Research project summary

Assessing the site and mechanism of Parkinson's disease initiation in vivo

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- Awarded $761,175 from the Canadian Institutes of Health Research (CIHR) in May 2017
- Summary reproduced from the CIHR website in the language provided

Parkinson's disease (PD) is an age-related movement disorder whose familiar features of tremor and rigidity result from the loss of neurons in characteristic regions of the brain. There is a growing body of evidence that these symptoms are preceded by other abnormalities that may arise decades before the movement issues become obvious. Notable amongst these abnormalities are a diminished sense of smell and persistent constipation, which are attributable to a loss of function of neurons in the nose and gut respectively. It has been postulated that PD is actually initiated at these sites by the exposure of neurons to some environmental agent (viruses or pesticides, for example) which promotes misfolding of a critical protein in susceptible individuals. The misfolded protein (alpha synuclein) may aggregate and spread from one neuron to another and act as a template to promote the misfolding of additional molecules of alpha synuclein. Over the course of decades the misfolding problem may reach the brain, having traversed neuronal connections from the distant sites of disease initiation. If true, this mechanism would provide a large window of opportunity for interventions to delay or eliminate the disease. We propose to test the hypothesis using a mouse line that we have created specifically for this purpose. We have engineered this line such that the aggregation of the misfolded protein generates a fluorescent signal that can be detected by microscopy. We will use known genetic or environmental triggers to initiate the process, and determine where in the gut or nasal lining the fluorescence is first detected. We will follow the fluorescent signal over time and determine if there is spread to the brain. We will also use clinical samples to determine whether the forms of misfolded alpha synuclein that are present in subtypes of human neurodegenerative disease initiate spread in our mouse model.

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