeneration due to  $\alpha$ syn aggregates (Halliday and Stevens, 2011; Wang et al., 2015; Dzamko et al., 2016; Harms et al., 2017).

The harmful effect of inflammatory response has placed neuroinflammation as a potential therapeutic target in PD. However, it would be misleading if we did not consider an important point, that neuroinflammatory responses can also be beneficial as they are in charge of removing cell dead bodies or  $\alpha$ syn aggregates. So, therapies should consider both the possibility to control the damaging neuroinflammatory response and to promote the beneficial one.

## Facing Parkinson's disease at the clinical stage

### *Clinical stages and diagnostic tests*

Basic research and *postmortem* studies in PD patients have revealed that the disease starts years before its motor clinical manifestation, first affecting non-dopaminergic areas such as the ENS or the olfactory bulb (Braak and Del Tredici, 2017; Obeso et al., 2017). However, to date, the gold clinical classification methods are still based on motor alterations, which means that the neurodegenerative process is already extended (Lang and Espay, 2018). Non-motor manifestations involve a multitude of altered functions like sleep disorder, olfaction (reduced olfactory ability), autonomic dysfunction (constipation), mood dysfunction (anxiety, depression) and cognitive decline (memory deficits, dementia) that may end in psychiatric disorders with visual, tactile and olfactory hallucinations (Onofrij et al., 2007; Borgemeester et al., 2016). The main clinical motor features are muscular rigidity, postural instability, bradykinesia and resting tremor, as a consequence of a 30-50% loss of DA population in the SNpc and around 80% of DA terminals in the striatum (Obeso et al., 2017). Both motor and non-motor symptoms become more severe as the disease progresses (Obeso et al., 2017; Poewe et al., 2017) (Fig. 1C). Additional collateral symptoms appear in the middle and late stages of the disease, derived from the side effects of the drug-based therapies: psychiatric alterations, hypersexuality or punding, among others (Fig. 1C) (Kulisevsky et al., 2009).

When it comes to diagnostic methods, of special relevance are neuroimaging approaches such as magnetic resonance imaging (MRI), which allows the determination of morphological changes and atrophy of the different brain areas affected in PD, quantitative iron mapping, detection of neuromelanin (oxidized DA), DA depletion (functional MRI), measurement of cortical thickness and volumetric calculations (Poewe et al., 2017). Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) are also neuroimaging tools that have enormously developed in recent years (Lang and Espay, 2018) and, to date, they are used to study DA levels, glucose (hexokinase activity),  $\beta$ -amyloid deposits presence and acetylcholine esterase activity, among others (Obeso et al., 2017).

Another issue that is receiving increasing attention from the scientific community in the field of diagnostic tests is the early disease-associated biomarkers that can be found in blood and cerebrospinal fluid (CSF), although at the moment there are no biomarkers available to use for clinical diagnosis (Oertel and Schulz, 2016). Examples of molecules that have been found to be different in PD patients and normal subjects that could develop as potential clinical biomarkers are reduction of orexin A (responsible for sleep disturbances), increase in 8-hydroxyguanine (indicating DNA damage due to oxidative stress), changes in DA and DA transporters levels and low apolipoprotein A1 (Emamzadeh and Surguchov, 2018). In some cases, immunohistochemical analysis for  $\alpha$ syn in biopsies of olfactory and gastrointestinal tissues (Poewe et al., 2017).

### *Treatments*

PD is associated with a large list of different additive factors and despite all the great contributions to its understanding, to date, its cause remains unknown. Consequently, the current diagnostic methods are not able to predict an early onset of the disease and the therapies are symptomatic in order to ameliorate motor and non-motor dysfunction, trying to slow down the progression of the neurodegenerative process, but they are not able to stop it (Fahn, 2018). In this line, diverse therapeutic strategies are used according to the clinical stage of the disease, which aim to cover the alterations associated with each one. It is noteworthy that the sooner the treatments are applied, the better the prognosis is (Olanow et al., 2009; Lang and Espay, 2018).

#### Early stages treatments

The early stages' therapies for PD are focused on the treatment of the non-motor symptoms (Fig. 1B), such as Domperidone for hypotension, Citalopram for depression, Clonazepam or Melatonin for sleep disturbances (Connolly and Lang, 2014).

