Bari, 21-23 settembre 2023

ABSTRACT BOOK

P37 - VCP modulation rescues C9ORF72 pathological features in ALS-neuronal models

Veronica Ferrari [(1)] - Barbara Tedesco [(1)] - Marta Cozzi [(1)] - Marta Chierichetti [(1)] - Elena Casarotto [(1)] - Paola Pramaggiore [(1)] - Guglielmo Patelli [(1)] - Laura Cornaggia [(1)] - Margherita Piccolella [(1)] - Valeria Crippa [(1)] - Mariarita Galbiati [(1)] - Riccardo Cristofani [(1)] - Paola Rusmini [(1)] - Angelo Poletti [(1)]

Università degli studi di Milano, Dipart. Scienze Farmacologiche e Biomolecolari, Milano, Italia [(1)]

Amyotrophic Lateral Sclerosis (ALS) is a fatal neurodegenerative disease, in which upper and lower motorneurons are affected and die during the course of the disease. Different pathological mechanisms concur to motorneuronal death, e.g.: accumulation of toxic misfolded protein aggregates and/or alterations in lysosome functionality and stability. Several familial ALS (fALS) cases are linked to an hexanucleotide sequence (G_4C_2) repeated expansion in the *C9ORF72* gene, which results in the aberrant translation of five different dipeptide repeat proteins (DPRs) prone to aggregate and detrimental for cells. DPRs induce organelle alterations and protein quality control (PQC) system misfunctioning. VCP is an ATPase protein involved in several pathways of the PQC system. Here, we analyzed the biochemical behavior of each single DPRs in immortalized motoneurons, confirming their accumulation and intracellular localization and studying their impact on lysosome stability. All DPRs induced lysosome membrane damage and alterations in lysosome activity, that was exacerbated by a detrimental misregulation of autophagy induction. Indeed, we found that DPRs prevented the activation of autophagy that is normally triggered to remove damaged lysosomes, by impeding the nuclear localization of different transcription factors (TFEB and TFE3) regulating autophagy and lysosome biogenesis. In addition, by overexpressing VCP in these models we found a rescue in the accumulation of the most toxic DPRs. Data show an increase in the clearance mediated by VCP through either UPS or/and autophagy. VCP overexpression is also associated with a decrease in lysosome alterations which could be strictly correlated with DPRs aggregates clearance mediated by VCP. Thus, together these findings suggest VCP modulation as a possible target to decrease DPRs-mediated toxicity and rescue motoneuron viability.