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Mitochondrial Dysfunction in the Mechanism of Neurodegeneration of Familial Form of Parkinson's Disease

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The mitochondria are not only the largest producer of cellular energy but regulator of the cell death calcium and redox signalling. Mitochondrial dysfunction shown to be a trigger for neurological and neurodegenerative disorders and mitochondrial diseases manifests themselves with wide-ranging neurological symptoms. Parkinson's Disease (PD) is a common neurodegenerative disease characterised by progressive loss of dopaminergic neurons, leading to dopamine depletion in the striatum. Alpha synuclein aggregations have been shown to be a pathological hallmark in histological staining of PD patients. Missense mutations, and duplications or triplications of the SNCA gene, which encodes α-synuclein, lead to autosomal dominant early onset PD, that is clinically and pathologically similar to sporadic PD. Monomeric α-synuclein exerts a role in the regulation of mitochondrial ATP synthase. During Parkinson's disease, the monomer aggregates to generate oligomers, and these aggregates maintain an interaction with the ATP synthase. However, the oligomeric structure is uniquely redox active and targeted oxidation in close proximity to ATP synthase induces its conversion to the Permeability Transition Pore (PTP), triggering mitochondrial swelling and ultimately cell death. Inhibition of the oligomer-induced oxidation event prevents the pathological induction of PTP. Human stem cell derived neurons with elevated intracellular α-synuclein, and iPSC derived neurons bearing a SNCA triplication, generate α-synuclein aggregates that interact with ATP synthase and induce PTP opening, leading to neuronal death. This ability of the α-synuclein to directly induce ROS is a key point in triggering lipid peroxidation and ferroptosis. These findings bring new insight into the mechanism of neurodegeneration, emphasizing the importance of mitochondrial dysfunction in PD.

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