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Review

Role of genomics in translational research for Parkinson's disease

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ABSTRACT

Research on Parkinson's disease (PD) has made remarkable progress in recent decades, due largely to new genomic technologies, such as high throughput sequencing and microarray analyses. Since the discovery of a linkage of a missense mutation of the α-synuclein (αS) gene to a rare familial dominant form of PD in 1996, positional cloning and characterization of a number of familial PD risk factors have established a hypothesis that aggregation of αS may play a major role in the pathogenesis of PD. Furthermore, dozens of sensitizing alleles related to the disease have been identified by genome wide association studies (GWAS) and meta-GWAS, contributing to a better understanding of the pathological mechanisms of sporadic PD. Thus, the knowledge obtained from the association studies will be valuable for "the personal genome" of PD. Besides summarizing such progress, this paper focuses on the role of microRNAs in the field of PD research, since microRNAs might be promising as a biomarker and as a therapeutic reagent for PD. We further refer to a recent view that neurodegenerative diseases, including PD, coexist with metabolic disorders and are stimulated by type II diabetes, the most common disease among elderly populations. The development of genomic approaches may potentially contribute to therapeutic intervention for PD.

Contents

1. Introduction

First described by Dr. James Parkinson in his historic publication, "Shaking palsy", in 1817, Parkinson's disease (PD) is now known as the second most common age-related neurodegenerative disease after Alzheimer's disease (AD) in super-aged societies [1]. PD is clinically manifested by motor dysfunctions, such as rigidity, resting tremor, bradykinesia, and postural instability, as well as by non-motor symptoms, including cognitive deficits, depression, and sensory, sleep, and emotional problems [2]. These symptoms of PD appear due to a deficiency of dopamine caused by dopaminergic neuronal degeneration in the substantia nigra pars compacta. In addition to neuronal cell death, the degenerating neurons are histopathologically distinguished by the formation of Lewy bodies, the

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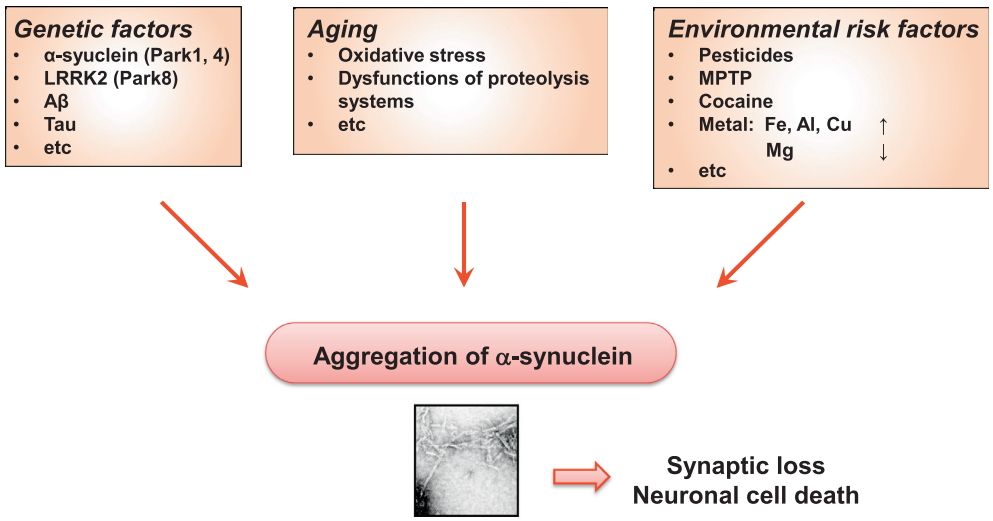

Fig. 1. Schematic of the pathogenesis of PD: αS may be situated at the center of the pathogenesis of PD.

intracellular inclusions which are composed of various molecules, including α-synuclein (αS), ubiquitin, and neurofilaments [3]. Similar pathologies are observed in the α-synucleinopathies, such as dementia with Lewy bodies (DLB), and Lewy variants of AD, while in multiple system atrophy (MSA), Lewy bodies are frequently localized in the oligodendrocytes [3,4].

Recently, there has been much progress in understanding the pathophysiological mechanisms of PD with the development of newer technologies. Since the linkage of missense mutations in the αS gene to a rare familial dominant PD was identified [5], a wealth of new studies has been performed, leading to the established view that aggregation of αS, a presynaptic protein with unknown functions, may play a central role in the pathogenesis of PD (Fig. 1). Consistent with this notion, further studies on a number of familial PD risk factors have shown that deregulation of these molecules may result in stimulation of pathological αS aggregation [6]. Moreover, results of genome wide association studies (GWAS) have corroborated the association of sporadic PD with variety of genes including *SNCA* (a gene encoding αS), leucine-rich repeat kinase 2 (*LRRK2*), and *MAPT* (a gene encoding tau) [7]. It is expected that the knowledge obtained from these association studies will be valuable for early diagnosis/treatment of PD and for the personal PD genome in the future.

