LECTURE 1

Proteotoxic responses in amyotrophic lateral sclerosis

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Amyotrophic Lateral Sclerosis (ALS) is a fatal neurodegenerative disease, in which upper and lower motorneurons are differentially affected and are selectively lost during during the course of the disease. This results in muscle atrophy and gradually to death of the patients mainly for respiratory failure.
ALS mainly occurs as sporadic (s)ALS form. Only 10% of cases are familial (f)ALS; of these, 40% involve the Chromosome 9 Open Reading Frame 72 (C9orf72) gene; other fALS associate to mutations in genes encoding for the proteins SOD1, TDP-43, FUS, SQSTM1/p62, TIA-1, optineurin, ubiquilin, and others, that are causative of motorneuronal death by different pathological mechanisms. One of the most studied is the proteotoxic stress triggered by potentially toxic misfolded proteins that accumulate perturbing several fundamental cell processes. In fact, both as wild type, but particularly when mutated, most of the protein products of these fALS genes (including the aberrant dipeptides (DPRs) arising from unconventional (RAN) translation of the G9ORF72 transcripts) are prone to misfold and to aggregate.
The intracellular proteotoxic response to these misfolded proteins and DPRs is based on the coordinate action of chaperones and the degradative systems, mainly the proteasome and the autophagy. Modulators of both the chaperones and of the degradative systems have been found able to modulate misfolded protein toxicity in a variety of preclinical models of fALS.
We tested compounds that are able to enhance the autophagy activity and/or to ameliorate the capability of chaperone assisted selective autophagy (CASA) in the removal of ALS associated misfolded proteins including C9ORF72 RAN translated neurotoxic DPRs and their aggregated species. Some of these have been recently clinically tested as potential therapeutic approach to treat different type of neurodegenerative diseases.
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