Neurobiology of Aging xxx (2014) 1–14

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

Review

The link between the SNCA gene and parkinsonism

Wei Xu [a], Lan Tan [a,b,c,*], Jin-Tai Yu [a,b,c,*]

[a] Department of Neurology, Qingdao Municipal Hospital, School of Medicine, Qingdao University, Qingdao, Shandong Province, China
[b] Department of Neurology, Qingdao Municipal Hospital, College of Medicine and Pharmaceutics, Ocean University of China, Qingdao, Shandong Province, China
[c] Department of Neurology, Qingdao Municipal Hospital, Nanjing Medical University, Nanjing, Jiangsu Province, China

ARTICLE INFO

Article history:
Received 5 April 2014
Received in revised form 30 October 2014
Accepted 31 October 2014

Keywords:
SNCA
Parkinsonism
Genetics
Epigenetics
Mechanism
Therapy

ABSTRACT

The groundbreaking discovery of mutations in the SNCA gene in a rare familial form of Parkinson's disease (PD) has revolutionized our basic understanding of the etiology of PD and other related disorders. Genome-wide Association Studies has demonstrated a wide array of single-nucleotide polymorphisms associated with the increasing risk of developing the more common type, sporadic PD, further corroborating the genetic etiology of PD. Among them, *SNCA* is a gene responsible for encoding α-synuclein, a protein found to be the major component of Lewy body and Lewy neurite, both of these components are the pathognomonic hallmarks of PD. Thus, it has been postulated that this gene plays specific roles in pathogenesis of PD. Here, we summarize the basic biological characteristics of the wild type of the protein (wt-α-synuclein) as well as genetic and epigenetic features of its encoding gene (*SNCA*) in PD. Based on these characteristics, *SNCA* may be involved in PD pathogenesis in at least 2 ways: wt-α-synuclein overexpression and its mutation types via different mechanisms. Associations between *SNCA* mutations and other Lewy body disorders, such as dementia with Lewy bodies and multiple system atrophy, are also mentioned. Finally, it is necessary to explore the influences which *SNCA* exerts on clinical and neuropathological phenotypes by promoting the transfer of scientific research into practice, such as clinical evaluation, diagnosis, and treatment of the disease. We believe it is promising to target *SNCA* for developing novel therapeutic strategies for parkinsonism.

1. Introduction

As an umbrella concept, parkinsonism (also known as Parkinson's syndrome) is defined as a movement-related neurologic syndrome characterized by asymmetrical resting tremor, hypokinesis, rigidity, and postural instability, all of which can be typically found in Parkinson's disease (PD) (Massano and Bhatia, 2012). Among all heterogeneous causes of parkinsonism, PD (also known as idiopathic or primary parkinsonism) is the most common one and also the second most prevalent progressive neurodegenerative disease after Alzheimer's disease.

PD was historically referred to as a solely environment-mediated disease. Since 1997, the groundbreaking demonstration of the genetic background of rare familial PD (accounting for 5%–10% of PD patients) via linkage analyses and of more common sporadic PD (90%–95% of PD cases) via association studies has refreshed our knowledge about the entity and complexity of genetic underpinning of PD (Burbulla and Kruger, 2011; Tsuboi, 2012). Although, hundreds of single-nucleotide polymorphisms (SNPs) located in *SNCA* have been reported to be associated with sporadic PD with distinct *p*-values. Also, missense (A53T, A30P, E46K, H50Q, and G51D) (Appel-Cresswell et al., 2013; Kiely et al., 2013; Kruger et al., 1998; Polymeropoulos et al., 1996; Zarranz et al., 2004) and multiplication mutations (duplication and triplication) (Chartier-Harlin et al., 2004; Singleton et al., 2003) of the gene have been reliably linked to early-onset autosomal dominant familial PD. On the other hand, core role of synucleinopathy in etiology of PD has been established (Mullin and Schapira, 2013), and the expression product of the gene (α-synuclein) has been confirmed as the major component of Lewy body (LB) and Lewy neurite which are pathognomonic hallmarks of PD. Also, evidence shows that these proteins contribute to the selective and progressive loss of dopaminergic neurons in substantia nigra pars compacta in PD (Hoehn and Yahr, 1998). It is thus of substantial significance to investigate the roles of *SNCA* in parkinsonism, particularly in PD.