Despite the many efforts made to understand the pathogenesis of PD, there are still no treatments available that cure PD. Consequently, huge expenditures on medical and nursing care of these patients have become a serious problem for our society. Therefore, a solution to this issue has become a high priority in research on neurodegenerative diseases. In this context, since it is expected that the development of genomic approaches may play a key role in the development of a therapeutic intervention for PD, we present this important issue in this review. We first summarize the advances made using positional cloning and GWAS in PD research whereby genomic approaches have played central roles. We then discuss the possibility that the development of advanced genomic technologies, such as a next-generation sequencing and array technology, may lead to a therapeutic intervention for PD. In this respect, special attention will be paid to the relevance of microRNA (miRNA) to PD pathogenesis since accumulating evidence suggests that deregulation of miRNA expression may play an important role in the pathogenesis of PD, and manipulation of miRNA may potentially lead to a therapy. We further discuss a recent view that neurodegenerative diseases, including PD, have aspects of metabolic disorders and are exacerbated by type II diabetes mellitus (DM), the most common disease among aged-populations. We suggest that genomic studies may contribute to our understanding of the mechanism by which DM stimulates PD, leading to new therapeutic approaches for PD.

2. The mechanism of PD is revealed by genomic research (1): the synuclein family of peptides

PD research greatly benefited from the progress in molecular biology technologies when in 1996 Polymeropoulos and his associates discovered a linkage of a missense mutation (A53T) of the αS gene to a rare familial PD case (referred to as PARK1) [8] (Fig. 2). Subsequent to the A53T discovery [5], another missense mutation A30P [9] was reported in PD and E46K was reported in DLB [10] (Fig. 2). In 2013, an additional four cases of mutations, A18T, A29S, H50Q, and G51D, were reported for both PD and DLB [11–13], while another A53E mutation was found in MSA [14]

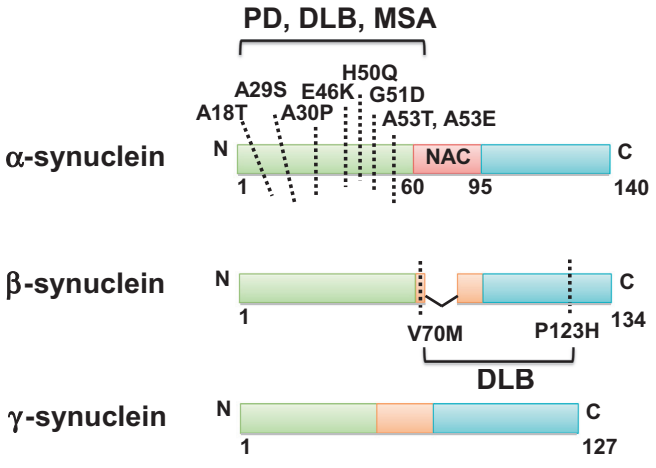

Fig. 2. Missense mutations of the synuclein peptide family (α, β, γ). Synucleins are composed of N-terminal basic regions with a repeating motif (KTKEGV) and divergent C-terminal acidic regions. The central region of α-synuclein includes a strongly hydrophobic NAC (*n*on-β-*a*myloid *c*omponent of the AD amyloid) domain, whereas the majority of the corresponding region in β-synuclein is naturally deleted and the same region in γ-synuclein is less hydrophobic [21]. For α-synuclein 8 mutations (A18T, A29S, A30P, E46K, H50Q, G51D, A53T and A53E) have been found from PD, DLB and MS, respectively [17]. For β-synuclein, two mutations (V70M and P123H) have been reported in sporadic and familial DLB [17].

(Fig. 2). In addition to the missense mutation of the αS gene, duplications and triplications of the locus containing the αS gene have been found in familial PD (referred to as PARK4), accounting for around 2% of the familial cases. Numerous studies have been conducted to characterize αS since the A53T missense mutation in αS was discovered, leading to the establishment of a hypothesis that αS is a central player in the pathogenesis of PD [15]. αS is a presynaptic protein with unknown functions. αS is an aggregate-prone protein, which may be more aggregated in various pathological conditions, such as missense mutations of other familial PD factors (as described later), deregulation of oxidative stress, and compromised protein degradation in the pathogenesis of familial and/or sporadic PD [16].

Notably, missense mutations of βS, another member of the synuclein family of peptides, have been identified in DLB. A substitution at position 70 (V70M) was found in a sporadic DLB case in Japan, while a proline to histidine mutation (P123H) was identified in a familial DLB pedigree in the USA (Seattle) [17] (Fig. 2). These amino acid changes occurred at highly conserved residues in important domain regions of βS, and did not appear to be single nucleotide polymorphisms, as they were not found in more than 330 controls. Statistically, the βS mutant proteins may be classified as "rare mutations that may have strong effects on the onset of PD". Based on cosegregation analysis of the Seattle pedigree, inheritance of the P123H mutation suggested that it could be a dominant trait with incomplete penetrance.

