

Chapter 2

In Pursuit of Cure for Parkinson's disease: Recent Advances and Future Perspectives

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Abstract

Mutation and alteration in the gene/protein are one of the crucial powers that “nature” has imparted to the evolution process. The proteins present today have seen some degree of transformation during evolution since the dawn of these biomolecules. As we know, the retaining of the 3D structure is the quintessential property for normal functioning of the proteins. Any alteration in nature, folding or the conformation will render the protein inoperable, altogether a diverse function or sometimes pathologically detrimental attributes. Although harmful changes are rare in occurrence, unfortunately, if they persist these amyloid proteins generate deleterious conditions that result in various disorders. Few examples that these deleterious proteins rake up are Alzheimer's disease, PD, Amyotrophic lateral sclerosis and Prion-mediated diseases, etc. Among these PD stands out as a burdensome illness, challenging the scientific domain since its discovery. It's a devastating neurodegenerative disorder characterized by a selective destruction of the nigrostriatal dopaminergic neurons. It's almost two century after the discovery of PD, how far we have reached with therapeutic implications? Sadly, we have virtually failed to tackle this debilitating disease. As unfortunate it might sound, nearly all the scientific efforts since its identification have been futile. However, frontiers in clinical biology developed over few decades have driven our knowledge to the equation and helped in understanding the multifarious molecular interplay between genetic, transcriptional and translational factors during

the PD. Recent years have seen an explosion in the progress of tools and techniques to understand and positively challenge this disorder. The voluminous data provided by these novel technologies are believed to furnish the required change in the pace of PD research that drives the discovery of new therapeutic approaches that dramatically impacts the care of PD patients. In this book chapter, we intend to provide a distilled summary of the experimental, genetics, and neuroclinical discoveries that occurred in the PD research so far. Further, we brief the potential strategies that can bring the granularity to the clinical entanglement of PD, which may bring the essential improvement in the diagnostic preciseness, clinical management and might embark into the long awaited pharmacological and nonpharmacological intervention for PD.

Keywords

PD; Diagnostics; Neurodegeneration; Therapeutic interventions; Future perspectives

Introduction

Parkinson's disease (PD) has become an unchallenged menace to the scientific world. It is a multisystem, pernicious, chronic disorder, affecting 1-2% of the population over the age of 65 years [1]. The dopaminergic neuron degeneration is a unique feature of PD which leads to a drastic depletion of the dopamine (DA) levels, dopamine transporter (DAT; high-affinity membrane carrier of DA) and

tyrosine hydroxylase (an enzyme involved in the synthesis of DA) [2]. The pathological hallmarks of PD include formation and accumulation of Lewy bodies in the dopaminergic neurons especially in pars compacta of the mesencephalon. Lewy bodies are agglomerates of α -synuclein, neurite filaments, α -crystallin and in addition, they may also contain tau protein [3]. Though α -synuclein is a major constituent of Lewy bodies, numerous other factors have been identified signifying the participation many cellular signalling pathways including lysosomal, mitochondrial, microtubules, and apoptotic pathways [3]. These multifaceted interactions suggest that Lewy bodies are formed as a consequence of vesicular accumulation due to lock horns of multiple trafficking pathways and plausibly not because of cytosolic accumulation of the unbound protein [4]. They are a dysfunctional aggresome of the cytosol in response to proteolytic stress to facilitate the clearance of sequestered proteins. One speculation is that α -synuclein fibrils and aggregation are more neurotoxic in nature, and when they are sequestered in the vesicle aggregation, they lose their harmful neuronal activity [5]. This new body of speculation suggests that Lewy bodies represent "protective sequestration" gone wrong.

PD was first described by the physician James Parkinson in 1817. Before this, the information about the PD symptoms was remarkably limited which led many researchers to theorise that this disease may have been a product of the Industrial Revolution which occurred that

time. James described this condition that menaced elderly, in his 'Essay on the Shaking Palsy' [6]. PD has been linked to genetic mutation nearly two decades ago, in 1996 first mapping of PD stricken brain revealed that small percentage of PD is beyond doubt hereditary in origin. In the later years, more genes were identified, but these genes were not linked to the earlier discovery, mounting the idea that PD is a pathologically complex disorder. The hereditary forms of PD have been associated with alterations of genes including PARK1, PARK8, PARK2, PARK6, PARK7 and PARK9. Nearly two decades after their first identification, 28 distinct chromosomal loci have been identified more or less plausibly related to PD [7,8]. However, the monogenic mutations occur only in six specific loci thereby responsible of PD. Altogether, only an incomplete number (4–6%) of total PD occurrences are explained by the mutations of these six genes. Hence, the PD etiology is multifarious, which believably occurs from an intricate interaction of mostly unidentified facets- numerous genes, environmental factors and protein-environment interactions (e.g., impact of environmental mediators on gene expression) and impact of these aspects on the ageing brain [9].

To date, there are no reliable curative therapies for PD, and even there is a conspicuous lack of early prognosis markers and diagnosis which completely relies on the clinical examination of the patient. In the past, the majority of the PD therapeutic were mainly directed towards amelioration of dopaminergic motor deficits. This strategy was later deemed as an improper approach since PD

pathophysiology is not only limited to the dopaminergic neuro-disintegration but also deals with other non-motor complications such as the cognitive deficit, dementia, hallucinations, etc., due to the failure of the autonomic nervous system in PD patients. Therefore, clinical research development focused on developing neurotherapeutic intervention/s which aimed to treat non-motor failures while countering parkinsonian motor dysfunction [6,10]. Accordingly, a vast amount of research has been dedicated to the formulation of therapeutic implications, the potential of defending the normal functioning of the brain from damage following PD. Unfortunately, virtually all the strategies have failed to cater suitable protection in human clinical trials.

In this article, we have summarised the elementary genetic principles of monogenic PD forms, current knowledge and understanding of the diagnostics of PD. Further, this review enumerates some of the key developments in neuroprotective therapy, potential glitches leading to the failures of these strategies and possible improvement of those mistakes, which might pave the way for future anti-parkinsonian trials.

