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Parkinson's Disease: Insights from the Laboratory and Clinical Therapeutics

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1. Introduction

Parkinson's disease (PD), a neurodegenerative disorder that was first described by James Parkinson (1755-1824) in 1817, is characterized partly by a progressive loss of dopaminergic neurons in the substantia nigra pars compact. It affects approximately 1.5% of the global population over 65 years of age. PD is the type of Parkinsonism that is defined as any combination of six specific and independent motoric features: bradykinesia, resting tremor, rigidity, loss of postural reflexes, flexed posture and the freezing phenomenon. Current dopamine replacement strategies, which include levodopa (L-DOPA, the precursor of dopamine) and dopamine receptor agonists, as well as monoamine oxidase B and catechol O-methyltransferase inhibitors, can effectively improve these symptoms. Many reviews of this field are available elsewhere; therefore we focus here on the most recent outcomes regarding the identification of key biomedical progress in PD, describe the most promising biological research targets that are currently being assessed to find ideal treatments, and provide insights from progress in laboratory research and clinical therapeutics.

2. The pathogenesis of Parkinson's disease

Decades of research have not found a single cause for PD and therefore a single factor is unlikely to emerge. Current research is mainly carried out on animal models of PD induced by intoxication with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and models of postencephalitic parkinsonism, neither of which has fully reproduced the clinical and pathological features of true PD. However, it is believed that PD is a multifactorial disease caused by both environmental factors and genetic susceptibility. Aging is an obvious factor because PD mainly targets elderly people. Studies have shown that the incidence of PD is around 10-15 cases per 100 000 person–years (1), but this figure increased to 93.1 in people aged between 70 and 90 years (2). Male sex appeared to be another risk factor, because the incidence of PD in men was 1.5 times higher than that in women (3). Geographically, China has a similar prevalence of PD to western countries (4), whereas Africans have a lower rate compared with African Americans (5).

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2.1 Environmental factors

Many environmental factors may increase the risk of developing PD. Priyadarshi et al. (6-7) showed the association between PD and farming, professional pesticide use, and drinking well-water in a meta-analysis. Other environmental factors, such as metals, solvents, electromagnetic fields and lifestyles, have also been determined as possible risk factors (8). Studies over the past two to three decades have provided more supportive findings. Tanner and Goldman (9) linked the consumption of well-water to the occurrence of PD. Living in rural areas was associated with farming and pesticide use, which led to an increased incidence of PD patients (10-11). This was association was clarified by another study that demonstrated that the effect of pesticide use was independent from that of farming (12). A lifestyle study found similar evidence of increased herbicide exposure in patients with PD (13). The discovery that exposure to MPTP induced parkinsonian syndromes initiated a new field in PD research – the study of exposure to pesticides (14-15). Many different pesticides have been investigated. MPTP has a similar structure to paraquat, a herbicide that is widely used in many countries. Paraquat was found to be associated with PD based on a 20-year exposure study (16). In a study in Germany, organochlorine pesticides were identified as risk factors for PD (17). Dithiocarbamates, which have been shown to enhance MPTP toxicity (18), were considered to be another risk factor for PD (19). Manganese, a constituent of several pesticides and herbicides, induced parkinsonism in humans following chronic exposure (20). Pesticides and herbicides may be used in combination, which results in a higher level of toxicity. One study showed that exposure to paraquat plus manganese ethylenebis-dithiocarbamate (maneb) resulted in 4.17-fold greater risk for PD compared with unexposed populations (21).

In addition to the above agricultural risk factors, industrial factors also play an important role in the development of PD. Chronic exposure to copper, manganese, and lead was associated with the risk for PD (22) and PD patients who had worked in factories that used chemicals, iron or copper had higher death rates (23). A German study also reported an association between exposure to lead and PD (17). Furthermore, the relationship between PD and head trauma has been investigated: a history of head trauma was associated with onset of PD at an earlier age (24-25).

As discussed above, many risk factors are involved in the development of PD; however, two environmental factors could lower this risk: cigarette smoking (26) and coffee drinking (27), although their mechanisms are unknown. Studies of twins showed an inverse association between cigarette smoking and PD (28-29), and similar results were reported by a study that compared PD cases with their unaffected siblings (30). A meta-analysis reported an inverse association between PD and coffee drinking which was independent of smoking (31). However, this was seen in men but not in women (27).

2.2 Genetic susceptibility

Most cases of PD are sporadic, but some patients (10-15%) show a positive familial history of the disease (32). Although the cause of PD is still unknown, both environmental and genetic factors are considered to be important. The discovery of several causative mutations and genes (33) has allowed a better understanding of PD.