Histological analysis of the postmortem brain with the P123H βS mutation showed typical Lewy bodies that were immunoreactive with anti-βS antibody, but not with anti-βS antibody, suggesting that an alteration in βS due to the missense mutation may lead to αS aggregation [17]. In support of this hypothesis that is based on the observation of human brains, subsequent studies showed that expression of βS mutant proteins (P123H, V70M) resulted in enhanced aggregation in both *in vitro* cell free- and cell culture-systems [18]. Furthermore, transgenic mice expressing P123H-βS displayed significant neuropathological abnormalities, including axonal swellings and astrogliosis, indicating that this βS mutation is indeed pathogenic in vivo [19]. Taken together, these results supported a role of this βS missense mutation in the pathogenesis of PD.

The number of patients with missense mutations of the synuclein family of peptides will likely increase greatly as the "personal genome" becomes more widely used in the near future. Nevertheless, the physiological functions of synuclein proteins are still obscure. The situation is similar to that in Alzheimer's disease (AD) research, where the physiological functions of amyloid precursor protein (APP) and Aβ are yet to be clarified [20]. The functions of synuclein proteins need to be clarified given that alteration of these proteins may play a critical role in the early stage of PD pathogenesis.

3. The mechanism of PD is revealed by genomic research (2): various familial PD risk factors

Not only synuclein genes but also a number of genes encoding risk factors were identified from the familial PD pedigrees by positional cloning approaches. At this time, a total of ~20 risk factors are known to conclusively cause hereditary PD [8,15,21–46] (Table 1). Some of these factors were identified in autosomal-dominant PD (Table 1). In addition to *SNCA*, *LRRK2* (dardarin, PARK8) may be the most extensively studied PD-related genes. LRRK2 is a large, multi-domain GTPase/kinase protein, and is characterized by the presence of a ROC domain, a COR domain, and a MAPKKK domain [47–50]. These domains control several pivotal cellular functions, such as proliferation, differentiation, and survival. Furthermore, LRRK2 plays a significant role in regulating neural functions, including vesicle trafficking and neurite formation [51]. The exact mechanism of LRRK2-stimulation of neurodegeneration is not understood. Although the mechanism is unclear, phosphorylation of αS may be deregulated by LRRK2, leading to initiation of PD pathogenesis. Similar to αS and LRRK2, the ubiquitin carboxy terminal hydrolase L1 (*UCHL1*, PARK5) gene may be responsible for an autosomal dominant form of typical PD [23]. However, only a single family has so far been identified with this gene mutation. Furthermore, it is interesting that this gene with another missense mutation, S18Y, is protective against PD [52]. Indeed, the role of PARK5 in the pathogenesis of PD is controversial since recent association studies have failed to show that *UCHL1* is susceptible to PD [53].

On the other hand, several gene products that are known to confer an autosomal-recessive trait in PD have been identified (Table 1), including *parkin* (PARK2) [21], PTEN-induced putative kinase 1 (*PINK1*, PARK6) [24], *DJ-1* (PARK7) [25,26], and *ATP13A2* (PARK9) [30,31]. A recent study suggests that parkin and PINK1 cooperate to regulate the quality of mitochondria [54,55], while DJ-1 may provide protection from oxidative stress [56,57]. The physiological function of ATP13A2 is obscure. However, since ATP13A2 is immunopositive on lysosomal membranes [30], this molecule might be important in the function of lysosomes. Thus, it is possible that the mechanism of neurodegeneration in PD may include these dysfunctions as well as a decrease in mitochondrial activity. Furthermore, since iron accumulation in the substantia nigra is typically observed in conjunction with the protein inclusions [58], PD may be related to oxidative stress and protein aggregation.

Taken together, the presence of either different loci or different causative genes strongly suggests that PD is not a single entity but a highly heterogeneous disorder. However, it is reasonable to speculate that the functions of proteins encoded by the causative genes may share a common pathway in the pathogenesis of PD. Evidence has accumulated to suggest that an ubiquitin-proteasome pathway and a pathway involving control of the mitochondria are particularly important because compromised functions of these pathways may lead to aggregation of αS. Thus, identification of the causative genes of PD and elucidation of the gene products should enhance our understanding of the pathogenesis in familial PD. Furthermore, the results are also applicable to the pathogenesis of sporadic PD. Therefore, it is expected that this knowledge may also help us to create a new treatment strategy for PD.

4. The mechanism of PD is revealed by genomic research (3): GWAS and meta GWAS

A number of gene variants or single nucleotide polymorphisms (SNPs) modulate the risk of PD [7]. These variants of SNPs are studied in two types of association studies. First, association studies are performed on the SNPs of known genes, including a REP1 polymorphism of located in the *SNCA* gene promotor, SNPs near both the *SNCA* or *LRRK2* genes and mutations of glucocerebrosidase gene [59,60]. Numerous exonic variants of *LRRK2* have been shown to influence PD risk in various ethnic populations, while mutations of glucocerebrosidase gene are observed in Gaucher disease, being reminiscent of the pathological link between this pediatric disease and PD. In contrast to these types of association studies, genome wide association studies (GWAS) are high throughput studies that cover all the SNPs on the whole genome [61,62]. The sample number of GWAS becomes larger if each GWAS is combined together in a multi-centered collaboration; so called, meta-analysis of GWAS [63]. Thus, GWAS and meta-GWAS are advantageous in that the results are unbiased compared to the association studies of the known genes. Thus, GWAS and meta GWAS may provide more information than was previously known.

