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Review article

Parkinson's disease: Mechanisms, translational models and management strategies

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ABSTRACT

Parkinson's disease is a progressive neurodegenerative disorder. The classical motor symptoms include resting tremors, bradykinesia, rigidity and postural instability and are accompanied by the loss of dopaminergic neurons and Lewy pathology. Diminished neurotransmitter level, oxidative stress, mitochondrial dysfunction and perturbed protein homeostasis over time worsen the disease manifestations in elderly people. Current management strategies aim to provide symptomatic relief and to slow down the disease progression. However, no pharmacological breakthrough has been made to protect dopaminergic neurons and associated motor circuitry components. Deep brain stimulation, stem cells-derived dopaminergic neurons transplantation, gene editing and gene transfer remain promising approaches for the potential management of neurodegenerative disease. Toxin or genetically induced rodent models replicating Parkinson's disease pathology are of high predictive value for translational research. This review addresses the current understanding, management strategies and the Parkinson's disease models for translational research. Preclinical research may provide powerful tools to quest the potential therapeutic and neuroprotective compounds for dopaminergic neurons and hence possible cure for the Parkinson's disease.

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder commonly affecting elderly people worldwide [1]. It affects around 0.3% of the general population and 1–3% of the population over the age of 65 and its number is going to rise from 8.7 to 9.3 million by 2030 [2,3]. The PD symptoms were described two hundred years ago by James Parkinson in 1817 [4]. Manifestations of PD primarily include dysfunctions of the somatomotor system (i.e., rigidity, bradykinesia, postural instability, gait dysfunction and tremors) [5]. At its core, PD involves progressive degeneration of the nigrostriatal dopaminergic pathway with substantial loss of substantia nigra pars compacta (SNpc) neurons and depletion of dopamine (DA) [6,7]. Impairments in non-motor functions are often accompanied (such as dementia, hyposmia and gastrointestinal alterations) during the disease course [8–10].

The pathological hallmark of PD is the accumulation of filamentous, cytoplasmic inclusions consisting mainly of α-synuclein aggregations in the form of Lewy bodies (LB) or Lewy neurites (LN). α-Synuclein phosphorylation and fibrillization lead to LB formation and induce neuron death [11–13]. LB are found in certain areas of the CNS, e.g. basal ganglia, the dorsal motor nucleus of the vagus (DMV), the olfactory bulb (OB), the locus coeruleus (LC) and the intermediolateral nucleus in the spinal cord (IML), and of the peripheral nervous system (PNS) e.g., celiac ganglia and enteric nervous system (ENS) of PD patients [14–16].

Early symptoms may include sleep and associated disorders such as, mild tremors, soft speech, postural difficulty, impairments in normal facial expressions, reduced limb movement, focus loss, general fatigue and depression without any obvious cause [17]. With the passage of time the onset of unilateral resting tremors is generally noticed by the close members and it is accompanied by a noticeable reduction in voluntary activities and postural difficulties. ***Bradykinesia*** refers to the slowness of a voluntary movement and is possibly due to slow programming to formulate instructions and/or slow execution of such instructions [18]. Quantitative evaluation of bradykinesia tasks (e.g., hand grasping and finger tapping) demonstrates slow performance of PD patients [19]. ***Resting Tremor*** is a rhythmic, involuntary oscillatory movement of a body part (limb, hand or foot), when it is not voluntarily activated and completely supported against gravity. Clinically, one out of four PD patients never develops tremors [20]. ***Rigidity*** is defined as increased resistance experienced during passive mobilization of body parts (such as distal limb). Stiffness and disturbance are experienced, and patient feels as if someone else is facilitating its movements. ***Postural instability*** refers to balance impairments compromising the

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ability to maintain posture [21]. At advanced stages of disease, patients experience higher fall rates and loss of independence (Supplemental Fig. 1A).

In addition to above mentioned primary motor function impairments, secondary motor symptoms such as gait impairments, micrographia, speech difficulties, dysphagia, dystonia and precision grip impairments worsen the quality of life of affected persons.

The non-motor symptoms (NMS) include neuropsychiatric symptoms (depression, cognitive dysfunctions and dementia), sleep disorders (insomnia, rapid eye movement disorders, vivid dreaming) and autonomic symptoms (bladder disorders, orthostatic hypotension, erectile impotence) [10,22]. *Cognitive Impairments & Dementia* are reported among 80% of PD patients after 15–20 years of disease progression [23–25]. Severe cognitive impairments are significantly associated with motor, depressive and autonomic dysfunctions in PD patients [26]. *Depressive disorders* are common among 50% of PD patients. Evidence indicates PD pathology extends beyond dopaminergic neurons and the discrete loss of serotonergic and noradrenergic neurons is observed [27]. It suggests dysregulation of neuronal circuits associated with mood regulation and reward systems are probable reasons of depressive disorders [28]. *Sleep impairments* in around 25% of PD patients are observed. Generally, insomnia (insufficient amount of sleep duration) is having a higher prevalence (up to 90%) among PD patients [29,30]. *Gastrointestinal dysfunctions* involve dysphagia (difficulty in swallowing) due to the mouth, pharynx and esophagus dysfunctions and bowel dysfunction (slowed colonic transit and constipation). *Orthostatic hypotension* is reduction of 20 mmHg systolic and 10 mmHg diastolic blood pressures within 3 min of standing [31]. A considerable percentage (40% to 60%) of patients with multi-decade PD manifestations is affected with orthostatic hypotension, possibly due to insufficient norepinephrine release [32].

In PD patients, α- synuclein aggregates are detected in the dorsal motor nucleus of the vagus (DMV), vagus nerve, spinal sympathetic preganglionic neurons and nerves of the epicardium [33,34]. *Urinary tract disturbances* are reported in 60% of PD patients suffering from bladder hypersensitivity and lead to urgency, frequency and incontinence in voiding [35] (Supplemental Fig. 1B).

The severity of PD is categorized into a five stage scale known as Hoehn-Yahr (HY) scale [36]. The HY-scale based comparison of PD patients provides disease progression assessment ranging from no signs of disease (stage 0) to wheelchair bound/bedridden (stage 5) condition. Although HY scale presents detailed description of disease onset and progression from 802 patient's data spanning over 15-years, however, its limitations such as non-linearity and mixing of impairments are debatable [37] (Supplemental Fig. 2).

Currently, Movement Disorder Society suggests using a modified form of *Unified Parkinson Disease Rating Scale (UPDRS)* for rating PD progression [38]. As per recommendations, the patients are assessed based on cognition and mood (Part I: non-motor), daily living activities (Part II: motor experiences), motor examination (Part III) and complications encountered in motor examinations (Part IV). The responses are scaled, such as 0 = normal, 1 = slight, 2 = mild, 3 = moderate, 4 = severe accordingly [38].

Autopsy studies and histology procedures have improved our understandings of PD progression and underlying pathological hallmarks, particularly in CNS neurons. However, major disadvantage associated with such approaches is analyzing neurons in real-time. Thus, neuroimaging technological advancements such as magnetic resonance imaging (MRI), single-photon emission computed tomography (SPECT) and positron-emission tomography (PET) are employed to analyze the extent of damage in the CNS [39].

Additionally, many lines of evidence provide substantial data that PD pathology includes mitochondrial dysfunction in the CNS. Inhibition of mitochondria complex I is widely reported in PD etiology [40,41]. Thus, compounds like rotenone and MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) are successfully used to generate pre-clinical models of PD owing to strong inhibition of mitochondria complex I activity [7]. Mounting evidence suggests that PD models are actively used in different laboratories to understand the onset and progression of disease symptoms using a battery of neurobehavioral tests [42]. Comparably, genes involved in mitochondrial dynamics/energetics such as *Pink1, Parkin* and *DJ-1* are manipulated (e.g., mutated or expression is masked) in cell cultures or rodents to induce PD features [43–45].

Current review aims to highlight the mechanisms of PD, management strategies to cope the challenges and translational models for the assessments and possible cure of disease manifestations.

2. Neurochemical and neuropathological features of PD

The depleted DA levels, dopaminergic neurons loss and intraneuronal cytoplasmic inclusions termed as “Lewy Bodies” (LB) in surviving SNpc neurons are the pathological hallmarks of PD (Fig. 1). The SNpc contains the soma of nigrostriatal neurons and project them to the putamen. The pattern of SNpc cell loss appears parallel to the expression levels of the dopamine transporter (DAT) transcript and is consistent with the finding that DA loss is most pronounced in the dorsolateral putamen, the main site of projection for these neurons. At the onset of symptoms, putamen DA is depleted ~80%, and ~60% of SNpc dopaminergic neurons has already been lost. However, the cell bodies of mesolimbic dopaminergic neurons adjacent to SNpc are affected to a limited extent in PD [46,47]. Consequently, there is significantly less depletion of DA in the caudate [48]. Thus, the selective loss of DA in striatum primarily contributes to PD pathology.

