Title
Abandoning the Proteinopathy Paradigm in Parkinson Disease—Not So Fast

Journal
JAMA Neurology, 80(8)

ISSN
2168-6149

Authors
Bronstein, Jeff M
Zeiger, William A
Peng, Chao

Publication Date
2023-08-01

DOI
10.1001/jamaneurol.2023.1694

Abandoning the Proteinopathy Paradigm in Parkinson's Disease: Not so Fast

Espay and Okun recently proposed abandoning the proteinopathy paradigm in Parkinson's disease in favor of a "proteinopenia" hypothesis. Loss-of-function as a possible mechanism for PD and other neurodegenerative diseases is not a new idea and we agree that multiple potential mechanisms underlying neurodegeneration should be investigated. Although their theory is provocative, they vastly oversimplify complex topics and selectively cite/interpret studies with serious limitations to reach an ill-supported conclusion that would stifle our best developed line of therapeutic investigation. From the first sentence, the authors flatten all the complexity of the protein folding field. In fact, many proteins only function once assembled into higher order structures and numerous studies have uncovered physiological functions that emerge when proteins form amyloidogenic structures[1]. A complex field cannot be oversimplified into such black-and-white opposition as "proteinopathy" vs "proteinopenia".

The authors offer several ill-supported claims to advance their hypothesis. First, opposite to the statement presented, many studies have found that there are correlations between α-Syn pathology in specific regions and the presence or progression of specific cognitive or motor symptoms[2]. Second, they conflate CSF levels of total or soluble protein with intraneuronal protein levels. In fact, in AD, lower CSF Aβ actually correlates with brain amyloid accumulation, while in PD, oligomer specific antibodies and Rt-Quic have demonstrated increased levels of aggregated α-Syn in CSF of PD patients[3]. Next, regarding knock-down α-Syn the authors don't mention that many other studies have reduced α-Syn without toxicity, knocking out the *α-Syn* gene (or even all three synuclein genes) in mice does not recapitulate features of PD, and knock-down/out of *α-Syn* is protective against toxin or pre-formed fibril-induced neuron loss[4]. Moreover, they ignore that overexpression (via multiple approaches) or induction of α-Syn aggregation in animal models recapitulates many clinical and pathological correlates of PD across hundreds of studies. Finally, the REP1 genotype mentioned actually leads to increased risk of developing PD and faster progression[5].

The failure of recent Phase 2 trials does not invalidate the entire proteinopathy hypothesis. Remember that multiple anti-Aβ trials failed before some demonstrated target engagement and showed evidence of slowing clinical progression. No one theory will explain all aspects of PD and other pathogenic processes are likely at play, but completely discarding the proteinopathy hypothesis is not supported by an objective assessment of the available science. We should take an all-of-the-above, rather than an either-or, approach to developing treatments for this important disease.

1. Saad, S. & Jarosz, D. F. Protein self-assembly: A new frontier in cell signaling. *Curr Opin Cell Biol* **69**, 62–69 (2021).
2. Beach, T. G. *et al.* Unified Staging System for Lewy Body Disorders: Correlation with Nigrostriatal Degeneration, Cognitive Impairment and Motor Dysfunction. *Acta Neuropathol* **117**, 613–634 (2009).
3. Majbour, N. *et al.* Disease-Associated α-Synuclein Aggregates as Biomarkers of Parkinson Disease Clinical Stage. *Neurology* **99**, e2417–e2427 (2022).
4. Cole, T. A. *et al.* α-Synuclein antisense oligonucleotides as a disease-modifying therapy for Parkinson's disease. *JCI Insight* **6**, e135633, 135633 (2021).
5. Ritz, B., Rhodes, S. L., Bordelon, Y. & Bronstein, J. α-Synuclein genetic variants predict faster motor symptom progression in idiopathic Parkinson disease. *PLoS ONE* **7**, e36199 (2012).