2.2.1 α-Synuclein (PARK1)

α-Synuclein, also called PARK1, was the first gene to be linked to PD (34), and mutations in α-synuclein gene have been linked to rare cases of familial PD (35-37). Genomic multiplications have been reported and both mRNA and protein levels of α-synuclein were increased in the brain (38). However, a large screening study has shown that α-synuclein multiplication is a rare cause of parkinsonism (39). Nevertheless, there is a link between α-synuclein level and age at onset and severity: when α-synuclein duplication causes the disease at an earlier age, then PD has a more aggressive form (39-40). α-Synuclein is a small neuronal protein that is involved in neurotransmitter release and synaptic vesicle recycling. Without genetic changes, α-synuclein is an abundant protein and a major component of Lewy bodies (LBs) in idiopathic, apparently sporadic PD (41-42). This supports the role of α-synuclein in the pathogenesis of PD.

2.2.2 Parkin (PARK2)

The PARK2 gene was identified as parkin in autosomal recessive forms of familial juvenileparkinsonism (AR-JP) (43). AR-JP is most commonly seen in Japanese populations and typically has an onset before the age of 40 years (44-45). Interestingly, no LBs have been found in parkin-positive brains. Parkin was reported to act as an E3-ubiquitin ligase that targets cytoplasmic proteins for proteasomal degradation and plays a role in receptor trafficking (46-47). A wide variety of parkin mutations have been found including large homozygous deletions in exons (43); frame-shift mutations, point mutations, duplications and triplications of exons (48); and deletions in the promoter (49). Parkin mutations were identified in nearly 50% of familial cases with disease onset before the age of 45 years (50) and in 15% of sporadic young-onset cases (51). In the subset of cases with onset before the age of 20 years, this proportion increased to 70% (51).

2.2.3 Ubiquitin carboxyl-terminal hydrolase L1 (UCH-L1; PARK5)

UCH-L1 is an enzyme that hydrolyzes the C-terminus of ubiquitin to generate ubiquitin monomers that can be recycled to clear other proteins. A single missense mutation in UCH-L1 was reported in two siblings with typical PD in a German family (52). A second rare mutation was reported in French families but was not restricted to PD (53). No other carriers of this mutation and no other mutations in UCH-L1 have been identified (54-55), which has raised doubts about the relevance of UCH-L1 to PD.

2.2.4 PTEN-induced kinase 1 (PINK1; PARK6)

PINK1 encodes a widely expressed protein kinase that is localized in mitochondria. PINK1 is the second most common cause of AR-JP (56) and may play an important role in sporadic PD (57). Several mutations have been identified including transitions (56), single heterozygous mutations (57), and heterozygous deletion of the PINK1 gene plus a splice site mutation on the remaining copy (58). One study suggested that heterozygous mutations are a significant risk factor in the development of PD (59). Briefly, PINK1 mutations may cause loss of function in patients with recessively inherited forms of PD because most mutations fall in the kinase domain (60).

2.2.5 Oncogene DJ-1 (PARK7)

The DJ-1 gene encodes a ubiquitous and highly conserved protein, and has been identified as a causative gene for early-onset autosomal recessive PD (61). A couple of mutations have been reported but these were found in only a few patients with early-onset PD (61-62). DJ-1 protein is not an essential component of LBs but is localized in mitochondria that protect against neuronal death (63).

2.2.6 Leucine-rich repeat kinase 2 (LRRK2; PARK8)

LRRK2 mutations are the most common mutations identified in either familial or sporadic PD. Although other LRRK2 mutations have been described, the G2019S mutation has been found to be the most common pathogenic cause of PD, and has been reported in 5–6.6% of cases of autosomal dominant PD (64-65) and 2–8% of sporadic cases (66-67). Penetrance in G2019S patients was age dependent, and increased from 17% at the age of 50 years to 85% at the age of 70 years (68). Nigral neuron loss and LB formation have been observed in the brains of sporadic PD patients with G2019S mutations (66).

2.2.7 Adenosine triphosphatase type 13A2 (ATP13A2; PARK9)

ATP13A2 has been identified as the causative gene in Kufor-Rakeb syndrome (69), a rare form of juvenile-onset parkinsonism caused by autosomal recessive neurodegeneration. Studies in PD patients have reported mutations of 22bp duplication in exon 16 (70) and missense mutation in exon 15 (71), indicating that they are possible causes of PD.

2.2.8 OMI/HTRA serine peptidase 2 (OMI/HTRA2; PARK13)

A missense mutation in the OMI/HTRA2 gene has been found in sporadic PD patients (72). The OMI/HTRA2 gene is located within the PARK3 linkage region, but its role in PD is unknown.

Other genetic factors, such as glucocerebrosidase (73), microtubule-associated protein tau (74) and progranulin (75), have shown an association with PD but their causality has yet to be elucidated.

