Mol Neurobiol (2013) 47:460–465
DOI 10.1007/s12035-012-8369-3

The Central Theme of Parkinson's Disease: α-Synuclein

Mehmet Ozansoy · A. Nazli Başak

Received: 22 October 2012 / Accepted: 22 October 2012 / Published online: 23 November 2012

Abstract Parkinson's disease (PD) is the second most common neurodegenerative disorder, defined by the presence of resting tremor, muscular rigidity, bradykinesia, and postural instability. PD is characterized by the progressive loss of dopaminergic neurons within the substantia nigra pars compacta of the midbrain. The neuropathological hallmark of the disease is the presence of intracytoplasmic inclusions, called Lewy bodies (LBs) and Lewy neurites (LNs), containing α-synuclein, a small protein which is widely expressed in the brain. The α-synuclein gene, SNCA, is located on chromosome 4q22.1; SNCA-linked PD shows an autosomal dominant inheritance pattern with a relatively early onset age, and it usually progresses rapidly. Three missense mutations, A53T, A30P, and E46K, in addition to gene multiplications of the SNCA have been described so far. Although it is clear that LBs and LNs contain mainly the α-synuclein protein, the mechanism(s) which leads α-synuclein to accumulate needs to be elucidated. The primary question in the molecular pathology of PD is how wild-type α-synuclein aggregates in PD, and which interacting partner (s) plays role(s) in the aggregation process. It is known that dopamine synthesis is a stressfull event, and α-synuclein expression somehow affects the dopamine synthesis. The aberrant interactions of α-synuclein with the proteins in the dopamine synthesis pathway may cause disturbances in cellular mechanisms. The normal physiological folding state of α-synuclein is also important for the understanding of pathological aggregates. Recent studies on the α-synuclein protein and genome-wide association studies of the α-synuclein gene show that PD has a strong genetic component, and both familial and idiopathic PD have a common denominator, α-synuclein, at the molecular level. It is clear that the disease process in Parkinson's disease, as in other neurodegenerative disorders, is very complicated; there can be several different molecular pathways which are responsible for diverse and possibly also unrelated functions inside the neuron, playing roles in PD pathogenesis.

Keywords Parkinson's disease · Genetics · α-Synuclein · Protein aggregation · Dopaminergic neurons

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease, affecting more than 1 % of the world population, aged 65 years. It has been traditionally suggested that PD is a multifactorial disease, a combination of genetic inheritance, aging, and environmental factors; but up to date, no environmental risk factor leading directly to PD pathogenesis has been found. Clinically, PD is defined by the presence of cardinal motor signs: resting tremor, muscular rigidity, bradykinesia, and postural instability. In addition, there are nonmotor characteristics like cognitive impairment, depression, olfactory deficits, psychosis, and sleep disturbance during the disease course [1–6].

Neuropathologically, PD is characterized by the progressive loss of dopaminergic neurons within the substantia nigra pars compacta of the midbrain. The motor deficit related to the disease becomes evident after approximately 80 % of striatal dopamine and 50 % of nigral neurons are lost [3, 6, 7]. The neuropathological hallmark of the disease is the presence of intracytoplasmic inclusions, called Lewy bodies (LBs) and

M. Ozansoy · A. N. Başak (✉)
Department of Molecular Biology and Genetics,
Neurodegeneration Research Laboratory (NDAL),
Boğaziçi University, Bebek,
Istanbul, Turkey
e-mail: basak@boun.edu.tr

Lewy neurites (LNs). The main component of LBs is α-synuclein, a small protein which is widely expressed in the brain [3, 7]. LNs are nerve cell processes containing protein aggregates which are also α-synuclein positive, and they are most widespread in the CA2/3 of the hippocampus and in the substantia nigra. LBs and LNs can be both characterized by using an α-synuclein specific antibody [7, 8].

A proposed and well-established six-stage progression of PD shows that the pathology is initially restricted to the medulla oblongata, pontine tegmentum, and olfactory bulb (stages 1–2). As the disease progresses, the nuclei in the midbrain, including substantia nigra, become affected (stages 3–4), and in later stages of PD (stages 5–6), the disease pathology spreads into the neocortex [1, 8].

