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Research Report

Post-translational modification of α-synuclein in Parkinson's disease

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ABSTRACT

Parkinson's disease (PD) is the second most common neurodegenerative disease, and the most prevalent degenerative movement disorder. It is estimated that the prevalence of such age-related neurodegenerative diseases will double in the next 25 years. While the etiology of Parkinson's disease is not entirely clear, a common link between both inherited and sporadic forms of disease is the protein α-synuclein. In PD brains, α-synuclein is typically found in large, insoluble protein aggregates referred to as Lewy bodies and Lewy neurites. The exact role of α-synuclein is still unknown, but it has been shown to undergo a variety of post-translational modifications, which impact α-synuclein aggregation and oligomer formation in different ways. This review highlights key post-translational modifications and the impact they have on α-synuclein aggregation and toxicity, elucidating potential mechanisms for PD pathogenesis and targets for future therapeutics.

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1. Introduction

Parkinson's disease (PD) is the second most prevalent neurodegenerative disease, currently affecting more than 1% of the world-wide population over the age of 65 (Hatcher et al., 2008). PD is characterized, in part, by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc), resulting in striatal depletion of the neurotransmitter dopamine (DA). Depleted DA levels manifest in the physical symptoms commonly associated with PD, including rigidity, resting tremors, and bradykinesia (slowing of movement). The mechanism leading to specific dopaminergic neuronal loss in the SNpc is still unknown, though a common feature found in most PD cases, both sporadic and genetic, is the presence of large, insoluble protein rich inclusions known as Lewy bodies. These inclusions are composed of multiple proteins and lipids, but the most prevalent component is the protein, α-synuclein.

The physiological function of α-synuclein is still poorly understood. It is expressed throughout the body, but has highest expression levels within the brain, and specifically in dopaminergic neurons of the SNpc (Xu et al., 2002). In neurons, α-synuclein is localized to nerve terminals (Maroteaux et al., 1988), suggesting a role in vesicle recycling (Burre et al., 2010). In support of this hypothesis, α-synuclein can bind anionic lipids, indicating the potential for

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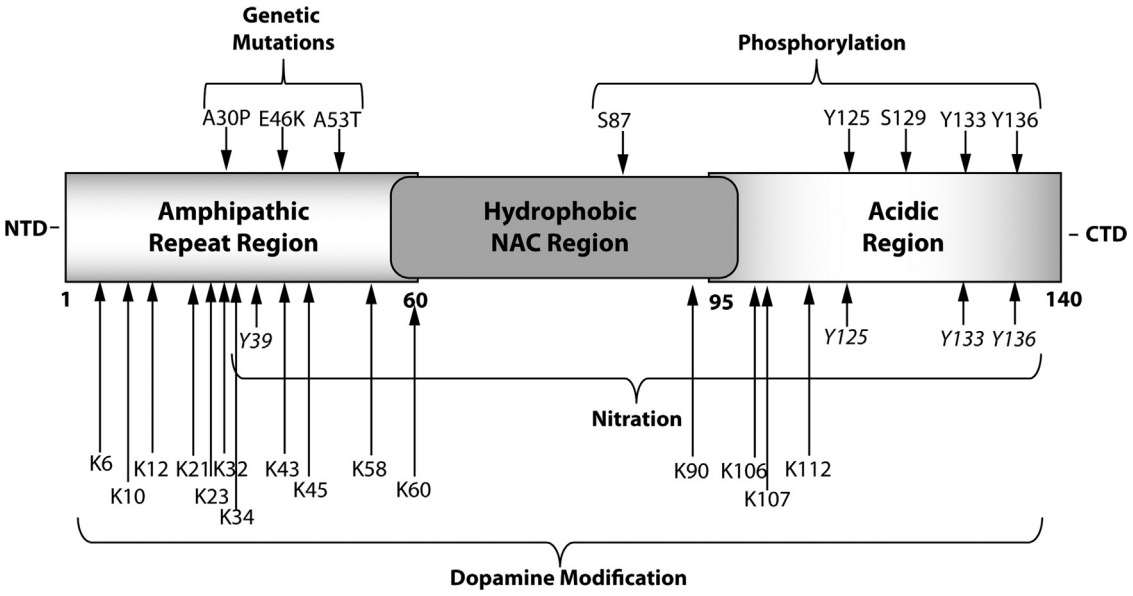

