

What's Hot in Parkinson's Disease? January 2010

Is Parkinson's Disease a Prion Disease?

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There have been more than a few theories over the span of many years regarding the pathogenesis of Parkinson's disease (PD). Recent findings have implicated problems with mitochondrial dysfunction, oxidative stress, and protein misfolding/aggregation along with genetic/environmental issues. Additionally, PD is now appreciated to be more than a single disorder, and is now considered a syndrome that may have multiple underlying causes usually occurring with similar clinical manifestations. Still, there is always a humanistic draw to attempt to outline a single unifying hypothesis underlying the cause of PD. Recently, in an issue of *Proceedings of the National Academy of Sciences (PNAS)*—Desplats, Olanow and Prusiner all discuss a new “prion disease” hypothesis.

It is widely accepted that in PD, there is an accumulation of misfolded proteins (i.e. usually alpha-synuclein). Alpha-synuclein formulates an important part of the Lewy Body inclusion that is pathologically present in many motor and non-motor regions within the PD brain. Why these inclusions occur and how they spread from one brain region to another remains unknown.

Interestingly, recent post-mortem brain samples from PD patients treated with embryonic cell transplants revealed the presence of Lewy body protein inclusions within previously disease-free transplant cells. This observation sparked a great deal of speculation as to how unaffected cells might acquire PD. This is where the story has become very interesting from a scientific perspective. Diseases such as Creutzfeldt-Jakob and Bovine Spongiform Encephalopathy (e.g. Mad-Cow Disease) are caused by the propagation of misfolded proteins that are referred to as prions. Desplats and colleagues reported in PNAS that nerve cells found to over-express tagged alpha-synuclein could change their conformation and transmit themselves from cell to cell. These investigators posited a prion hypothesis to explain the spread of PD, and also suggested that specific targeting of alpha-synuclein misfolding may provide a viable treatment for the disease.

It is important to keep in perspective that hundreds of expert investigators have been hard at work for many years on these issues. It is the work of the collective PD scientific community that has provided the back-drop for the protein misfolding hypothesis. The addition of the notion that alpha-synuclein may act like a prion protein and potentially explain the progression of PD is, however, a

relatively new idea. Like all new ideas, PD as a prion disease has its champions and its critics. The important thing is that we move, as a PD community, toward a better understanding and toward better treatments for this disabling condition.

Selected references:

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 Aug 4;106(31):13010-5. Epub 2009 Jul 27.

Olanow CW, Prusiner SB. Is Parkinson's disease a prion disorder? *Proc Natl Acad Sci U S A*. 2009 Aug 4;106(31):12571-2. Epub 2009 Jul 28.