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OC.4-DYSREGULATION OF AUTOPHAGY HAS A POTENTIAL ROLE IN SYNJ1-ASSOCIATED EARLY-ONSET PARKINSONISM

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Several genes responsible for some of the hereditary forms of Parkinson's disease are implicated in distinct steps of the intracellular trafficking regulating the endo-lysosomal pathway. Among the others, we have recently reported how SYNJ1 mutations, which cause an early-onset parkinsonism (PARK20) are associated to an alteration of endosomal trafficking. In particular, we revealed a crucial role for Synaptojanin 1 (Synj1) in regulating the homeostasis and functions of early endosomal compartments. Importantly, the same alterations of early endosomal compartments and trafficking defects occur in fibroblasts derived from PARK20 patients, highlighting defective cellular pathways in PARK20 mutant cells. Furthermore, we also found that the structure of lysosomes resulted slightly altered in Synj1-deficient cells, despite any substantial difference in the levels of two lysosomal markers, Lamp-1 and cathepsin D. Because trafficking toward lysosomes is unaffected upon Synj1 silencing, the alteration of lysosomes could be due to changes in the autophagic pathway, whose activity is critical in many neurodegenerative diseases. Our results show how autophagy is indeed up-regulated in Synj1 silenced cells, as observed by measuring the levels and number of autophagosomes. The increase in autophagosome biogenesis can be, at least in part, explained by the alteration of the mTORC1 signaling, a key upstream modulator of the pathway. Nevertheless, the clearance of autophagy substrates results reduced in Sinj1 depleted cells, suggesting therefore a more complex scenario, which will need further investigations. Overall, our preliminary data corroborate the existence of a functional link between endosomal trafficking, autophagic pathway and Parkinson's disease.