



Editorial

Beyond L-DOPA: hope for Parkinson's treatment and diagnosis



Parkinson's disease (PD) is a highly prevalent neurodegenerative disease, affecting more than ten million people worldwide. Although we do have some preliminary insight into possible mechanistic underpinnings, we are far from fully understanding the etiology of the disease, and current treatments are only effective for treating symptoms in the short term. Disease-modifying treatments are clearly needed, particularly given that the global burden of PD is expected to grow as the population ages. Although several exciting developments have recently emerged on the PD treatment front, an additional major unmet need is a specific diagnostic test or biomarker for PD. There is currently no objective test for the disease, and clinicians must rely on symptomatic analyses and costly brain imaging tests to make a subjective diagnosis.

PD is associated with cell death of dopamine-secreting neurons in the substantia nigra of the brain, and current treatments for PD, such as levodopa (L-DOPA), are mainly aimed at improving the characteristic motor symptoms resulting from the reduced dopamine levels associated with neuronal loss. Research has suggested the possibility that these dopaminergic neurons may be intrinsically vulnerable to disruptions in metabolic signaling. Mitochondrial dysfunction and errors in protein folding quality control have long been suspected to contribute to PD, although precise pathophysiological mechanisms are not yet clear. Both the rarer genetic (familial) and more prevalent sporadic forms of the disease have been linked to a breakdown in mitochondrial function and/or cellular stress responses within the cell. Several recent studies have therefore directly targeted metabolic pathways for PD therapeutic development.

A randomized controlled clinical trial published on August 3, 2017 in *The Lancet* found that stimulating the glucagon-like peptide-1 (GLP-1) receptor signaling pathway with exenatide resulted in a significant improvement of motor function in treated patients, mirroring results from earlier preclinical studies using rodent models of PD. GLP-1 signaling is well known to play a role in glucose homeostasis, and agonists such as exenatide have long been used in the treatment of diabetes. Whether GLP-1 receptor targeting in these patients is merely inducing symptomatic effects or if it is treating the underlying disease in a neuroprotective manner remains to be seen. Interestingly, GLP-1 receptor signaling has in some studies been directly linked to mitochondrial biogenesis and function, raising the compelling possibility that exenatide could be neuroprotective in patients by correcting aberrant mitochondrial function in PD dopaminergic neurons. Although we await the precise mechanism of action for how GLP-1 receptor modulation is affecting PD, we are encouraged by the new therapeutic possibilities of approaching the disease from the angle of manipulating cellular metabolism.

Another recent study in the August 30, 2017 issue of *Nature* has shown that neurorestorative therapy may also be a viable approach

for PD treatment. Using a non-human primate model of PD, the authors injected human induced pluripotent stem cell (iPSC)-derived dopaminergic neuron progenitors into the diseased animals' brains, and saw a marked improvement in movement with a decrease in tremors in the treated monkeys. Interestingly, the authors saw a positive symptomatic effect using both iPSCs from normal and PD patients, which provides hope that patients may someday be the source of their own neuroregenerative treatment.

An important question in the field is whether PD has an autoimmune component. Scientists have speculated about this possibility, particularly since PD susceptibility has been genetically linked in some instances to specific major histocompatibility complex (MHC) alleles. A study in the June 29, 2017 issue of *Nature* may provide some insight into this connection, as the authors showed that PD patients (but not healthy controls) can raise cytotoxic T cells (CTLs) against alpha-synuclein, which is known to produce protein aggregates in some forms of PD. Since CTLs recognize antigen presented within the MHC complexes, this may explain the MHC genetic linkage. Whether and to what degree these CTLs contribute to disease pathology will take further studies, but this work brings to light the important question of how the immune system may fit into PD, and whether therapeutic manipulation of immune cells may have the potential to affect disease outcome.

Although the number of potential therapeutic avenues for the treatment of PD seem to be expanding rapidly, diagnostic tools for identifying the disease and monitoring its progression are still lagging behind. A positive response to L-DOPA treatment is currently one of the best indications clinicians have available for PD diagnosis, but we need a definitive blood test. In 2010, the Parkinson's Progression Markers Initiative (PPMI) was launched by the Michael J. Fox Foundation as a major international observational study in an effort to identify biomarkers of PD. A central goal of the PPMI is to create a repository of standardized, longitudinal biological samples and imaging datasets, and make them available to both academic and industry researchers. Given its scale, it is the hope that this large databank will reveal biological patterns unique to PD—giving clinicians tools for PD diagnosis, and giving researchers new insights into pathophysiological mechanisms of disease onset and progression.

Although L-DOPA has been the gold standard for treatment and diagnosis in the PD field—we clearly need to strengthen our arsenal of disease-modifying treatments and diagnostic tools. We are heartened by recent developments in treatment possibilities and look forward to where the field will go in the coming months.

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