Table 1
Familial PD risk factors.

Name	Chromosomal location	Gene	Potent physiologic functions of protein	Inheritance	Clinical phenotype	References
PARK1/4	4q21–q23	SNCA	Maintaining a supply of synaptic vesicles	AD	Late-onset parkinsonism	[5,6]
PARK2	6q25–q27	Parkin	Ubiquitin-protein ligase	AR	Juvenile-, Early-onset parkinsonism	[22]
PARK3	2p13	?		AD	Late-onset parkinsonism	[23]
PARK5	4p14	UCH-L1	Ubiquitin hydrolase	AD	Late-onset parkinsonism	[24]
PARK6	1p36.12	PINK1	Regulating mitochondrial quality control	AR	Early-onset parkinsonism	[25]
PARK7	1p36.23	DJ-1	Antioxidative stress reaction	AR	Early-onset parkinsonism	[26,27]
PARK8	12q12	LRRK2	Multi-domain protein kinase which regulates wide variety of biological processes	AD	Late-onset parkinsonism	[28–30]
PARK9	1p36.13	ATP132A	Lysosomal ATPase	AR	Juvenile-onset parkinsonism	[31,32]
PARK10	1p32	?			Late-onset parkinsonism	[33]
PARK11	2q37.1	GIGYF2	Cooperate with GRB10 to regulate the IGF1 and insulin receptors signaling	AD	Late-onset parkinsonism	[34]
PARK12	Xq21–q25	?			Late-onset parkinsonism	[35]
PARK13	2p13.1	HTRA2	Mitochondrially-located serine protease	AD	Late-onset parkinsonism	[36]
PARK14	22q13.1	PLA2G6	Hydrolyzes phospholipids and release free fatty acids	AR	Early-onset parkinsonism	[37]
PARK15	22q12.3	FBXO7	Cell cycle, genome stability, development, synapse formation, and circadian rhythms	AR	Juvenile-onset parkinsonism	[38,39]
PARK16	1q32	Rab7L1	Regulates the vesicle traffic		Late-onset parkinsonism	[40,41]
PARK17	16q11.2	VPS35	Involved in *endosome-to-Golgi* transport	AD	Late-onset parkinsonism	[42]
PARK18	3q27.1	EIF4G1	Translation initiation factor which involved in mitochondrial activity	AD	Late-onset parkinsonism	[43]
PARK19	1p31.3	DNAJC6	Regulates the molecular chaperone activity	AR	Juvenile-onset parkinsonism	[44], [45]
PARK20	21q22.11	SYNJ1	Synaptic vesicle recycling	AR	Early-onset parkinsonism	[46], [47]

AD: autosomal dominant, AR: autosomal recessive.
Juvenile-oncet (age; <20), Early-onset (age; 20–40), Late-onset (age; >40).

GWAS from different populations have already been reported for PD, in which the association of *SNCA* to PD was confirmed by the majority of these studies [39,40,63–72] (Table 2). It is known that ethnic differences are a critical issue frequently associated with GWAS. Consistent with this notion, two collaborative studies of GWAS revealed that association of *MAPT* with PD was observed for a Western population but not for an Asian population [39,40]. Indeed, the haplotype (H1, H2) of the Asian population is different from that of the Western population, suggesting that the difference in association of the *MAPT* and PD was due to the different ethnic populations. Notably, the two GWAS have identified three new PD susceptibility genes that reached genome wide significance. In the Asian population, GWAS identified two new susceptibility loci PARK16 on chr1q32 and BST1 (bone marrow stromal cell antigen 1) on 4p15 [39], and the HLA (human leukocyte antigen) region was identified as a susceptibility locus in a late-onset sporadic PD population from North America [68]. Furthermore, several novel genes were identified by a recent meta-analysis which include *SYT11, ACMSD, STK39, MCCC1/LAMP3, GAK*, and *CCDC62/HIP1R* [73]. Thus, it is expected that the number of genes identified by GWAS will increase even more as GWAS is used more universally and improved.

It is anticipated that the knowledge obtained from these genomic analyses will be applied to early diagnosis based on genetic testing in the future. Nevertheless, it should be born in mind that GWAS are frequently associated with specific problems which must be overcome. A few of limitations of GWAS are known and must be overcome. First, as is the case with *MAPT*, the heterogeneity of SNPs across the population is a critical problem. Second, 'the multiple, rare variants in common diseases', do not reach significance in GWAS. Third, other genetic mechanisms, such as methylation, are not well captured by current GWAS approaches. Finally, if SNPs are associated with the disease, this does not necessarily mean that the genes in the vicinity are associated with the disease. Indeed, many of the genes identified by GWAS have not been conclusively shown to be involved in the pathogenesis of PD.