Genetics of PD

PD was initially thought to be mainly sporadic without any genetic component. However, recent studies have shown that this is not true; approximately 20 % of patients with PD have a family history of the disease. The first gene linked to PD is α-synuclein (SNCA, PARK1 locus) which was discovered by Polymeropoulos et al. [9] through linkage analysis of a large multigenerational Italian family (the Contursi kindred) exhibiting an autosomal dominant inheritance pattern. Today, 18 chromosomal loci have been described for PD (Tables 1 and 2). Mutations occurring in six genes (SNCA, Parkin, DJ-1, PINK1, LRKK2, and ATP13A2) have been demonstrated to cause familial PD, while common polymorphisms in SNCA and LRRK2 are established as well-validated risk factors for the disorder [1, 2, 5].

This review will focus on the SNCA gene, its protein product α-synuclein, and its marked role in the molecular pathology of PD.

SNCA (PARK1/4)

SNCA, located on chromosome 4q22.1, has six exons encoding a 140-amino acid protein. The N-terminus of the protein consists of an amphipathical α-helical domain which associates with membranes such as presynaptic vesicles. The central part and the C-terminus contain fibrillization and aggregation inhibition regions, respectively (Fig. 1).

SNCA-linked PD shows an autosomal dominant inheritance pattern with a relatively early onset age, and it usually progresses rapidly [5]. Three missense mutations, duplications, and triplications of the SNCA have been described so far (Fig. 1). The A53T mutation of the Contursi kindred is the first α-synuclein mutation identified. Subsequent to the discovery of A53T, two further mutations in α-synuclein, A30P and E46K, were described in a German and a Spanish family, respectively [9–11]. Although rare, multiplications of the normal α-synuclein gene, e.g., duplications and triplications as a cause of PD, are of major relevance, because

Table 1 Genes/chromosomal loci linked to parkinsonism

Name of locus	Chromosome position	Gene	Inheritance pattern	Type of parkinsonism
Well-validated genes/loci				
PARK1/4	4q21	SNCA	AD	EOPD
PARK2	6q25.2-q27	Parkin	AR	Juvenile/EOPD
PARK6	1p35-p36	PINK1	AR	EOPD
PARK7	1p36	DJ-1	AR	EOPD
PARK8	12q12	LRRK2	AD (IP)	LOPD
PARK9	1p36	ATP13A2	AR	Kufor–Rakeb syndrome
Putative genes/loci				
PARK3	2p13	Unknown	AD	LOPD
PARK5	4p14	UCHL1	AD	LOPD
PARK10	1p32	Unknown	Not clear	LOPD
PARK11	2q36-q37	GIGYF2	AD (IP)	LOPD
PARK12	Xq21-q25	Unknown	Not clear	Not clear
PARK13	2p12	Omi/HTRA2	Not clear	Not clear
PARK14	22q13.1	PLA2G6	AR	AO dystonia–parkinsonism
PARK15	22q12-q13	FBXO7	AR	EO parkinsonian pyramidal syndrome

AD autosomal dominant, *AR* autosomal recessive, *EOPD* early-onset PD, *LOPD* late-onset PD, *IP* incomplete penetrance, *AO* adult onset, *EO* early onset [1]

Table 2 Susceptibility genes/loci for PD

Name of locus	Chromosome position	Gene	Risk variants
Well-validated genes/loci			
PARK1/4	4q21	SNCA	REP1 repeat polymorphism and multiple SNPs in 3′ half of the gene
PARK8b	12q12	LRRK2	G2385R, R1628P
Not assigned	17q21.1	MAPT	H1 haplotype
Not assigned	1q21	GBA	>300 mutations including N370S and L444P
Putative genes/loci			
PARK16	1q32	Unknown	Multiple SNPs from GWAS
PARK17	4p16	GAK	Multiple SNPs from GWAS
PARK18	6p21.3	HLA-DRA	Multiple SNPs from GWAS

SNP single nucleotide polymorphism, *GWAS* genome wide association studies [1]

they prove that not only the mutated but also the wildtype α-synuclein is pathogenic if overexpressed [3, 12–14].