* Corresponding authors at: Department of Neurology, Qingdao Municipal Hospital, School of Medicine, Qingdao University, No.5 Donghai Middle Road, Qingdao, Shandong Province 266071, China. Tel./fax: +86-0532-88905659.
E-mail addresses: dr.tanlan@163.com (L. Tan), yu-jintai@163.com (J.-T. Yu).

0197-4580/$ – see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.neurobiolaging.2014.10.042

Herein, we will summarize the biochemical properties of SNCA (α-synuclein) as well as the genetics and epigenetic modulations of SNCA gene in PD. Special focus will be put on the preliminary discussion of the potential mechanisms by which *SNCA* contribute to occurrence of parkinsonism. We also review *SNCA* mutation in other LB disorders such as dementia with Lewy bodies (DLB) and multiple system atrophy (MSA). At last, clinical features and neuropathological findings in *SNCA*-associated parkinsonism are outlined. Potential values of *SNCA* in clinical evaluation, diagnosis, and treatment for PD are emphasized. (Fig. 1).

2. Biochemical properties of SNCA

α-Synuclein was initially identified in senile plaque and thus initially named nonamyloid component of plaque. This protein is encoded by *SNCA*, which contains 114 kb and located on chromosome 4q22.1 (ENSG00000145335, chromosome 4: 90,645,250–90,759,466 reverse strand). (Fig. 2) UCSC gene data (http://genome.ucsc.edu/index.html) show that *SNCA* comprises 6 exons, the latter 5 of which correspond with a coding region as translational initiation codon (autophagy-related genes, ATG) are situated in exon 2, whereas termination codon (TAA) is located in exon 6. (Fig. 2) The full length and also the major transcript are composed of 140 amino acids (aa). At least 3 other truncated transcripts which have distribution of regional characteristics in PD (Cardo et al., 2014; McLean et al., 2012) are produced via alternative splicing (in-frame deletions of exon 3 and/or 5): 126 aa (5^+, 3^-), 112 aa (5^-, 3^+), and 98aa (3^-, 5^-) (Pihlstrom and Toft, 2011) (Fig. 2). Additionally, according to Ensembl Genome (http://www.ensembl.org) and Vega Genome database (http://vega.sanger.ac.uk), another 2 transcripts (67 aa and 115 aa) exist, although we have not found their way of transcription yet. Also, it is inconclusive whether there is difference among these isoforms in influencing pathogenesis in PD.

In the whole synuclein family (including α-, β-, and γ-synuclein), α-synuclein is by far the sole member found to be implicated in etiology of neurodegenerative diseases (such as Alzheimer's disease, PD, DLB, and MSA) in a manner known as synucleinopathy. α-Synuclein, comprising 140 amino acid residues, is a natively soluble fibrillogenic protein, and it is predominantly enriched in the presynaptic terminal either in soluble unstructured form or in connection with phospholipid membranes, particularly with synaptic vesicles (Clayton and George, 1998). These 2 existing states have a close relationship with synucleinopathy. First, the junction state will protect the protein from further aggregation. When binding to the water-lipid interface carrying a negative net charge, it can be transformed into a specific conformation comprising 3 subsections: the N-terminus of the protein composed of an amphipathic α-helical domain which binds the membranes in a parallel way, the central part region (non-amyloid β component, NAC) and the glutamate-rich acidic C-terminus which harbors fibrillation and aggregation inhibition region (Ozansoy and Basak, 2013). Furthermore, it is worthy to note that intracellular α-synuclein binds preferentially to structures with constrained size and high curvature (such as vesicles and mitochondria) (Nuscher et al., 2004) (Fig. 3).