It is generally perceived that the neuropathology of PD is characterized solely by the dopaminergic neuron loss and DA depletion, however neurodegeneration extends well beyond dopaminergic neurons [49]. Neurodegeneration and LB formation are found in noradrenergic (LC), serotonergic (raphe), and cholinergic (nucleus basalis of Meynert and DMV) systems, as well as in the cerebral cortex (especially cingulate and entorhinal cortices), optic bulb, and autonomic nervous system. Degeneration of hippocampal structures and cholinergic cortical inputs contribute to the high rate of dementia that accompanies PD, particularly in older patients. Currently, the lesions of the serotonergic and noradrenergic pathways are not clinically correlated with PD manifestations as clearly as being those of the dopaminergic systems.

2.1. Molecular events underlying PD

Epidemiological, genetic, post-mortem analysis, in vitro and in vivo modeling studies have significantly unveiled underlying mechanisms of PD. Protein homeostatic impairments (inducing protein aggregations) and mitochondrial dysfunctions (leading to impaired bio-energetics and oxidative stress) are primary underlying reasons of SNpc neuronal loss. Additionally, pathogenic genetic mutations, dopamine dysregulation, calcium channels altered activity and neuro-inflammation are culprits contributing to PD development [50].

2.1.1. Aberrant protein homeostasis and PD

Protein homeostasis is under intrinsic surveillance mechanisms (such as ubiquitin-protease, chaperone mediated process and autophagy system) for rapid detection of altered protein and its processing or elimination [51,52]. Several lines of evidence support that the failure of above mentioned surveillance mechanisms leads to aggregation of native and non-native proteins and hence affecting cellular homeostasis [50,53]. α-Synuclein interactions with the chaperone proteins, ubiquitin proteasomal and lysosomal proteins provide details of how it interacts natively and its mutated forms lead to failure of surveillance mechanisms [54–56]. Phosphorylated α-synuclein (at serine 129) enhances the formation of LB inclusions [57]. Similarly, misfolding of α-synuclein is known to cause its aggregation [58]. It suggests alterations in α-synuclein native structure may contribute in LB pathology and hence damage to the SNpc neurons.

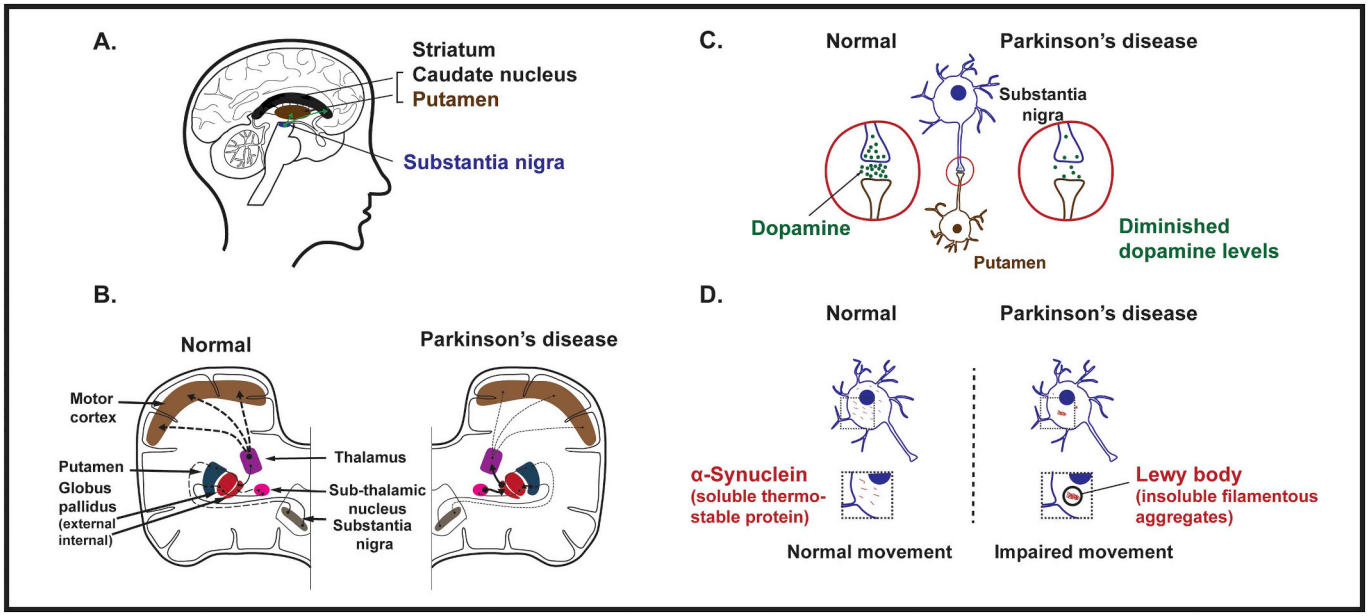

Fig. 1. The dopaminergic pathways, neurochemical and neuropathological basis of Parkinson's disease. Sketch illustrating dopamine production from Substantia nigra (blue) and synaptic transmission (green) to the striatum (A). The dopaminergic pathway with the normal target stimulation (dashed-lines) and target suppression (continuous-line) in normal brain, while degenerated substantia nigra in Parkinson's disease impairs cortico-striatal circuits leading to induction of the associated symptoms (B). Reduced dopamine production from Substania nigra dopaminergic neurons (C) and formation of α-synuclein aggregates as Lewy body (D) lead to the movement disorders, characterized as PD symptoms.

The α-synuclein aggregation is reported to restrict the surveillance mechanisms such as heat shock protein 70 (Hsp70) and Hsp40 are sequestered along the α-synuclein in the LB and hence are functionally unavailable for the cell [59]. Additionally, α-synuclein aggregation may contribute to the autophagy impairments by inhibiting RAB1A protein and inhibition of the proteasome complex through chymotrypsin-like 20S/26S protein cleavage restriction [60,61].

These studies clearly demonstrate impaired protein homeostasis through either failure of surveillance mechanisms or through α-synuclein mediated failure is a key event in PD pathology (Fig. 2).

2.1.2. Mitochondrial dysfunction and oxidative stress in PD

Histology of post-mortem human brains reveals signs of mitochondrial dysfunction, particularly oxidative stress is a common pathological mechanism employed in PD pathology [62,63]. In fact, a toxin 1-methyl-4-phenyl-1,2,3,4-tertahydropyridine (MPTP) exposure showed striking Parkinsonian features due to irreversible mitochondrial complex I inhibition and suggested the involvement of mitochondrial dysfunctions in PD manifestations [64,65]. Quantitative estimation of mitochondrial electron transport chain (ETC) components from PD brain subjects reveals a 34% loss of complex I 8 kDa subunit while other complexes remain unchanged [66]. Importantly, the degeneration of dopaminergic neurons induced by loss of mitochondrial complex I activity in PD models [40] is successfully implicated in preclinical research. The complex I inhibitors (e.g., MPTP or rotenone) induce PD features in animal models and hence provide an opportunity to unveil the PD facts [7,67].

Dopaminergic neurons are susceptible to mitochondrial reactive oxygen species (ROS) [68]. The main sites of ROS production in mammalian cells are mitochondria [69], and its generation is initiated by the electron leak primarily at complex I through partial reduction of molecular oxygen (O_2) to superoxide radical (O_2^{*-}) by a single electron uptake, in turn, it leads to either hydroxyl radical (OH^*) generation through iron catalyzed Fenton reaction or to peroxynitrite ($ONOO^-$) (Fig. 3). Superoxide radical (O_2^{*-}) is also converted to hydrogen peroxide (H_2O_2) by superoxide dismutase 2. H_2O_2 is subsequently broken down to H_2O and O_2 by catalase to maintain its homeostasis [70]. Accumulation of ROS is reported to induce widespread damage to cellular components [69]. Additionally, mitochondrial DNA alterations under ROS stress may lead to huge burdens as genetic removal of TFAM (transcription factor A, mitochondrial) a major transcriptional factor is reported to induce neurodegeneration in mice [71]. This mouse model is known as MitoPark and exhibit cardinal PD features.

Dopamine in PD brain is oxidized to form dopamine quinones and free radicals either by self-oxidation or by mitochondrial outer membrane bound monoamine oxidases (MAO) such as MAO-A (in neurons) and MAO-B (in glia). Oxidation products of dopamine may cyclize to form aminochromes, and are reactive enough to produce superoxide radicals [72].