Burden of Parkinson's Disease

PD is the second most common neurodegenerative disorder after Alzheimer disease and imposes an increasing social and economic burden on the societies with ageing populations. The age of onset of PD is usually over 60 years. However, approximately one in ten patients is

younger than 50 years at the time of diagnosis [10]. It is opined that PD even in the meekest form is a disastrous experience to the patient and close relatives. Even though there is no complete loss of motor function in the earlier stages, the experience of transition from healthy to physical deficits impart devastating psychological effect, which impacts totality and the quality of patient's life. Since the victims of PD are persons in the dusk of their life, hence, the emotional impact caused by PD, tragically, is of no essential interest to society. But, the cost of PD treatment has maximum impact on the society, it has its own component within the societal tax burden, it diverts resources from other diseases, and it demands the creation of highly specialised units, raising the cost of hospital operations. It is a member of the high-cost diseases, not only in requiring the long-term clinical interpositions but also as an imposer of persistent and more often than not, a continuous economic burden. Rehabilitation period followed by often lifelong disability that may severely affect the continuation of one's previous life. In its severe form, PD-related deficits may prevent the execution of even the simplest daily functions, requiring advanced nursing care and specialised facilities [11].

Today, more than 10 million people agonise from this disease worldwide and this number is expected to grow substantially over the next 25 years [11]. Mortality rates in patients with PD are relatively high, compared to those of the general population. In the early-onset form of PD, where the disease begins to develop before age 50,

the average total life expectancy is shorter, compared to that of the general population. However, these differences become smaller as the age of onset increases [12]. Even though reports are conflicting, most studies show a greater occurrence in men. In 2004, Wooten et al. demonstrated 1.5 times higher age-dependent increased frequency in men compared to women. A possible explanation might be that female steroid hormones protect women from developing neurological conditions [13].

Lo et al, in 2009 identified that reduced cognitive function immediately after the emergence of PD symptoms is the important predictor of death, implicating a bi-fold rise in the mortality [14]. The more severe the cognitive impairment the higher the mortality risk. Furthermore, hallucinations that occur early in the development of PD seem to be associated with an increased mortality risk. Other studies have revealed that bronchitis (44.1%), malignant neoplasms (11.6%), heart diseases (4.1%), cerebral infarction (3.7%) and septicemia (3.3%) are common causes of death in PD patients [15].

Genetics of Parkinson's Disease

Autosomal-Dominant Forms of Mendelian Parkinson's Disease

Human α -synuclein (α -syn)

The α -synuclein family members are mainly expressed in neuronal cells of craniates and composed of naturally misfolded proteins with a 15–20 kDa molecular

weight (MW)[16]. Its primary sequence can be classified into amino-terminal, non-β amyloid component (NAC) and carboxy-terminal (CT) regions (Table 1). The mutations that are associated with PD mainly occur in the N-terminus region of the protein (p.A30P, p.E46K, p.H50Q, p.G51D, and p.A53T) [17]. The non-β amyloid component contains a specific amino acid sequence “GVTA-VAQKTVE” which makes the protein highly hydrophobic thereby directly responsible for the formation of amyloid fibrils. The apolipoprotein binding motif [EGS]-K-T-K-[EQ]-[GQ]-V-XXXX which are characteristic feature of synuclein occurs as semi-conserved repeats in the NT and NAC regions that allow α-syn to acquire α-helix structure and bind to lipid membranes. The c-terminus is involved in the recruitment of proteins [18,19].

Table 1: Autosomal-dominant forms of Mendelian Parkinson's disease.

Gene/Locus	Properties
SNCA (PARK1)	
Size:	140 amino acids
MW:	14460 Da
Chromosome:	4q21
SNCA occurs both in monomeric and oligomeric forms. They comprise alpha helix and β-sheet conformations, as well as morphologically diverse aggregates, ranging amorphous to amyloid-like fibrils. SNCA functions in presynaptic signaling and membrane trafficking. Lewy bodies, hallmark entities of synucleinopathies comprise modified alpha-synuclein.	
LRRK2 (PARK8)	
Size:	2527 amino acids
MW:	286103 Da
Chromosome:	12p11-q13
LRRK2 is a homodimer, and comprise an ankryin repeat region, a leucine-rich repeat (LRR) domain, a kinase domain, a DFG-like motif, a RAS domain, a GTPase domain, a MLK-like domain, and a WD40 domain. This protein is present largely in the cytoplasm but also found associated with the mitochondrial outer membrane.	

α-syn in normal physiological setup exists in several forms it can be monomeric, few α-syn can form oligomers, or they can form a mature fibril. An oligomeric form of α-syn is the most toxic form generated at the surface of the cell membranes. Three-point mutants tend to form stable beta-sheets in NAC fragment and thus exacerbate the formation of toxic oligomers [20,21]. It has been theorised that many neurodegenerative disorders including PD and other synucleinopathies follow the mechanistic feature of “prion-like” disorders, with effector molecules such as α-syn being functioning as “infectious prions”. Mounting evidence demonstrates that α-syn might disseminate as monomers or oligomers from the “source cell” neighbouring “host cell” or via exocytosis in vesicles. Once in the acceptor cell, α-syn may serve as a “pathogen” which induces misfolding of the stable proteins to ‘prion-like’ structure, continuing the cycle of pathology [22].

Leucine-Rich Repeat Kinases (LRRK2; PARK8)

The leucine-rich repeat kinase2 is a complex protein with MW 286 kDa. It is a multimer comprising two enzymatic domains at its centre [23]. The Ras of complex protein (ROC); a GTPase domain, separated by a spacer region called the C-terminal of the Roc domain (COR), flanked by a kinase moiety. It belongs to the serine/threonine kinases and has a multiple-domain architecture comprising of Armadillo repeats (ARM), leucine-rich repeats (LRR), Ankyrin repeats (ANK) and WD40 repeats (Table 1).

Till date five PD-associated mutations in LRRK2 have been identified which include p.R1441C/G/H, p.G2019S, p.I2020T p.Y1699C and p.N1437H [24,25]. The G2019S is the most recurrent form among these mutations, represents for 13.3% of sporadic and 29.7% of familial PD in Ashkenazi Jewish, 40.8% of sporadic and 37.0% of familial PD in Arab-Berber populations. The G2019S represent ~ 1–7% of familial PD subjects from the US and European origin and for 1–3% of sporadic PD from Caucasian populations [26]. Additionally, this genic alteration explains 0.7% of the sporadic and 7.7% of the familial cases of PD in Russian patients [27]. Site specific studies have disclosed that p.G2019S mutation occurs in the kinase domain resulting in the overactive enzyme, thereby intensifying the propensity of autophosphorylation and phosphorylation of other substrates [27].

Recessive Forms of Mendelian PD

Autosomal Recessive Mutations in the Parkin (PARK2)

The PARK2 (MIM 602544) is first of the three recessive PD genes identified in relation to PD. This gene encodes for 456 amino acid protein which functions as an E3 ubiquitin ligase in the ubiquitination of proteins (a post-translational modification that conjugates ubiquitin to target proteins, thereby controls the fate of the cell) [28]. It comprises of ubiquitin-like domain (UBL) domain (62% homologous to ubiquitin), which plays a vital role in stabilising the structure (Table 2).