3. Experimental models in PD research

3.1 Neurotoxin models

The development of experimental models is essential for a better understanding of the etiopathogenesis of PD and to provide effective therapeutic agents. Neurotoxins that target the dopamine (DA) system, such as 6-hydroxydopamine (6-OHDA) and MPTP were used in early animal models for PD research and are still widely in current use (76).

3.1.1 6-OHDA

6-OHDA was the first agent used in an animal model of PD (77). Because of its structural similarity to DA and norepinephrine, 6-OHDA can enter and accumulate in both dopaminergic and noradrenergic neurons. Catecholaminergic structures are destroyed by 6-

OHDA through reactive oxygen species (ROS) and quinines (78-79). Because 6-OHDA crosses the blood-brain barrier (BBB) poorly, it is usually injected directly into the brain stereotaxically. Intraventricular and intracisternal administrations of 6-OHDA to rats produce a bilateral loss of DA and motor abnormalities that can be partially corrected by dopaminergic receptor agonists (80). However, the motor deficits induced are caused by considerable depletion of DA that requires high doses of 6-OHDA. Thus, animals often die due to aphagia and adipsia from severe stress (77, 81). In contrast, a unilateral intracerebral injection is more practical and useful. This model provides an approach to measure asymmetrical turning behavior in response to DA agonists with an internal control – the unlesioned contralateral side of the brain. To induce unilateral lesions, 6-OHDA is typically injected into the striatum, substantia nigra or the median forebrain bundle. Striatal injection of 6-OHDA produces slow retrograde degeneration of the nigrostriatal system over 1 month (82) and apoptotic morphology in the neurons that die (83-84). After injection of 6-OHDA into the substantia nigra or the medial forebrain bundle, dopaminergic neurons die more quickly than after striatal injection and no apoptotic morphology is seen (85). It should be noted that no typical LB formation has been demonstrated in this model (86). Unilateral lesions produce typical asymmetric circling motor behavior, especially after injection into the substantia nigra or the medial forebrain bundle which leads to more readily detectable behavioral deficits. The quantification of this circling behavior has been applied widely to evaluate new anti-parkinsonian drugs, and stem-cell and gene therapies (86).

6-OHDA has mainly been used in small animals, such as rodents, but has also been administered to non-human primates (86) and has been applied *in vitro* in various different models (87). The unilateral lesion induced by 6-OHDA in rats is one of the most popular models of PD (88-89). This model has advantages for testing cell replacement therapies and investigating regenerative therapies (90). However, 6-OHDA models demonstrate only one dimension of a complex illness: one type of cell loss and cellular stress. Moreover, 6-OHDA causes an acute model and cannot replicate many features of PD (90).

3.1.2 MPTP

MPTP was discovered in the early 1980s (14). Unlike 6-OHDA, MPTP is highly lipophilic and can cross the BBB easily after systemic administration. In the brain, it is metabolized to the 1-methyl-4-phenylpyridinium ion (MPP^+), which can enter dopaminergic neurons via the DA transporter (DAT) (91), and results in mitochondrial complex I inhibition and ROS formation (92). No LBs have been observed in MPTP-induced parkinsonism in either human or animal models (93-94).

Systemic administration of MPTP to many different species satisfies most of the requirements for an ideal parkinsonian model (90). The most commonly used PD model is the MPTP mouse model cause of the relatively low cost and acceptable timing for research. Acute administration of MPTP caused depletion in striatal DA (95), whereas the subacute model showed striatal DA depletion and cell loss in the substantia nigra (96-97). However, the acute model showed a greater loss of striatal DA than the subacute model. Moreover, the mechanism of cell death appears to differ in these two models: non-apoptotic mechanisms after acute (98) versus apoptotic mechanisms after subacute administration of MPTP (99). In addition, Acute treatment of animals with MPTP induced clear microglial activation in the striatum and the substantia nigra (100-101) and over-expression of inducible nitric oxide

synthase (102), whereas the subacute model showed only minimal microglial activation (101). Consequently, anti-inflammatory and anti-microglial compounds could be potential neuroprotective agents for PD and have been investigated using the acute MPTP model.

Although the mouse model has been used extensively in PD research, the non-human primate model is considered to be the "gold standard" for assessment before clinical trials because it reproduces the main pathological defect of PD, and the parkinsonian symptoms induced match many clinical features of PD. Acute and chronic non-human primate models are available, and both show similar motor symptoms of parkinsonism, although the mechanisms differ. Schneider et al. reported that the acute MPTP monkey model inuced increased binding to striatal DA D1 and D2 receptors and increased striatal prepronkephalin mRNA expression. In contrast to these findings, striatal preprotachykinin mRNA expression was decreased in both acute and chronic MPTP monkey models. Notablely, chronic administration of MPTP to animals with cognitive but no motor deficits induced no changes in preprotachykinin expression in the striaturn (103).