When the first motor symptoms appear, before

resorting to the use of DA agonists (for DA replacement) there is a great bet for the use of inhibitors of monoamine oxidase isoform B (MAO-B), the enzyme that degrades DA. In the late 60's, selegiline was found to be a very potent and selective MAO-B inhibitor, and from 1975 was finally defined as a treatment in PD (Szoko et al., 2018). Additionally, posterior studies found that the benefits of selegiline were not only the preservation of DA but also the anti-apoptotic effect and the neuroprotection it exerts against PD-related neurotoxins as MPTP (Szoko et al., 2018). The second inhibitor of MAO-B that was used for PD treatment was rasagiline (first synthesized by TEVA Neuroscience), with similar properties to selegiline but showing a higher neuronal survival in the toxin-based experimental models of the disease (Riederer and Muller, 2018). Selegiline and rasagiline are irreversible inhibitors of MAO-B and the suggested mechanisms of action of selegiline and rasagiline include acting as neurotrophic factors, decreasing oxidative stress and promoting anti-apoptotic systems (Bainbridge et al., 2008).

In recent years, there is an increasing interest in the development of reversible MAO-B inhibitors, such as safinamide, which acts as a competitive substrate for the enzyme (Tipton, 2018).

#### Middle-stages treatments

As the motor symptoms aggravate, pharmacological approaches to PD aim to restore DA depletion. George Cotzias was the pioneer in L-DOPA administration to PD patients in 1966 (Lees et al., 2015). Since then, L-DOPA is still the gold standard for PD treatment and several drugs are approved by the Food and Drug Administration (FDA) such as Sinemet, Xadago, Rytary and Duodopa (Connolly and Lang, 2014; Emamzadeh and Surguchov, 2018). Oral L-DOPA neuroprotective effect can be potentiated when it is administered with DA agonists and MAOB (including safinamides) and/or catechol-O-methyltransferase (COMT) enzyme blockers, as well as systemic inhibitors (Herrero et al., 2011). It is noteworthy that the mentioned enzyme's inhibitors show better safety and tolerability properties than DA agonists (Riederer and Muller, 2018).

#### Late stages treatments

In the late stages of the disease, medication must face the more severe motor and non-motor symptoms, especially cognitive decline and hallucinations (see below). In these cases, patients do not show a good response to the previous mentioned treatments and start to present secondary effects, motor symptoms aggravation and resistance complications (Espay et al., 2017). This need prompted the development of additional treatment strategies such as Deep brain stimulation (DBS), subcutaneous apomorphine administration or the L-DOPA-carbidopa intestinal infusion (duodopa), which, for the moment, have shown

positive results including motor and non-motor symptoms (Antonini and Nitu, 2018). DBS has developed in recent years and it consists of the implantation of an electrode in specific brain areas (good candidates are the subthalamic nucleus, the globus pallidus internus and the pedunculopontine nucleus) that will provide electrical stimulation with frequencies between 100-200 Hz (Guridi et al., 1993; Blanco et al., 2013; Lang and Espay, 2018; Thevathasan et al., 2018). DBS has proved to be very effective for improving motor symptoms in patients with early onset PD and the ones with a positive response to L-DOPA treatment (Espay et al., 2017). The subcutaneous delivery of apomorphine uses pump systems and allows acute and continuous administration of the drug, while L-DOPA-carbidopa intestinal infusion is based on gels that substitute the oral format and shows an increase in the useful time of the treatment (Antonini and Nitu, 2018). Apomorphin and duodopa are last-term treatments that are resorted to when the PD patient does not show a good response to previous treatments, but both strategies have demonstrated to improve the quality of life of the patients that encounter severe complications.

