**Abstract**

**Title:** RBPome – RNA-binding proteins in Machado-Joseph disease: from pathogenesis to therapy

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Machado-Joseph disease (MJD), or spinocerebellar ataxia type 3 (SCA3), is a rare, uncurable neurodegenerative disease, belonging to the group of polyglutamine diseases. Despite the huge research effort made in the last years, the complete molecular mechanisms of pathogenesis that lead to neurodegeneration are not fully understood. Moreover, there is no treatment available for the patients that can stop or delay the disease progression. Therefore, there is an unmet and urgent need to continue research that characterizes the molecular pathology and to develop new therapies that are disease modifying.

RNA processing events play a major role in the regulation of brain development and normal functioning, which are highly regulated by RNA binding proteins (RBPs). Moreover, more than 50% of known RBPs are expressed in the brain, where they are involved in different processes such as alternative splicing, transport, localization, stability, and translation of RNAs. Reflecting these facts and their importance, RBPs have now been implicated in the pathogenesis of several neurodegenerative diseases. In 2015, we showed that two RBPs, Ataxin-2 and PABP, relevant for MJD/SCA3 pathogenesis, could be targeted for therapeutic strategies (Nóbrega et al., 2015, Brain). More recently, we showed that other RBP, G3BP1, is also very important for the pathogenesis of MJD/SCA3, and that its use through gene therapy can reduce several disease-associated hallmarks (Koppenol et al., 2021, Brain). These studies clearly highlight that RBPs must be investigated in MJD/SCA3, with focus on their possible involvement in the disease pathogenesis, but also to unveil new targets for therapy development. Therefore, we studied the RBPome (RBPs expression) in an MJD/SCA3 transgenic mouse model, identifying differentially expressed RBPs that could impact the disease pathogenesis. Several of these RBPs are recruited to stress granules (SGs), which we proposed as cellular foci potentially involved in MJD/SCA3 pathogenesis (Marcelo et al., 2019, Cell Death Dis). Others RBPs recruited to SGs are HSPA8 and CARHSP1 that were found to be dysregulated in MJD/SCA3. Their modulation led to the mitigation of behavior deficits and neuropathological abnormalities in different MJD/SCA3 mouse models. Altogether, our data point to an overall dysregulation of RBPs expression in MJD/SCA3 and that several RBPs are promising targets for the development of disease-modifying therapies.