Table 2: Autosomal-Recessive forms of Mendelian Parkinson's disease.

<p>PARKIN (PARK2)</p> <p>Size: 465 amino acids</p> <p>Mw: 51641 Da</p> <p>Chromosome: 6q25.2-q27</p> <p>Encodes parkin, a protein that belongs to the “ring between ring fingers” (RBR) family of E3 ubiquitin ligases. The RBR domain is composed of 2 RING fingers linked by a cysteine-rich “in-between-RING” (IBR) motif. The RBR domain interacts with ubiquitin-conjugating enzymes (E2s) to catalyze attachment of ubiquitin to protein targets, thus tagging these proteins for destruction by the proteasome.</p>
<p>PINK1(PARK6)</p> <p>Size: 465 amino acids</p> <p>Mw: 51641 Da</p> <p>Chromosome: 1p36.12</p> <p>Encodes PINK1 with an N-terminal mitochondrial targeting sequence, a transmembrane helix, a serine/threonine kinase domain, and a C-terminal domain of unknown function.</p>
<p>DJ-1 (PARK7)</p> <p>Size: 189 amino acids</p> <p>Mw: 19891 Da</p> <p>Chromosome: 1p36.23</p> <p>DJ-1 belongs to PfpI superfamily and a homodimeric protein containing of two monomers. Incisively, DJ-1 subunits possess a flavodoxin-like Rossmann fold, which contains six-strand parallel β-sheet forming a core sandwiched by α-helical layers.</p>
<p>ATP13A2 (PARK9)</p> <p>Size: 1180 amino acids</p> <p>Mw: 128794 Da</p> <p>Chromosome: 1p36.13</p> <p>ATP13A2 is a member of the P5 subfamily of ATPases which transports inorganic cations as well as other substrates. Mutations in this gene are associated with Kufor-Rakeb syndrome.</p>

The carboxy-terminal comprises of three “Really Interesting New-Gene” (RING) domains (RING0, RING1 and RING3), In-between-ring (IBR) domain and interacts with the ubiquitination complex [29]. Nearly 50% of the

mutations occur in the region between exons 2–4 (52%, 459/887) that encodes UBL domain, the linker region, and the starting part of the RING0 domain. Mutations in the Park2 includes simple mutations (nonsense, missense and splice site mutations, indels), as well as copy number variations (CNVs) of the promoter sites and single or multiple exons. PARK2 mutations occur across the entire gene in both homozygous, compound heterozygous or heterozygous state in familial and sporadic cases from different countries [30,31].

Other Rare Forms of Autosomal Recessive Mutations Causing PD

P-TEN-induced Putative Kinase 1 (PINK1; PARK6)

The PINK1 protein is a putative serine/threonine kinase with a size of 581-amino-acid and crucial in anti-apoptotic, antioxidant, pro-survival and cytoprotective pathways. PINK1 controls mitochondrial machinery thereby regulates ATP synthesis, oxygen intake, and reactive oxygen species (ROS) production [32]. Further, PINK1 acts as an indirect key effector that controls the AKT-mTOR pathway to regulate inflammation, metabolism, survival and proliferation along with multiple additional functions [33].

Mutations in PINK1 represent the second most common cause of autosomal recessive Parkinsonism. PINK1

families exhibit an earlier onset of disease (range of 9–52 years), accompanied by sustained responses to levodopa treatment [34]. The PINK1 mutations frequency is in the range of 1–9%, with significant dissimilarity between diverse ethnicity. In contrast with Parkin, PINK1 mutations are mainly missense or nonsense variations. Only three families with complete-exon deletions (exons 4–8, 6–8 and 7) and one with a heterozygous whole-gene deletion have been reported. Till date, More than 60 missense and nonsense mutations have been identified in nearly 170 patients [35]. These mutations span all the 8 PINK1 exons at a closely equal rate (in each of the exons 5–10 diverse mutations have been identified). The exon 7 represents the genomic site with the largest number of mutations (in more than 50 patients), and the most common mutation is p.Q456X [35].

DJ-1 (PARK7)

DJ-1 belongs to PfpI superfamily and is a homodimeric protein containing two monomers of 189 amino acids each. DJ-1 is a universally coded by PARK7 gene, initially recognised as an oncogene responsible for cancer and male infertility. DJ-1 subunits possess a flavodoxin-like Rossmann fold, which contains six-strand parallel β -sheet forming a core sandwiched by α -helical layers. Mutations in PARK7 gene, leading to loss of function of the protein, were later associated with early-onset recessive forms of PD [36].

Even though, clear-cut details about the functioning of DJ-1 remain obscure, several lines of evidence specify that protein is involved in diverse biological functions, specifically regulating the ROS and free radical induced cell death. The DJ-1-mediated PD phenotype follows the path exactly similar to parkin or PINK1 mutation phenotype which shows early-onset and late disease development [37]. Van Duijn et al. first reported the occurrence of two families with mutations in the PARK-7 locus in a family-based linkage analysis [38]. The first family was a Dutch family with a large homozygous deletion of exons 1–5 and the second was an Italian family comprising a homozygous missense mutation, the p.Leu166Pro, in an extremely conserved coding site of the protein. Two members of a Chinese family in their 30s developed PD with DJ-1 and PINK1 genes showing heterozygous mutations implicating the digenic inheritance; bizarrely, another sibling with the similar genotype completely unaffected. Because of the rarity of the DJ-1 associated PD, relatively few cases have been described in the literature [39].

ATP13A2 (PARK9)

ATP13A2 (PARK9, MIM# 610513) was discovered as a gene encoding P (1B)-type ATPase, a polytopic membrane transporter protein with unidentified ion specificity. Mutations in this gene result in an autosomal recessive L-DOPA-responsive Parkinsonism (juvenile onset) demonstrating the clinical features of PD. The highest encod-

ing of ATP13A2 occurs in pars compacta of the substantia nigra (SNc) of the brain, a region that suffers an utmost loss of DA during PD. Mutations in ATP13A2 is also affiliated with early onset of autosomal levodopa responsive Parkinsonism, known as Kufor–Rakeb syndrome (KRS, MIM# 606693) [40]. This syndrome is characterised by all the specific features of PD including other clinical characteristics such as spasticity, supranuclear gaze palsy, and facial-facial myoclonus. These mutations follow an autosomal recessive trend concerning two mutant alleles (homozygotes or compound heterozygotes) which result in mRNA degradation, protein modification and degradation. Cloning studies have led to the discovery of compound heterozygous mutations, three homozygous and two heterozygous mutation forms [41].

