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PROGRAMMA

MECHANISM OF PAROXETINE-MEDIATED AUTOPHAGIC INDUCTION IN CELL MODELS OF AMYOTROPHIC LATERAL SCLEROSIS AND FRONTOTEMPORAL DEMENTIA

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Protein aggregation is a hallmark of neurodegenerative diseases, including amyotrophic lateral sclerosis and frontotemporal dementia (ALS/FTD). The *C9ORF72*-hexanucleotide expansion G4C2 represents one of the most frequent genetic causes of ALS/FTD diseases. One molecular mechanism underlying *C9ORF72*-pathology is the accumulation of dipeptide repeats (DPRs) encoded by the G4C2 expansion. Additionally, TDP-43 inclusions are present in 98% of ALS and 50% of FTD cases. Persistent aggregates cause physical damage and sequester intracellular components, leading to cell damage. For this reason, enhancement of the proteostasis network represents a therapeutic approach in ALS/FTD.

Here, we dissected the mechanism of autophagic induction of the antidepressant paroxetine in motoneuron-like cells. We show that paroxetine induced the expression of autophagic markers LC3, SQSTM1/p62 and LAMP1, and enhanced the autophagic flux. Further analyses revealed that paroxetine was able to induce lysosomal membrane permeabilization. This event triggered the activation of Transcription Factor EB (TFEB), a master regulator of autophagy, previously shown to induce lysophagy, a selective form of autophagy for the turnover of damaged lysosomes.

Therefore, we tested if paroxetine-mediated autophagic induction favored the clearance of protein aggregates. Indeed, we observed a decrease in high molecular weight insoluble species and aggregates of proteins associated with ALS/FTD. In conclusion, these results indicate that the mechanism underlying paroxetine effects on autophagy involves TFEB-activity in response to lysosomal permeabilization. By activating autophagy, paroxetine displays a beneficial effect in cell models of ALS/FTD.