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Review article

Deregulation of α-synuclein in Parkinson's disease: Insight from epigenetic structure and transcriptional regulation of *SNCA*

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ABSTRACT

Understanding regulation of α-synuclein has long been a central focus for Parkinson's disease (PD) researchers. Accumulation of this protein in the Lewy body or neurites, mutations in the coding region of the gene and strong association of α-synuclein encoding gene multiplication (duplication/triplication) with familial form of PD have indicated the importance of this molecule in pathogenesis of the disease. Several years of research identified many potential faulty pathways associated with accumulation of α-synuclein inside dopaminergic neurons and its transmission to neighboring ones. Concurrently, an appreciable body of research is growing to understand the epigenetic and genetic deregulation of α-synuclein that might contribute to the disease pathology. Completion of the ENCODE (Encyclopedia of DNA Elements) project and recent advancement made in the epigenetic and trans factor mediated regulation of each gene, has tremendously accelerated the need to carefully understand the epigenetic structure of the gene (SNCA) encoding α-synuclein protein in order to decipher the regulation and contribution of α-synuclein to the pathogenesis of PD. We have also analyzed the detailed epigenetic structure of this gene with knowledge from ENCODE database, which may open new avenues in α-synuclein research. Interestingly, we have found that the gene contains several transcriptionally activate histone modifications and associated potential transcription factor binding sites in the non-coding areas that strongly suggest alternative regulatory pathways. Altogether this review will provide interesting insight of α-synuclein gene regulation from epigenetic, genetic and post-transcriptional perspectives and their potential implication in the PD pathogenesis.

Contents

Abbreviations: α-SYN, α-synuclein; CGI, CpG island; CTD, c-terminal domain; DA, dopaminergic neurons; DLB, Diffuse Lewy Body; ENCODE, Encyclopedia of DNA Elements; EOPD, early onset Parkinson's disease; GWAS, genome-wide association studies; H3K4me1, Histone H3-lysine 4 monomethylation; H3K4me3, Histone H3-lysine 4 trimethylation; H3K27me3, histone H3 lysine 27 trimethylation; H3K9ac, hitone lysine 9 acetylation; H3K27ac, histone lysine 27 acetylation; H3K36me3, histone H3 lysine 36 trimethylation; L-DOPA, L-3,4-dihydroxyphenylalanine; LD, linkage disequilibrium; miRNA, micro RNA; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; PD, Parkinson's disease; PARP-1, Poly (ADP Ribose) Polymerase-1; PTM, post translational modification; QTL, Quantitative Trait Locus; SAM, S-adenosyl methionine; SAH, S-adenosyl homocysteine; *SNCA*, [synuclein, alpha (non A4 component of amyloid precursor)]; SNpc, substantia nigra pars compacta; SNP, single nucleotide polymorphisms; UTR, untranslated region.

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1. Introduction

Parkinson's disease (PD) is a late-onset neurodegenerative disease that affects a significant portion of elderly populations worldwide (Beitz, 2014). Recent epidemiological data suggests this disease is increasing every year, with 50,000 to 60,000 new cases in the USA alone in addition to the 1 million patients already suffering (National Parkinson's Disease Foundation; http://www.pdf.org/en/parkinson_statistics) (Beitz, 2014). The clinical features of the disease include cardinal motor dysfunctions, such as postural instability, resting tremor, bradykinesia, and rigidity (Beitz, 2014; Sherer et al., 2012; Thomas and Beal, 2011). In conjunction, several non-motor symptoms are also associated with the disease: anosmia, sleep disturbances, anxiety or depression, loss of bladder control, constipation, etc. (Beitz, 2014; Sherer et al., 2012; Thomas and Beal, 2011). PD cases are generally classified under two categories based on its origin. The first type contains a known or inherited familial genetic abnormalities, called familial PD (autosomal dominant or recessive). This accounts for only 10% or less of the total cases. The second type is called sporadic PD cases without any known familial history and consists of around 90% or more of the cases, (Gasser, 2009). Generally, degeneration of around 70% dopaminergic (DA) neurons in the *substantia nigra pars compacta* (SNpc) of the midbrain region takes place before the clinical symptoms sets in (Heisters, 2011; Morrish et al., 1998; Postuma et al., 2010). Recently Kordower et al. in a report studied 28 *post-mortem* brain samples ranging from 1 to 27 years post diagnosis of PD and showed that 50% to 90% of tyrosine hydroxylase(TH)-positive DA neuronal death in the SNpc occurs within relatively early years after the disease diagnosis and negligible loss (<20%) thereafter. Interestingly, although a variable degree of loss (33%-80%) of nigral melanin-containing neurons was observed across the disease duration, there was higher number of melanin containing neurons remained as compared to TH-positive neurons at any point analysis (Kordower et al., 2013).