Second, the role of free-state protein in synucleinopathy may depend on the concrete form of α-synuclein. Although debates concerning the native conformation of wild-type α-synuclein (wt-α-synuclein) exist, depicting it either as a helically folded tetramer against aggregation (Bartels et al., 2011; Wang et al., 2011) or as a disordered monomer (Fauvet et al., 2012; Gould et al., 2014) with a propensity of aggregation, recent studies suggest that meta-stable helical tetramer of α-synuclein keeps a dynamic equilibrium with unfolded monomers (Coelho-Cerqueira et al., 2013; Selkoe et al., 2014). This suggests that the tetrameric state may provide a potential protective mechanism by tuning up total quantity of α-synuclein monomers and therefore inhibiting its further aggregation (Gurry et al., 2013). Also, it can be postulated that disassociation of the tetramer acts as an obligatory gateway for formation of pathologic inclusion (Fig. 3).

In terms of its physiological functions, increasing evidence shows that α-synuclein plays an important role in transmembrane transport and intracellular trafficking (Eisbach and Outeiro, 2013). For example, α-synuclein may promote the cellular transport by facilitating the accumulation of synaptic vesicles at the active zone (Diao et al., 2013), interacting with heat shock proteins (Witt, 2013) and prenylated Rab acceptor protein 1 (Lee et al., 2011), thus sustaining normal SNARE-complex assembly (Burre et al., 2010) and modulating the state of actin polymerization (Bellani

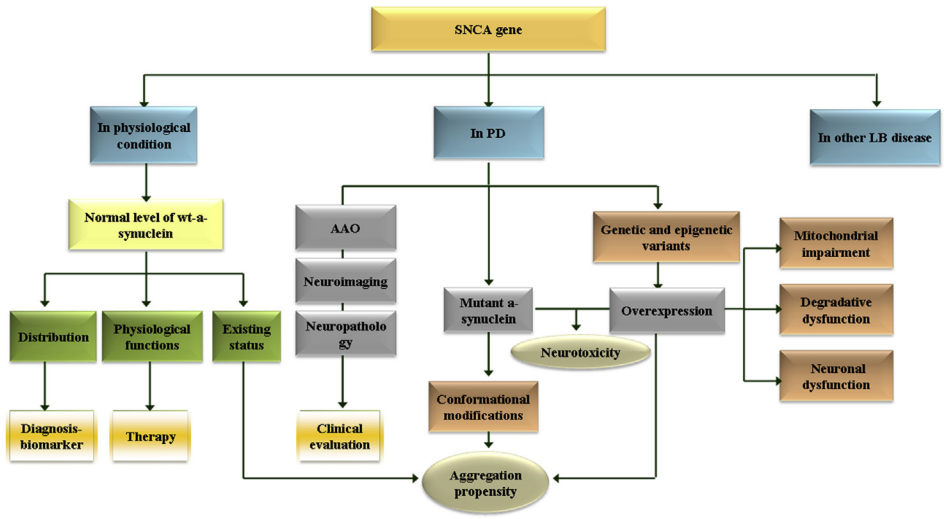

Fig. 1. Graphic abstract. In this article, we summarized the biochemical properties of SNCA (α-synuclein) as well as the genetics and epigenetic modulations of SNCA gene in PD. Accordingly, SNCA gene may be involved in PD pathogenesis via 2 main manners: overexpression of wt α-synuclein and its mutant types per se. We also review *SNCA* mutation in other LB disorders. Finally, potential values of *SNCA* in clinical evaluation, diagnosis, and treatment for PD is emphasized. Abbreviations: AAO, age at onset; LB, Lewy body; PD, Parkinson's disease. (For interpretation of the references to color in this figure, the reader is referred to the Web version of this article.)