The progression of PD exhibits mutation-specific differences. Patients carrying the A53T mutation, for example, have a relatively early onset age and severe parkinsonism with a frequent dementia, while carriers of the A30P mutation show typical late-onset PD with late and mild form of dementia [10, 15]. E46K patients, on the other hand, have a very similar clinical picture of A53T carriers [11]. In addition to the differences in clinical picture of point mutations in the SNCA, duplications and triplications of the gene also display differences. SNCA duplications cause late-onset typical PD with dopa-responsiveness, whereas triplications of the gene lead to more severe disease with dementia, rapid progression, and earlier onset age [16, 17]. These differences may be caused by the dosage differences of the SNCA.

In addition to the mutations in the SNCA gene, there are some variants identified in genome-wide association studies (GWAS), conferring susceptibility to PD. The effects of these susceptibility variants include altered control of the level of transcription of the SNCA gene, regulation of alternative splicing, or altered mRNA stability through post-transcriptional mechanisms. REP1 is a polymorphic dinucleotide repeat site, located 10 kb upstream of the transcriptional start site of SNCA, and five different alleles of REP1 have been identified (Fig. 2). This polymorphic region has been found to be related to PD susceptibility through affecting the expression level of the SNCA. In addition, there are SNPs located at the 3′-end of the gene, and two of them are outside the coding region. The striking point is that a risk allele of REP1, which affects the SNCA expression in cell culture and animal models, is in linkage disequilibrium with the SNPs identified at the 3′-end. Thus, it is unclear whether the REP1 allele alone or the haplotype including the REP1 allele and these SNPs together confer genetic risk for PD [18, 19].

Another possible mechanism related to SNPs is the alteration of gene expression by changes in alternative splicing. Recent studies show that alternatively spliced isoforms of SNCA lead to the generation of four different SNCA protein isoforms, depending on the inclusion of exons 3 and 5: exon $3^{+}5^{+}$ (140 aa; SNCA140), exon $3^{-}5^{+}$ (126 aa; SNCA126), exon $3^{+}5^{-}$ (112 aa; SNCA112), and exon $3^{-}5^{-}$ (98 aa; SNCA98) (Fig. 3). One isoform, SNCA112, has been shown to occur only in the brains of patients with Lewy body disease, and it has also been demonstrated that SNCA112 is found to be upregulated in cell culture studies when the parkinsonian toxins, MPTP and rotenone, are applied [6–10].

The third proposed mechanism is the presence of three SNPs located around the 3′-UTR of the gene. The 3′-UTR of SNCA consists of binding sites for two miRNAs (mir-7 and mir-153), and it is also known that these miRNAs are widely expressed in neurons and control the downregulation of the SNCA gene [9–12, 14, 18].

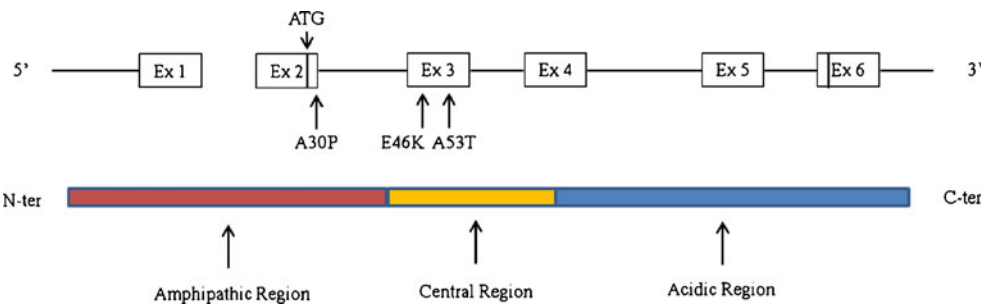

Fig. 1 The SNCA gene and its protein structure. ATG indicates the start codon. *Ex* exon [1]

