Abstract Book

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Molecular pathways controlling unconventional non-AUG translated proteins levels in ALS and FTD.

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Intronic GGGGCC (G4C2) hexanucleotide repeat expansions within the human C9orf72 gene represents the most common cause of familial forms of amyotrophic lateral sclerosis (fALS) and frontotemporal dementia (FTD). Repeat-associated non-AUG (RAN) translation of resulting RNA leads to the production of neurotoxic dipeptide-repeat (DPR) proteins. DPR proteins aggregate into cytoplasm or nuclei of motor neurons, altering the proteotoxic response machinery. The protein quality control (PQC) system maintains protein homeostasis by re-folding (by chaperone) or by degradation (by autophagy or proteasome) of misfolded proteins to counteract proteotoxic events. In a previous high-throughput drug screen for the identification of modulators of DPR levels. We identified i) forskolin (FSK, a cAMP-elevating compounds) as DPR protein levels enhancer, and ii) geldanamycin (GELD, an HSP90 inhibitor) and spironolactone (SPL, an aldosterone antagonist), as reducer of DPR protein levels. Interestingly, FSK-increased cAMP levels may activate PKA. We demonstrated that PKA blockage (by H89 treatment) or knockdown reduced translation efficiency (polyribosome profile) of DPRs in neuronal cells overexpressing DPR proteins, and in C9ALS/FTD patient-derived iPSC motor neurons with endogenous DPR protein levels. In motor neuron like cells, we analysed the involvement of the two main degradative pathways. We demonstrated that proteasome and autophagy pathways are responsible for DPR proteins degradation in cells treated with GELD and with SPL. Even if GELD and SPL did not increase the activity of autophagy or proteasome, we observed that their activity is completely counteracted by autophagy or proteasome blockage respectively. Our results suggest the degradative systems and the selective modulation of RAN translation as molecular targets to reduce DPR protein levels and neurotoxicity in C9ALS/FTD.