MPTP has been used to produce the best-characterized model of PD (104) in many different species, including non-human primates, small vertebrates, such as mice, and even invertebrates, such as worms (105-107). However, rats are relatively resistant to MPTP-induced neurotoxicity compared with mice (108-109) and primates are the most sensitive model (110). MPTP models develop pathological and neurochemical changes similar to those of PD patients (111) and produce an irreversible and severe parkinsonian syndrome that includes rigidity, tremor, bradykinesia, posture abnormalities and even freezing (86, 112). PD is a slowly progressive illness but the MPTP mouse model is an acute or subacute process. The chronic administration of MPTP to primates induced the slow development of a parkinsonian syndrome (113).

3.1.3 Rotenone

Rotenone is one of the most recent neurotoxins to be used in PD models (114). It is widely used as an insecticide throughout the world, and the rotenone model was the first to use an environmental toxin. Rotenone is highly lipophilic and can thus move freely and rapidly across cellular membranes without transporters. In mitochondria, it interferes with the electron transport chain, resulting in mitochondrial complex I inhibition (115). Furthermore, it also inhibits the formation of microtubules from tubulin (116) and the excess of tubulin monomers may be toxic to cells (117). The complex I inhibition induced by rotenone led to increased levels of oxidative stress which occurred predominantly in dopaminergic regions including the striatum, ventral midbrain and the olfactory bulb (118). Rotenone is a mitochondrial complex I inhibitor and acts evenly throughout the brain (119), which indicates that dopaminergic neurons are uniquely sensitive to mitochondrial complex I inhibition. Sherer et al (120) detected microglial activation in the striatum and substantia nigra of rotenone-infused rats. In the same model, the hallmark of PD pathology – LBs – were observed (114, 121) in the ventral midbrain regions (122). Exposure of animals to rotenone caused selective nigrostriatal dopaminergic neurodegeneration but had minimal effects on neurons of other brain regions (114, 121). It has been reported that parkinsonian symptoms in humans, such as rigidity and bradykinesia, are caused by reduced striatal dopaminergic activity (123); this change in motor behavior has also been reported in rotenone-exposed rats (114, 121). Rats treated with rotenone displayed a significant increase in abnormal motor behavior and decline in locomotor activities (124).

Rotenone-treated animal models reproduce all the pathological and behavioral features of typical human PD. Rotenone has been used successfully in a variety of species, including non-human primates, mice, and snails. However, there is some variation between the models and not all treated rats displayed these features. Briefly, this model provides very similar clinical features to typical PD but the low reproducibility and high mortality rate (88) may limit its practical use (117). Interestingly, rotenone was found to be involved in a multisystem disorder (125): enteric nervous system dysfunction (126) and loss of myenteric neurons in rats (127).

3.1.4 Other neurotoxins

Other neurotoxins used in PD models include paraquat and maneb. Paraquat is a common herbicide, has a similar chemical structure to MPP^+, the oxidized metabolite that mediates MPTP neurotoxicity, and has been suggested to be a risk factor for PD (128). Epidemiological studies have also indicated that exposure to paraquat may play an important role in the development of PD (16). After crossing the BBB, paraquat inhibits mitochondrial complex I in dopaminergic neurons (129). The treatment of mice with paraquat caused destruction of dopamine neurons in the substantia nigra (130). The paraquat-induced neurodegeneration is probably triggered by c-Jun N-terminal kinase signaling pathways (131). In this model, microglial activation has been identified and may act as a risk factor for dopaminergic cell death (132). Further investigations showed that the activated microglia produce potentially harmful molecules, such as superoxide anion and nitric oxide, resulting in redox cycling reactions and ROS formation which enhance tissue vulnerability in the paraquat model (133-135). In addition, oxidative stress plays an important role in nigrostriatal degeneration (136-137). The paraquat model demonstrated *a*-synuclein up-regulation and aggregation associated with dopaminergic cell death in the substantia nigra pars compacta in mice (138).

Maneb is a fungicide that is always used in combination with paraquat in agriculture. In PD research, maneb potentiates the DA toxicity of paraquat in mice (139). Maneb alone inhibits mitochondrial complex III and causes selective dopaminergic neurodegeneration (140). The combination of maneb and paraquat induced more pronounced behavioral and pathological changes than paraquat alone (141-142). Barlow et al. (143) explained that this effect could be due to the ability of maneb to modify the biodisposition and thus increase the concentration of paraquat. Findings in co-exposure models have important implications for the risk of PD in humans because they are liable to be exposed to the synergistic mixtures in agricultural or residential areas where both agents are applied jointly (139).

