Alteration of autophagy and lipid metabolism in MPAN: what we know and still don't know.

Pathogenic variants in the C19orf12 gene cause Mitochondrial membrane protein-associated neurodegeneration (MPAN), a progressive neurodegenerative disorder. This study investigates the cellular mechanisms underlying MPAN pathogenesis, focusing on lipid metabolism, autophagy, and mitochondrial function. Extensive investigations in patient fibroblasts revealed no significant mitochondrial dysfunction, contrary to expectations based on the protein's mitochondrial localization. However, patient-derived fibroblasts exhibited defective autophagy activation and, when differentiated into adipocytes, showed abnormal accumulation of lipid droplets (LDs). We employ a combination of lipidomics and proteomics approaches to elucidate the relationship between impaired autophagy and LD accumulation. This research opens up novel avenues for therapeutic interventions by providing new insights into MPAN pathogenesis.