The role of the PQC system in managing misfolded protein in motoneuronal and muscular models of ALS and SBMA

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ABSTRACT

Motorneuronal diseases are fatal neurodegenerative diseases which include spinobulbar muscular atrophy (SBMA). Recent studies have demonstrated that both motorneuron and muscle cells are directly affected in SBMA patients. SBMA is caused by a poliglutammine stretch in the N-terminal region of the androgen receptor (AR) protein. In presence of testosterone ARpolyQ lose the proper conformation, misfolds and becomes toxic to cells. The protein quality control (PQC) system is in charge of protein homeostasis. The chaperone system maintains proteins in the proper conformation; if it fails misfolded proteins are directed to the degradative systems: the ubiquitin proteasome system (UPS) and the autophagy. We have already demonstrated that autophagy stimulation reduces protein aggregation in motorneuronal models of SBMA. Here we studied the involvement of the PQC system in the muscular response to misfolded toxic proteins and in the removal of aggregates, hallmark of the disease.

We tried to potentiate the autophagic response with trehalose in muscle C2C12 cells stably expressing AR with a stretch of 100 glutamine (C2C12_ARQ100). By filter retardation assay (FRA) we observed that ARpolyQ aggregation was reverted by trehalose. By RTq-PCR analysis we found that trehalose increased the expression of the small heat shock protein B8 a molecular chaperone involved in the autophagic machinery.

Overexpression of HspB8 in C2C12_ARQ100, interestingly, caused a significative reduction of ARpolyQ aggregation in FRA.

We extend our findings to a SBMA-related motorneuronal disease: the amyotrophic lateral sclerosis (ALS). As model of sporadic ALS we studied the TAR-DNA-Binding Protein of 43 kDa (TDP43) and its truncated form TDP43-25 that aggregates in the cytoplasm. Trehalose treatment of muscle C2C12 cells expressing both TDP43 and TDP43-25 caused no aggregate reduction.

In conclusion we demonstrate that the enhancement of autophagy is a possible therapeutical strategy for treating SBMA; in the case of sporadic ALS other degradative pathways should to be investigated as autophagic facilitation can not prevent aggregate formation.

GRANTS: Regione Lombardia; AFM-TELETHON, FRANCE; FONDAZIONE TELETHON, ITALY; FONDAZIONE CARIPLO, ITALY; FONDAZIONE ARISLA, ITALY; Ministero della Sanità, ITALY.