Nature Reviews Neuroscience | AOP, published online 2 September 2011; doi:10.1038/nrn3106

NEURODEGENERATIVE DISEASE

α-synuclein gets a new look

Misfolded α-synuclein is heavily implicated in the pathogenesis of Parkinson's disease. In its native state, α-synuclein is widely believed to be a 14-kDa unfolded monomer. Selkoe and colleagues now challenge this view. In a study published in *Nature*, they show that α-synuclein primarily exists as a tetramer that has an α-helical secondary structure.

Neil Smith

The authors first examined the native state of α-synuclein using native PAGE, which avoids the destabilizing effect of detergent on protein complexes that is observed when SDS–PAGE is used. They analysed cell lysates from four different cell lines, human red blood cells (RBCs) and mouse frontal cortex. In all samples, the predominant species of α-synuclein that was detected on native gels migrated at 55–65 kDa, approximately fourfold the expected size of 14 kDa. Thus, these data suggest that α-synuclein primarily exists as a tetramer in its native state.

Protein conformation can influence the mass determined by PAGE. Analysis of purified non-denatured α-synuclein from RBC lysates by scanning transmission electron microscopy, however, also indicated that native α-synuclein has a molecular mass of ~55 kDa. Moreover, a similar result was obtained following analysis of the purified protein by sedimentation equilibrium analytical ultracentrifugation.

Native α-synuclein is widely understood to exist in an unfolded conformation. Contrary to this view, the authors showed that α-synuclein purified from RBCs had an α-helical structure, as revealed by circular dichroism. Interestingly, this form of α-synuclein showed more resistance to aggregation than monomeric α-synuclein.

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Taken together, these results challenge the prevailing view of α-synuclein's native state. According to the authors, α-synuclein aggregation may follow tetramer destabilization in disease states and stabilization of the tetrameric conformation may be a novel therapeutic strategy for Parkinson's disease.

Darran Yates

ORIGINAL RESEARCH PAPER Bartels, T., Choi, J. G. & Selkoe, D. J. α-Synuclein occurs physiologically as a helically folded tetramer that resists aggregation. *Nature* 14 Aug 2011 (doi:10.1038/nature10324)