α-synuclein: The Driving Force Behind Neurodegenerative Diseases

don whitley scientific
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UNIVERSITY OF LEEDS

Abstract:

α-synuclein (α-syn) is a neuronal protein abundant in the brain with a key role in the pathogenesis of neurodegenerative diseases, in particular the synucleinopathies. Abnormal protein inclusions containing aggregated α-syn, such as Lewy bodies are the pathological hallmarks of the synucleinopathies. It is still unclear how α-syn causes neurotoxic effects, however evidence suggests the aggregation of α-syn into a β-sheet fibril conformation is the major pathological event. Understanding the structure, functions and aggregation of α-syn is important in the development of disease modifying therapeutics to combat disease.

Introduction:

- Neurodegenerative diseases are characterised by the progressive loss of specific nerve cell populations.
- Parkinson's disease (PD) is the second most common neurodegenerative disease caused by the loss of dopaminergic neurones in the subsantia nigra leading to significant disability.
- The aggregation of α-syn plays a central role in the pathology of diseases such as PD, MSA and DLB, however the precise mechanisms are not fully understood.

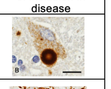
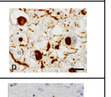
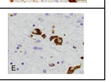
Disease	Brain region affected	Pathological inclusion	Microgram image of inclusion in disease
Parkinson's disease (PD)	Brain stem	Lewy bodies and Lewy neurites	
Dementia with Lewy bodies (DLB)	Cortex and brain stem	Lewy bodies and Lewy neurites	
Multiple system atrophy (MSA)	White matter	Glial cytoplasmic inclusions	

Figure 1 – Major neurodegenerative diseases with α-synuclein pathology

Structure of α-synuclein

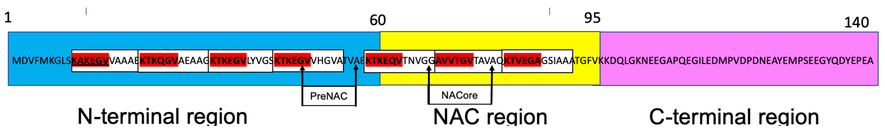


Figure 2- Human α-synuclein primary sequence. 140 amino acid protein encoded by SCNA gene. There are seven imperfect 11 residue repeats (white) with a conserved KTKEGV motif (red).

α-syn has three defined regions:

- N-terminal region is amphipathic and facilitates membrane binding
- NAC region is hydrophobic and promotes amyloid aggregation
- C-terminal domain is unstructured and mediates protein interactions.

- In its native structure α-syn exists in equilibrium between a monomeric conformation and an α-helical membrane bound state, however this is still debated.
- Identifying the structure of α-syn is important to aid the understanding of the proteins physiological functions and toxicity.

Functions of α-synuclein

- The normal function of α-syn remains poorly understood, however evidence suggests a role in stabilisation, sequestration and fusion of presynaptic vesicles.

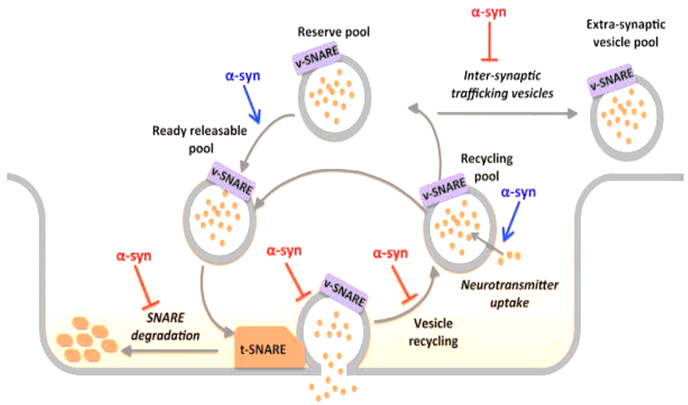


Figure 3 - Functions of α-synuclein at the pre-synaptic terminal (Lashuel, Hilal A. et al., 2013).
Blue represents normal concentrations of α-syn, red α-syn indicates accumulation / overexpression of the protein.

- α-syn proposed functions include; vesicle pool maintenance, vesicle trafficking and refilling, interacting with t-SNARE and v-SNARE for SNARE complex assembly, neurotransmitter release and synthesis, molecular chaperoning and lipid transport.
- The span of functions that α-syn exhibits are thought to influence its role in pathology.

Aggregation of α-synuclein

- α-synuclein aggregation and fibril formation have an important role in the pathology of neurodegenerative disease, the fibular protein inclusions are a common hallmark of disease.

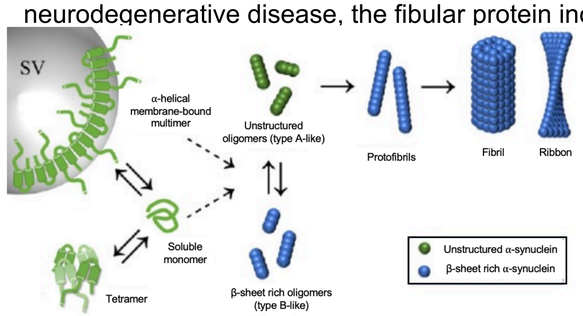


Figure 3 - α-synuclein aggregation process (Miraglia et al., 2018)
α-syn fibrils are formed via a nucleation reaction:
1. α-syn monomers form oligomers (**lag phase**)
2. monomer addition forms protofibrils and higher order aggregating structures (**elongation phase**)
3. α-synuclein fibrils with a β-sheet structure are formed (**stationary phase**)

- Evidence suggests the largest toxicity arises from oligomers which disrupt cellular functions and cause neuronal cell death.
- Different oligomeric species can give rise to different phenotypes in disease.
- Various factors have been identified to shift α-synuclein aggregation, including PD associated mutations, interactions with proteins and membranes and regions critical for aggregation including the NAC core and the P1 region in the N-terminus.
- Different factors cause different aggregation states in disease.

Conclusions and future perspectives

- Aggregation of α-syn is the main pathological event in neurodegenerative diseases, termed the synucleinopathies.
- α-syn has a multitude of functions with a regulatory function at the synapse.
- Despite detailed research into α-syn, the exact mechanisms of aggregation and physiological roles of α-syn remain unknown.
- There are limited therapeutics to cure neurodegenerative diseases - understanding α-syn functions, structure and aggregation is important for the development for disease modifying therapeutics.

α-syn could be a valid therapeutic target to cure these diseases, possible strategies include:

- Small molecules that stabilise the native state of α-syn, inhibit α-syn aggregation or cause disaggregation of fibrils and oligomers back to their monomeric form.
- Identifying compounds that promote α-syn aggregation, accelerating inclusion body formation, preventing the toxic effects of oligomers and misfolded protein build-up

Acknowledgements:

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Key references:

Lashuel, H.A., Overk, C.R., Oueslati, A. and Masliah, E. 2013. The many faces of α-synuclein: from structure and toxicity to therapeutic target. *Nature reviews. Neuroscience.* 14(1), pp.38-48.
Miraglia, F., Ricci, A., Rota, L. and Colla, E. 2018. Subcellular localization of alpha-synuclein aggregates and their interaction with membranes. *Neural regeneration research.* 13(7), pp.1136-1144.

Name: Emily Walbank
Supervisor: Professor Brockwell