Modulations in mitochondria dynamics (fusion/fission machinery and its transportation) are also under intensive investigations in neurodegenerative diseases. Mitochondria undergo fusion/fission dynamics to maintain a healthy mitochondria pool, and the cell sorts damaged population for mitophagy [73]. Mitophagy involves the activity of a mitochondrial kinase PINK1 and cytosolic Parkin to activate PINK1/Parkin pathway [74]. The loss of PINK1/Parkin based mitochondria quality control through genetic mutations or other factors contributes to PD pathogenesis [44].

2.2. Genetics underlying PD

So far, mutations in several genes are identified in hereditary forms of PD such as, mutated α-synuclein, LRRK2, UCHL1, DJ-1, ATP13A2, PINK1, Parkin, GBA1 and VPS35 are widely reported to cause familial PD manifestation through dopaminergic neurodegeneration [75,76].

Briefly, α-synuclein gene (*Scna/Park1*) mutations cause familial forms of PD and induce formation of LB causing severe damage in SNpc and persistent motor impairments in rodents [77]. Further, A53T mutation in α-synuclein inhibits chaperone-mediated autophagy and induce toxic effects due to α-synuclein accumulation [78]. Leucine-rich repeat kinase 2 (*Lrrk2*) contains GTPase activity domain and its mutated forms are related with late-onset familial PD [79]. Mitochondria morphology and autophagy is regulated by *Lrrk2* in neurons. *Lrrk2* G2019S mutation induces alteration in mitochondria dynamics in glial

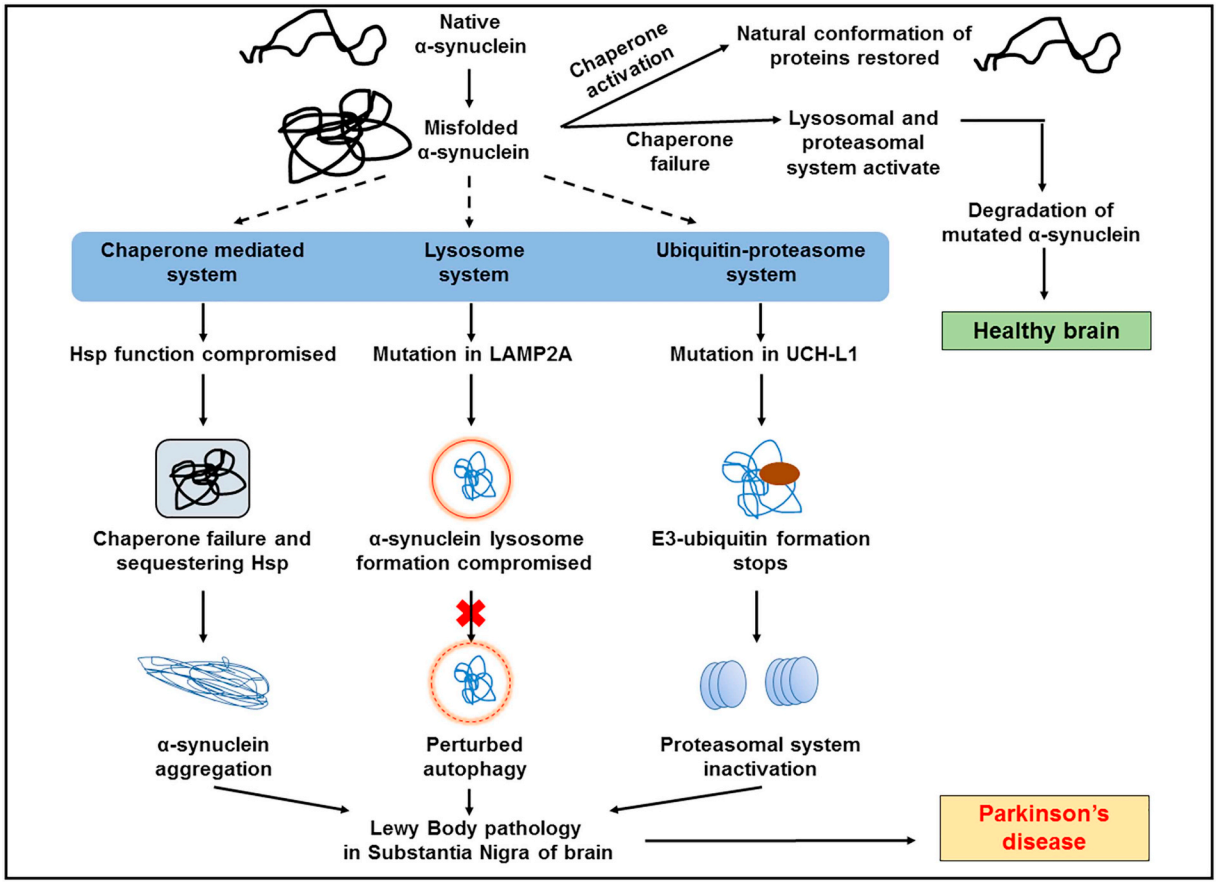

Fig. 2. Perturbed homeostasis of mutated α-Synuclein. Chaperone mediated system restores the configuration, however its failure leads to aggregation. Gene mutations (such as LAMP2A, UCH-LI) lead to aberrant protein clearance and Lewy body formation and hence Parkinson's disease development.

cells and brain lysates of such rodent demonstrated higher levels of pro-inflammatory TNF-α and Drp1 proteins thus modulating neuroinflammation [80]. Additionally, mutation in LRRK2 is reported to induce synaptic dysfunctions in human dopaminergic neurons through phosphorylation of auxilin protein [81]. *Uchl1* (ubiquitin carboxy-terminal hydrolase-L1) gene encode deubiquitinating enzyme and is required for axonal integrity. Immunohistological studies demonstrate colocalization of mutated UCH-L1 with α-synuclein in LB of PD nigrostriatal neurons. Similarly, post-translational modifications in UCH-L1 are linked to neurodegeneration underlying PD [82,83]. *Dj-1* is a deglycase protein and it can inhibit α-synuclein aggregation, while its deficiency results in increased α-synuclein aggregation in PD animal models [84]. Mutated *Dj-1* is associated with impaired mitochondrial quality control by enhancing mitochondria removal and its localization within mitochondrial matrix is linked to PD pathology [85,86]. A P5-type ATPase 13A2 protein is encoded by *Atp13A2* gene and localizes to lysosomal compartments with unknown functions. Mutated forms of *Atp13A2* are associated with cellular dysfunctions in the form of significant reduction in oxygen consumption rate and mitochondrial membrane potential [87]. The inheritance of *Atp13A2* mutations causes juvenile-onset of PD [88]. *Pink1* and *Parkin* genes play vital role in mitochondria quality control [89]. It involves selective recruitment of *Pink1* to damaged mitochondria and subsequent activation of Parkin's E3 ubiquitin ligase for its recruitment and triggering autophagy. Mutations either in *Pink1* or *Parkin* are reported to impair this process of selective autophagy [90]. Glucocerebrosidase 1 (*Gba1*) is lysosomal enzyme coding gene, and its mutations enhance the risk of GBA1-associated PD at earlier age [91]. *Gba1* mutation D409H shortens the lifespan and enhances the morbidity of A53T α-synuclein transgenic mice [92]. Vacuolar protein sorting 35 (*Vps35*) gene mutations account for familial PD. *Vps35* regulates transmembrane sorting between endosomes and Golgi bodies. Interestingly, D620N mutation in *Vps35* is reported to induce mitochondrial fragmentation and dysfunction through interaction with dynamin-like protein (DLP) 1 and accelerates removal of mitochondria via lysosomal degradation [93]. Gene mutations implications in PD pathology reveal that it could aggravate the symptoms and are broadly linked with dysfunctions of mitochondria and its dynamics, impaired autophagy and lysosomal functions.