Diagnosics Markers for PD

The biomarkers for PD are crucial in identifying the disease progress at an early phase which enables one to start the treatment early as well as monitor the efficacy of neuroprotective therapies. The recognized criteria for diagnosis are based on the detection of classical symptoms of parkinsonism, i.e. bradykinesia (diminution of normal quick movement which makes even simple tasks such as brushing the teeth or even walking painstakingly difficult), resting tremor (occurs in 70% of the PD patients, it occurs when muscles are in relaxed state), increased muscular rigidity and postural instability [42]. The assessment of the

state and progression of PD depends on diverse factors and clinical steps. These comprise of analysis of symptoms utilising structured scoring systems such as Short Parkinson Evaluation Scale, (SPES), Unified PD Rating Scale, (UPDRS), the Hoehn and Yahr (H&Y) staging scale, and “Scales for Outcomes in PDs” (SCOPA) [43].

Behavioral and Functional Manifestations

Early non-motor symptoms of PD include instabilities in sleep, visuospatial abilities, olfaction, cognition as well as behavioural alterations and these symptoms allegedly indicate the loss of extra-nigral domains of the brain prior to DA neurons. Assessment strategies targeting these symptoms are non-invasive, cost-efficient and easy to administer [44]. These comprise olfactory modality tests (e.g., the University of Pennsylvania Smell Identification Test -the UPSIT), the bradykinesia akinesia incoordination test (BRAIN), the REM sleep behaviour disorder screening questionnaire, a keyboard tapping test and accelerometer based exams. The results obtained from these tests can be employed along with other risk features to devise risk algorithms [45,46]. Though these strategies look promising in determining the PD risk at the initial stages, their real efficiency cannot be known until they have been completely affirmed. In addition, most of the features that are followed in these examinations are non-specific and still need exhaustive exploration, since there are questions with both false positive and negatives [47].

Biological Markers

The detection of the α -synuclein in the Lewy body and reduced DAT detected by PET imaging can be used as early biochemical markers. Given that α -synuclein is also found in other synucleinopathies, it should be used along with other diagnostic methods to increase the specificity and sensitivity for PD [48]. With the increasing relevance of miRNAs in biofluids, the development of circulating biomarkers for PD has a great potential. A research study utilising qRT-PCR advocated that levels of miR-1, miR-22-5p and miR-29 peripheral blood greatly differ that can assist to identify PD patients. The levels of miR-16-2-3p, miR-26a-2-3p and miR30a are different between treated and untreated patients [49]. A recent study employing ‘next generation sequencing’, showed that 16 miRNAs including miR-16, miE-20a and miR-320 were significantly altered in total blood leukocytes of PD patients. Since these markers were inconsistent with the results, a lot of efforts are being made to develop a precise “biological marker,” which can be employed as a blood test or an imaging scan [50].

Imaging as a Functional Biomarker of PD

Neuroimaging techniques such as positron emission tomography (PET), magnetic resonance imaging (MRI), single-photon emission tomography (SPECT) and transcranial sonography (TCS) can deliver significant evidence on the status of the brain's function and structure

in PD [51,52,53]. They provide specific information about the integrity of the DA system, the time frame of neuron loss and offer complete anatomical contours of the brain damage. As they are non-invasive techniques, they can be repeatedly employed. However, neuroimaging techniques at present are not cost effective, limiting their employment under the special diagnostic circumstances.

The above techniques have been successfully exploited in order to distinguish PD from other parkinsonian disorders. PET is regarded as the best tool for PD identification by reckoning the discharge of positrons in the brain from radioactive isotopes or tracers that have been administered through the blood stream. Clinical trials have shown the average uptake of 18F-DOPA compared to controls and patients with PD reduced to 40% in the striatum [52]. Since 18- DOPA is not widely available, most employed tracer is SPECT tracer (Ioflupane Iodine-123; DatSCAN) which can highlight the presynaptic dopamine receptor (DaT) system. The only difference between SPECT and PET is half-lives of isotopes that are used in tracing; SPECT employs isotopes with much longer half-lives. Recently a SPECT imaging trials showed that as the disease severity increased striatal absorption of 99mTc-TRODAT-1 reduced subsequently [54]. Transcranial sonography can identify an echo of increased density of midbrain in PD patients; hyperechogenicity emitted by midbrain might implicate the increased iron concentration in the SN of PD patients [55].

Advances in the PD Therapeutics Mechanism of L-DOPA Alleviating the Function of Basal Ganglia

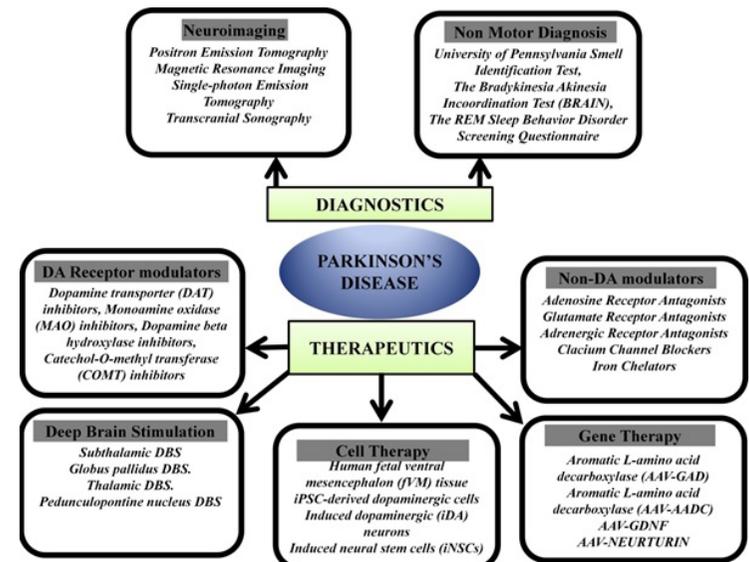


Figure 1: Diagnosis and therapeutic avenues for PD.

Levodopa (L-3, 4-dihydroxyphenylalanine, L-DOPA), is a precursor of DA and represent a most successful breakthrough in the symptomatic treatment of PD. Even after half a century of its introduction as an anti-PD agent, levodopa still remains the mainstay of PD therapy. The precise mechanism of action of L-DOPA is contradictory,

even though it is “the gold standard” for the symptomatic intervention of PD [56]. As the DA neurons are very plastic and robust, the DAergic functioning remains unharmed even after the destruction of most of the DA neuron. The primary symptoms of PD manifest only after the deterioration of ~30% of the pigmented SN neurons, and striatal DA terminal density is diminished to 50-70% [57]. Thus, at the time of L-DOPA administration, the usually large mass of the striatal DA will be on the verge of degeneration. It is established that L-DOPA produces a ~300% increase in quantal size (from 3,000 to 10,000 DA molecules) in the short duration of time. Further, L-DOPA increases vesicular DA storage ability by 240%. Thus, in intact DA axons, L-DOPA can be transported into the cytosol and converted to DA that is accumulated into synaptic vesicles. Further, the synaptic overflow of DA after the L-DOPA treatment increases dramatically (in the range of 20-fold) as DAT levels are drastically diminished [58].

