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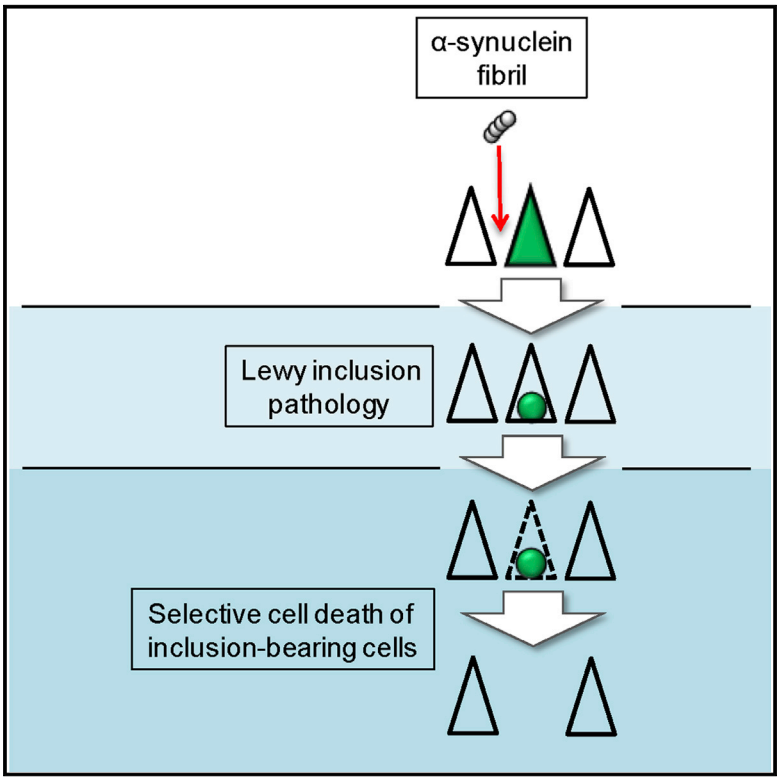
Report

Progressive Aggregation of Alpha-Synuclein and Selective Degeneration of Lewy Inclusion-Bearing Neurons in a Mouse Model of Parkinsonism

Graphical Abstract



Highlights

- Alpha-synuclein fibrils seed conversion of endogenous protein into Lewy pathology
- Lewy inclusions undergo a stage-like compaction in vivo
- Lewy inclusion-bearing neurons selectively die, whereas non-bearing neurons survive

Authors

Valerie R. Osterberg, Kateri J. Spinelli, ..., Randall L. Woltjer, Vivek K. Unni

Correspondence

unni@ohsu.edu

In Brief

Lewy inclusions are the pathological hallmark of several forms of Parkinsonism and are found in regions where cell loss occurs. However, their relationship to cell death of inclusion-bearing versus non-bearing neurons is not known. Osterberg et al. use in vivo multiphoton imaging in a fibril-seeded mouse model to show selective cell death of inclusion-bearing neurons.

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Progressive Aggregation of Alpha-Synuclein and Selective Degeneration of Lewy Inclusion-Bearing Neurons in a Mouse Model of Parkinsonism

Valerie R. Osterberg,[1,5] Kateri J. Spinelli,[1,5] Leah J. Weston,[1] Kelvin C. Luk,[2] Randall L. Woltjer,[3] and Vivek K. Unni[1,4,*]
[1]Jungers Center for Neurosciences Research, Oregon Health and Science University, Portland, OR 97239, USA
[2]Department of Pathology and Laboratory Medicine, Institute on Aging and Center for Neurodegenerative Disease Research, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA 19104, USA
[3]Department of Pathology, Oregon Health and Science University, Portland, OR 97239, USA
[4]Parkinson Center of Oregon, Department of Neurology, Oregon Health and Science University, Portland, OR 97239, USA
[5]Co-first author
*Correspondence: unni@ohsu.edu
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SUMMARY

Aggregated alpha-synuclein inclusions are found where cell death occurs in several diseases, including Parkinson's disease, dementia with Lewy bodies, and multiple-system atrophy. However, the relationship between inclusion formation and an individual cell's fate has been difficult to study with conventional techniques. We developed a system that allows for in vivo imaging of the same neurons over months. We show that intracerebral injection of preformed fibrils of recombinant alpha-synuclein can seed aggregation of transgenically expressed and endogenous alpha-synuclein in neurons. Somatic inclusions undergo a stage-like maturation, with progressive compaction coinciding with decreased soluble somatic and nuclear alpha-synuclein. Mature inclusions bear the post-translational hallmarks of human Lewy pathology. Long-term imaging of inclusion-bearing neurons and neighboring neurons without inclusions demonstrates selective degeneration of inclusion-bearing cells. Our results indicate that inclusion formation is tightly correlated with cellular toxicity and that seeding may be a pathologically relevant mechanism of progressive neurodegeneration in many synucleinopathies.

INTRODUCTION

Evidence suggests that many neurodegenerative diseases involve spreading aggregation of specific proteins through the nervous system, potentially via a prion-like mechanism (for review, see Jucker and Walker, 2013, Guo and Lee, 2014, and Fraser, 2014). Synucleinopathies are such a group typified by pathologically aggregated alpha-synuclein in specific neuronal (e.g., Parkinson's disease and dementia with Lewy bodies) or glial (e.g., multiple-system atrophy) populations where cell loss occurs. Recent work demonstrates that aspects of progressive alpha-synuclein aggregation can be recapitulated in model systems by exogenous introduction of in-vitro-generated, preformed fibrils (PFFs) of alpha-synuclein (Volpicelli-Daley et al., 2011; Luk et al., 2012a, 2012b; Masuda-Suzukake et al., 2013; Sacino et al., 2014a, 2014b, 2014c). PFFs seed the aggregation of endogenous alpha-synuclein, and this aggregation spreads along synaptically connected pathways (Luk et al., 2012a, 2012b). One hypothesis is that this seeding involves a prion-like mechanism where introduced PFFs directly convert endogenous alpha-synuclein into an aggregated form that then propagates through the brain. However, recent work questions the ability of PFFs to cause widespread seeding of endogenous alpha-synuclein (Sacino et al., 2014a) and other potential mechanisms for spreading have been proposed (for review, see Brundin et al., 2008 and Golde et al., 2013). In addition, the role inclusion development plays in a cell's ultimate fate has been difficult to determine using current techniques. Evidence supporting either an association between Lewy pathology development and compromised cell health (Lu et al., 2005; Greffard et al., 2010) or the opposite, relative neuroprotection (Gertz et al., 1994; Bodner et al., 2006; Tanaka et al., 2004), exists in the literature.

To test these mechanisms in vivo, we developed a multiphoton imaging approach to monitor conversion of endogenous alpha-synuclein into pathologically aggregated states in living mouse brain after PFF injection. Transgenic mice expressing GFP-tagged wild-type (WT) human alpha-synuclein (Syn-GFP; Rockenstein et al., 2005) were injected with mouse sequence PFFs in primary sensory cortex and neuronal aggregation of Syn-GFP monitored in vivo using multiphoton microscopy. Serial imaging of individual mice allowed us to determine the time course and pattern of inclusion development up to 13 months after PFF injection. In vivo multiphoton fluorescence recovery after photobleaching (FRAP) experiments allowed us to measure alpha-synuclein mobility in different somatic pools and detected a slow alpha-synuclein turnover rate within inclusions. These data suggest that exogenously introduced PFFs convert endogenous alpha-synuclein into an aggregated state structurally