Role of the autophagic pathway in a muscle model of Spinal and Bulbar Muscular Atrophy.

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Spinal and bulbar muscular atrophy (SBMA) is a motor neuron disease (MND) caused by a polyglutamine expansion in the androgen receptor (ARpolyQ) protein that interferes with the correct folding of the protein. Indeed, when ARpolyQ is activated by testosterone, it is released by the Heat Shock proteins and misfolds. In presence of misfolded proteins cells activate the protein quality control (PQC) system that is composed by a chaperone network, responsible for the refolding of proteins, and by two main degradative system the ubiquitin proteasome system (UPS) and the autophagy lysosome pathway (ALP). When chaperone system fails, misfolded proteins are addressed to the degradative pathways. If misfolded proteins are not correctly removed, they could aggregate in insoluble high molecular weight species. These inclusions are found in patient nervous system. Despite of being a MND recent data suggest that ARpolyQ exert toxicity also on skeletal muscle. Thus in this study we used muscle C2C12 cells stably trasfected with the AR carrying a tract of 100 glutammine to study the PQC system involvement in muscle during the disease.

Initially, we characterized the cellular model and by filter trap assay (FTA) we found that ARpolyQ accumulated after testosterone treatment. We also observed that after activation ARpolyQ is present in the insoluble NP-40 fraction. We inhibited the degradative pathways and observed that ARpolyQ is degraded by both UPS and ALP. As activators of the UPS are highly toxic we enhanced ALP with trehalose. We observed that trehalose treatment significantly reduced the accumulation of ARpolyQ. By real time PCR we observed that trehalose increased the expression of many ALP-related genes such as HspB8. HspB8 is a small heat shock protein that acts in the refolding of proteins or addresses them to ALP. We overexpressed HspB8 and found that it reduced ARpolyQ accumulation, while silencing HspB8 increased the accumulation in FRA.

These results demonstrate that modulating autophagy could be a promising therapeutical strategy for disease associated to misfolded and aggregation protein like SBMA.

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