2.3. Neuronal circuit in normal vs PD brain

The basal ganglia and motor cortex play crucial roles in the execution of motor activities. The basal ganglia in the brain include the striatum, which comprises the caudate nucleus, putamen, globus pallidus (divided into an external segment (GPe) and an internal segment (GPi)) and the substantia nigra (SN) (divided into a pars compacta (SNpc), a pars reticulata (SNpr)), and subthalamic nucleus (STN). The main input region of the basal ganglia is the striatum which receives afferents from many regions of the cerebral cortex, including motor and premotor, cingulate, and prefrontal cortices, and the intralaminar nuclei of the thalamus [94]. The major output regions of the basal ganglia are the GPi and the SN, which project to the thalamus modulating activity of cortical regions and to the brainstem. The input and output regions are connected via either the direct or the indirect pathways, both of which arise from striatum. Cortico-striatal projections, intrinsic basal ganglia circuits, and output pathways are functionally arranged according to the basal ganglia loop involved [95–97]. The main neurotransmitter of basal ganglia circuit is the inhibitory gamma

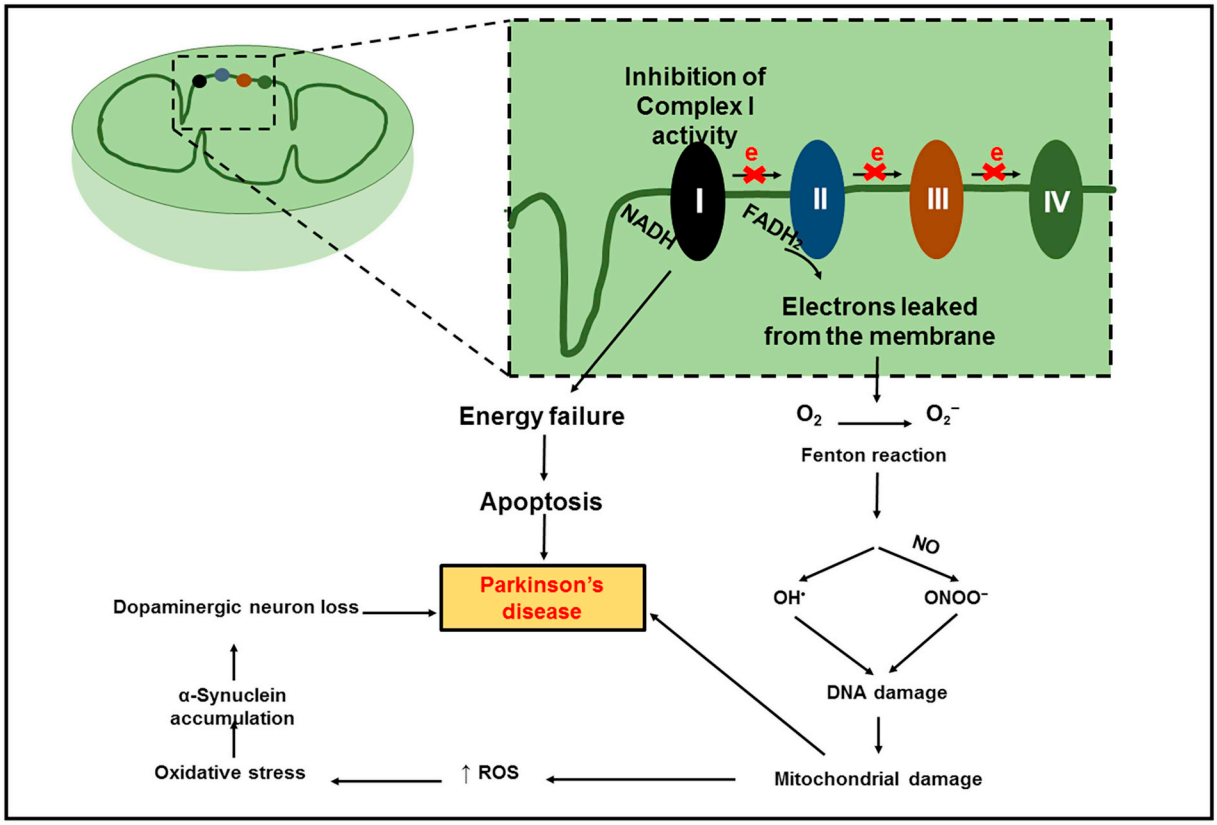

Fig. 3. Mitochondrial dysfunction and oxidative stress in Parkinson's disease. The mechanism of mitochondrial dysfunction and oxidative stress highlighting inhibition of mitochondrial complex I and associated ROS production leading to loss of dopaminergic neurons in Parkinson's disease.

aminobutyric acid (GABA), while neurons of the STN use excitatory glutamate, and those of the SNpc use dopamine [98,99].

The 'motor circuit' is most directly relates to the control and pathophysiology of movement functions and disorders, respectively. Its oversimplified organization is shown in Fig. 1B. Cortical motor areas project out in point to point fashion to putamen where they establish excitatory, glutamatergic synaptic connections with the neurons containing GABA. These neurons give rise to two pathways that connect the striatum to the output nuclei, the GPi and SN. Neurons in the 'direct pathway' project directly from the putamen to GPi/SN. They bear dopamine receptors and provide a direct inhibitory effect on GPi/SN neurons. Striatal neurons in the 'indirect pathway' connect the putamen with the GPi/SN via synaptic connections in the GPe and STN. They also contain dopamine receptors and project from putamen to GPe and from GPe to STN and are GABAergic and pose inhibitory effect on dopamine neurons.

Neurons originating in the STN use glutamate as a neurotransmitter and activate neurons in the GPi/SN. Stimulation of neurons in the indirect pathway leads to GPe inhibition, disinhibition of the STN and GPi/SNpr excitation. Thus, the basal ganglia output activity is influenced by the opposing effects of inhibitory inputs from the direct pathway and excitatory inputs from the indirect pathway. This, in turn, provides an inhibitory effect on the brainstem and thalamo-cortical neurons involved in motor activities. The basal ganglia and the cerebellum modulate the activity of largely overlapping cerebral cortical areas through multi-synaptic loops, which were traditionally assumed to be anatomically and functionally separate [100]. Recent study showed that the cerebellum projects to the striatum and to the GPe and that the STN has projections to the cerebellar cortex [101]. These reciprocal connections between the basal ganglia and the cerebellum, together with pathological changes in the cerebellum, reason the active involvement of the cerebellum in PD pathogenesis [100].

2.4. Theory of PD progression: Braak's hypothesis

PD is most likely caused by a combination of environmental and genetic factors. Predominantly, onset of PD is sporadic, however, 10–15% of patients have a positive family history of the disease [102]. It is postulated that an unknown pathogen (virus or bacterium) in the gut could be responsible for the initiation of sporadic PD, and a staging system based on pattern of α-synuclein spreading is formulated for PD progression [103]. As per Braak's hypothesis, a pathogen enters the body via nasal cavity and swallowed initiating Lewy pathology in the nasal cavity and gut lining. Then pathology spread from PNS to CNS. Later, a more encompassing dual-hit hypothesis was presented, stating that sporadic PD starts in the neurons of the nasal cavity and the neurons in the gut separately and now is known as Braak's hypothesis. It is suggested that pathology spread via the olfactory tract and the vagal nerve to the CNS. In this hypothesized spread of α-synuclein pathology the spinal cord is not potential route for disease spread and is only involved after the CNS has already become affected [104,105].

2.5. Translational research in PD

Preventing neurodegeneration of dopaminergic cells of SNpc is still unresolved challenge of PD despite tremendous drug and non-drug mediated symptomatic relieves. Multifactorial and heterogeneous PD manifestations involving multiple cellular pathways make it extremely challenging biological problem. Moreover, strategies to stop neurodegeneration are currently unavailable. To this grim situation, development of therapeutic compounds and evaluation of their respective protective capacities may lead to identification of potential compounds/strategies for clinical benefits of PD patients.

The rapid march of accumulating evidence on the protection of dopaminergic neuron research seems to identify a putative candidate

for human clinical trials and associated outcomes. Protection of dopaminergic neurons in pre-clinical studies by taurine, caffeine, Mfn2 overexpression, puerarin, progranulin gene delivery, nicotine receptor activation, estrogen in cell-culture study seems convincing and promising [106–110]. However, human clinical trials of coenzyme Q10 administration for slowing disease progression revealed no clinical benefits, thus convincing preclinical therapeutic investigations are debatable for their relevance to humans clinical situations [111].

Mounting evidence is suggesting a bunch of molecules with therapeutic value against oxidative stress, such as cinnamic aldehyde, curcumin and melatonin imparting protection to the dopaminergic neurons in MPTP and 6-OHDA rodent models of PD [112–114]. Additionally, mitochondrial dysfunction mitigation strategies are reported to enhance the neuronal cell survival in neurodegenerative disease [115]. Although preclinical translational studies unveil the potential protective capacities of molecules, however, clinical trials might not be predictive of positive outcomes. Thus, challenge for developing clinical neuroprotective strategies remains elusive.

2.6. In vitro models for PD

The PD involves multiple cellular pathways such as, α-synuclein misfolding and deposition, and dopaminergic neuron death (involving mitochondrial dysfunctions and ROS generation) during disease progression. The involvement of such cellular functions/pathways is extremely challenging to investigate under in vivo conditions, owing to the heterogeneous nature of the brain. Further, absence of in vitro human neuronal cell-line mimicking physiology of dopaminergic neurons poses greater challenges for translational research. So, it is inevitable to develop in vitro models recapitulating PD cellular features in pure culture of neurons to understand the cellular mechanisms and the possibility of identifying therapeutic target to cure the cardinal PD features [116]. In particular, cellular models of PD have enhanced the understandings of α-synuclein misfolding's and aggregation processes, mitochondrial impairments such as oxidative stress, fusion-fission dynamics, axonal transportation and bioenergetics upon toxin (such as MPP^+) insult [117].