Fig. 1 – α Synuclein is a 140 residue, soluble protein containing three distinct regions. These include an amphipathic repeat region which is known to bind anionic lipids and contains the KTKEGV repeats, the hydrophobic non-amyloid component region which is prone to aggregation, and an acidic c-terminal region. Locations for select point mutations and post-translational modifications are shown. Residues highlighted by italics (Y39, Y125, Y133, Y136) have been shown to be either nitrated or modified by dopamine.

interaction with biological membranes *in vivo*. When bound to lipids, the normally unstructured α-synuclein adopts an α-helical structure (Ulmer et al., 2005). This is of interest as recent evidence suggests that under physiological conditions α-synuclein exists in equilibrium between unstructured monomeric forms and tetrameric α-helical oligomers that are resistant to fibrillization (Bartels et al., 2011; Wang et al., 2011). These findings are important as they highlight the key fact that the dynamic structure of α-synuclein may play a role in PD pathogenesis. Aberrant α-synuclein function or structure may produce different oligomers, which may be toxic themselves, or fibrillize into toxic species, such as those seen in Lewy bodies. While the exact physiological structure of α-synuclein is still controversial (unstructured monomer versus helical tetramer), the monomeric protein can be divided into three distinct domains (Fig. 1). The N-terminal portion (residues 1–60) contains four 11-residue imperfect repeats with the highly conserved hexameric motif (KTKEGV). This region can adopt an amphipathic helical structure that may serve as/mimic a mitochondrial targeting sequence (MTS) peptide (Devi et al., 2008), potentially linking α-synuclein to mitochondrial dysfunction, a pathogenic factor in PD. The second domain is the non-amyloid component (NAC) region (residues 61–95), which is essential for α-synuclein fibrillization and Lewy body formation. Fibril formation requires a conformational change in the structure of α-Synuclein, from mainly random coil to β-sheet. Once in a β-sheet enriched state, monomeric α-Synuclein can begin to stack and form β-sheet fibril structures, similar to those found in Alzhiemer's and Huntington's disease. Lastly, there is an acidic C-terminal domain (residues 96–140) which is highly enriched in glutamate, aspartate, and proline residues. This region has been proposed to function as a solubilizing domain and contributes to the thermal stability of α-synuclein as well as serving as a domain for protein/protein interactions (Oueslati et al., 2010).

α-Synuclein was the first causal genetic factor linked with the disease, when mutations in the *PARK1* gene (which encodes α-synuclein) were discovered in patients with PD (Polymeropoulos et al., 1997). Further research has identified key mutations in the *PARK1* gene that lead to early onset of PD. In addition, it has been shown that simple gene duplications or triplications in the wildtype *PARK1* gene contribute to PD pathogenesis (Singleton et al., 2003). While the exact role these genetic alterations play in PD is still being examined, it is known that certain mutations, including A30P and A53T, can alter the rate at which α-synuclein oligomerizes and/or aggregates (fibrillizes) into Lewy bodies. It has been shown that while A53T accelerates the formation of large fibrillar aggregates, A30P stabilizes the "protofibril" state, that is, smaller oligomeric structures. Furthermore, it has been shown that the rate of fibrillization is concentration-dependent. It is generally believed that the rate of α-synuclein assembly into different molecular species plays a crucial role in PD etiology. While the exact impact of different α-Synuclein structural species is unresolved, the ability of the protein to undergo structural transitions is of high importance. Recent work has demonstrated that administration of pre-formed α-Synuclein fibrils not only leads to cellular death, but that the fibrils can be transmitted from cell to cell, generating a degernative cascade (Luk et al., 2012). Conversely, other studies have proven that stabilized protofibril states can permeabilize membranes, which may contribute to neuronal death (Volles and Lansbury, 2002), leading to contriversy of which structural species is the most toxic. This review will attempt to highlight key differences between both structures and the impact they have on α-Synuclein structure and toxicity.

In addition to genetic changes, α-synuclein is extensively post-translationally modified (PTM) in PD. These modifications