Probable Mechanisms of Dyskinesia Mediated by the Levodopa

The precise mechanism of levodopa-mediated dyskinesia is obscure. Several evidence specify that dyskinesia develops in reaction to the dose-dependent pulsatile stimulation of striatal DA receptors. The incidence of pulsatile stimulation is greatly influenced by the half-life of the dopaminergic drug and the PD severity [59]. Fluctuation in levodopa levels is more likely to induce variations in SN

dopamine and pulsatile stimulation of DA receptors; as there are less striatal DA terminals and reduced buffering ability. Continuous delivery of levodopa or short-acting agonists or long-acting agonists potentially attenuates the dyskinesias. Hence, a strategy involving pulsatile stimulation prevention is considered to have the potential approach to coping up with the development of dyskinesias [60]. This method consists of the dopaminergic mimetic with a comparatively long half-life, to thwart the deterioration of DA neurons, and employ trophic factors that induce the multiplication of DA terminals which can aptly buffer the variations in SN dopamine. Alternatively, strategies that counterbalance the postsynaptic molecular and neurophysiological fluctuations in the downstream neurons might confer antidyskinetic effects.

Treatment for PD

DA Receptor Agonists

Dopaminergic receptor modulators are subdivided based on their structural formulae as ergoline derivatives (bromocriptine, pergolide, cabergoline, lisuride and α -dihydroergocriptine (DHEC) and nonergoline derivatives (pramipexole, ropinirole, rotigotine and apomorphine) [61]. DA Receptor agonists exert their pharmacologic effect by the direct stimulation of DA receptors, shunting the presynaptic production of DA. The DA like effectors usually have a strong affinity to the receptor proteins, and have much longer half-life than L-DOPA, these

features results in continuous and more stable stimulation than L-DOPA [62]. Unlike DA, the DA receptor-effector molecules or their metabolites will not generate ROS or other free radicals that are toxic to neurons. To the contrary, free-radical scavenging is one of the protective mechanisms in their repertoire [63].

MAO Inhibitors as PD Therapeutics

The role of apoptosis in neuro cytotoxicity in PD have triggered the pursuit for anti-apoptotic agents as a credible neuroprotective therapy in PD. MAO-B inhibitors caught the attention as PD therapeutics, owing to their ability to hinder the breakdown of striatal dopamine. Several lines of studies indicate that rasagiline has high specificity and binds irreversibly to the MAO-B isoform [64]. The degree of inhibition of MAO-B has been estimated to be ~5 times and ~10 times greater when compared to selegiline. Investigations in the cell culture and animal models have demonstrated that anti-apoptotic effects of pargylamines derivatives appear to be conferred by the propargyl chain and are independent of MAO-B inhibition. In vitro, rasagiline thwarts negative impacts of a wide range of cytotoxic factors, including serum and growth factor deprivation instigated by 6-hydroxydopamine (6-OHDA) and MPTP [65].

The phase 1 pivotal TEMPO study was conducted for 6-months with randomised, placebo-controlled, double-blind paradigm to understand the efficacy, safety, and tol-

erability of rasagiline. A total of 404 treatment-naïve patients with early PD were randomised to obtain placebo, rasagiline (1-2 mg/day). The primary score was changed in the total United PD Rating Scale (UPDRS) score. After 26 weeks, motor and total UPDRS scores had considerably improved in groups treated with rasagiline. This TEMPO efficacy trial was further extended to 6 months in 317 patients from the original study. And the results from the second phase TEMPO trial confirmed the possible disease-modifying effect of rasagiline [66]. These results prompted delayed-start ADAGIO (Attenuation of Disease Progression with Azilect Given Once-daily) which suggested a potential disease-modifying effect for rasagiline 1 mg/day, though the clinical impact of this finding has yet to be established [67].

Coenzyme Q10 (CoQ10)

Coenzyme Q10 (CoQ10) is an antioxidant, lipophilic molecule, a membrane stabiliser, located in the inner membrane of mitochondria and functions as an electron carrier (from complexes I and II to complex III) in the electron transport chain assisting the generation of ATP. Coenzyme Q10 is most appropriate antioxidant for PD therapy, as preclinical studies support the significance of redox equilibrium perturbation in PD due to defective mitochondrial complex 1 activity [68]. When CoQ10 was orally administered 7–10 days before the treatment of malonate in rats, it controlled ATP decline (in dose-dependent manner), striatal lesions, and attenuated the

malonate-mediated increase in lactate. In a mice model, CoQ10 pre-treatment completely abolished the depletion of DA and tyrosine hydroxylase levels [69].

In human study, UPDRS score was measured in 80 patients to comparatively examine the dose-dependent effect of CoQ10 (300mg, 600mg or 1200mg) and placebo. There was a dose-dependent reduction in UPDRS score in patients treated with CoQ10 compared to placebo, at the highest dose CoQ10 showed utmost beneficial impacts when compared to others [70]. Further, an “open label futility study” comprising 17 patients was performed to evaluate the tolerability of high doses. In Patients administered with higher doses of CoQ10 (1,200 mg to 3,000 mg per day) Plasma levels plateau at 2,400 mg dose, implicating the 2,400 mg as the futility dose [71].

Creatine

Creatine is an endogenic metabolite produced from methionine, arginine, and glycine. This energy rich system not only involved in the metabolism but also embodies antioxidant and neuroprotective properties and plays a crucial role in brain energy homeostasis [72]. It is hypothesised that creatine might be a better therapeutic anti-PD agent as it plays an essential role in cellular energy metabolism, could alleviate the deterioration energy homeostasis which is rather impaired in Parkinson disease.

Neuroprotective administration of creatine was validated in MPP+ and 6-OHDA-treated in vitro model DA

degeneration, where it protected tyrosine hydroxylase immunoreactive dopaminergic neurons and their fibres [72]. Oral creatine supplementation in mice protected against MPTP-induced DA depletion, suggesting a neuroprotective effect. In early epidemiological studies, behavioural complications drastically improved in a clinical trial of 200 patients with PD (diagnosed within 5 years) [73]. In a follow-up study, creatine demonstrated the neuroprotective effect even after 18 months. However, while there were no modifications in the PD scores or DAT imaging, creatine improved mood behaviour in a placebo-controlled a two-year clinical study comprising 60 subjects. There is on-going phase III clinical trial (NIH funded) which involves 52 medical amenities and 1720 PD patients; where creatine is treated with a dose of 10 g in a large long-term study against PD [74,75].

