

Regulation of translation of Ataxin-3 by Ataxin-2

Clévio Nóbrega¹, Sara Carmo-Silva^{1,2}, David Albuquerque³, Ana Vasconcelos-Ferreira^{1,2}, Udaya-Geetha Vijayakumar¹, Liliana Mendonça¹, Hirokazu Hirai⁴, Luís Pereira de Almeida^{1,2}

¹CNC - Center for Neuroscience and Cell Biology, University of Coimbra, Rua Larga, FMUC, 3004- 504 Coimbra, Portugal

²Faculty of Pharmacy, University of Coimbra, 3004- 517 Coimbra, Portugal

³Faculty of Sciences and Technology, University of Coimbra, 3004- 517 Coimbra, Portugal

⁴Department of Neurophysiology, Gunma University Graduate School of Medicine, Maebashi, Gunma, Japan

In polyglutamine disorders, proteins carrying abnormally long polyglutamine tracts interact aberrantly with other proteins contributing to neurodegeneration. In this work we focus on Machado-Joseph disease (MJD), a disorder associated to the polyglutamine-expanded ataxin-3 (Atx3MUT). Aiming at clarifying the mechanism of neurodegeneration we investigated the interaction of Atx3MUT with wild-type ataxin-2, a protein recently involved in ALS and PD pathogenesis, and whose mutated form causes spinocerebellar ataxia type 2.

Using cell and animal models of MJD, we found that Atx3MUT aggregation in the cell nucleus leads to re-location of Atx2 to the nucleus and a downregulation of its mRNA and protein levels. Importantly, our results suggest a role of Atx2 in translational regulation of specific transcripts, by reducing the protein synthesis through interaction with PABP. Accordingly, abnormal reduction of Atx2 cytoplasmic levels, by freeing its natural interactor and translation activator PABP, leads to an overactive protein translation of specific transcripts, particularly of Atx3MUT. Conversely, the restoration of Atx2 levels represses Atx3MUT translation and rescues neuropathological MJD-related abnormalities, due to interaction with PABP through PAM2 motif.

These data indicate a clear function of Atx2 in the regulation of the translation of specific mRNAs, particularly ataxin-3 and point to a key physiological role of ataxin-2 in MJD pathogenesis opening a new avenue for therapeutic intervention in this and potentially other polyglutamine disorders.