Ekspression of circular RNA in myotonic dystrophy type 1 - implications to pathogenesis

Muscular dystrophies belong to a group of human neurodegenerative disorders associated with expansions of simple repetitive elements within specific genes. The most common form of muscular dystrophy is myotonic dystrophy type 1 (DM1). DM1 is caused by the expansion of an unstable (CTG)n repeat in the 3'-untranslated region (3'UTR) of the *DMPK* gene. The pathomechanism of DM1 is associated with the gain-of-function of mutant *DMPK* transcript containing expanded number of CUG repeats. Expanded CUG repeats interact with some RNA-binding proteins, affecting their activity. Examples of such proteins are muscleblind family proteins (MBNL) and CUG triplet repeat RNA binding protein (CUGBP), which are splicing factors. Alterations in the splicing factors result in aberrant splicing of their target genes.
Recent studies have discovered a new class of RNA molecules, whose generation depends on a non-canonical form of alternative splicing. They are called circular RNAs (circRNAs) Unlike the other types of RNA, circRNAs are covalently closed circular molecules. The function of the vast majority of circRNAs is still unknown. However, it is known that most circRNAs contain exons of protein-coding genes and that they are processed cotranscriptionally, which implies that their formation competes with the formation of linear transcripts. Recently it was proposed that an important role in circRNA biogenesis is played by MBNL1 protein. Taking into account the arguments mentioned above, i.e. sequestration of MBNL proteins in DM1 cells and the crucial role of MBNL1 in the circRNA biogenesis, we hypothesize that the level of at least some circRNAs is aberrantly regulated (downregulated) in DM1 and therefore circRNA may play a role in the pathogenesis of DM1. The objective of the proposed project is to investigate the expression level of selected circRNAs in DM1 and to establish the role of the potential alterations in the pathogenesis and development of the disease.

The proposed project encompasses two major research aims. In the framework of the first aim, the comparison of circRNA expression in DM1 and normal samples will be conducted. For this purpose, the expression of selected circRNAs (~20) will be analyzed in samples derived from muscle biopsies of DM1 patients and in DM1 myoblast cell lines, as well as in a similar number of corresponding control samples. The obtained profiles of circRNA expression will be compared with clinical data available for DM1 samples. In the framework of the second aim, the analysis of common genetic variation and conservation (the occurrence of SNPs) of circRNA splice sites will be conducted. I will perform this analysis with the use of data collected in the literature and in publicly available circRNA/SNP databases.

The results that will be obtained in the proposed project will shed more light on pathogenesis of DM1 and on the role of circRNAs in this disease. Identified circRNAs undergoing specific downregulation in DM1 may in the future become biomarkers or targets for DM1 therapy. This result may have more general implications also in the pathogenesis of other trinucleotide repeat expansion diseases (TREDs), such as Huntington disease, spinocerebellar ataxia, or DM2. It may add up new mechanism of circRNA-induced pathogenesis.
Moreover, regardless of whether circRNAs will be found associated with the pathogenesis of DM1, the analysis will add up to the knowledge on circRNAs biogenesis.