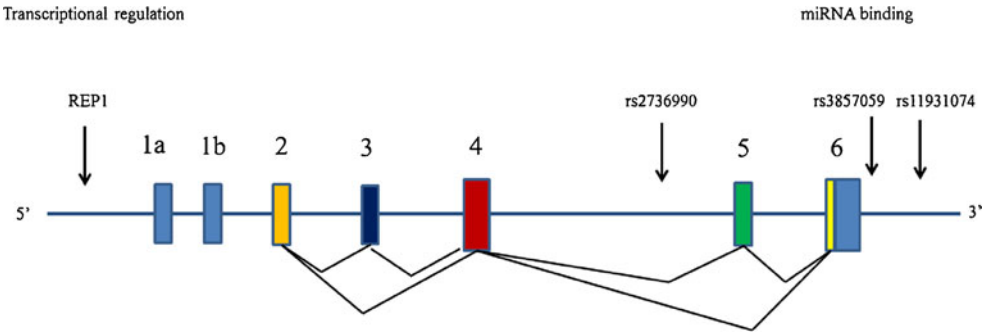

Fig. 2 Alternative splicing pattern of the SNCA gene. The positions of REP1 repeat region and SNPs in the 3′-end [18]

Protein Interactions of α-synuclein

Although α-synuclein is widely expressed in the brain, PD-associated degeneration occurs in specific regions of the central nervous system, affecting predominantly the substantia nigra pars compacta. Thus, the central question of PD pathology is why and how the genetic variation in the SNCA gene leads to the degeneration of a specific cell population (dopaminergic neurons) in the brain. One approach to this problem is that the main metabolic function of the relevant cells, namely dopamine production, may confer a vulnerability to the neurons degenerating in PD [2, 11, 12, 14, 18].

It has been shown that α-synuclein interacts with tyrosine hydroxylase (TH), which is the rate-limiting enzyme in dopamine synthesis, and, with this interaction, α-synuclein regulates the production of dopamine. Alpha-synuclein has been reported to bind to TH, preventing its phosphorylation, and, by increasing the activity of protein phosphatase 2A (PP2A), it inhibits the TH activation. In addition, α-synuclein overexpression has been shown to reduce the activity of the TH promoter in cell culture models. On the other hand, a decrease in α-synuclein expression leads to an increase in TH phosphorylation, and, by this way, TH activity increases. It has also been demonstrated that α-synuclein interacts with L-aromatic amino acid decarboxylase (AADC), an enzyme which catalyzes the conversion of L-DOPA to dopamine. Alpha-synuclein overexpression reduces the AADC activity by decreasing the phosphorylation of the enzyme [12, 18, 20, 21].

Several studies show that age could be an important factor in the dysfunction of dopamine metabolism. Alpha-synuclein null mice exhibit a slight dopamine decrease (~18 %) or no change at all. Dopamine decrease becomes more pronounced (~36 %) when the α-synuclein null mice age to 24–26 months compared to that in wild-type littermates. Dopamine reduction is observed with the decrease in TH and dopamine transporter expressions [18, 20–24]. Another important point, which may be related to the dopamine metabolism, is the possible link of α-synuclein and apoptosis. It has been demonstrated that α-synuclein accumulation in cultured human dopaminergic neurons results in apoptosis in the presence of dopamine synthesis and reactive oxygen species. Dopamine-related neurotoxicity is mediated by intracellular protein complexes (54–83 kDa) containing α-synuclein and the 14-3-3 protein in the substantia nigra pars compacta of the PD brain [25].

It has been shown that α-synuclein induces the fibrillization of tau protein in vitro, and in vivo studies on mice indicate that mutant α-synuclein expression leads to the filamentous inclusions of both α-synuclein and tau. These findings suggest that a possible interaction between α-synuclein and tau drives the formation of pathological inclusions [26]. The Lewy body inclusions in PD consist of a RING-type E3 ubiquitin ligase SIAH1 besides α-synuclein and other proteins, and it has been found that endogenous SIAH1 and α-synuclein co-localized in cell bodies and neurites of PC12 cells and mouse cortical neurons [27, 28]. Moreover, SIAH1 has been observed with UBCH8 (human brain-enriched E2 ubiquitin-conjugating enzyme), and it facilitates mono- and di-ubiquitination of α-synuclein [27]. This SIAH1-mediated ubiquitination of α-synuclein does not target it to proteasome for degradation, but it rather promotes its aggregation.

