Mitochondrial dysfunction in Parkinson's disease

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Parkinson's disease (PD) is a chronic and progressive neurodegenerative disorder that currently affects ~5 million people globally. For 90% of patients there is no known cause (idiopathic, iPD) and for all patients there is no cure. Diagnosis is late in the neurogenerative process when >60% of vulnerable neurons are already lost. There are few drugs available that target the numerous non-motor aspects of the disease and none that target the underlying degenerative process. Addressing these many deficits requires the discovery of the cellular pathways whose dysfunction initiates and/or contributes to neuronal death in PD. The involvement of mitochondrial dysfunction as a causal factor of PD is well supported by observations in patients. A number of familial forms of PD involve specific defects in mitochondrial proteins (Parkin, PINK1, DJ-1), while impaired OXPHOS activity has been observed in iPD patients. Further supporting the contribution of OXPHOS impairment to PD, OXPHOS complex I inhibition by MPTP or rotenone respectively produces PD symptoms in humans or acts as a PD mimetic in PD models.

We have discovered that elevated levels of PD protein alpha-synuclein or reduced expression of a PD-associated long non-coding RNA (lncRNA), both of which are observed in iPD patient brain samples, can impair OXPHOS function and might be responsible for the OXPHOS dysfunction detected in patients. It is anticipated that these discoveries will substantially improve our understanding of the underlying molecular mechanisms of iPD and identify potential targets for development into effective disease-modifying therapies for iPD patients.