The human dopaminergic neuron containing cultures have been successfully derived from induced pluripotent stem cells (iPSCs), neural stem cells (NSCs) and embryonic stem cells (ESCs) through different approaches. The fibroblast cells were reprogrammed using forced expression of Sox2, Klf4, Oct3/4 and c-Myc transcription factors [118]. Moreover, fibroblasts were directly reprogrammed to functional induced dopaminergic neurons through culturing on microgroove and nanogroove substrates [119]. Thus, animal models may be replaced initially through harnessing the translational value of dopaminergic neurons.

The baker's yeast *Saccharomyces cerevisiae* offers a humanized yeast model to investigate the neurodegenerative process modulated by the human proteins. Vectors (e.g., pRS426 with *GAL1* promoter) containing genes of interest (e.g., A53T mutated α-synuclein) are delivered and following expression of the transgene, the modulation of pathways (such as proteasome and autophagy) are monitored for possible involvement of the transgene on investigated pathways [120]. The screening of α-synuclein mutants for hindering the vacuolar degradation process revealed the formation of α-synuclein aggregates and associated toxicity [121]. The oxidative-damage induced mitochondrial autophagy associated with the *Parkin* expression in yeast cells indicated a higher degradation rate of damaged mitochondria through PARKIN translocation to mitochondria, thus offering a new in vitro PD model to dissect the disease pathogenicity with special emphasis on the autophagy of mitochondria [122]. Yeast models of PD greatly replicate the cellular and molecular events such as vesicular trafficking (replicating synaptic regulation), protein clearance and autophagy (protein homeostasis) and mitochondrial homeostasis [123].

2.7. Rodent models for PD

Animal models closely mimicking the PD symptoms (such as movement disorders) may provide a pre-clinical alternate for translational research. However, such animal models completely replicating the human PD features are yet to be developed. Importantly, animal models display core pathological hallmarks of human PD, such as a subset of motor symptoms, LB formation and dopaminergic SNpc neuron loss in a progressive manner. It provides an opportunity to be used as high predictive prerequisite for human PD manifestations and possible cure. Based on the objective of study, appropriate mouse model featuring PD subset is appropriately selected keeping in view the advantages and limitations of the model (Fig. 4).

2.7.1. Pharmacological and neurotoxic PD models

2.7.1.1. 1-methyl-4-phenyl-1,2,3,6-tetrahydroptridine (MPTP). A lipophilic toxin, MPTP is highly selective for SN of human and other primates and induces PD after crossing blood brain barrier [124]. In mice, following system administration, MPTP is converted by MAO-B to intermediate 1-methyl-4-phenyl-2,3-dihydroptridinium ($MPDP^+$) and finally to MPP^+ (through oxidation) in astrocytes. MPP^+ in turn, induces the formation of reactive oxygen species and it exerts toxicity in dopaminergic neurons of basal ganglia entering through the DA transporter (DAT). Additionally, ENS also displays dopaminergic neurons loss following MPTP insult [125]. It induces toxicity age-dependently through inhibiting the activities of complexes I, III and IV of electron transport chain in older mice and hence leads to the oxidative stress, which is the underlying reason of MPP^+ induced neurotoxicity of SNpc [126].

Mounting evidence suggests intraperitoneal or subcutaneous administration of MPTP (4 mg–32 mg) over 3–7 weeks duration (daily or 5-days a week) results in progressive dopaminergic neuron loss in SN [127]. Mice with MPTP administration demonstrate dose dependent PD symptoms and α-synuclein containing inclusions are made in remaining dopaminergic neurons [128].

2.7.1.2. Rotenone. Rotenone is a toxin of plant origin and is having high affinity with mitochondrial ETC complex I and inhibits its activity following repeated oral, subcutaneous, intravenous or intraperitoneal administrations in rodents. Rotenone induced PD models depict bradykinesia and postural abnormalities, dopaminergic neuron death in the SN and aggregation of α-synuclein [7]. Although, rotenone induce complex I inhibition throughout the brain, however SN neurons seems to have high sensitivity for complex I inhibition and thus it produces selective dopaminergic neuron death [129]. Collectively, rotenone-induced mice and rat models replicate behavioral impairments, elevated ROS levels, perturbed proteasome activity, degenerated SN neurons, reduced DA levels and aggregated LB-like α-synuclein inclusions. Conversely, it appears that rotenone induced PD symptoms are variable and reproducibility problems among various animal models exist. It limits the use of rotenone in translational research to some extent.

2.7.1.3. 6-Hydroxydopamine (6-OHDA). The dopamine analog 6-OHDA is used to induce monoaminergic neuronal toxicity. It is incapable of crossing blood brain barrier, thus it requires the direct administration using stereotaxic procedures to the substantia nigra. The stereotaxic procedures, administering 6-OHDA are generally operated in rats rather than in mice owing to ease of toxin delivery in relatively large brain area [130].

6-OHDA is specifically taken up from presynaptic terminals of dopaminergic neurons through DAT. In dopaminergic neurons, it is oxidized to produce free radicals, including hydrogen peroxide, thus leading to neuronal death through mitochondrial dysfunction and oxidative stress. It is preferably used to induce unilateral lesions in SN and associated motor function deficits [131]. However, it may be bilaterally administered to the dorsal striatum to induce NMS, such as olfactory deficits with signs of anxiety and depression [132]. The spectrum of PD

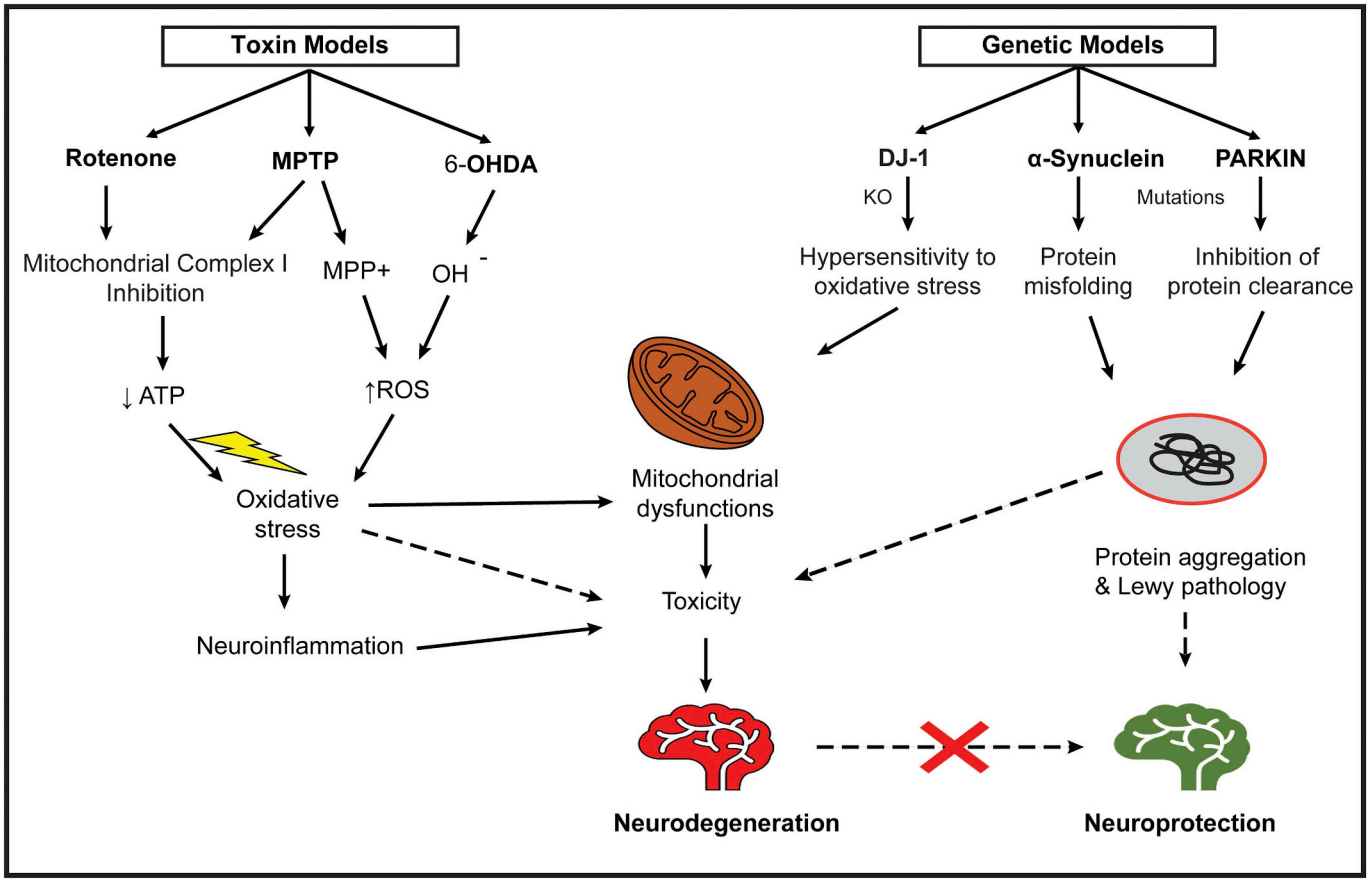

Fig. 4. The mechanisms of neurodegeneration for Translational research. Illustration of mechanism of dopaminergic neurons degeneration and induction of PD manifestations through administration of toxins and mutated genes. Mitochondrial dysfunction, oxidative stress and LBS formation impart huge burdens to dopaminergic neurons leading to induce sub-set of PD symptoms in rodents for translational research.

symptoms is not adequately elicited by the 6-OHDA induced model as it does not affect locus coeruleus and no depletion of norepinephrine is encountered as reported in PD patients, thus its use is study specific [133].

