National Meeting of
PhD Students in Neuroscience

"New Perspectives in Neuroscience: Research Results of Young Italian Neuroscientists"

National Meeting of PhD Students in Neuroscience

Naples, February 23, 2018

Congress Center of "Federico II" University of Naples
Aula Magna Partenope
Via Partenope 36, Naples

NOVEL ROLE OF VCP IN THE CLEARANCE OF MUTANT-SOD1 IN ALS

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Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disease with an incidence of 2-5 cases over 100 000 per year, for which no cure is aveilable. ALS is proteinopathy characterized by the presence of inclusions in the brain of affected individuals. Moreover, various mutations in genes bring to the expression of proteins that misfold and form aggregates. These aggregates are thought to be toxic for cell and concur to their death. Aggregates may form because of the failure of Protein Quality Control (PQC) system. The system recognises misfolded proteins, refolds them and where it is not possible it enhances their degradation mainly through the Ubiquitin-Proteasome System (UPS) or the autophagic pathway. SOD1 mutated is a clinical model of familiar form of ALS (fALS) linked to aggregation. SOD1 is the first gene found mutated in ALS and up to now are found more than 100 mutations of this gene that are correlated to 30% of fALS. SOD1 mutants misfold and are prone to form intracellular aggregates that are mainly degraded through UPS, but also through the autophagic pathway when the UPS is altered. Valosin Containing Protein (VCP) is an AAA^+ ATPase protein with a key-role in many pathways of the PQC system. VCP mutations in ALS and other neurodegenerative diseases is correlated with the presence of intracellular inclusions.
These date made us hypothesize a role of VCP in the clearance of these misfolded protein aggregates and in particular, we have studied VCP role in the removal of mutated SOD1 aggregates. In this work we demonstrate that the overexpression of VCP decreases the levels PBS-insoluble spices of mutated-SOD1 in a motor-neuron immortalized cell line (NSC-34). Moreover, studying these aggregates when VCP is overexpressed in a condition of inhibition of the UPS or the autophagic pathway, we define that VCP wild type mainly enhances SOD1 mutant degradation through the UPS. We also demonstrate that two point mutations of VCP correlated to ALS are not deleterious and do not alter VCP role in the removal of SOD1 mutant aggregates. However, these VCP mutants lose their function in this pathway when the UPS or the autophagic pathway are altered.
These data give a novel role to VCP in the removal of SOD1 mutant aggregates and once it will be well defined it could be studied as a target for these fALS cases. Moreover, it could be interesting to determine if this role of VCP is extended to other mutated protein found in intracellular inclusion, that are present in a higher percentage of ALS cases as TDP-43.

Grants: Fondazione Telethon, Italy; Fondazione Cariplo, Italy; Fondazione AriSLA, Italy; Association Française contre les Myopathies, France; Regione Lombardia; Fondazione regionale per la ricerca biomedica (FRRB) (TRANS_ALS), Regione Lombardia, Italy; Joint Programme on Neurodegenerative Diseases (JPND, CureALS); Università degli Studi di Milano e piano di sviluppo UNIMI - linea B; Italian Ministry of Health; PRIN - Progetti di ricerca di interesse nazionale.