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Review

Pathogenic effects of α -synuclein aggregation

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Abstract

Biochemical and genetic evidence point towards α -synuclein aggregation as having a pivotal role in the onset and progression of several neurodegenerative disorders, including Parkinson's disease, multiple system atrophy and Lewy body dementia. We review recent data on how α -synuclein aggregates may impact on cellular homeostatic mechanisms including cellular transport and degradation and transcriptional regulation. α -Synuclein aggregates can exist as several molecular species and their different features are discussed in the context of the methodologies used for their study and the many chemical and physical factors that influence their formation. \mathbb{O} 2004 Elsevier B.V. All rights reserved.

Theme: Disorders of the nervous system *Topic:* Degenerative disease: Parkinson's

Keywords: Parkinson disease; Lewy body dementia; Multiple systems atrophy; Lewy body; Protein aggregation; Filaments; Amyloid; Oligomers; Synuclein; Neurodegeneration

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1. Introduction

The group of α -synucleinopathies comprises the neurodegenerative disorders, Parkinson's disease, Lewy body dementia, Lewy body variant of Alzheimer's disease, multiple system atrophy, and neurodegeneration with brain iron accumulation type I [4,34,103,104,122,123]. They are all brain amyloidoses unified by pathological intracellular inclusions of aggregates having the α -synuclein protein as a key component [103,122]. The inclusions are designated Lewy bodies when found in the neuronal cell body, Lewy neurites in axons, and glial cytoplasmic inclusions when found in oligodendrocytes. The latter is the pathognomonic cellular lesion in multiple system atrophy [32,89].

A direct role for α -synuclein in the neurodegenerative processes in Parkinson's disease and Lewy body dementia is demonstrated by genetic evidence. Autosomal dominant early-onset Parkinson's disease and Lewy body dementia can be induced by hyper expression of the wild type α synuclein protein due to gene triplication [30,99] and expression of mutated α -synuclein wherein single amino acids have been exchanged [65,93,127]. At the tissue level, the genetically induced diseases are paralleled by the development of Lewy inclusions wherein aggregates of insoluble α -synuclein is present [65,93,127], and the A53T and A30P mutations stimulate aggregation of α -synuclein in vitro [19,28]. The presence of aggregated α -synuclein in Lewy inclusions is shared with the common sporadic Parkinson's disease and Lewy body dementia as well as other neurodegenerative disorders but its pathogenic role in the sporadic cases is not clear. However, the strong correlation between α -synuclein-induced diseases and

aggregation of α -synuclein justifies the study of putative pathogenic effects of α -synuclein aggregates.

This raises the key question as to which molecular species represent the toxic culprits on the pathway of α -synucleins aggregation from soluble monomers via smaller oligomers to insoluble filaments. This is by no means a trivial matter as a large effort is exercised to develop models of α -synuclein-induced neurotoxicity.

This review will focus on the process of α -synuclein aggregation and the functional impact of α -synuclein aggregates. The literature in this field is vast and rapidly growing so we have been forced to select those references that we feel highlight the points we want to make. Accordingly, we apologize to all of those having made significant contributions forming part of the basis for our presentation but not been cited in this paper.

2. The α -synuclein aggregation process

 α -Synuclein is a 140-amino acid protein that frequently is divided in three overlapping regions: the N-terminal repeat region of about 100 amino acids containing six 11residue repeats some of which display amphipatic properties; the hydrophobic NAC region from amino acids 61–95; the acidic C-terminal region [37,111] (Fig. 1). α -Synuclein displays a high degree of structural plasticity that is governed by its environment. Structural studies have demonstrated α -synuclein to be monomeric and natively unfolded in solution [124], whereas its N-terminal repeat region acquires a α -helical conformation upon interacting with phospholipid membranes [14,24]. α -Synuclein aggreDownload English Version:

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