# Characterising the role of alpha synuclein in Ferroptosis in the context go Parkinson's disease

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**Résumé**

**Objective:**
Despite the involvement of alpha synuclein (a-syn) in Parkinson's disease (PD) pathology, the exact function of this protein and the mechanisms involved in the neuropathology remain unclear. Here we aim to demonstrate a pivotal interplay between a-syn, iron metabolism and ferroptosis in PD. By modifying endogenous a-syn we aim to determine whether there are changes in susceptibility to ferroptosis.

**Background:**

Iron accumulation and intracellular inclusion of aggregated alpha synuclein (a-syn) are two main hallmarks in Parkinson's disease (PD). Mutations in the SNCA gene encoding a-syn result in familial PD. Iron deposition in the brain tightly correlates with a-syn deposition in the dorsal substantia nigra and cortex. Recently, we have shown that a novel regulated cell death pathway termed ferroptosis, defined by iron-dependent lipid peroxidation, is predominant in pro-oxidant models of PD.

**Methods:**

Via CRISPR/Cas 9 we have modulated endogenous a-syn and created stable cells lines from LUHMES cells, a human neuronal cell line, which can be differentiated into dopaminergic neurons. Cell death in response to two different ferroptosis inducers - Erastin and RSL3, which act on different parts of the pathway, was measured by resazurin assay. Levels of lipid peroxidation were equally assessed with C11-BODIPY by flow cytomery.

**Results:**

We have observed that the absence of wild type a-syn conferred a protection against two

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ferroptosis inducers - Erastin and RSL3. This difference in cell viability was specific to ferroptosis since no difference was observed when inducing apoptosis or autophagic cell death by staurosporine or rapamycin respectively. Levels of lipid peroxidation in response to Erastin or RSL3 were significantly less in the dopaminergic neurons lacking wild type asyn.

**Conclusion:**
For several years, anti-apoptotic drugs have failed to afford any improvement in neuroprotection. For the first time, ferroptosis could represent the missing part to the puzzle in explaining the vicious circle between synucleinopathy, iron accumulation and subsequent cell death in Parkinson's Disease.

**Mots-Clés:** Alpha synuclein, Ferroptose, mort neurone, Fer, stress oxidant, peroxidation lipidique