

DESCRIPTION FOR THE GENERAL PUBLIC (IN ENGLISH)

Spinocerebellar ataxia type 3 (SCA3), also known as Machado-Joseph disease, is the most frequent form among the autosomal dominantly inherited spinocerebellar ataxias worldwide. SCA3 belongs to the group of at least nine polyglutamine diseases, which share specific mutation i.e. an abnormal expansion of CAG repeats located in the coding region of the functionally unrelated genes. In case of SCA3, *ATXN3* encoding ataxin-3 is the affected gene. Despite extensive research, the exact molecular and cellular pathways underlying the SCA3 neurodegeneration remain elusive, and no preventive treatment is available. It is presently believed that expanded CAG triplets exert their pathogenic effect in SCA3 at protein and RNA level. Mutant ataxin-3 harboring long tracts of glutamine has the propensity to fold abnormally and form aggregates, that may be harmful for neuronal cells. On the other hand, mutant CAG repeats accumulate as intranuclear RNA *foci*, that sequester RNA-binding proteins and lead to a loss of their normal function. The recent data suggest that there might exist also another pathogenic pathway for SCA3. It turned out that expanded repeats, located mainly in the non-coding regions, trigger unconventional translation called repeat-associated non-AUG (RAN) translation, and in complete absence of AUG start codon, lead to the production of various homopolymeric or dipeptide repeats proteins. Many reports provide strong evidence that these unusual proteins might be involved in the pathogenesis of the expanded repeat diseases.

In this project we intend to achieve two important goals. First, to demonstrate that RAN translation occurs at CAG repeats in SCA3. Second, to provide evidence that RAN-translated proteins contribute to SCA3. To address these tasks, we will perform comprehensive analyses using various experimental models of SCA3. We will determine expression pattern, cellular distribution, aggregation capacity and cell death-inducing ability of individual RAN-translated proteins. To gain deeper insight into RAN translation involvement in SCA3, we will analyze putative RAN translation toxicity markers in studied disease models. In addition, we will use proteomics approach to identify proteins which specifically interact with RAN-translated proteins.

The research proposed herein will broaden existing knowledge about the pathways underlying CAG toxicity in SCA3, and may reveal RAN translation as a new player on the stage of SCA3 pathogenesis. This information will open new, promising avenues for developing novel therapeutic strategies for this devastating and fatal polyQ disease.