#### Treatment of non-motor symptoms

Depression, autonomic impairment and cognitive decline are extremely common non-motor symptoms in the late stages of PD (Kalia and Lang, 2015). Non-motor symptoms are not alleviated with dopaminergic treatments and in some cases they indeed show more complications (Lang and Espay, 2018). Thus, non-dopaminergic pharmacological therapies are targeted, including afferent and efferent anatomical basal ganglia and cortical connections and projections, as well as other targets outside the CNS, where other neurotransmitter and neuromodulators that have been described in non-motor symptoms of PD are important (Marsden and Obeso, 1994; Lang and Espay, 2018). These non-dopaminergic pathways include noradrenergic, glutamatergic, serotonergic, GABAergic, cholinergic, adenosinergic, opioidergic and histaminergic (Poewe et al., 2017). Patients suffering from depression have shown positive results in the treatments consisting of serotonin uptake, such as primavanserine (Brundin et al., 2015; Aaseth et al., 2018). Autonomic impairment is usually treated with mineralocorticoids (such as fludrocortisone), adrenergic compounds (like midodrine and etilefrine), pro-kinetic therapies (like lubiprostone) and antimuscarinics (like tolterodine or oxybutynin) (Espay et al., 2017; Poewe et al., 2017). Regarding psychiatric alterations, the most used drugs are clozapine and the quetiapine (Poewe et al., 2017). Among the non-motor alterations linked to PD, of special relevance is cognitive impairment, which is more and more frequent and aggravated by the aging factor (Reid et al., 2011); patients that develop the disease before 50 years old will not manifest cognitive decline, while the cognitive alterations are almost

ensured if PD appears after the decade of the 60's (Reid et al., 2011). In this sense, cholinesterase inhibitors notably improve cognitive impairment and dementia (Connolly and Lang, 2014).

### New approaches to PD treatment

#### Antibiotics

Antibiotics are a great example of “old drugs for new therapies”. Initially used for killing pathogenic microorganisms, in recent years compelling evidence has demonstrated their neuroprotective properties (Reglodi et al., 2017). In the particular field of PD therapies, the use of antibiotics has a beneficial effect on  $\alpha$ syn toxicity, mitochondrial dysfunction and neuroinflammation. Several studies have shown that toxicity of  $\alpha$ syn fibrillar aggregates is reduced by the use of the macrolide Rifampicin (Zhu et al., 2013) and also antibiotics of the  $\beta$ -lactam family, such as Ceftriaxone and Rapamycin (Jiang et al., 2013; Bisht et al., 2014). Interestingly, other antibiotics (mainly Rapamycin, D-Cycloserine, Ceftriaxone and Minocycline) seem to have a protective effect on mitochondrial dysfunction by regulating glutamate imbalance (Reglodi et al., 2017). Additionally, Rifampicin administration was shown to reduce DA damage induced by MPTP and paraquat, inhibitors of Complex I of the mitochondrial electron chain (Oida et al., 2006). Finally, recent studies have demonstrated that the use of antibiotics is able to reduce the inflammatory component, thus having a beneficial effect on the neurodegeneration in PD (Reglodi et al., 2017). Tetracyclines possess potential anti-inflammatory properties (Reglodi et al., 2017). Particularly, Doxycycline and Minocycline promoted neuroprotection *in vivo* against MPTP and 6-hydroxydopamine (6-OHDA) by blocking microglial activation. In addition, Rifampicin's anti-inflammatory effect relies on its ability to inhibit the release of pro-inflammatory compounds such as TNF- $\alpha$ , nitric oxide (NO), IL-1 $\beta$  and prostaglandin E2 (PGE2) (Zhu et al., 2011; Reglodi et al., 2017).

#### Physical exercise

Recent studies have claimed that regular and moderate-intensity physical exercise has a beneficial effect on PD. On one hand, physical exercise improves the motor condition of the patients increasing muscle strength and aerobic capacity, as well as reducing balance and gait dysfunction (Lang and Espay, 2018). Together with this, evidence has shown that exercise displays a neuroprotective effect through its anti-inflammatory properties, promoting and improving the regulation of glucose metabolism, which in the long term means a lower DA neuronal loss in the SNpc (Spielman et al., 2016; Aaseth et al., 2018). For this, physiotherapeutic therapies have started to be included since PD is diagnosed, in order to reduce symptoms and

improve the quality of life of the patients (Aaseth et al., 2018; Gil-Martinez et al., 2018b).