As a model of environmental exposure, administration of paraquat/maneb reproduces neurodegenerative changes and is useful for the investigation and understanding of the neurotoxic mechanisms of risk factors for PD. Although this model cannot achieve the severe nigrostriatal neurodegeneration induced by MPTP and 6-OHDA, it is a good complement for the comprehensive understanding of PD.

3.2 Genetic models

The majority of PD cases are sporadic but several causative genes and mutations have been discovered and have led to new approaches in the investigation of the mechanisms involve in PD. Several genetic animal models of PD reported in recent years are discussed below.

3.2.1 α-Synuclein

Many different transgenic mice models that over-express human α-synuclein have been generated and applied to pathogenesis and drug research. Transgenic mice induced by the tyrosine hydroxylase promoter expressed α-synuclein containing A30P and A53T mutations and showed a progressive decline in locomotor activity and loss of substantia nigra neurons and striatal DA content (144-145). When transgenic mice were induced by the neuron-specific platelet-derived growth factor β promoter, α-synuclein over-expression was observed, together with reduced tyrosine hydroxylase immunoreactivity and DA content in the striatum and impaired motor performance (146). Mice that over-expressed A53T mutant α-synuclein under the mouse prion promoter (PrP) developed an adult-onset progressive neurodegenerative disorder (147-148). Another neuron-specific promoter, thymocyte differentiation antigen 1 (Thy1), was used in mice to induce a high level of widespread expression of α-synuclein in most neuronal populations (149-150). Both Thy-1 and PrP mice are the only models that have intraneuronal inclusions, degeneration and mitochondrial DNA damage in the neurons (151).

A rat model that over-expresses wild-type or mutant α-synuclein induced by adenoassociated viruses in substantia nigra neurons, displayed progressive age-dependent loss of DA neurons, motor impairment, and α-synuclein-positive cytoplasmic inclusions (152). In Drosophila, α-synuclein over-expression led to age-dependent loss of dorsomedial dopaminergic neurons, accumulation of LB-like inclusions with α-synuclein immunoreactivity and compromised locomotor activity (153). α-Synuclein over-expression in Caenorhabditis elegans caused accelerated dopaminergic neuronal loss and motor impairment (154-155).

PC12 cells have been widely used in PD research to understand the regulation of the neuronal level of α-synuclein. α-Synuclein expression in PC12 cells was low but could be greatly increased by treatment with nerve growth factor (NGF) (156). NGF signal transduction was indicated via the MAP/ERK and PI3 kinase pathways (157). Another study with PC12 cells reported that wild-type α-synuclein was selectively translocated into lysosomes and degraded by the chaperone-mediated autophagy pathway (158). However, the mutant α-synuclein bound to the receptor on the lysosomal membrane inhibited both its own degradation and that of other substrates (158). PC12 cells over-expressing mutant α-synuclein showed impaired proteasomal activity and enhanced sensitivity to proteasomal inhibitors (159). Endoplasmic reticulum stress and mitochondrial dysfunction played important roles in increased cell death (160). The same model in another study showed impairment in both proteasomal and lysosomal functions, a high level of autophagic cell death and loss of chromaffin granules (161).

Yeast has been widely used to investigate the role of α-synuclein toxicity in human diseases, including PD. When expressed in yeast, α-synuclein became cytotoxic in a concentration-dependent manner (162). α-Synuclein in yeast was highly selectively associated with the plasma membrane and formed cytoplasmic inclusions (162). The growth inhibition induced by α-synuclein was accompanied by cellular consequences, such as proteasome impairment, heat-shock and oxidative stress, formation of ubiquitin-positive α-synuclein inclusion bodies, and emergence of apoptotic markers (162-164). Because the molecules that inhibit α-synuclein toxicity are potential therapeutic agents, α-synuclein toxicity in the yeast model has been used for genetic screening to identify genetic modifiers (165-166) and for small molecule or chemical screening to identify novel compounds.

Studies of α-synuclein in cell-free systems have focused on its aggregation pathway, post-translational modification, self-assembly and structure characterization. Test-tube models are critical for the investigation of PD-related protein α-synuclein and its related molecules as they provide more detailed information than any other approaches. However, some findings may not fully account for the biological complexity of α-synuclein *in vivo*. Therefore, further validation in cell cultures or *in vivo* is required.