Recent studies also showed that α-synuclein plays a role in the trafficking of presynaptic vesicles. Burre et al. [29] reported that presynaptic SNARE complex assembly requires the presence of α-synuclein, which binds to the synaptobrevin-2/vesicle-associated membrane protein-2 (VAMP2).

It has long been considered that α-synuclein is a "natively unfolded" protein, and it only gains a secondary structure (α-helical) when it binds to presynaptic vesicles. However,

Fig. 3 Different isoforms of SNCA produced from alternative splicing [18]

Bartels et al. [30] proposed that this definition could be a result of in vitro studies which obviously have some built-in disadvantages, for example, widespread use of bacterial expression protocols and denaturing conditions of experimental procedures. This laboratory demonstrated that, under non-denaturing conditions, endogenously expressed α-synuclein, isolated from living human cells, exists as a folded tetramer of 58 kDa. Recombinantly expressed α-synuclein forms amyloid-like fibrils, whereas native α-synuclein tetramers show no amyloid-like aggregation pattern. According to this finding, it appears that misfolding and aggregation of α-synuclein could not be the primary cause of PD pathology, and the destabilization mechanisms, preceding α-synuclein misfolding of natively folded tetramers, may be the new starting point for PD pathology [30].

Conclusion

It is well established that Parkinson's disease has a strong genetic component, and its neuropathology is also widely known. On the other hand, the molecular mechanisms responsible for the degeneration of dopaminergic neurons remain largely elusive. Although it is clear that LBs and LNs contain mainly the α-synuclein protein, the mechanism(s) which leads the α-synuclein to accumulate needs to be elucidated. One of the burning questions concerning the molecular pathology of PD is how wild-type α-synuclein aggregates in sporadic PD cases, and related to this question, which interacting partner(s) plays role(s) in the aggregation process. Another important point is the cellular context in which degeneration occurs, namely the dopaminergic neurons. It is known that dopamine synthesis is a stressfull event, and several studies have shown that α-synuclein expression somehow affects the dopamine synthesis. The aberrant interactions of α-synuclein with the proteins in the dopamine synthesis pathway may cause small disturbances, which can be corrected by the neuron, but as the neurons age, the repair/correction mechanisms are overwhelmed and the accumulated abnormalities may cause the neuron to degenerate and die. This "accumulated errors" approach is also supported by the late-onset nature of PD and its possible relation to aging.

The gene encoding α-synuclein (SNCA/PARK1) was the first gene to be associated with Parkinson's disease. This discovery not only transformed the whole field of PD research, but it also converted the historically pure idiopathic PD to a complex disorder with a non-negligable genetic component. Subsequent research efforts in the last decade yielded remarkable insights into the role of α-synuclein in neurodegeneration, and, today, several lines of evidence demonstrate a central role of α-synuclein in the pathogenesis of Parkinson's disease. This is because α-synuclein is not only the principal component of LBs in both familial and idiopathic PD and further the first gene mutations/multiplications in which unambiguously linked to Parkinson's disease, but α-synuclein is also one of the major genes most consistently associated with PD in the GWAS studies conducted recently. These findings have started to blur the distinction between familial and idiopathic disease and may pave the ways to understand the complicated and partly overlapping molecular mechanisms effective in both familial and idiopathic Parkinson's disease.

Acknowledgment We would like to thank Boğaziçi University Research Funds and TÜBİTAK (108T179) for their financial support. The invaluable contribution of Suna and İnan Kıraç Foundation to our research is especially acknowledged.