5. Strategy for PD therapy

5.1. Conventional concept of PD therapy

Despite active research, no treatments have been developed that may delay PD progression. Accordingly, medications, such as l-dopa, are usually used to improve the dopaminergic function on the clinical stages of the disease [73]. In addition, other medications, such as monoamine oxidase B inhibitors and dopamine agonists are used in the hope of delaying the onset of dyskinesias, side-effects by l-dopa [74]. When medications are not effective to control symptoms anymore, alternative, such as brain stimulation, can be selected [75].

Since there are currently no treatments that cure PD, the concept of the prevention of PD may be important. Indeed, PD appears to be affected by various environmental and non-genetic factors [76]. Some factors are also protective against PD. Coffee and

Table 2
Genome-wide association studies (GWAS) in PD.

Study (References)	Exploratory		Replication		SNPs	Chromosome/Main associated genes (SNP)
	PD	Controls	PD	Controls		
Maraganore 2005 [64]	443	443	332	332	198,345	5/***SEM5A*** *(rs7702187)*, 2/***GALNT3*** *(rs16851009)*, 1/***PRDM2*** *(rs2245218)*, X/***PASD1*** *(rs7878232)*
Fung 2006 [65]	267	270	–	–	408,803	4/***BRDG1*** *(rs11946612)*, 4/***DLG2*** *(rs10501570)*
Satake 2009 [40]	1078	2,628	993	15,753	435,470	4/***SNCA*** *(rs11931074)*, 1/***PARK 16*** *(rs947211)*, 12/***LRRK2*** *(rs1994090)*, 4/***BST1*** *(rs453875)*
Simón-Sánchez 2009 [41]	1745	4047	3452	4756	463,185	4/***SNCA*** *(rs2736990)*, 17/***MAPT*** *(rs393152)*, 1/***PARK 16*** *(rs823128)*, 12/***LRRK2*** *(rs1491923)*
Pankratz 2009 [66]	857	867	–	–	328,189	4/***GAK/DGKQ*** *(rs11248060)*, 4/***SNCA*** *(rs356229)*, 17/***MAPT*** *(rs1724425)*
Edwards 2010 [67]	604	619	–	–	491,378	4/***SNCA*** *(rs2736990)*, 17/***MAPT*** *(rs11012)*
Hamza 2010 [68]	2000	1986	–	–	811,597	4/***SNCA*** *(rs356220)*, 17/***MAPT*** *(rs199533)*, 6/***HLA-DRA*** *(rs3129882)*, 4/***GAK*** *(rs11248051)*,17/***MAPT*** *(rs11012)*
Spencer 2011 [69]	1705	5175	1,039	1984	1,733,533	4/***SNCA*** *(rs356220)*, 17/***MAPT*** *(rs8070723)*, 4/***BST1*** *(rs4698412)*, 4/***GAK*** *(rs1564282)*, 1/***PARK16 (rs823128)***
Saad 2011 [70]	1039	1984	3232	7064	492,929	4/***BST1***(rs4698412), 4/***SNCA***(rs11931074), 12/***RFX4***(rs4964469)
Do 2011 [71]	3426	29,624	6,584	15,407	522,782	12/***LRRK2*** *(rs34637584)*, 1/***GBA*** *(i4000416)*, 4/***SNCA*** *(rs356220)*,17/***MAPT*** *(rs12185268)*, 3/***MCCC1/LAMP3*** *(rs10513789)*, 4/***SCARB2*** *(rs6812193)*, 4/***GAK*** *(rs6599389)*, 17/***SREBF1/RAI1*** *(rs1186035)*, 1/***SLC41A1*** *(rs823156)*, 18/***RIT2/SYT4*** *(rs4130047)*, 21/***USP25*** *(rs282335)*
Liu 2011 [72]	268	178	1782	1658	525,124	5/***SLC25A48*** *(rs4976493)*, 9/***UNC13B*** *(rs10121009)*, 15/***SLCO3A1*** *(rs7171137)*, 17/***NSF*** *(rs183211)*, 17/***WNT3*** *(rs415430)*, 17/***MAPT*** *(rs1981997)*, 4/***SNCA*** *(rs356220)*, 12/***LRRK2*** *(rs1427271)*, 1/***GBA*** *(rs2049805)*, 1/***PARK16*** *(rs823114)*, 4/***BST1***(rs4538475), 2/***STK39*** *(rs2102808)*, 3/***MCCC1/LAMP3*** *(rs1171141)*
Nalls 2011 [73]	5333	12,019	7053	9007	7,689,524	17/***MAPT*** *(rs2942168)*, 4/***SNCA*** *(rs356219)*, 6/***HLA-DRB5*** *(chr6:32588205)*, 4/***BST1*** *(rs11724635)*, 4/***GAK*** *(chr4:911311)*, 12/***LRRK2*** *(rs1491942)*, 2/***ACMSD*** *(rs6710823)*, 2/***STK39*** *(rs2102808)*, 3/***MCCC1 /LAMP3*** *(rs11711441)*, 1/***STY11*** *(chr1:154105678)*, 12/***CCDC62/HIP1R*** *(rs12817488)*

tobacco use have been associated with a lower risk of idiopathic PD in many epidemiological studies [77]. It is known that caffeine appears protective against PD with decrease in risk occurring with a larger intake of coffee. It is interesting that smoking tobacco it may reduce the risk of PD, because tobacco smoke contains the compounds which may inhibit the monoamine oxidase B [78,79].

