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Parkinson's disease as a member of Prion-like disorders

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ABSTRACT

Parkinson's disease is one of several neurodegenerative diseases associated with a misfolded, aggregated and pathological protein. In Parkinson's disease this protein is alpha-synuclein and its neuronal deposits in the form of Lewy bodies are considered a hallmark of the disease. In this review we describe the clinical and experimental data that have led to think of alpha-synuclein as a prion-like protein and we summarize data from *in vitro*, cellular and animal models supporting this view.

1. Parkinson's disease and other alpha-synucleinopathies

Parkinson's disease (PD) is the second most common neurodegenerative disease and the most common movement disorder. It principally affects people over the age of 50 and its prevalence increases with age. The majority of PD cases are sporadic but a small percentage is familiar and in these cases the age of onset can be much earlier (Thenganatt and Jankovic, 2014).

Patients with PD show characteristic motor symptoms such as postural instability, bradykinesia, rigidity and resting tremor. However, clinical studies have evidenced a wide range of other non-motor symptoms, including anosmia, sleep problems, constipation and psychological alterations as depression with around 40% of the patients developing dementia (Khoo et al., 2013).

PD belongs to a group of diseases named alpha-synucleinopathies due to the presence of alpha-synuclein aggregates. These diseases include among others Dementia with Lewy Bodies (DLB) and Multiple System Atrophy (MSA). DLB is clinically characterized by progressive dementia with visual hallucinations, and hyper-sensitivity to neuroleptic medications (McKeith et al., 1996). MSA is the third most common parkinsonism syndrome with a great variety of symptomatology comprising autonomic dysfunction parkinsonian movement disorders, cerebellar ataxia (Gilman et al., 1999).

Neuropathological, biochemical and genetic evidences (Spillantini et al., 1998, 1997; Vekrellis et al., 2011) have supported the implication of alpha-synuclein as the cause of these diseases. More specifically, mutations, duplications and triplications of the alpha-synuclein gene (SNCA) locus are causes of familial forms of PD and DLB (Houlden and Singleton, 2012) and SNCA has also been identified as a risk factor in all the PD genome wide association studies (Singleton et al., 2013).

Additionally, alpha-synuclein deposits can be found with other proteinaceous aggregates (Tau, Aβ, prions, etc.) characteristics of other neurodegenerative diseases (Arima et al., 1998; Charles et al., 2000; Doherty et al., 2004; Forman et al., 2002; Haïk et al., 2002; Lippa et al., 1999; Spillantini et al., 1998; Takeda et al., 1998; Wakabayashi et al., 2000).

2. The alpha-synuclein protein

Alpha-synuclein is a small protein of 140 amino acids highly expressed in the brain, with a pre-synaptic localization (Iwai et al., 1995; Jakes et al., 1994), but has been reported to be expressed in other organs including kidney, liver and heart (Baltic et al., 2004) besides been present in blood cells (Nakai et al., 2007). It is part of the synuclein family, which has two other members with different percentage of homology to alpha-synuclein, beta-synuclein with 63% and gamma-synuclein with 55% homology. The alpha-synuclein gene, SNCA, resides in chromosome 4 and although three alternative spliced transcripts have been described, proteins have been identified only for the full length 1–140 protein (Tofaris and Spillantini, 2007). Structurally alpha-synuclein can be divided in

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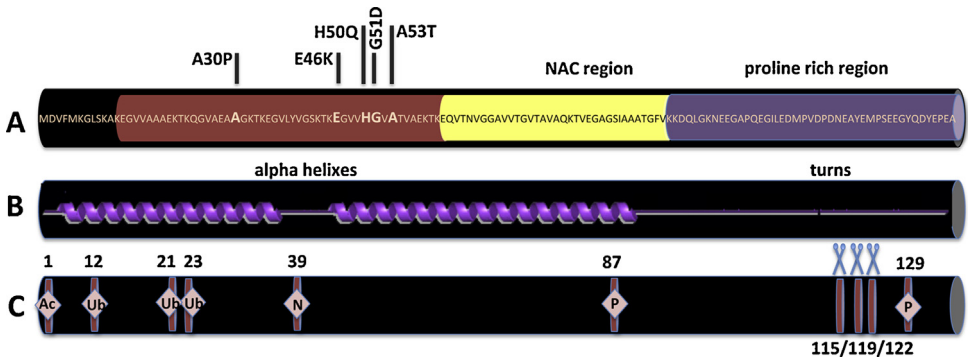

Fig. 1. Schematic of alpha-synuclein featuring: sequence with regions of interest and most abundant mutations (A), tertiary structure of the protein (B) and post-translational modifications (C) where Ac is acetylation, Ub = ubiquitinilation, P = phosphorylation and scissors show some of the truncated epitopes.

three regions: the N-terminal part containing 7 imperfect repeats of 11 amino acids with a highly conserved KTKEGV motif and with propensity to form alpha-helical structures (Chandra et al., 2003; Eliezer et al., 2001) (Fig. 1B). The alpha-synuclein gene mutations A30P, E46K, A53T, H50Q and G51D that are associated with disease are concentrated in this N-terminal region (Appel-Cresswell et al., 2013; Kiely et al., 2013; Krüger et al., 1998; Lesage et al., 2013; Polymeropoulos, 1997; Proukakis et al., 2013; Zarranz et al., 2004).

