The role of protein quality control system in Amyotrophic Lateral Sclerosis

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Amyotrophic lateral sclerosis (ALS) is the most common adult-onset motor neuron disease. ALS is sporadic (sALS) in the 90% of patients, while it develops in familial (fALS) forms in the remaining 5-10% of the cases. In fALS, specific gene mutations (i.e. SOD1, TDP-43, FUS, UBQLN2, C9ORF72) lead to the production of neurotoxic proteins or peptides prone to misfold, which then accumulate into aggregates. Notably, some of these proteins aggregate also in sALS, even if they are not mutated. To prevent aggregates-induced proteotoxic stresses, misfolded and/or aggregated proteins must be rapidly removed by the protein quality control (PQC) system. PQC system is composed by the chaperones, together with the degradative pathways (i.e the proteasome and the autophagy). We demonstrated that a member of the mammalian family of small Heat Shock Proteins (HSP), the chaperone HSPB8, plays an important role in misfolded proteins removal. HSPB8 is a chaperone induced by harmful events like proteasome inhibition. HSPB8 is expressed both in motoneuron and muscle cells, which are both targets of misfolded protein toxicity in ALS. HSPB8 interacts with the HSP70 co-chaperone BAG3 and enhances the degradation of misfolded proteins by autophagy. To efficiently remove misfolded proteins, the HSPB8-BAG3-HSP70 complex needs an active retrograde transport, mediated by dynein. Surprisingly, we demonstrated that inhibition of this transport does not increase misfolded proteins aggregation. Rather, dynein inhibition correlates with a reduced accumulation of mutant fALS proteins. This reduction is mediated by the proteasome, rather than by autophagy and correlates with the upregulation of the HSP70 cochaperone BAG1. In fact, BAG1 and BAG3 compete for HSP70-bound clients for their disposal by the proteasome or autophagy, respectively. When the misfolded proteins cannot be efficiently retro-transported to be stored into the aggresomes for autophagy degradation, the cells activate a compensatory mechanism that relies on the induction of BAG1 to target the HSP70-bound cargo to the proteasome in a dynein-independent manner.

Our data suggest that approached aimed at potentiating both HSPB8-BAG3 and/or BAG1 may contribute to the maintenance of proteostasis in ALS.

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