Principal Investigator: Massimo Aureli

Grant Title: Dissecting the molecular mechanism linking GCase-dependent lysosomal impairment with Parkinson's disease

Abstract

Objectives: The project aimed to uncover the molecular mechanisms linking lysosomal accumulation of uncatabolized substrates to neuronal damage and to study glial activation due to the release of compounds from impaired lysosomes.

Methods Used: Induced pluripotent stem cells (iPSCs) were cultured, characterized, and differentiated into dopaminergic neurons and midbrain organoids. Various assays, including cell viability, immunoblotting, immunofluorescence, and LC-MS/MS proteomics, were used to evaluate protein and lipid expression and enzymatic activities. Glial cells were treated with vesicles from pathological neurons to assess glial activation.

Results: Differentiated iPSCs into dopaminergic neurons exhibited significant GlcCer accumulation and neurodegenerative changes upon CBE treatment. Proteomic and lipid analyses showed disrupted neuronal proteostasis and altered lipid composition. Enhanced lysosomal exocytosis and metabolic adaptations were observed. Glial cells treated with vesicles from pathological neurons showed increased inflammatory markers, suggesting potential propagation of neurodegeneration in Parkinson's disease. These findings provide insights into neuronal damage mechanisms and therapeutic targets for neurodegenerative disorders.