The second region is the NAC region, which stands for non-amyloid component and has this name because it was first described in amyloid plaques in Alzheimer's disease brains (Uéda et al., 1993), location that was not confirmed later (Culvenor et al., 1999). This hydrophobic region of 35 amino acids is indispensable for the aggregation of alpha-synuclein (Crowther et al., 1998; Giasson et al., 2001) and it has a degree of sequence similarity with other amyloidogenic peptides such as β-amyloid (El-Agnaf and Irvine, 2002). The third region is the C-terminal part, a proline rich area, negatively charged and highly unstructured (Fig. 1A and B) where several proteins have been reported to bind (Burré et al., 2012; Dev et al., 2003).

The alpha-synuclein protein undergoes a number of post-translational modifications mostly pathology associated. These include N-acetylation and nitration in tyrosine 39 (Giasson et al., 2000; Trexler and Rhoades, 2012). There are several ubiquitinylated residues in lysines 12, 21 and 23, as well as fragments truncated at Asp-115, Asp-119, Glu-120, Asn-122, Tyr-133, and Asp-135 (Anderson et al., 2006; Baba et al., 1998; Hasegawa et al., 2002) (Fig. 1C) that have been detected. Also phosphorylation, mainly in Ser-129 and Ser-87 have been strongly associated with pathology (Fujiwara et al., 2002; Paleologou et al., 2010).

The alpha-synuclein protein is considered to be a natively unfolded protein that can become misfolded and aggregates forming β-sheet structures (Fauvet et al., 2012; Weinreb et al., 1996). However it has also been reported that alpha-synuclein can be natively in a tetrameric form as suggested by data obtained using recombinant, cell or brain extracted alpha-synuclein (Bartels et al., 2011; Selkoe et al., 2014; Wang et al., 2011). It is known that alpha-synuclein structure is stabilized by its binding to lipid membranes (Davidson et al., 1998) and a recent report has shown that multimers are found only when alpha-synuclein is bound to cell membranes, not finding tetramers or other oligomers when the protein is in its cytosolic not-bound state (Burré et al., 2014). These discrepancies might be explained by different methods of producing or extracting the alpha-synuclein (Coelho-Cerqueira et al., 2013). The events that could lead to alpha-synuclein aggregation and gain of pathological function have been summarized (Anichtchik et al., 2013). Despite a debate is ongoing about the structural physiological characteristics of alpha-synuclein, in the pathological condition the protein becomes insoluble with amyloid characteristics and with, features similar to prions as summarized in Table 1. Misfolded alpha-synuclein has been described to have different conformations or strains and to be able to transmit the pathology from cell to cell explaining the progression of PD in affected individuals. However, although fidelity of transmission of strain characteristics has been suggested (Watts et al., 2013) more evidences are needed to definitely prove it (Table 1).

3. The prion protein

Prions, (from proteinaceous infectious particles) are the causal agent of the Transmissible Spongiform Encephalopathies (TSEs). They are misfolded isoforms from an ubiquitiously expressed protein, PrP^{C} (Prusiner et al., 1998). Prions occur as distinct strains, which share the sequence of the underlying PrP^{C} but exhibit diverse phenotypes, including incubation period, clinical symptoms as well as biochemical and neuropathological features. It is generally accepted that prion strains differ in regard to the conformation of their PrP^{Sc}, which is propagated with high fidelity by seeded conversion (Weissmann, 2009). Biochemically, prions are characterized by a high content in β-sheet as compared with the fundamentally helical conformation of the PrP^{C}, and high but not total resistance to proteinase K digestion. Purified prions are insoluble even in mild detergents and they form oligomers and fibrils named prion rods that can be observed using electron microscopy (Riesner, 2003).

In addition to been self-propagating inside cells, prions are transmitted from cell to cell within individuals and between individuals. In cells several mechanisms of transmission have been reported, including release of exosomes and uptake by recipient cells and tunnelling nanotubules connecting donor and recipient cells (Fevrier et al., 2004; Gousset et al., 2009; Vella et al.,

Table 1
Comparison of prion and alpha-synuclein biochemical and transmission properties. *Although *in vitro* generation of alpha-synuclein fibril "strains" has been reported (Guo et al., 2013) their serial transmission in a prion-like manner has not been demonstrated.

	Prions	Alpha synuclein
Biochemical characteristics		
Oligomer and fibril formation	Yes	Yes
High content in β-sheet	Yes	Yes
Insolubility in mild detergents	Yes	Yes
Partial resistance to PK	Yes	Yes
Conformation diversity	Yes	Yes
Transmission properties		
Spread cell to cell	Yes	Yes
Spread in an organism	Yes	Yes
Transmission among individuals	Yes	No
Spread of strains	Yes	No