References

1. Bekris LM, Mata IF, Zabetian CP (2010) The genetics of parkinson disease. J Geriatr Psychiatry Neurol 23:228–242
2. Dickson DW, Fujishiro H, Orr C, DelleDonne A, Josephs KA, Frigerio R, Burnett M, Parisi JE, Klos KJ, Ahlskog JE (2009) Neuropathology of non-motor features of parkinson disease. Parkinsonism Relat Disord 15(Suppl. 3):S1–S5
3. Gasser T (2010) Identifying PD-causing genes and genetic susceptibility factors: current approaches and future prospects. Prog Brain Res 183:3–20
4. Gasser T, Hardy J, Mizuno Y (2011) Milestones in PD genetics. Mov Disord 26(6):1042–1048
5. Spillantini MG, Schmidt ML, Lee VM, Trojanowski JQ, Jakes R, Goedert M (1997) Alpha-synuclein in Lewy bodies. Nature 388:839–840
6. Wolters E (2009) Non-motor extranigral signs and symptoms in Parkinson's disease. Parkinsonism Relat Disord 15(Suppl. 3):S6–S12
7. Gasser T (2009) Molecular pathogenesis of Parkinson disease: ınsights from genetic studies. Expert Rev Mol Med 11:E22
8. Sulzer D (2007) Multiple hit hypotheses for dopamine neuron loss in Parkinson's disease. Trends Neurosci 30:244–250
9. Polymeropoulos MH, Lavedan C, Leroy E, Ide SE, Dehejia A, Dutra A, Pike B, Root H, Rubenstein J, Boyer R, Stenroos ES, Chandrasekharappa S, Athanassiadou A, Papapetropoulos T, Johnson WG, Lazzarini AM, Duvoisin RC, Di Iorio G, Golbe LI, Nussbaum RL (1997) Mutation in the alpha-synuclein gene ıdentified in families with Parkinson's disease. Science 276:2045–2047
10. Krüger R, Kuhn W, Müller T, Woitalla D, Graeber M, Kösel S, Przuntek H, Epplen JT, Schöls L, Riess O (1998) Ala30Pro mutation in the gene encoding alpha-synuclein in Parkinson's disease. Nat Genet 18:106–108
11. Zarranz JJ, Alegre J, Gómez-Esteban JC, Lezcano E, Ros R, Ampuero I, Vidal L, Hoenicka J, Rodriguez O, Atarés B, Llorens V, Gomez Tortosa E, del Ser T, Muñoz DG, de Yebenes JG (2004) The new mutation, E46K, of alpha-synuclein causes Parkinson and Lewy body dementia. Ann Neurol 55:164–173
12. Chartier-Harlin MC, Kachergus J, Roumier C, Mouroux V, Douay X, Lincoln S, Levecque C, Larvor L, Andrieux J, Hulihan M, Waucquier N, Defebvre L, Amouyel P, Farrer M, Destée A (2004) Alpha-synuclein locus duplication as a cause of familial parkinson's disease. Lancet 364:1167–1169
13. Pirkevi C (2009) Parkinson's disease in Turkish patients: molecular defects in familial and isolated cases. Boğaziçi University, Dissertation