3.2.2 Parkin

Parkin mutations have been found in a number of cases with recessive juvenile onset (167) and are the second genetic cause of PD. In a rat model, over-expression of parkin protected against the toxicity of mutant α-synuclein as demonstrated by a reduction in α-synuclein-induced neuropathology (168). In addition, parkin over-expression through viral transduction protected mice from mild MPTP-induced lesions (169). However, parkin knockout mice showed no impairment in the dopaminergic system (170-171). A parkin knockout Drosophila model exhibited locomotor defects and male sterility (172). These tissue-specific phenotypes were due to mitochondrial dysfunction. Further studies showed that oxidative stress components and genes involved in innate immunity were induced in parkin mutants, which indicated that oxidative stress and/or inflammation may play a fundamental role in the etiology of AR-JP (173). Another study showed that the expression of mutant human parkin in Drosophila caused age-dependent, selective degeneration of dopaminergic neurons accompanied by progressive motor impairment (174). Both the loss of function and toxicity of parkin have been demonstrated in the Drosophila model.

In experiments using cell-free models, mutant forms of parkin associated with AR-JP were reported to have reduced ubiquitin ligase activity (175-176). Catechol-modified parkin in the substantia nigra – a vulnerability of parkin to modification by dopamine – suggested a mechanism for the progressive loss of parkin function in dopaminergic neurons (177). Another modification – phosphorylation by cyclin-dependent kinase 5 – may contribute to the accumulation of toxic parkin substrates and decrease the ability of dopaminergic cells to cope with toxic insults in PD (178).

3.2.3 PINK1

PINK1 knockout mice had no dramatic abnormalities in the dopaminergic system (179). In Drosophila models, compared with the loss of parkin, the loss of PINK1 showed a strong similarity in phenotype: shortened lifespan, infertility and wing postural defect; in addition, identical loss of mitochondrial integrity was found in both cases (180-182). However, one difference was also observed: up-regulation of parkin rescued PINK1 mutants, whereas PINK1 up-regulation could not rescue parkin mutation (180-182). Cell-free models have been used to investigate the enzymatic function of PINK1 and the effects of mutations.

PINK1 was shown to phosphorylate downstream effector tumor necrosis factor receptor-associated protein 1 directly and prevent oxidative stress-induced apoptosis (183). It was also reported that the PINK1 kinase domain catalyzed the phosphorylation of artificial protein substrates, including α-casein (184) and histone H1 (60). Kinase assays suggested that multiple PINK1 mutants associated with autosomal recessive PD have reduced kinase activity (60, 183-185).

3.2.4 DJ-1

DJ-1 knockout mice exhibited a deficit in scavenging mitochondrial hydrogen peroxide due to its function of atypical peroxiredoxin-like peroxidase (186). Further studies have been carried out using Drosophila. DJ-1 knockout caused selective sensitivity to the oxidative toxins, paraquat and rotenone (187-189). DJ-1 protein undergoes oxidative modification on cysteine residue, which was also seen in Drosophila (189), and the oxidative modification occurred with aging and after exposure to paraquat (190). Cell-free models have helped researchers to characterize the crystal structure of DJ-1, investigate its function and activity, and reveal the effect of oxidative modifications on the stability and function of DJ-1.

3.2.5 LRRK2

In cell models, LRRK2 mutations significantly increased autophosphorylation activity (191-194). Over-expression of mutant LRRK2 caused condensed and fragmented nuclei, resulting in increased cellular toxicity (191). Because the cellular toxicity induced by mutant LRRK2 can be prevented by inactivation of the kinase domain in cell models, the kinase domain could be a therapeutic target for LRRK2-associated PD. Cell-free systems have been used to investigate the kinase function and how it is affected by pathogenic mutations. Reports indicated that LRRK2 catalyzed its autophosphorylation or the phosphorylation of artificial substrates (191-192, 195). This suggested that LRRK2-mediated phosphorylation was regulated by the binding of guanine triphosphate (GTP); in addition, both GTP binding and protein kinase activity are necessary for LRRK2 neurotoxicity (192, 196).

4. Clinical therapeutic insights

From the traditional view, PD is considered to be a single clinical entity, but this is currently under scrutiny (197-198). Clinically, the subtypes of this heterogeneous disease can be recognized on the basis of age at onset, predominant clinical features and progression rate. There are two major clinical subtypes: the tremor-predominant form which is often observed in younger people, and generally leads to a slow decline in motor function; in the other type, known as “postural imbalance and gait disorder” that is often observed in older people (>70 years old), motor function declines more rapidly, and is characterized by akinesia, rigidity, and gait and balance impairment. (198).

4.1 Dopamine replacement therapies

During the years of disease progression, the treatment of PD has to be adapted to alternating periods of reduced mobility and abnormal involuntary movements and is complicated by the onset of motor fluctuations and dyskinesia (199). PD was essentially an untreated motor disorder before L-DOPA was developed as a treatment. For the next two decades, the symptoms of hallucinations and delirium or other motor complications and psychiatric manifestations became the prevailing clinical problems in PD after treatment with L-DOPA. However, bradykinesia, resting tremors and rigidity which are the major symptoms of PD (200) can be controlled by long-term use of L-DOPA and other dopaminergic agents. Although the dopamine precursor, L-DOPA, and dopamine agonists are very effective in treating motor symptoms, they can cause substantial motor and behavioural adverse effects. Many reports have claimed that some patients treated with dopaminergic drugs develop

impulse control disorders, a dopamine dysregulation syndrome or other abnormal behaviors (201). Because of these flaws, new treatments for PD should be developed to tackle two unresolved problems: the alternation between therapies that alleviate symptoms and those that modify the disease; and reduction of the real causes of disability in long-term PD, which include autonomic dysfunction, balance loss, cognitive impairment and the growing prevalence of other non-motor symptoms.