2.7.1.4. Paraquat. The repeated low dose intraperitoneal or subcutaneous administration of paraquat (N,N`-dimethyl-4-4-4`-bipyridinium) in mice and rats replicates PD pathology, particularly, the dopaminergic neuron loss in the substantia nigra, and associated motor deficits. Paraquat induced rodent models are useful predictive tool to investigate the LB pathology in dopaminergic neurons [134]. It enters the DA neurons through DAT and exerts its toxic effects through elevated ROS levels, such as hydrogen peroxide, hydroxyl radical and superoxide radicals and damaging nucleic acids [135,136].

In addition to above toxin-induced PD models, other such models have been used previously and involve reserpine (preventing storage of dopamine in presynaptic terminals), and trichloroethylene (a solvent, inducing dopaminergic neuron loss similar to MPP^+) administrations. The choice of appropriate models of PD depends on the set of questions being asked as well as the specific predictive powers and limitations of the each animal model. Moreover, the toxin-induced PD symptoms might be experienced in one species rather than others, such as rats being resistant to MPTP fail to replicate cardinal features of PD, however MPTP induced PD mouse models are well-established in the field [137].

2.7.2. Genetic models for PD

The genetic manipulations (site specific mutations, modulated expression levels, genetic ablation or transgene expression) of PD genes are used to induce genetic models. Genetic models mimic the phenotype of PD patients and demonstrate both motor and non-motor symptoms. The advantage of gene-based PD models is the certainty of molecular event/pathway involved in disease manifestations, the wider challenge encountered in toxin-induced PD models.

2.7.2.1. α-Synuclein model. The mutations identified in familial PD were discovered in the α-synuclein encoding gene (A53T and A30P) for the first time [138,139]. Additionally, rare duplication and triplication of the said gene are observed in PD patients [140–142]. Rodent model by overexpressing human wild-type α-synuclein gene through adeno-associated virus (AAV) vector having synapsin-1(neuron-specific) promoter demonstrate higher transgene expression associated with PD cardinal features like, synucleinopathies, dopaminergic neuron loss in SN, dystrophic axon terminals and motor functional impairments [143]. Comparatively, forced expression of A53T mutated α-synuclein in DA producing neurons lead to early-onset PD symptoms involving mitochondrial dysfunctions leading to dopaminergic neuron loss [144]. Thus, α-synuclein transgenic mice potentially provide pre-clinical tool to investigate the therapeutic strategies aimed at α-synuclein aggregation based PD impairments.

2.7.2.2. LRRK2. The most common genetic cause of PD is mutation in leucine-rich repeat kinase 2 (*LRRK2*) gene. Its genetic ablation in mice replicates the α-synuclein aggregation, LB-like pathology and hampers the protein degradation pathways [145] without affecting the survival of dopaminergic neurons [146]. Similarly, its ablation from rat demonstrates similar phenotype and points to its little or no direct effect on dopaminergic neurodegeneration. The spurious phenotype

(such as renal tubule injury), encountered in LRRK2 knockout rodents and replication of a narrow spectrum of PD etiology are limitations and hence should be considered while deciding pre-clinical investigation [146,147].

2.7.2.3. Parkin, PTEN-induced putative kinase 1 (Pink1), and Dj1. Mutations in *Parkin* or *Dj1* cause the autosomal recessive form of PD. *Parkin* functions are associated with proteasomal degradation of damaged mitochondria. It encodes E3 ubiquitin ligase Parkin which recognizes a protein target for E2 recruitment and mediates the transfer of ubiquitin for proteasomal degradation of target protein [148]. Overexpression of mutant Parkin (Q311X) in mice dopaminergic neurons through bacterial artificial chromosome containing DAT promoter demonstrated progressive motor deficits associated with dopaminergic neuron loss [149]. In sharp contrast, another study reports the overexpression of *Parkin* having targeted deletion of exon 2 in mice does not exhibit signs of PD such as nigrostriatal cell loss, cognitive impairments and noradrenergic dysfunctions due to uncertain reasons [150]. Similarly, mutated *Pink1* impairs the axonal transport of mitochondria contributing to peripheral neuropathy symptoms observed in some PD patients [151].

DJ-1 is a stress sensor and its neuroprotective roles are evident under oxidative stress conditions [152]. Identification of DJ-1 mutations from familial forms of PD suggests its role in the PD etiology [153]. Dj1 knockout mice do not show apparent pathology in dopaminergic neurons [154]. However, Dj1 knockout mice exhibit hypersensitivity to oxidative stress induced by MPTP [155] and functional deficits in medium spiny neurons of the striatum [156]. These findings suggest the critical involvement of Dj1 in development of PD. Subsequently, it was shown that Dj1 deficient mice present a progressive loss of dopaminergic neurons in SNpc and display locomotor dysfunction as they age. Thus, it seems that Dj1 deficient mice may serve as predictable model in pre-clinical studies to investigate the PD pathology at early stages [157].

2.8. Management of PD

The PD is still an incurable, progressive neurodegenerative disease affecting quality of life, however it is not life-threatening [158]. It involves the death of post-mitotic CNS neurons and hence it adds more challenges while opting management strategies. PD is multi-factorial and heterogeneous disease and it underlies multiple cellular processes of degeneration. Thus, multiple approaches are used for symptomatic relief [159].

2.9. Drug therapies for PD

The PD management aims to improve the quality of life of affected persons. One of widely used approaches is drug treatment. Additionally, allied health professionals assist PD patients through physical, language or occupational therapies in an attempt to enable patients to perform activities independently for longer durations. Drug based management strategies are carefully selected to provide symptomatic relief with considerations of the side-effects and tolerance levels of the patient (Table 1).

2.9.1. Initial PD management

The onset of PD symptoms is linked to the profound reduction in dopamine (DA) levels and associated SNpc cell death, and it worsens over time. Thus, neuroprotection approaches could delay the disease progression and strategies to maintain DA levels of dopaminergic neurons could provide symptomatic relief at an earlier stage of PD. Based on the patient's status at earlier stages having mild-to-moderate disability, *mild potency drugs* are suggested. Monoamine oxidase (MAO) B inhibitors (selegiline and rasagiline), NMDA receptor blocker (amantadine) and anticholinergic drugs (benztropine and ethopropazine) are mild potency drugs used to delay the levodopa therapy for months [160,161].

Another consideration is *tolerance of medication* by patient undergoing treatment. Younger patients (age < 65 years) generally have reduced risk of side-effects. Briefly, MAO-B regulates the degradation of DA in brain and MAO-B inhibitors irreversibly inhibit its activity and prolong the duration of DA levels in brain. Enhancing cholinergic tone through inhibition of cholinesterase can improve motor function of PD patients [162].

Dopamine agonists provide a better choice following mild potency drugs, as they directly mimic the role of DA through binding with dopamine receptors. Further, DA agonist (bromocriptine and pramipexole) treatment postpones the administration of L-dopa and is considered as first-line treatment for younger patients.

2.9.2. Advanced PD management

Advanced PD management involves the optimization of the L-dopa containing formulations and multiple drug administrations, in addition to possible surgical and advanced approaches to provide better health benefits. Patients at stage 4 and 5 of HY scale are considered at advanced PD. As advanced PD manifestations involve severe motor impairments and extreme non-motor challenges, the optimization requires the precise analysis of risks and benefits of the treatments [163].