Neurotrophic Factors

Even though the cellular and molecular mechanisms underlying their neuroprotective action remains largely unknown, there has been a foresightful maxim in the potentials of neurotrophic factors as an anti-PD therapy.

Glial Derived Neurotrophic Factor

Glial-derived neurotrophic factor (GDNF) belongs to the transforming growth factor- β superfamily [76]. GDNF injected directly into the striatum either before or after (7 and 16 days) MPTP improved the TH immunoreactivity density and DA levels, demonstrating the pro-

tective and reviving potentials of GDNF on dopaminergic neurons [77,78]. The anti-PD potentials of GDNF have been established in primate models [79]. Intracerebroventricular GDNF injections in MPTP-treated primate resulted in diminished Parkinsonism in a dose-dependent manner, weakened dyskinesias, and amplified the generation of the DA. In a Phase I human trial, GDNF infused continuously into the putamen for 6 months significantly ameliorated the motor deficits and quality of life in 10 PD subjects [80]. In contrast, a Phase II clinical study carried by AMGEN of continuous injection of GDNF into the putamen, the therapy which was well-tolerated did not meet the primary endpoint at 6 months [81].

Neurturin

Neurturin (NTN), a close homologue of GDNF, is another neurotrophic factor which has emerged as a potential therapeutic target. Similar to GDNF, the recombinant NTN has shown a varying impact in animal models of PD [82]. In one study, the delivery of NTN into the striatum after 6-OHDA lesioning in rats resulted in a 72% protection of nigral DA neurons but failed to rescue DA levels in the striatum. In contrast, another study demonstrated that NTN administered 12 weeks following 6-OHDA failed to protect nigral neurons but increased striatal DA fibres [83]. The viral vector-mediated infusion has delivered the most effective procedure for the administration of NTN. Ceregene Inc. has recently developed AAV2-based vector

which encodes human NTN (CERE-120) when administered into the striatum in rats it significantly enhanced the NTN expression which in turn delivers nigral neurons protection of against 6-OHDA-induced degeneration in a dose-responsive manner [84]. The Phase I human trial study with a small sample size was performed to examine the safety and tolerability of putamen administration of CERE-120. According to this study administration of CERE-120 resulted in a significant decrease in UPDRS "off" scores, with no dyskinesias and least side effects [85]. However, in a double-blind, large Phase I/IIB trial CERE-120 when administered both intraputamally and intranigally showed no changes in UPDRS "off" scores and no marked favourable differences between treatment and control groups were found [86].

Deep Brain Stimulation (DBS)

DBS has been recognised as a most powerful therapeutic alternative when pharmacological approaches no longer satisfactorily regulate the motor dysfunction in advanced stages of PD. Since the first application of DBS for PD in 1993, more than 12,000 patients across the world have received DBS. Prior to levodopa, surgical treatments were the most effective therapeutic strategies for PD. Initially, these procedures targeted the pyramidal tracts mainly focused on the lessening the tremor [87]. In 1987, Benabid and colleagues demonstrated that prolonged electrical transmission to the subcortical brain (DBS) was as effective as thalamotomy for tremor suppression. Fol-

lowing this use of DBS other basal ganglia locations were explored [88].

DBS rapidly overhauled lesioning better choice over many pharmacological interventions due to its several advantages. Generally, it is damage-proof and the presence of numerous stimulation parameters (location, size, intensity and the shape of the stimulating current field) which can be attuned subsequent surgical grafting. The first trial conducted in Germany and Austria, comprised 156 patients with advanced PD and severe movement deficits [89]. Subjects were assigned to undertake an unblinded trial with a randomized-pairs design; bilateral DBS of the subthalamic nucleus versus to receive optimized and individualised drug therapy. After 6 months, the patient group assigned to receive DBS had better quality life by 24% (50 of 78 pairs mean Parkinson's disease questionnaire -39, 31.8 vs. 40.2) while the group administered with the best pharmacotherapy did not change. Correspondingly, the motor scores according to the Unified PD Rating Scale (UPDRS-III) enhanced consistently in the DBS group (55 of 78 pairs, mean UPDRS-III 28.3 vs. 46.0). Further, dyskinesia in the pharmacotherapy group remained unaltered, whereas in the DBS group "off" state reduced by 54% [89].

Dietary Components and Beverages as Protective Agents

Growing body of evidence suggest that excessive oxidative stress may be a causative factor in the development

of Parkinson disease. As the knowledge of the mechanisms has enhanced researchers understood the importance of oxidative stress and lipid peroxidation in the pathogenesis of PD [90].

Vitamins

The emerging role of various nutritional components has been comprehensively reviewed recently [91]. Antioxidants such as vitamin E expected to protect against the development of Parkinson disease. Pre-treatment of neuronal cells with vitamin E relieved MPTP-mediated dopaminergic neurotoxicity. In another research study, investigators found out that vitamin E alleviated oxidative stress induced by iron in the mouse brain, suggesting that vitamin E may be neuroprotective against PD. Additionally, vitamin E was neuroprotective in 6-OHDA-treated animals [92].

Initial studies to examine the consumption effect of vitamin-E and bioactives were conducted in 106 PD patients and their spouses. This research work concluded that PD patients are less likely to eat vitamin E-containing foods than those without PD. In another study, it was showed an insignificant trend towards an association of high total vitamin E intake with decreased risk of PD [93]. Further, a meta-analysis of eight epidemiological studies portrayed that moderate intake of vitamin E is protective with a relative risk. Vitamin E supplement has been employed as a protective agent against PD in the DATATOP study [94]. In this study, 800 subjects were administered

with α -tocopherol, the physiologically active constituent of vitamin E, for more than a year. However, α -tocopherol was unable to bestow any beneficial effect on PD mediated motor deficits.

Coffee - Caffeine

Common sources of caffeine are coffee, tea (especially black tea), soft and energy drinks, and chocolate. Caffeine is known to be a CNS stimulant and an adenosine receptor antagonist. A body of epidemiological data clearly demonstrate the health promoting benefits of caffeinated beverages [95] and a clear inverse association between PD and coffee has been reported. The ability of caffeine to down-regulate NO production, neuroinflammation and microglial activation through these pathways are speculated to contribute to neuroprotection. Recent evidence indicates that caffeine reduces dopaminergic toxicity and slows disease progression through the antagonism of adenosine vA2A receptors [96]. Hence, currently, clinical studies are underway to evaluate several 1A2A receptor antagonists for symptomatic relief and slowing of disease progression [97]. Estrogen is shown to significantly modulate the neuroprotective potential of caffeine and epidemiological studies have consistently demonstrated a greater improvement in male than female PD patients.