Peak-dose dyskinesia, diphasic dyskinesia and off-period dystonia are the three forms of dyskinesias that commonly occur with L-DOPA use and negatively affect the quality of life of patients in the advanced stages of the disease (202). Peak-dose dyskinesia occurs when plasma L-DOPA levels are highest; diphasic dyskinesia refers to the abnormal involuntary movements that occur transiently at the onset and end of L-DOPA efficacy; and off-period dystonia occurs when a patient receives subtherapeutic levels of L-DOPA. Recent advances in the treatment of severe disabling dyskinesias have lessened but not entirely eliminated their effects. Specific examples of such advances include deep brain stimulation (DBS) of the subthalamic nucleus, continuous subcutaneous infusion of apomorphine and continuous duodenal infusion of L-DOPA. Currently, a major focus of drug development is the identification of agents that can acutely suppress existing disabling dyskinesias and of agents that do not induce dyskinesias.

More than 80% of patients who have had PD for 20 years develop dementia. Once this occurs, irrespective of their age or the duration of the disease, death follows shortly (203). From an anatomopathological point of view, PD dementia is believed to be due to a combination of the extension of Lewy bodies into limbic and cortical structures with concomitant Alzheimer's disease(AD)-related neurofibrillary tangles and amyloid-β plaque pathology (203-204). The recent observation that lower levels of amyloid-β_{1-42} in the cerebral spinal fluid may predict a more rapid cognitive decline supports the contribution of AD-related pathologies to the cognitive impairment that is seen in patients with PD (205). Relief from neuropsychiatric cognitive and behavioral symptoms without worsening motor impairment or altering the relief of symptoms that is provided by L-DOPA are the goals of current treatment in PD dementia. To achieve these goals, reliance is placed on fine-tuning the balance between dopaminergic and non-dopaminergic (prominently cholinergic) neurotransmission strategies.

4.2 Surgical treatment and deep brain stimulation (DBS)

In recent years, DBS has become an established treatment for the advanced stages of PD. It is efficacious and is approved by the US Food and Drug Administration for the treatment of advanced, L-DOPA-responsive PD and medically refractory essential tremor. New anatomical targets for DBS, such as the pedunculopontine nucleus, are currently being explored in patients with PD who have gait disorders. In the search for new targets, smart DBS techniques such as coordinated reset stimulation are currently under development (206).

Many reports have enlarged described the long-term outcome of DBS in PD, but, as with L-DOPS treatment, flaws still remain. Subthalamic nucleus DBS (STN DBS) can substantially improve motor function and quality of life in some patients with PD; however, a minority of patients experience cognitive and emotional difficulties after surgery. Better controlled

randomized trials that compared STN DBS with the best medical therapy failed to substantiate the findings of widespread or marked cognitive deterioration (207-208).

Smeding and colleagues (209) reported on predictors of the cognitive and psychosocial effects of STN DBS in patients with PD. Varied mood outcomes were observed: 16 patients treated with STN DBS (15%) showed improvements, but the same percentage showed deterioration. Strutt and colleagues (210) have shown that mood (depression) changes cannot be attributed solely to symptoms of somatic depression that overlap with those of PD.

The pre-operative selection of patients who are suitable for STN DBS is critical; response to L-DOPA is considered to be not only a predictor of motor outcomes, but perhaps also of neurocognitive and quality of life outcomes. As pre-operative impairments can predict neuropsychological outcomes after therapy, neuropsychological evaluation should be undertaken before surgery. Mood states should also be evaluated, but reliance on self-reported questionnaires should be discouraged (211).

Although aging is suggested to be a prognostic factor of neurosurgical outcome (212-213), studies that trace the long-term clinical evolution among subgroups of patients with early-onset versus late-onset PD after STN DBS are still lacking. The latest study of a cohort of 19 subjects treated with subthalamic nucleus DBS after more than 20 years of disease reported clinical and neuropsychological data up to a mean of 30 years after disease onset (214). A higher prevalence of axial and non-L-DOPA-responsive symptoms was observed during long-term evaluations compared with other STN DBS follow-up studies. This confirms that, even in patients with an early onset of disease and a previous long-lasting response to dopaminergic therapies, several complex aspects underlie the development of non-motor symptoms and other features of the progression of PD. Therefore, the surgical option of STN DBS should be proposed earlier, since the progression of PD might not follow a single direction, and it is possible that age might affect the development of non-motor features more than the duration of the disease.