Increasing amounts of L-dopa and its agonists need to administer frequently at advanced stages as motor symptoms (dyskinesia, freezing) worsen and patients show a shorter and limited response (wearing off) to treatments [164]. Higher doses of L-dopa in early and moderate stages lead to increased risk of dyskinesia as the report shows, < 400 mg per day of L-dopa dose is the most effective treatment and with least risk of dyskinesia [165]. A recent study reports the levodopa induced enhancement of nigral plasticity lowers the severity of motor symptoms in PD [166]. A combination of carbidopa-levodopa (Sinemet

Table 1
Drug used in Parkinson's disease Treatment.

Drug classes	Specific drugs	Mechanism of action
Anticholinergic	Trihexyphenidyl Benztropine Ethopropazine	Block acetylcholine receptors and prevents the dopamine degeneration
Monoamine oxidase (MAO) inhibitors	Selegiline	Blocks MAO-B receptors to reduce dopamine metabolism
Antiviral drugs	Amantadine	Blocks NMDA and acetylcholine receptors and promotes release of dopamine
Dopamine agonists	Bromocriptine Pergolide, Ropinirole Pramipexole	Directly stimulates dopamine receptors
L-dopa combinations	L-dopa / Carbidopa L-dopa/ Benserazide Sinemet CR	Metabolism of dopamine in cells containing dopa-decarboxylase
Catechol-*O*-methyl transferase (COMT) inhibitors	Entacapone	Blocks peripheral COMT activity to retain catecholamines

CR) is administered for sustained release to increase the retention time of sufficient DA in patients. Additionally, entacapone, selegiline, amantadine and DA agonists are often administered along with Sinemet CR. Catechol-O-methlytransferase (COMT) inhibitors administration ameliorate the weaning off symptoms in PD patients [167], however, if patients experience NMS, such as hallucinations, then catechol *O*-methyltransferase (COMT) inhibitors treatment is stopped.

2.10. Physical therapy for PD

In addition to drug-based PD management, physical activity in the forms of exercise substantially improves gait-related activities (such as stride length, step variability) and NMS (such as cognition). PD patients are trained for various activities such as aerobic, strength and flexibility, balance and agility trainings for beneficial outcomes [168].

It suggests that physical activity such as treadmill training, dance or exercise not only improve the motor functions, but also cognitive functions and NMS in moderate-to-severe PD patients and improve their quality of life [169–171]. A recent systematic review highlights the improvements in cognitive functions of PD patients owing to physical exercise programs (over 10-years duration) through sustained attention, processing speed and mental flexibility [172]. Importantly, PD patients trained for 6-min Walking Test demonstrated an increase in step length and reduced step variability [170]. Following training, execution of improved talking with walking was observed in PD patients thus, improving gait, cognition and balance [173]. Music-based movement therapy harness the enjoyment coupled cognitive movements of the patients to access change in gait-related activities and appears beneficial for stride length [174].

2.11. Strategies and future perspectives of PD

The marked improvements in PD symptoms upon L-dopa and related drugs administrations are not consistent over time and patients must face severe movement and cognitive impairments. Thus, non-drug based strategies such as ablative surgeries, electric stimulations, cell therapies and gene editing are currently gaining increased attention (Fig. 5).

The basal ganglia physiology gained a lot of intention, prior to the development of surgical treatments for PD. The chance observation of surgical destruction of caudate nucleus resulting in improvements in PD motor manifestations leads to the targeted ablation surgeries. [175]. With the development of L-dopa based therapies, attention to such ablative surgeries shifted to drug based symptomatic relief of PD. However, owing to short term drug induced benefits in PD patients, ablative surgeries regained attention in 1990s. Technological developments in the form of stereotactic techniques improved the precision of brain surgeries upto 1 mm scale.

2.11.1. Ablative surgeries

Ablative surgeries have a long history of clinical practice rooted back in 1950s and later such surgeries were completely abandoned due to drug therapies. However, with the technological developments and non-persistent drug therapeutic effects coupled with associated side effects, ablative surgeries reemerged in 1990s. These surgeries may be performed unilaterally or bilaterally owing to the PD symptoms concerned (Fig. 5A). Principally, removal of the targeted brain area does not affect the body functioning, but alleviates the disease symptoms. The surgical ablation of the thalamus (thalamotomy), globus pallidus internal (pallidotomy) and subthalamic (subthalamotomy) regions have

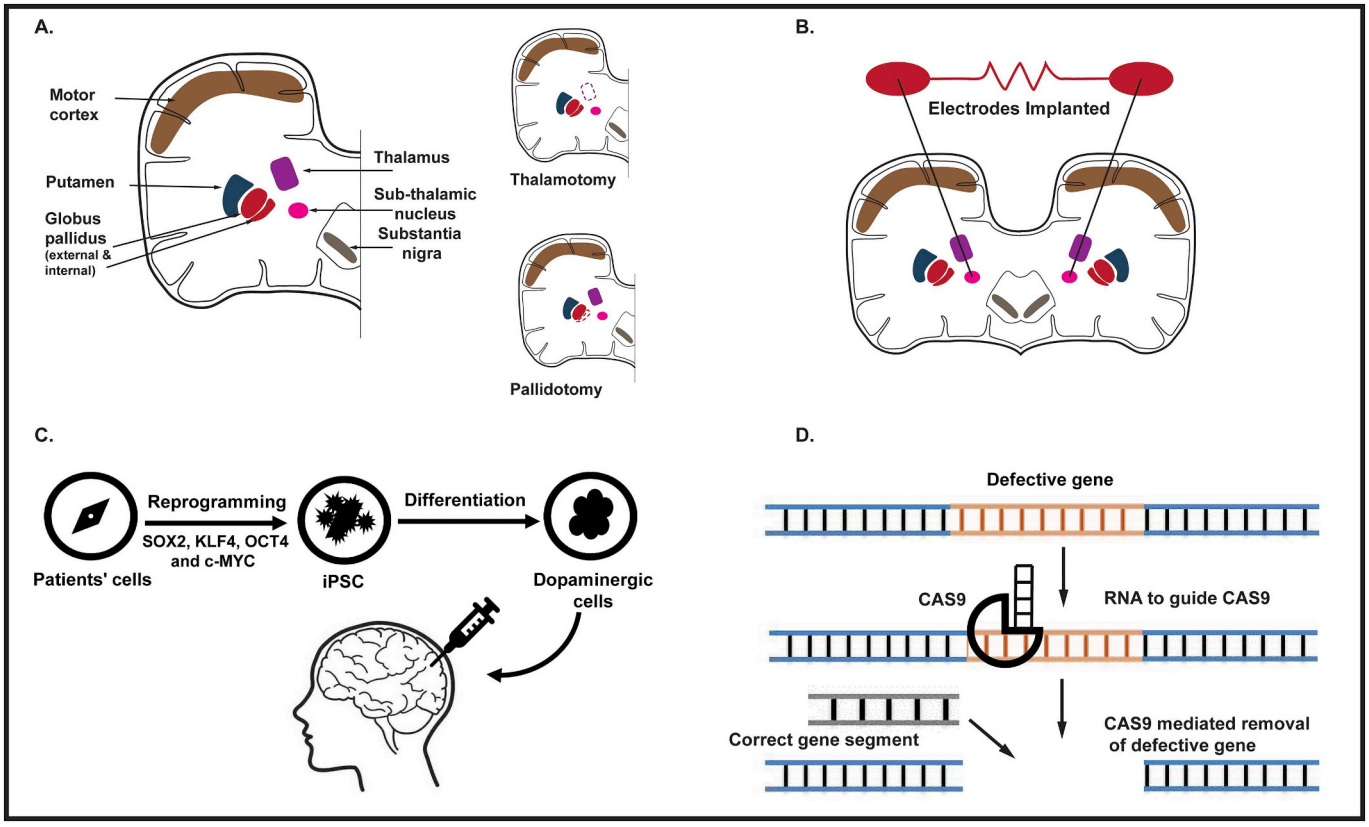

Fig. 5. Surgical and molecular approaches for PD management involving Ablative surgeries (A), bilateral deep brain stimulation installation (B), induced pluripotent stem cell derived dopaminergic cells transplantation (C) and gene-editing technology CRISPR-Cas9 (D) to provide long term benefits.

been considered for clinical benefits. A study of around 200 patients with thalamotomy revealed sustained improvements in 24.5% patients, and mild-to-moderate improvements in 45.2% patients over 7.9 years follow-up [176]. GP has strong synaptic connections with the thalamus and striatum, while in PD patient's physiological regulations it seems altered and results in motor function impairments [177].

2.11.2. Deep brain stimulation (DBS)

Mounting evidence reports the remarkable role of deep brain stimulation in alleviating the Parkinsonian motor symptoms. The advances in DBS technology and stereotaxic procedures have led to substantial considerations for its applications in PD patients and hence marginalizing the ablative surgeries [178].