5.2. Dosage reduction of amyloid: a therapeutic paradigm for neurodegenerative disease

It has been well characterized that aggregation of amyloidogenic proteins is stimulated under various conditions [80], including high protein concentrations. Consistent with this notion, the concept of 'dosage reduction of amyloidogenic protein' has been a therapeutic paradigm in the neurodegenerative disease field [81]. Indeed, there is strong evidence from animal studies that merely over-producing a wild type or mutant amyloidogenic protein can result in a "neurodegenerative disease" phenotype. The amount of amyloidogenic proteins has been reduced at their mRNAs levels with various strategies including RNA interference (RNAi) [82]. In particular, allele-specific gene silencing by RNAi is useful for inhibiting the expression of disease-associated alleles without suppressing the expression of corresponding wild-type alleles [83]. To realize such allele-specific RNAi (ASP-RNAi), the design and assessment of small ASP-RNAi and efficient delivery of ASP-RNAi to the target is required. In this context, preclinical trials performed on mice with amyotrophic lateral sclerosis due to a superoxide dismutase 1 mutation or on mice expressing polyglutamine-expanded proteins (in either Huntington's disease or spinocerebellar ataxia), and these studies have yielded dramatic successes when the expression level of the toxic protein is reduced [84,85].

More recently, the evidence is accumulating to support a relevance of miRNA in the pathogenesis in PD [86–95] (Table 3). MiRNAs are small non-coding RNAs that have been recently identified as post-transcriptional regulators of gene expression with relevant roles in the physiological and pathological aspects of the various tissues including central nervous system [96–98]. MiRNAs mediate targeted-mRNA degradation or translational inhibition through complete or partial binding to the open reading frames and to the 3′untranslated regions (3′UTR) of mRNAs. Deregulation of miRNAs may play important roles in the pathology of PD and of other α-synucleinopathies [99–101]. Furthermore, manipulation of miRNAs may potentially lead to therapy of these diseases. MiRNA might be more promising compared to other strategy of RNAi because miRNA is more relevant to pathophysiologically of PD (See Fig. 3).

It has been reported in a number of neurodegenerative diseases. In PD, abnormal function of several miRNAs has been shown (Table 3). For instance, the expression of miR-133b, a miRNA that regulates the maturation and function of dopaminergic neurons

Table 3
Involvement of miRNAs in PD pathology.

miRNAs (References)	Function	Targets	Changes
miR-133b [85]	Survival of dopaminergic neurons	Pitx3	Down-regulated in PD brain
miR-433 [86]	Regulates the expression of α-synuclein	FGF20	–
miR-7 [87]	Regulate oxidative stress and cell death	α-Synuclein	–
miR-153 and miR-7 [88]	Regulates the expression of α-synuclein	α-Synuclein	–
miR-184 and let-7 [89]	Regulate dopaminergic neurons survival and activity	DP and E2F1	Influence by mutant LRRK2
miR-34b/c [90]	Modulating expression of DJ1 and Parkin	Unknown	Down-regulated in PD brain
miR-205 [91]	Suppressed the expression of LRRK2	LRRK2	Down-regulated in PD brain
miR-126 [92]	Suppressed the IGF-1/PI3K signals	p85β, IRS-1 and SPRED1	–
miR-1, miR-22, miR-29 [93]	Biomarkers for PD in blood	–	Down-regulated in PD blood
miR-1826, miR-450b-3p, miR-626, miR-505 [94]	Biomarkers for PD in plasma	–	Up-regulated in PD Plasma

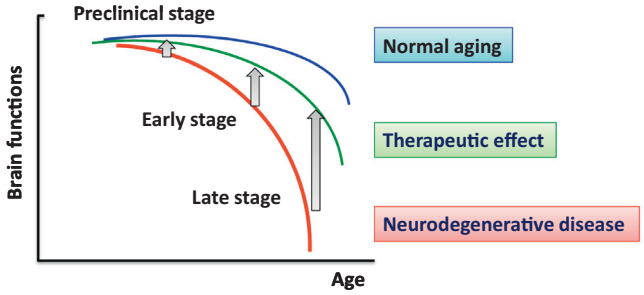

Fig. 3. Schematic of the progression curve of the neurodegenerative diseases, such as AD and PD. Diagnosis and treatment in the early-stage may be more efficient for the therapy of the diseases compared to those in the late-stage.