Tea

Previously regular tea drinking was reported to reduce the risk for PD and protect against PD in Chinese

patients A large prospective study also showed a reduced risk of PD incidence among subjects who habitually drank three or more cups of tea per day and a recent retrospective study reported a delayed onset of motor symptoms in Israeli PD patients [98]. The polyphenol theaflavin (TF) present in black tea, possess a wide variety of pharmacological properties including antioxidative, antiapoptotic, and anti-inflammatory effects [99]. TF-mediated neuroprotection against MPTP-induced dopaminergic neurodegeneration in rodents was evidenced by increased expression of nigral TH, DAT and reduced expression of apoptotic markers [100].

Novel Frontiers of the PD Therapy

Adenosine Receptor Antagonists

Adenosine is a modulator of neuro signals that directs the functions of DA and other neurotransmitters that are required for the motor function and learning and memory. Four adenosine receptors (A1, A2A, A2B and A3) have been identified of which the A2A subtype is densely focalized in the basal ganglia system, with the highest abundance found in the striatum. They are predominantly co-expressed with D2 receptors in enkephalin-expressing striatopallidal neurons and consequently are extremely appropriate to the purpose of the indirect efferent pathway of the basal ganglia system. In these neurons, the A2A closely interrelates structurally and functionally with the D2 receptor. A2A and D2 receptors display interlinked in-

hibitory reactions, as they form receptor heteromers and target composite signalling cascades, therefore believed to play a significant role in the dopaminergic ordinance in the basal ganglia. Postmortem studies of PD patients have demonstrated a 2.95-fold increase in A2A-receptor expression in the putamen compared to healthy subjects and increased levels in dyskinetic patients treated with L-DOPA compared to L-DOPA-treated patients that displayed no dyskinesias [101].

A2A antagonists have demonstrated their neuroprotective efficacy in animal models. Numerous studies have been conducted employing in vivo models of PD to explore A2A-receptor inhibitors as feasible neurotherapeutics. The A2A antagonists (caffeine, theophylline, SCH58261, DMPX and KF17837) inhibited motor deficits such as catalepsy and reduced movement accelerated by haloperidol-induced dyskinesia models in rodents. Further oral administration of preladenant and SCH412348 potentiated contralateral rotation behaviour in animals lesioned with 6-OHDA. Further, oral infusion of the A2A-receptor inhibitor preladenant and SCH412348 inhibited L-DOPA-induced contralateral rotation behaviour, signifying that preladenant and SCH412348 may lessen the risk of dyskinesias progression [102].

In a first Phase I trial, the A2A receptor antagonist KW-6002 compounded the concomitant effects of low dose L-DOPA treatment with progress in the extent of time spent "on" without any aggravation of dyskinesias

[103]. Consequently, Phase II large, double-blind, randomised, placebo-controlled trials in advanced PD patients displayed substantial diminutions in the expanse of time spent "off" over a 12 week period. Similar conclusions were later drawn by a large Phase III trial in PD patients in late stage, where KW-6002 intervention resulted in reduced daily "off" times and further resulted in favourable "on" time (104). Reduction in "off" time was continual for a considerable period, with patients demonstrating advances from baseline scores up to 1 year later. However, KW-6002 treatment was consociated with the escalation in "on time with dyskinesias" and the occurrence of dyskinesias was accounted as an unfavourable effect in the KW-6002 groups [104]. In Phase II clinical trial, A2A antagonist preladenant treatment was also examined in PD patients with motor variations. There was a marked decline "off" time and preladenant enhanced the "on" time with dyskinesias. Thus, similar to KW-6002, preladenant mediated A2A inhibition might not reduce dyskinesias [105].

Glutamate Receptor Modulators

Glutamate receptors such as NMDA receptor are recognized as facilitators of excitotoxic neuronal death triggered by glutamate, so blocking of these receptors in the SNc hinders neuronal deterioration induced by the extreme action of STN [106]. Direct intranigral infusion of MK-801, NMDA receptor antagonist provides protection against degeneration of the SNc induced by MPP+ deliv-

ered to the nigral or striatal regions of the rats. Uninterrupted systemic intra-nigrostriatal treatment of MK-801 of degeneration in rats, curbs the neuronal degeneration in the SNc induced by 6-OHDA [107]. Prolonged administration of BZAD-01 (the NR2B-selective NMDA receptor antagonist) not only reduces SNc degeneration but also improves motor dysfunction induced by 6-OHDA dopaminergic-lesions in rats. These studies clearly affirm that hyperactive NMDA receptor conduces neurodegeneration in PD and its modulation by antagonists may serve as disease-altering therapy for decelerating the neurodegeneration in PD patients [108].

α -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors play a crucial role in synaptic plasticity in the brain and also control most of the excitatory neurotransmission. Several studies in rodent models of PD indicate that exclusive activators of AMPA receptors may be useful for protection against SNc degeneration [109]. Various categories of AMPA receptor potentiators have been described- benzothiazides (cyclothiazide), benzylpiperidines (CX-516, CX-546) pyrrolidones (piracetam, aniracetam) and biarylpropylsulfonamides (LY503430, LY450108, LY451395 LY404187 and LY392098) [110]. Preclinical and Clinical studies have demonstrated the potentiation of AMPA receptors may be an efficacious intervention in the treatment of neuronal and cognitive deformities. For instance, SNc degeneration and motor discrepancies caused by 6-OHDA lesion in rats and MPTP

in mice were effectively blocked by the AMPA receptor agonists LY404187 and LY503430 [111,112]. Interestingly, AMPA receptor activators redeem these protective effects even after the manifestation of toxin-mediated SNc lacérations, hinting the neurotrophic actuation provided by these compounds. In addition, age-mediated loss of substantia nigra neurons is protected by S18986, suggesting that augmenting AMPA receptor pathways may block the age-related loss of these neurons, and possibly avert the SNc degeneration that causes PD [113].

