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Clearance of misfolded proteins in motoneuron disease: the case of Spinal and Bulbar Muscular Atrophy

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In order to control the cellular homeostasis and survival, the newly synthesized proteins are directed to Protein Quality Control system (PQC) to ensure the correct folding. PQC requires the coordinated action of molecular chaperones and proteolytic systems, the ubiquitin–proteasome system (UPS) and the autophago-lysosomal pathway (ALP). Although the PQC system efficiently remove all the intracellular proteins, some misfolded proteins might escape from PQC defence. The accumulation of misfolded and aggregated proteins is a common hallmark of several motoneuron diseases (MNDs), including spinal bulbar muscular atrophy (SBMA) and amyotrophic lateral sclerosis (ALS). SBMA is caused by a polyglutamine-expanded tract (polyQ) in the androgen receptor protein (AR). The binding of the ligand testosterone to the ARpolyQ induces protein misfolding and aggregation. The expanded polyQ tract confers to mutant AR a toxic gain-of-function that alters a cascade of several downstream pathways, including the PQC.

Using SBMA cellular and knock-in mice models, we observed that insufficient or impaired PQC activity contribute to ARpolyQ accumulation. In particular, ALP plays a crucial role in the clearance of ARpolyQ. We studied the activity of HSPB8-BAG3 complex, which acting with Hsc70 and CHIP, can direct ARpolyQ to ALP-mediated clearance. Analysing the expression of these genes in muscle of symptomatic SBMA mice, we found that HSPB8-PQC machinery is highly increased suggesting that ALP might be the preferential degradative pathway rather than UPS.

In this line, we analysed compounds able to activate or potentiate the HSPB8 machinery and ALP, in SBMA cell model. We have already tested the disaccharide trehalose, an m-TOR independent ALP inducer. Even the mechanism of action of trehalose is still unclear, we demonstrate that it is able removed the ARpolyQ misfolding also via induction of HSPB8 expression. However, the enzyme trehalase digest trehalose into glucose, reducing its bioavailability. Therefore, we used two trehalase-indigestible dysaccharides, lactulose and melibiose. We found that lactulose and melibiose counteract ARpolyQ aggregation with effects comparable to trehalose. Recently, we also tested another interesting compound Berberine, a traditional herbal medicine. Berberine reduced the ARpolyQ aggregates facilitating the clearance of the mutant proteins activating the PQC system.

These data suggest that the autophagy/PQC inducers might have therapeutic potential for SBMA and other misfolding-related MNDs.

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