

Introduction

Is α -synuclein the culprit of the Parkinsonian neurodegeneration?

The discovery of point mutations and multiplications of the normal coding region of the *alpha-synuclein* (α -syn) gene as causative for familial forms of Parkinson's disease (PD) and dementia with Lewy bodies and the observations that all PD patients show abnormal accumulations of the α -syn protein as a major component of Lewy bodies have had a profound impact on PD research. These findings not only shifted our attention toward understanding the normal function of α -syn and what kind of pathological α -syn species are formed in the diseased brain, but also created a foundation on which new hypotheses regarding the mechanisms of disease in PD were built. Yet today, we still do not have unequivocal evidence to answer a critical question on the role of α -syn: What are the pathogenic α -syn species in PD?

In this issue of *Experimental Neurology* three articles provide a review of what we have learned from cell systems to animal models and human postmortem brain specimens. Reviewing the evidence from cellular model systems, Cookson and van der Brug highlight that although the overall hypothesis that mutations or increased concentrations of α -syn are damaging to neurons, the details of this process are not yet clarified and we have a major challenge in determining the critical primary effects and distinguishing them from secondary phenomena. These authors propose a framework in which the toxicity of α -syn can be understood. They suggest that aggregation of α -syn into small soluble oligomeric species may be responsible for its ability to damage the cells, and downstream of this comes degenerative changes caused by putative toxic effects such as pore formations, ER stress, and synaptic dysfunction. Finally, cell death is triggered. While this framework is appealing to many in the field, as Cookson and van der Brug also acknowledge, the experimental evidence supporting this framework in *in vivo* systems is very limited.

The development of appropriate animal models is currently a serious concern and limitation in the field not only for testing this pathogenic hypothesis, but also for developing novel therapeutics. In the second review, Chesselet critically assesses the validity of α -syn overexpression as a useful model for PD. She first identifies that the more widely used toxin-based models (e.g., 6-OHDA and MPTP) have limitations in development of neuroprotective therapies, as it is yet unclear if the mechanism of action of these toxins is relevant to the pathophysiological process occurring in PD patients. Identifi-

cation of the genetic mutations causing familial forms of PD brought rapid development of several transgenic mouse lines expressing the human mutated proteins, especially human α -syn protein. Reviewing the various promoters used and α -syn constructs expressed in the mouse, Chesselet highlights that either a double mutation or a truncation of the α -syn protein was necessary to obtain cell loss and/or decreased dopamine levels in the mouse, while many other lines expressing wild-type or single mutant forms failed to show significant effects in the dopaminergic system. The use of viral vectors to overexpress α -syn has been more successful in replicating the protein inclusions and neurodegeneration in the nigrostriatal neurons seen in PD. Despite this unique advantage in resembling parkinsonian pathology, this approach has not been widely used in laboratories. This is most likely because it requires stereotaxic injection of the vector in the ventral midbrain, which might be considered labor-intensive, as well as variability in preparations of viral vectors (see also the review by Ulusoy et al. in the Gene Therapy special section of this issue). Nevertheless, it is important to stress that while currently available models are worth exploring for drug development, further work should be done to generate models that more accurately recapitulate true parkinsonian pathology and the behavioral phenotype.

The third paper, by Halliday and McCann, details the current knowledge and debates the interpretation of human postmortem brain tissue analysis from PD patients. In their view, one of the critical questions still to be answered is whether the insoluble aggregates are the toxic species. The current tissue-processing techniques on samples obtained from patients favor the visualization of the aggregated species, forming the basis for the interpretation that inclusions represent the primary pathology. However, this view can be challenged by findings that argue soluble oligomers could as well be the pathogenic species and inclusions are a means for the cells to protect themselves. Along the same lines, if the tissue processing can be misleading, then staging the disease based on these data may be biased. Thus even if the human brain tissue is the best source we have to better understand the underlying pathological changes occurring in PD brains, the interpretation of the information from this material is not trivial. If we then raise the bar and search for definitive evidence for the presence of toxic insoluble α -syn species or modifications of α -syn protein, e.g., by interaction with dopamine, in the patient material, it rapidly becomes

apparent that this field warrants further studies and in-depth analysis.

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