Adrenergic Receptor Antagonists

α 2 adrenergic receptor antagonist yohimbine and idazoxan significantly lowered L-DOPA-mediated hyperkinesia and alleviated the expression of abnormal involuntary movements (AIMs) in 6-OHDA-lesioned rats [114]. Similar results were evidenced when MPTP-lesioned non-human primates were administered with α 2 adrenergic receptor inhibitors, as they significantly shortened the L-DOPA Induced dyskinesia (LID)s without affecting the anti-parkinsonian properties of L-DOPA. Fipamezole, a most recently formulated adrenergic inhibitor, has also been described to expand both the duration and quality of L-DOPA properties with “on time devoid of dyskinesia” amplified by up to 98% in MPTP-lesioned macaques and total favorable “on” time improved by up 75% [115]. Both fipamezole and idazoxan have consequently advanced to clinical trial examinations. The effects of oral administra-

tion of idazoxan on motor dysfunction and LIDs ensuing after an acute treatment of L-DOPA was evaluated in 18 PD patients, this randomized, placebo-controlled trial, showed that idazoxan reduced the asperity of LIDs without hindering the antiparkinsonian properties of L-DOPA [116].

In Phase II double-blind, placebo-controlled, randomized trial dose-intensifying effect of fipamezole was assessed in PD patients experiencing LIDs. Though no salient endpoint difference was observed between fipamezole and placebo, it was concluded that adverse results may have been attributed because of the non-homogeneity of the total population as the study comprised the patients from two diverse populations. In another study, evaluation of a subgroup of US patients administered with fipamezole, demonstrated that fipamezole attenuated LIDs in a dose-responsive mode. However, it also induced mild, transient blood pressure, which is regarded as moderately tolerable adverse profile [117].

Gene Therapy for PD

First gene therapy trial against PD was an anti-symptomatic strategy which directed at transfection of aromatic amino decarboxylase (AADC), an enzyme producing dopamine from levodopa. In preclinical studies, it had been successful as even smaller doses of levodopa carried similar antiparkinsonian potential as high doses with coalesced action of AADC transfected through gene therapy

[118]. Further, exogenous AADC delayed the progression of DOPA-mediated dyskinesias. Here, ten patients with progressive PD received an AAV2-hAADC vector administered through bilateral putaminal infusions. UPDRS scores among AADC treated subjects improved in the first 12 months, but exhibited a slow decline in successive years. These data specify a continued transgene expression over 4 years after vector transfer and extended safety, but highlight the necessity of a meticulous efficacy trial and the transfer of a higher vector dose [119-121].

Preclinical trials in primate and rodent models administering lenti-DA confirmed a substantial antiparkinsonian result. A phase 1/2 open-label trial was conducted to ascertain the safety and effectiveness of ProSavin after bilateral infusion into the putamen of subjects with moderate PD. The major endpoints of this trial were the score and severity of adverse effects linked with ProSavin and motor functions as measured with Unified PD Rating Scale (UPDRS) part III (off medication) scores (after 6 months of vector injection) [122]. Another series of studies assesses the effect of AAV2-GAD after the bilateral infusion into the subthalamic nucleus in patients with advanced PD. In this double-blind, phase 2, randomised, controlled trial subjects aged 30-75 years with advanced levodopa-responsive PD were registered for the bilateral infusion of AAV2-GAD. The expected outcome was changed in the UPDRS motor scores at the 6-month after infusion of AAV2-GAD. However, the degree of the GAD efficacy

was, unfortunately, negligible and it is uncertain whether this method is going forward [123]. Recently, gene therapies for disease-modifying approaches have hinged upon the glial cell family of ligands (GFLs), namely, GDNF and neurturin. Phase 2 clinical trials evaluating the potency of gene delivered neurturin have failed miserably. A novel trial employing vector-mediated gene delivery of GDNF is presently on-going.

miRNA: Future Therapeutic Agents for Parkinson's Disease

Since PD is a multifaceted and complex disease it might need equally complex strategies for its treatment. Early diagnosis, a combination of therapies, and lifestyle modification are more likely backers for the effective eradication of the pathology. Recent studies show that miRNAs are playing an important role in the pathophysiology of PD. They are endogenous, short noncoding RNAs, measuring 12-22 nucleotides, associated with post-transcriptional machinery during the progression of PD. The micro RNAs are emerging as strong governing factors in a wide array of disorders and it might be possible to exploit potential therapeutic avenues ensued by these entities. Animal and even human efficacy data indicate that anti-miR compounds that inhibit specific miRNAs have the potential to become a whole new class of drugs [124].

In order to modify the expression levels of disease-associated miRNAs in the hope of curing the disease, two

strategies are being explored viz., 1. Mature miRNA mimics 2. Employing anti-miRNA candidates based on RNA interference (RI) [125]. RI is a simple and rapid method of silencing the transcription of target genes and blocking the expression of proteins associated with PD for e.g., blocking the production of α -synuclein by the introduction of short interfering RNA markedly decrease synuclein levels and protects from neurodegeneration.

Mature miRNA mimics are small RNA moieties that acts as miRNA precursors which can block the formation and maturation of specific target proteins. Here gene of the target might be any gene containing pathogenic mutation involved directly or indirectly in the pathophysiology of PD. There is a long-standing anticipation that RNA-interference-based therapies will be one of the major classes of drugs in the future. As miRNA drugs do not appear to have the same issues with toxicity as short interfering RNA or small hairpin RNA-based therapies, they are gaining more attention for their special potential in PD therapy [126].

Another strategy involves usage of synthetic anti-miRNA molecules (antagomirs) in order to inhibit the functions of specific miRNAs [127]. These anti-miRNAs are antisense oligonucleotides that bind to and inactivate the miRNA target, thus obstructing the function of over-expressed miRNAs. Several studies have shown that infusion of specific synthetic oligonucleotides against several miRNAs led to a drastic downregulation of miRNA levels,

and miRNA silencing is specific, efficient, and long-lasting [128]. Although, miRNA-mediated strategies unexplored completely and often demonstrate many challenges, including the organ/tissue specificity of the miRNA and inaccessibility of specific delivery approaches to the central nervous system, they represent powerful strategies to tackle the humankind's most devastating diseases.

Conclusion

The main source of the pharmaceutical therapy has been our understanding of the mechanisms of the disease. As soon as L-DOPA emerged as a potent neurotherapeutic 50 years ago, it changed the quality and extent of patient's life. However, soon it was deemed failure as the "trustworthy" L-DOPA showed side effects, this changed our perception of PD pathophysiology. Since then scientific arena is frantically searching for novel disease-modifying therapeutic agents or strategies. Lately, there is an upsurge of treatments and novel strategies that have moved away the importance of from dopamine-mimetic treatments to a new block of agents/approaches that work in completely novel ways. Altogether, widespread progress has been made with some of the longstanding challenges in our pursuit of efficient disease-modifying therapies for PD. In this review, we have tried to cover a broad range of strategies that could be used to prevent the progressive neurodegeneration seen in PD. Further, we have provided condensed details of the experimental, genetics, and neuroclinical discoveries that occurred in the PD research so far.

Conflict of Interest

The authors report no conflict of interest.

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