14. Singleton AB, Farrer M, Johnson J, Singleton A, Hague S, Kachergus J, Hulihan M, Peuralinna T, Dutra A, Nussbaum R, Lincoln S, Crawley A, Hanson M, Maraganore D, Adler C, Cookson MR, Muenter M, Baptista M, Miller D, Blancato J, Hardy J, Gwinn-Hardy K (2003) Alpha-synuclein locus triplication causes Parkinson's disease. Science 302:841
15. Spira PJ, Sharpe DM, Halliday G, Cavanagh J, Nicholson GA (2001) Clinical and pathological features of a parkinsonian syndrome in a family with an Ala53Thr alpha-synuclein mutation. Ann Neurol 49:313–319
16. Fuchs J, Nilsson C, Kachergus J, Munz M, Larsson EM, Schlüle B, Langston JW, Middleton FA, Ross OA, Hulihan M, Gasser T, Farrer MJ (2007) Phenotypic variation in a large swedish pedigree due to SNCA duplication and triplication. Neurology 68(12):916–922
17. Ibáñez P, Lesage S, Janin S, Lohmann E, Durif F, Destée A, Bonnet AM, Brefel-Courbon C, Heath S, Zelenika D, Agid Y, Dürr A, Brice A (2009) Alpha-synuclein gene rearrangements in dominantly ınherited parkinsonism: frequency, phenotype and mechanisms. Arch Neurol 66(1):102–108
18. Venda LL, Cragg SJ, Buchman VL, Wade-Martins R (2010) Alpha-synuclein and dopamine at the crossroads of Parkinson's disease. Trends Neurosci 33:559–568
19. Simón-Sánchez J, Schulte C, Bras JM, Sharma M, Gibbs JR, Berg D, Paisan-Ruiz C, Lichtner P, Scholz SW, Hernandez DG, Krüger R, Federoff M, Klein C, Goate A, Perlmutter J, Bonin M, Nalls MA, Illig T, Gieger C, Houlden H, Steffens M, Okun MS, Racette BA, Cookson MR, Foote KD, Fernandez HH, Traynor BJ, Schreiber S, Arepalli S, Zonozi R, Gwinn K, van der Brug M, Lopez G, Chanock SJ, Schatzkin A, Park Y, Hollenbeck A, Gao J, Huang X, Wood NW, Lorenz D, Deuschl G, Chen H, Riess O, Hardy JA, Singleton AB, Gasser T (2009) Genome-wide association study reveals genetic risk underlying Parkinson's disease. Nat Genet 41(12):1308–12
20. Baptista MJ, O'Farrell C, Daya S, Ahmad R, Miller DW, Hardy J, Farrer MJ, Cookson MR (2003) Coordinate transcriptional regulation of dopamine synthesis genes by alpha-synuclein in human neuroblastoma cell lines. J Neurochem 85:957–968
21. Yu S, Zuo X, Li Y, Zhang C, Zhou M, Zhang YA, Uéda K, Chan P (2004) Inhibition of tyrosine hydroxylase expression in alpha-synuclein-transfected dopaminergic neuronal cells. Neurosci Lett 367:34–39
22. Kirik D, Rosenblad C, Burger C, Lundberg C, Johansen TE, Muzyczka N, Mandel RJ, Björklund A (2002) Parkinson-like neurodegeneration ınduced by targeted overexpression of alpha-synuclein in the nigrostriatal system. J Neurosci 22:2780–2791
23. Masliah E, Rockenstein E, Veinbergs I, Mallory M, Hashimoto M, Takeda A, Sagara Y, Sisk A, Mucke L (2000) Dopaminergic loss and ınclusion body formation in alpha-synuclein mice: ımplications for neurodegenerative disorders. Science 287:1265–1269
24. Peng X, Tehranian R, Dietrich P, Stefanis L, Perez RG (2005) Alpha-synuclein activation of protein phosphatase 2A reduces tyrosine hydroxylase phosphorylation in dopaminergic cells. J Cell Sci 118:3523–3530
25. Xu J, Kao SY, Lee FJS, Song W, Jin LW, Yankner BA (2002) Dopamine-dependent neurotoxicity of alpha-synuclein: a mechanism for selective neurodegeneration in Parkinson disease. Nature Med. 8:600–606
26. Giasson BI, Forman MS, Higuchi M, Golbe LI, Graves CL, Kotzbauer PT, Trojanowski JQ, Lee VM-Y (2003) Initiation and synergistic fibrillization of tau and alpha-synuclein. Science 300:636–640
27. Lee JT, Wheeler TC, Li L, Chin L-S (2008) Ubiquitination of alpha-synuclein by Siah-1 promotes alpha-synuclein aggregation and apoptotic cell death. Hum Molec Genet 17:906–917
28. Liani E, Eyal A, Avraham E, Shemer R, Szargel R, Berg D, Bornemann A, Riess O, Ross CA, Rott R, Engelender S (2004) Ubiquitylation of synphilin-1 and alpha-synuclein by SIAH and ıts presence in cellular ınclusions and Lewy bodies ımply a role in Parkinson's disease. Proc Nat Acad Sci 101:5500–5505
29. Burre J, Sharma M, Tsetsenis T, Buchman V, Etherton MR, Sudhof TC (2010) Alpha-synuclein promotes SNARE-complex assembly ın vivo and ın vitro. Science 329:1663–1667
30. Bartels T, Choi JG, Selkoe DJ (2011) Alpha-synuclein occurs physiologically as a helically folded tetramer that resists aggregation. Nature 477:107–111