One of the most prominent pathophysiological hallmarks of this disease is the presence of intracytoplasmic inclusion bodies called Lewy bodies, or Lewy neurites (Spillantini et al., 1997). These inclusion bodies are present in the neurons containing α-synuclein (α-SYN) aggregates (Spillantini et al., 1997). The dynamic process of α-SYN aggregation through the formation of different intermediate species mainly contributes to α-synucleinopathy in PD (Stefanis, 2012). The contribution of α-SYN in the disease pathogenesis is further highlighted by the discovery of the genetic components in PD, which first came into the picture through genetic abnormalities in the α-SYN coding gene called *SNCA*, when familial mutations and gene multiplications were discovered in that particular locus (Farrer et al., 2004; Ibanez et al., 2004; Kruger et al., 1998; Polymeropoulos et al., 1997; Singleton et al., 2003; Zarranz et al., 2004). Later on, numerous other genetic or environmental factors—such as imbalances in genetic dosage, post-translational modifications, exposure to toxins and pesticides/herbicides, oxidative stress and more recently, epigenetic deregulation—have been implicated in dysregulation of α-SYN in PD (Basu et al., 2015; Cristovao et al., 2012; Guhathakurta et al., 2017; Mouradian, 2012; Tanner et al., 2011; Venda et al., 2010). These factors have been either implicated in increased α-SYN protein expression or in the generation of misfolded intermediates of the protein, which ultimately contribute to α-synucleinopathy in PD. Altogether, it can be said that environmental factors and age-associated changes—along with some common genetic variants identified through candidate gene approach or whole genome association studies—play important roles in the pathogenesis of the sporadic form of the disease (Gasser et al., 2011).

A lot of effort has been made over the years to understand what factor(s) instigate α-SYN protein aggregation and how this event leads to neurodegeneration. However, significant progress has not been made in understanding the epigenetic or transcriptional regulation of α-SYN through considering its detailed genetic structure. Several single nucleotide polymorphisms (SNP) in the regulatory element of *SNCA* have been identified as genetic risk factors for PD, but their contribution to the aberrant regulation of α-SYN has only been investigated by using *in vitro* systems where implications from epigenetic underpinnings were largely overlooked (Basu et al., 2017). With the completion of the ENCODE project (Encyclopedia of DNA Elements), we can now understand the complex gene regulation pattern of eac h gene by considering all *cis* and *trans* elements associated with DNA (Consortium, 2012). In this review, the present understanding of genetic and epigenetic regulation of *SNCA* will be discussed and it will also highlight the importance of the enormous amount of ENCODE data in *SNCA* regulation. This will open a new avenue for research related to the regulation of α-SYN expression in dopaminergic neurons, helping researchers understand the behavior of this molecule under severe pathological conditions such as PD.

2. Regulation of α-synuclein expression and Parkinson's disease

α-SYN is a synaptic protein consisting of 140 amino acids (Maroteaux et al., 1988). The gene coding for this protein resides on chromosome 4 in humans and spans around 114 kb region in the genome (Touchman et al., 2001). α-SYN belongs to a family of synuclein proteins where two other members, such as β and γ synuclein, are also present and the genes coding for them are well-conserved across the species (George, 2002). Expression of α-SYN can be regulated at various stages of its development like any other gene expression system. Interestingly, deregulation of this gene has long been associated with PD (Stefanis, 2012; Venda et al., 2010).

The first piece of evidence pointing to the fact that α-SYN gene deregulation is directly associated with PD came from familial PD cases where coding region mutation resulted in the 53rd amino acid substitution from alanine to Threonine in Italian and Greek families (Polymeropoulos et al., 1997). Subsequently, two other mutations at the 30th (Alanine to Proline) and the 46th (Glutamine to Lysine) were discovered in families of Greek and Spanish descent, which led to an autosomal dominant pattern of the disease inheritance along with early-onset (Kruger et al., 1998; Zarranz et al., 2004). These coding mutations altered amino acids in the N–terminal domain of the protein, which has a role in this protein's aggregation (Gallegos et al., 2015; Recchia et al., 2004). Involvement of α-SYN gene deregulation in pathogenesis of PD was further strengthened by the findings of *SNCA* locus multiplication.