in the SN, was reduced in midbrain samples from patients with PD [86]. It was also showed that a mutation of the binding site for miR-433 on the FGF20 gene has been associated with PD, and that increased FGF20 up-regulate the αS level [87]. Furthermore, miR-7, which was deceased in a PD mouse model, has been shown to down-regulate the expression of αS [88]. Moreover, it was reported that miR-7 and miR-153 showed similar distribution to αS expression [89]. However, it is unclear that miR-7 deceased in Parkinson's brains. Additionally, some of the miRNAs were reported as a marker for PD (up-regulated in PD; miR-1826, miR-450b-3p, miR-626, miR-505, down-regulated in PD; miR-1, miR-22, miR-29) [94,95]. Although, these findings suggest that miRNAs may be involved in the pathogenesis of PD, the mechanism are unclear. One possibility is that aggregated αS might interfere with the miRNA in nucleus. In support of this notion, αS was primary identified as the molecule which expressed in nucleus of nervous system of torpedo (Fig. 4-i). Moreover, nuclear inclusions of αS were frequently observed in the transgenic mice expressing human αS (Fig. 4-ii).

5.3. Early diagnosis/treatment of PD: a paradigm for PD therapy

Recently, a number of clinical trials far AD have been completed. This includes the vaccination of Aβ peptides and use of secretase inhibitors [102–104]. Despite the huge efforts of these trials, none have been so far successful. Consequently, one interpretation is that accumulation of amyloidogenic proteins may not be related to the neurotoxicity in AD. Alternatively, it might be that the therapy should have been initiated in an earlier stage of the disease. If the latter view is the case, detection of the disease and treatment in the early stages is essential for having a cure for AD. According to a view that preclinical detection of AD depends on the utilization of biomarkers and is critical for selection of patients who are likely to benefit from amyloid-targeting therapies, it is predicted that preclinical detection of AD pathology will have a major impact on entry criteria into trials as well as on assessment of the efficacy of current and future treatments. Based on such an idea, the Alzheimer's Disease Neuroimaging Initiative (ADNI) was started in 2003 to speed drug development by validating imaging and biomarkers for AD clinical trials [105,106].

Similar to AD, early diagnosis and early treatment may also be crucial in PD, since it has been well-documented by pathological studies that the majority (more than 90%) of the dopaminergic neurons in midbrain are already non viable at the time when clinical symptoms are manifested in PD patients. In this context, the Parkinson Progression Marker Initiative (PPMI) was started similar to the AD initiative [107].

6. PD as a metabolic disease

Recently, there has been a global increase in the prevalence of obesity, with obesity-related diabetes currently affecting over 366 million adults worldwide by 2030 [108], and Type II DM is increasing as a consequence of the obesity epidemic. In this context, DM might act as a risk factor for other diseases among elderly populations. Consistent with this notion, it has been shown that for many types of diseases, such as atherosclerosis [109], cancer [110], osteoporosis [111], and chronic pulmonary obstructive disease [112], that DM is a risk factor. In the nervous system, cerebral ischemia and depression have been found to be triggered by DM [113,114]. In a similar context, it is of a note that the risk of neurodegenerative disorders, such as AD and PD, are significantly higher when the patient has the coexisting condition of type II DM [115,116]. Furthermore, neurodegenerative disorders are frequently associated with alterations of the glycolytic systems [117], suggesting that neurodegenerative diseases may have aspects related to metabolic disorders. It is therefore possible that type II DM therapy might have a beneficial effect on downstream diseases, including PD. In support of this notion, recent studies have shown that incretin, a group of gastrointestinal hormones that exhibit anti-diabetic actions, were effective in ameliorating PD in experimental models [118,119].

As for the mechanism by which PD is triggered by type II DM disease, one may speculate that common pathological mechanisms may underlie both DM and PD. Indeed, many pathologies, such as oxidative stress, inflammation, and amyloidoses, are commonly observed in both of these disorders. However, the situation may be not so simple. If stimulation of PD by DM may contribute to

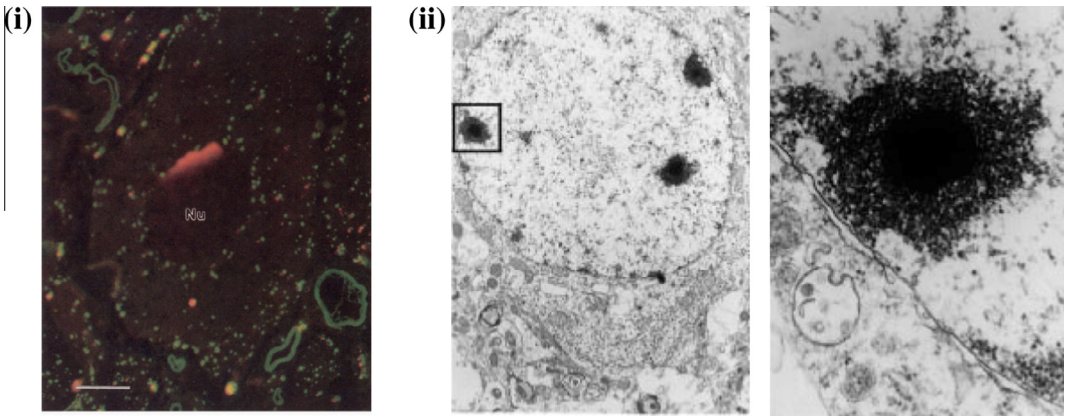

Fig. 4. Nuclear staining of synuclein. (i) Synuclein (*red*) was identified in torpedo as the molecule which is expressed abundantly in presynapse areas and in the nucleus. (Reprinted from *J. Neurosci.*, Maroteaux et al., 1988, 8(8) 2804–2815 with permission) [125]. (ii) Nuclear inclusion formation is frequently observed in transgenic mice expressing human αS. Boxed areas in left panel indicate areas shown in right panel. (Reprinted from *Science.* Masliah et al., 2000, 287(5456) 1265–1259 with permission) [126].

