

α -Synuclein in neurodegeneration – a good protein that may go bad

Henrik Zetterberg^{1,2,*} & Ann Brinkmalm¹

- 1. Institute of Neuroscience and Physiology, Department of Psychiatry and Neurochemistry, the Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden*
- 2. Department of Molecular Neuroscience, UCL Institute of Neurology, Queen Square, London, UK*

*Corresponding author: henrik.zetterberg@gu.se

Parkinsonian disorders represent a large group of age-related neurodegenerative diseases. In addition to common Parkinson's disease (PD), they include the more rare atypical parkinsonian disorders, such as multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and dementia with Lewy bodies (DLB) [1]. The differential diagnosis may be challenging, especially in early disease stages. As an accurate initial diagnosis has profound implications for the management of these devastating disorders, there is an unmet need for better diagnostic tools. Additionally, biomarkers are critical in objectively evaluating PD progression and assessing treatment effects. More knowledge is also needed on pathogenic mechanisms.

Predominantly expressed in the pre-synapse, 140 amino acid-long α -synuclein has been found to be the major constituent of the intracellular aggregates in Lewy bodies, the pathological hallmark of PD and DLB, and in the glial cytoplasmic inclusions of MSA [2, 3]. These

diseases have accordingly been grouped as *synucleinopathies*, which differentiates them from the other parkinsonian disorders. Intracellular α -synuclein has been shown to be released into the extracellular space [4] and may be transmitted between neurons [5]. The exact role of α -synuclein in neurotoxicity remains unclear but genetic data (duplications and triplications of the α -synuclein-encoding *SNCA* gene in PD) clearly suggest a primary involvement of the protein in neurodegeneration [6-8]. In addition, recent data show that Lewy bodies are highly prevalent in the brains of individuals who have died in the course of disorders that are not normally classified as synucleinopathies, *e.g.*, Alzheimer's disease [9]. Such accumulations are unlikely to be simply coincidental; to delineate their role in the disease process and how they interact with tau and A β pathologies and microglial activation accurate *in vivo* biomarkers are needed.

This mini-symposium consists of 4 chapters dealing with most aspects of α -synuclein in the context of neurodegeneration. In Chapter 1, Berkhoudt Lassen and co-workers describe interaction partners to α -synuclein, which may either prevent or promote α -synuclein misfolding and aggregation, likely depending on a stochastic process that initiates on a background of selective vulnerability [10]. Chapter 2, by Emmanouilidou and Vekrellis, details normal α -synuclein production, secretion and clearance, and how disrupted α -synuclein homeostasis may initiate pathology spreading over the brain. Chapter 3 discusses the role of α -synuclein aggregates in triggering inflammatory responses from microglia. Finally, Chapter 4 Atik and co-workers give an updated account of the diagnostic utility of α -synuclein detection and quantification in clinically accessible tissue specimens (biopsies from salivary glands and the gastrointestinal tract mucosa), as well as in biofluids, such as cerebrospinal fluid (CSF), plasma and saliva.

Altogether, the volume summarizes a large body of recent literature on the relevance of α -synuclein as a diagnostic and prognostic biomarker, as well as a disease-promoting agent when its normal homeostasis and important physiological functions are disrupted. The editors are to be congratulated for assembling a strong team with diverse expertise to give us a coherent picture of the current state of art in α -synuclein-focused research. The volume is to be read by both clinical researchers and those who are focused on basic research on neurodegeneration.

References

1. Tolosa E, Wenning G, Poewe W: **The diagnosis of Parkinson's disease.** *Lancet Neurol* 2006, **5**(1):75-86.
2. Spillantini MG, Schmidt ML, Lee VM, Trojanowski JQ, Jakes R, Goedert M: **Alpha-synuclein in Lewy bodies.** *Nature* 1997, **388**(6645):839-840.
3. Gai WP, Power JH, Blumbergs PC, Blessing WW: **Multiple-system atrophy: a new alpha-synuclein disease?** *Lancet* 1998, **352**(9127):547-548.
4. El-Agnaf OM, Salem SA, Paleologou KE, Cooper LJ, Fullwood NJ, Gibson MJ, Curran MD, Court JA, Mann DM, Ikeda S *et al*: **Alpha-synuclein implicated in Parkinson's disease is present in extracellular biological fluids, including human plasma.** *Faseb J* 2003, **17**(13):1945-1947.
5. Desplats P, Lee HJ, Bae EJ, Patrick C, Rockenstein E, Crews L, Spencer B, Masliah E, Lee SJ: **Inclusion formation and neuronal cell death through neuron-to-neuron transmission of alpha-synuclein.** *Proc Natl Acad Sci U S A* 2009, **106**(31):13010-13015.

6. Singleton AB, Farrer M, Johnson J, Singleton A, Hague S, Kachergus J, Hulihan M, Peuralinna T, Dutra A, Nussbaum R *et al*: **alpha-Synuclein locus triplication causes Parkinson's disease**. *Science* 2003, **302**(5646):841.
7. Simon-Sanchez J, Schulte C, Bras JM, Sharma M, Gibbs JR, Berg D, Paisan-Ruiz C, Lichtner P, Scholz SW, Hernandez DG *et al*: **Genome-wide association study reveals genetic risk underlying Parkinson's disease**. *Nat Genet* 2009, **41**(12):1308-1312.
8. Fuchs J, Nilsson C, Kachergus J, Munz M, Larsson EM, Schule B, Langston JW, Middleton FA, Ross OA, Hulihan M *et al*: **Phenotypic variation in a large Swedish pedigree due to SNCA duplication and triplication**. *Neurology* 2007, **68**(12):916-922.
9. Schneider JA, Arvanitakis Z, Yu L, Boyle PA, Leurgans SE, Bennett DA: **Cognitive impairment, decline and fluctuations in older community-dwelling subjects with Lewy bodies**. *Brain* 2012, **135**(Pt 10):3005-3014.
10. Lodato MA, Woodworth MB, Lee S, Evrony GD, Mehta BK, Karger A, Chittenden TW, D'Gama AM, Cai X, Luquette LJ *et al*: **Somatic mutation in single human neurons tracks developmental and transcriptional history**. *Science* 2015, **350**(6256):94-98.