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ABSTRACT BOOK

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The role of extracellular vesicles in the removal of aggregated TDP43 responsible for ALS/FTD diseases

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Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD) are two related neurodegenerative diseases. ALS is caused by the death of both upper and lower motoneurons, while FTD is characterized predominantly by circumscribed atrophy of the frontal and temporal lobes. ALS and FTD overlap each other. This is demonstrated by the presence of cognitive and behavioral dysfunction in up to 50% of ALS patients and by the presence of frontotemporal atrophy in patients with ALS. Moreover, these diseases are both characterize by the presence of TAR DNA binding protein 43 (TDP43) inclusions in affected cells. These inclusions, observed in 97% of patients with ALS and 50% of patients with FTD, are composed by TDP43 and its C-terminal fragments of 35 kDa (TDP35) and 25 kDa (TDP25). These fragments are highly aggregation-prone and probably neurotoxic. Thus, their removal is protective for cells.

The mechanism responsible for the clearance of aggregates and misfolded proteins is the intracellular protein quality control (PQC) system. It consists of molecular chaperones/co-chaperones and the degradative pathways. PQC controls the folding status of proteins and prevents the aggregation of misfolded proteins by refolding them or degrading.

Recent data demonstrated that also extracellular secretory pathway, represented especially by exosomes (EXOs) and microvesicles (MVs), might be involved in the removal of misfolded proteins from affected cells.

Thus, we evaluated the role of EXOs and MVs in the secretion of TDP43 and its C-terminal fragments, using neuronal cell models.

We used ultracentrifugation, that allowed us to separate MVs from EXOs on the basis of their dimension. Then we analyzed them through i) Nanoparticle Tracking Analysis (NanoSight) to establish their number and sizes, and ii) western blot analysis, to characterize their protein content.

Our preliminary results show that TDP43, TDP35 and TDP25 are all secreted, mainly by MVs. In particular, we found that MVs are enriched of insoluble forms of TDPs and also of superoxide dismutase 1 (SOD1), another ALS-related protein. Finally, both in EXOs and in MVs, we observed the presence of some important PQC-components, suggesting an interplay between the two pathways.

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