#### Anti-inflammatory therapy

The design of therapeutic strategies based on the use of anti-inflammatory agents is of increasing interest considering that chronic neuroinflammation plays an important role in the progressive neurodegenerative process in PD. Epidemiological studies have evidenced that the use of non-steroidal anti-inflammatory drugs (NSAIDs) like aspirin, ibuprofen, celecoxib and sialic acid, reduces the incidence of PD and protects DA neurons from cell loss (Wang et al., 2015; Aaseth et al., 2018; Lang and Espay, 2018). At the moment, numerous immunomodulators are included in clinical trials for their use as potential treatment in PD and other neurodegenerative disorders (Lang and Espay, 2018), such as minocycline (a tetracycline analog), glucocorticoids (Wang et al., 2015; Tiwari and Pal, 2017; Lang and Espay, 2018).

#### Gene therapy

Gene therapy is a technique for genome editing and consists of the introduction of specific genes in the cells of the patient in order to restore expression deficit. This is a growing field in PD treatment and, at the moment, two gene therapy approaches are being tested, both based on the use of viral vectors. Regarding the first one, several clinical trials have been carried out, consisting of the injection of viral expression vectors of growth factors that have been demonstrated to exert a neuroprotective effect on animal models of the disease and *in vitro* tests, directly into the putamen and/or the SNpc (Bartus and Johnson, 2017; Poewe et al., 2017). The two gold growth factors that have been tested are the glial cell line-derived neurotrophic factor (GDNF) and neurturin, both preventing DA neurons from death and promoting axonal restoration in experimental models (Bartus and Johnson, 2017). However, there are not enough randomized clinical trials that confirm the efficacy of this therapy approach, and by the end of 2018 a study on the expression of GDNF mediated by the adeno-associated virus is predicted to be published (Poewe et al., 2017). The second gene therapy strategy is the use of viral vectors to express key enzymes in the DA metabolism (Bjorklund et al., 2009), like TH and co-factors into the striatum (Carlsson et al., 2005) and glutamate decarboxylase into the subthalamic nucleus (LeWitt et al., 2011). This approach has already passed to phase II clinical trial and shows promising results improving DA availability and reducing and preventing motor symptoms (Bjorklund et al., 2009).

#### Stem cells and cell reprogramming

Another biotechnology-based therapeutic strategy of increasing interest in the last decades is the use of human

stem cells (hSC), which consists of the reprogramming of these kind of cells to produce a determined cell type of interest (Hagell et al., 2002). This method comes as a solution to the problems derived from the adrenal and fetal implants in the SNpc and the striatum of PD patients (Madrazo et al., 1991). At the moment, it is possible to obtain dopaminergic neurons from embryonic hSC and pluripotent induced hSC (Lindvall et al., 1990; Hagell et al., 2002). Results from experimental research are very promising and the current trials are focused on the aspects regarding clinical translation, such as safety protocols or successful implantation of the induced cells.

## Conclusions

PD is a chronic and progressive neurodegenerative disorder affecting 2-3% of the population aged more than 65 years old and showing an increasing worldwide impact, both social and economic. Cell death of SNpc neurons and  $\alpha$ syn deposits are the core neuropathological features, accompanied by a number of contributing factors such as mitochondrial dysfunction, protein homeostasis impairment and neuroinflammation, but other nuclei and systems are affected probably before symptoms appear at a subclinical stage. A minor percentage of the cases are directly related to a genetic cause; however, 23 loci are currently linked to PD development, providing new insights regarding the possible implicated pathways. An important emerging concept is that there is no single cause of PD, but a set of causes that are added and aggravate the progression of the neurodegeneration, finally converging in a *domino effect*. Importantly, all pieces are specially predisposed to fall within the most important contributing factor: aging. Although great advances have been made, the cause that initiates the neurodegenerative process is currently not known and many questions remain unresolved, reducing treatment possibilities to palliative strategies. Therefore, one of the great challenges in the field is to understand what factors accelerate and promote dopaminergic neuronal death, as well as the rest of the contributors to the pathology of PD. It is noteworthy to consider that dopaminergic deficits and detectable PD features appear when the disease has already passed its first stages. For that reason, a great objective both for understanding the disease and for fighting against it is to develop early disease associated markers. Another important trial is not to assume that all PD patients suffer from the same stage or subtype of the disease and thus, personalized medicine should be defended. To achieve this, one of the key elements is to consider PD as multiple converging diseases, in which many systems and pathways are implicated. A major challenge is the development of predictive factors to identify individuals at risk and early manifestations that precede the onset of the defining motor symptoms in order to establish effective therapies that could slow down the neurodegenerative process.

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