Electric stimulation of the ventral intermediate (VIM) nucleus of the thalamus (unilateral) coupled with thalamotomy (in most affected area) lead to marked improvements in PD tremors. However, the tremors were not completely alleviated because stimulator frequency was limited to 130 Hz instead of optimized 200 Hz [179]. Subsequently, the idea of chronic DBS stimulation at high frequency abandoned the need of brain lesions in the majority of patients. Currently, > 100,000 DBS devices are available to treat movement disorders [180]. It is achieved through the stereotactic procedures of fine electrodes installation in targeted basal ganglia regions such as GPi and STN and stimulation at higher frequencies, while the device (containing battery) is housed just below the clavicle bone. DBS installation is recommended to the patients tolerant to medication effects and with no significant cognitive impairments. DBS surgery associated infections are most commonly reported complications and proper monitoring of DBS programming is recommended for optimized regulations of motor functions (Fig. 5B).

Based on the symptoms evaluation, neurobiologist manually adjusts the stimulation parameters every 3–12 months (in the open-loop system) following DBS installation. The DBS device development leads to the manufacturing of closed-loop DBS containing a feedback signal alleviating the needs of manual adjustments as encountered in the open-loop system. It involves the detection of biomarkers such as electroencephalogram and electromyogram by the sensors integrated in DBS and it consumes 44% less electric stimulation, thus reducing repeated surgeries and enhancing battery life [181,182]. Stimulation of the STN or GP results in reduction of the rigidity, bradykinesia and drug-induced dyskinesias severity [183,184]. Although, DBS has great potential to restore quality of life of PD patients, however, its implications are limited to early-to-mild PD stages, cognitive impairments and related NMS [185]. Further, patients have to undergo repeated surgeries, which enhance the chances of infection and socioeconomic burdens.

2.11.3. Transplantation therapy: induced pluripotent stem cells (iPSC)

Endogenous repair systems of the CNS have limited capacity. Cell transplantation strategies involve the replacement or supplementation of dopaminergic neurons in PD patients with reprogrammed DA producing neurons derived from neural stem cells, embryonic stem cells or fibroblasts (Fig. 5C). The dopaminergic cells transplantation strategy aims to graft dopaminergic neurons into DA-deficient striatum to reverse the major PD symptoms.

Successful reprogramming of mouse skin fibroblasts into iPSC through a cocktail of transcription factors (*Sox2*, *Klf4*, *Oct4* and *c-Myc*) forced expression provides a potential approach to obtain induced dopaminergic neurons [186]. However, these transcription factors are reported to overexpress in cancerous cells, thus there is increased risk of developing tumors while considering iPSC to be used for PD cure. The potential of poly (ADP-ribose) polymerase 1 to form iPSC without *c-Myc* provides an alternative method to develop safer iPSC [187], however the risk cannot be abolished completely. Transplantation of fetal dopaminergic graft into putamen of PD patient tremendously improved motor deficits and associated L-dopa treatment withdrawal for 3-years following transplantation, such grafted dopaminergic neurons were viable even after 24-years of transplantation. The patient enjoyed clinical benefits for 14 years beyond which the gradual loss in graft-induced benefits reappeared [188,189]. It suggests that the long-term benefits of grafted tissue in the putamen of PD patients are not life-lasting and hence other strategies are warranted for life-lasting clinical improvements.

2.11.4. Gene editing CRISPR-Cas9

The recently developed gene editing technology, Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) uses the RNA-guided endonuclease CAS9 to cut the double-stranded DNA providing the opportunity of editing genes to treat familial PD [190] (Fig. 5D). So, mutations underlying familial PD can be reversed through stereotaxic injection of RNA-guided editing tool. The Cas9 generates the double-stranded breaks at specific DNA location, triggering the cellular repair process to edit the mutation [191]. CRISPR-Cas9 technique, signifies the possibility of manipulation of the germ cell line DNA to get rid of the familial Parkinsonism in future generations [192]. A recent study reports the use of fluorescent labelled markers for editing the mutated PD gene through fluorescence-activated cell sorting (FAC)-assisted CRISPR/Cas9 editing to treat PD associated mutations (A30P and A53T) of α-synuclein gene [193].

2.11.5. Viral vectors-mediated gene delivery strategy

Substantial consideration of genetic manipulations is evident in PD management strategies, as nine clinical trials using virus mediated gene delivery to putamen and SN have been completed, yielding promising results and considerable benefits. Strategies harness the capacities of adeno-associated virus vector serotype 2 (AAV2) and lenti-vector expression system to deliver the foreign gene into the host genome. The trials involved multiple approaches to prevent neurodegeneration and associated functional outcomes through delivering (i) neurotransmitter gamma-aminobutyric acid producing enzyme genes (AAV2-GAD-65, AAV2-GAD-67), (ii) L-dopa converting enzyme, aromatic L-amino acid decarboxylase (AAV2-AADC), (iii) Tricistronic lenti-vector to transfer three genes, including tyrosine hydroxylase (TH), GTP cyclohydrolase 1 (GTP-CH1) involving dopamine synthesis and AADC, and (iv) genes providing trophic support such as neuturin (AAV2-NRTN) and glia cell-derived neurotrophic factor (AAV2-GDNF) into putamen and SN, bilaterally in majority of trials [194–197]. Gene therapy provides a potential approach to deal and restore the detected mutation in the PD associated genes, even before the onset of PD manifestations. Collectively, PD management strategies involve the use of feasible options largely depending upon the patient's response (Table 2).

3. Conclusions

The PD is a multifactorial neurodegenerative disease and involves impairments of various cellular processes and hence effective management is extremely challenging. It increases the socioeconomic burdens and affects the independence of the patient. Despite the drug triggered symptomatic relief, strategies for the prevention of dopaminergic neuron death are lacking. Strategies involving DBS, controlled reprogramming of iPSC and differentiation into dopaminergic neurons, CRISPR-Cas9 gene editing and virus-mediated gene transfer provides hope for future endeavors in successful PD therapy. Although striking differences in brain structure of rodents and humans limit the predictive power of pre-clinical studies to human trials, however, they may be carefully used to unveil the potential therapeutic targets for the disease. Translational research using laboratory animals with behavioral signs of PD symptoms provides powerful tools to quest the potential therapeutic and neuroprotective compounds.

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Table 2
Summary of Management Strategies in PD.

Parkinson's disease stages		Symptoms	% Loss of neurons		Available treatments	Response of patients	Side effects	Mitigation measures
			SN	**DA cells**				
Mild PD	**Stage I**	Unilateral tremors Postural changes Walking and Facial expression alterations	62–82%	40–60%	**Age < 65** • Benzhexol = 0.5-2 mg tid • Procyclidine = 2.5-10 mg tid	Reduced tremors and rigidity.	Dry mouth, Urine retention, Constipation, Blurry vision and sometimes Cardiac arrhythmia	Dose reduction and adjustments with renal impairment medications.
	Stage II	Bilateral tremors and rigidity. Walking problems with poor posture.	85%	75%	**Age > 65** • Amantadine = 100 mg bid			
Moderate PD	**Stage III**	Loss of balance and slowness of movement. Impaired activities, such as eating.	88%	82%	**Age < 65** • Sinemet (L-dopa250mg + carbidopa 25 mg) = half to 1 tablet tid	Improved hypokinesia and reduced tremors.	Nausea, Vomiting, Hypertension, Dyskinesia and Cardiac arrhythmia.	Reduce dose and take them with meals only, Physical exercise, DBS surgery may be recommended.
	Stage IV	Person cannot stand on its own. Posture instability.	89%	90%	**Age > 65** • Madopar (levodopa 25 mg + benserazide 50 mg) = half to 1 tablet tid • Selegiline = 5 mg with breakfast and lunch			
Severe PD	**Stage V**	Bradykinesia, Rigidity, Hallucinations, delusions and muscle spasms are common.	95%	95%	Levodopa ± Selegiline ± Bromocriptine Bromocriptine (40 mg) • Week 1 = 1/2 tablet at bedtime • Week 2 = 1 tablet at bedtime • Week 3 = 1 tablet bid • Week 4 = 1 tablet tid	Improved postural instability, Reduced muscle rigidity and tremors.	Nausea, Dry mouth, Vomiting, Hallucinations, Dizziness and Diarrhea.	Reduce dose at first and titrate in upward slowly, DBS is recommended.

Abbreviations: PD, Parkinson's disease; SN, Substantia nigra; DA, Dopamine; tid, Thrice a day; bid, Twice a day; DBS, Deep brain stimulation.

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Chand Raza conceived and wrote the manuscript. Rabia Anjum and Noor ul Ain Shakeel prepared and revised the figures. All the authors read the review before submission.

Competing interests

We, authors, declare no competing financial interests.

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