4.3 Transplantation treatment

Pharmacological agents that increase DA can alleviate motor symptoms as mentioned above; however, patients develop severe effects with long-term use. Cell transplantation therapy has therefore been investigated as an alternative treatment in recent years. Since only one cell type is affected in a distinct location of the brain, cell replacement therapy is liable to be successful for PD, and has already been used in many other diseases. Transplantation treatment is considered to be an on-going alternative strategy for an effective cure for PD.

Stem-cell replacement therapy has been suggested as a treatment for neurodegenerative diseases caused by the degeneration of DA neurons in the substantia nigra of the brain, and especially for PD (215). Stem cell-derived DA neurons can replace endogenous degenerated neurons. Clinical studies using fetal midbrain tissue proved the principle that cell transplantation could be a feasible treatment for PD(216).

Although it has shown promise for the treatment of PD, the safety and efficacy of transplanted stem cells induced by different methods are variable. Fetal-tissue transplants

have gained some success, but their availability is limited. Human induced pluripotent stem cells (hiPSCs) are a promising alternative for personalized therapy; many cells can be generated and the chances of immunorejection are low. Several reprograming methods can generate hiPSCs, the most common of which are lentiviral and retroviral methods, but these can generate mutations and lead to chromosomal aberrations.

Recently, Rhee and colleagues (217) compared the safety of several types of hiPSCs, and found that they were able to generate healthy DA neurons. Neural precursor cells from protein-based hiPSCs were transplanted into a rat model of PD. The transplanted tissue not only survived well but also was able to rescue motor deficits in the model animals. These findings suggest that protein-based hiPSCs can be considered as a safe, viable alternative to virus-induced cells; moreover, they could potentially be used for transplantation and treatment in patients with PD (218).

4.4 Neuroprotective effects

DA substitution therapy and DBS do not completely relieve the symptoms of PD. Hence, there is still a need to identify neuroprotective agents that can modify the progression of the underlying disease processes.

Due to its robust effects in preventing degeneration of the nigrostriatal system in commonly used neurotoxin-based pre-clinical models of the disease, glial cell line-derived neurotrophic factor (GDNF) has gained most attention as a candidate neuroprotective molecule in PD. GDNF may be used in two ways to afford substantial neuroprotection in rodent and primate models of PD induced by either 6-OHDA or MPTP: infusion and viral-mediated delivery of GDNF, and transplantation of GDNF-producing cells (219-222).

Because of these promising pre-clinical results, more clinical trials to evaluate the efficacy of GDNF and neurturin in patients with PD are now in progress. However, the results obtained from these trials to date remain inconclusive (223-225).

Another recent study demonstrated that viral vector-mediated delivery of GDNF is unable to prevent the degeneration of the nigrostriatal DA neurons induced by over-expression of human wild-type α-synuclein at levels that have been shown to be efficient in the toxin models; this highlights the importance of performing pre-clinical tests on potential therapeutic compounds in mechanistically different models of PD (226).

5. Conclusions

As is the case for many other diseases that humans have been fighting for decades, there is a common gap between laboratory research and the ideal clinical therapy: how to ensure that products derived from laboratory experiments are both efficacious and safe. Although various studies have made progress towards a definitive solution for PD, several unresolved areas still remain. A better understanding of its biochemical pathogenesis is the best method to develop new disease-modifying therapies. However, through novel therapies and the refinement of old treatments, the management of this disease has been considerably up-graded over the past 20 years. Clinical experience shows that most patients who have accepted treatment now have a relatively good quality of life despite having suffered the effects of PD for many years. We should be confident that all these new developments will

provide advances for PD treatment, and give us a hope of a final triumph in fighting the disease.

6. References

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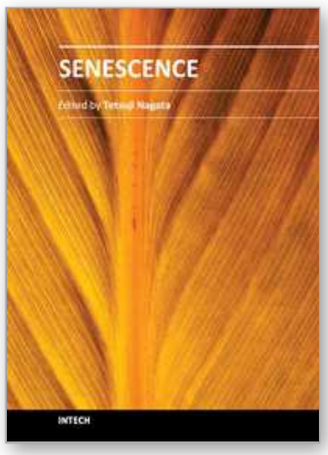
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The book "Senescence" is aimed to describe all the phenomena related to aging and senescence of all forms of life on Earth, i.e. plants, animals and the human beings. The book contains 36 carefully reviewed chapters written by different authors, aiming to describe the aging and senescent changes of living creatures, i.e. plants and animals.

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