THE CONTRIBUTION OF PROTEIN QUALITY CONTROL IN THE PATHOGENESIS OF SBMA.

Rusmini P.[1]*, Polanco M.[2], Crippa V.[1,3], Cristofani R.[1], Cicardi M.E. [1], Meroni M. [1], Galbiati M.R. [1], Pennuto M. [2], Poletti A[1].

[1] Dipartimento di Scienze Farmacologiche e Biomolecolari (DiSFeB) Centro di Eccellenza per lo studio delle Malattie Neurodegenerative (CEND), Università degli Studi di Milano, Via Balzaretti 9, 20133 Milano,Italia.

[2] Centre for Integrative Biology (CIBIO), Università di Trento,Italia.

[3] Present address: Laboratorio di Neurobiologia Sperimentale, Istituto Nazionale Neurologico C. Mondino, via Mondino 2, 27100 Pavia, Italia

phone: 02.50318214 email: paola.rusmini@unimi.it

Spinal and bulbar muscular atrophy (SBMA) is a motoneuronal diseases caused by an elogated polyglutamine (polyQ) tract in the androgen receptor (AR). The intracellular accumulation of ARpolyQ, induced by the ligand testosterone, altered the protein quality control system (PQC) and impaired the protective mechanisms deputed to refolding and clearance of misfolded proteins. Emerging evidence reveal that ARpolyQ toxicity is not related only to motoneuron degeneration but also to skeletal muscle damage. Using SBMA knock-in mice (113Q SBMA mice), we analysed the role of PQC in skeletal muscle. All mice were analysed both at a pre-symptomatic stage (8 weeks) and at symptomatic stage (24 weeks). At symptomatic stages, the skeletal muscle of SBMA mice showed an increased expression of muscular markers (MYOG, TGF-beta1, AchR) suggesting that there is atrophy accompanied by denervation. In this condition, we have analysed the transcriptional regulation of several proteins involved in the PQC system. We found no variations of the autophagic master key regulator TFEB expression, while all autophagic markers analysed were specifically induced in skeletal muscle of symptomatic tg SBMA male mice (p62, LC3 Beclin-1 ATG10). Moreover, we have analysed the expression of HSPB8, a pro-autophagic chaperone, and of the co-chaperones BAG3 and BAG1, involved in the autophagic and proteasomal removal of the misfolded proteins, respectively. We found that HSPB8, BAG1 and BAG3 were transcriptionally up-regulated in symptomatic tg SBMA male mice. Moreover, the ratio BAG3:BAG1, index of which PQC degradative pathways is preferred to clear misfolded proteins, was increased in favor of the BAG3. Collectively, these data might suggest that in the skeletal muscle of SBMA mice autophagy is highly activated and the data might elucidate how muscle responds to ARpolyQ toxicity.

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