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VCP: a novel regulator of SOD1-G93A clearance in a ALS model

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Valosin Containing Protein (VCP) is AAA+ ATPase protein involved in many pathways of the Protein Quality Control (PQC) system. One of VCP roles is to extract misfolded proteins from cytoplasmic aggregates and to cooperate in their refold processes or, if it fails VCP routes them to the Ubiquitin Proteasome System or to the autophagic pathway to be degraded. In many neurodegenerative diseases, like ALS and IBMPFD, mutations of VCP are found and have been correlated to the pathology. VCP mutations are associated to the presence of intracellular inclusions in the brain of affected individuals. Intracellular inclusions are one of the clinical features of ALS. These inclusions can be positive to SOD1 mutated or to TDP-43 in its wild type form. ALS is a proteinopathy due to mutations of genes that express protein which can misfold, form aggregates that can bring toxicity and eventually cell death.
In this context, knowing VCP key role in regulating proteinostasis and that VCP mutation and malfunctioning is related to the presence of intracellular inclusions in ALS, we have studied VCP role in the clearance of a mutant form of SOD1 (SOD1-G93A). This work demonstrates that overexpressing VCP in NSC-34, motor-neuron immortalized cell line, that transiently express SOD1-G93A, brings to a significant decrease of SOD1-G93A aggregates. Moreover, by studying the same features in conditions of inhibition of the UPS or the autophagic pathway we have determined that VCP contribute in SOD1-G93A clearance is mainly through the UPS. These data demonstrate that VCP is novel regulator of the degradation of SOD1 mutated.