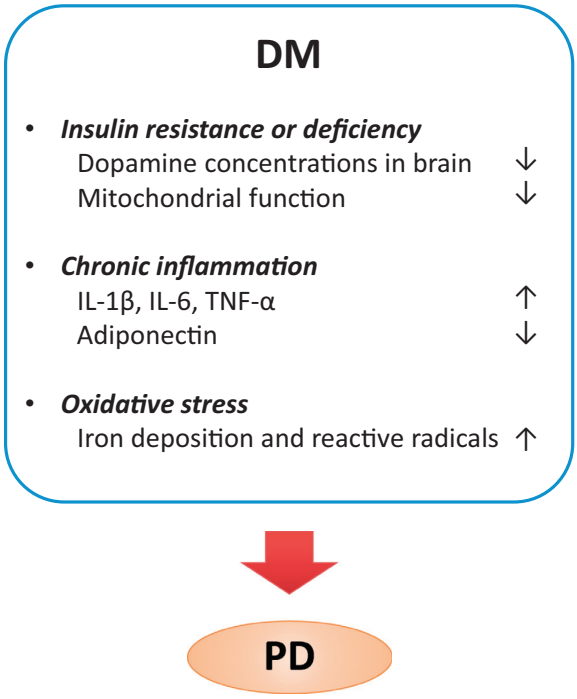

Fig. 5. Schematic of the relationship between DM and PD. DM may stimulate PD by various mechanisms.

the common pathologies between these two diseases, then it is probable that the progression of these diseases stimulate each other [120–122]. However, to the best of our knowledge, there are no reports showing that the progression of DM has been enhanced by neurodegenerative disorders. Therefore, a question is "Why is DM a risk factor for PD, while PD is not a risk factor for DM?" Since PD, a relatively common disease, is triggered by the more common DM, it is generally thought that PD may be situated downstream of DM. Such a relationship may be applicable to many types of diseases triggered by DM. Similar questions may arise for other diseases that are triggered by DM.

We hypothesize that one possible explanation for this question of how DM may be a risk factor for PD, is that some negative regulator systems, such as the adiponectin (APN) signaling pathway [123], might be involved (Fig. 5). We observed that APN was localized in Lewy bodies in postmortem brains derived from both PD and DLB patients, suggesting that APN might be involved in neurodegeneration. Furthermore, neurodegeneration was significantly ameliorated by APN treatment in both *in vitro* (neuronal cells) and *in vivo* (transgenic mouse) models of α-synucleinopathies. Collectively, these results suggest that APN, 'an anti-DM molecule' might be 'an anti-neurodegenerative molecule' and be could be a therapeutic candidate for the protection of α-synucleinopathies [124]. We hypothesize that expression of APN might be up-regulated under neurodegenerative conditions (This can explain the reason why PD does not trigger DM). However, increased levels of APN gradually become less protective until they are sequestered by αS into Lewy bodies (This may explain why APN is localized in the Lewy bodies in PD). Our hypothesis may provide an idea for a new type of therapy for PD. We need to investigate whether our hypothesis can be validated using the new genomic research tools, such as PD/DM GWAS.

7. Summary

Genomic approaches, such as positional cloning and GWAS, have greatly contributed to a better understanding of the mechanism of PD. The knowledge obtained from these studies will be valuable in the future for early diagnosis of PD, which will be essential to early treatment of PD. Furthermore, genomic research may play a key role in the therapy of PD. For example, some genomic approaches might be useful for identifying specific miRNAs as biomarkers and/or as therapeutic agents.

Although it is expected that development of new genomic tools will continue to profoundly change the field of PD, at least two issues must be emphasized. First, it is important to bear in mind that genomic approaches will not solve all the problems. Indeed, PD is not a simple disease that can be completely understood from only the point of genomic analyses. Although genomic studies usually can definitively confirm that the diagnosis of PD is correct, the correct diagnosis of PD is not easy. Indeed, PD is affected by a number of environmental factors. Furthermore, a recent study suggests that PD is stimulated by other age-associated disorders, such as type II DM. In this context, genomic studies on PD must progress cooperatively with other research tools, such as histology, cell biology, and biochemistry. Second, privacy and ethical concerns will become more important in the future. The availability of large genomic data sets raises concerns over information access, data security, and subject/patient privacy that must be addressed. Thus, the progress of genomic research may generate other issues which are rarely highlighted in research with conventional methodologies.

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