

Proper body development is underlain by a multi-faced regulation of diverse and complex biochemical processes. Considering molecular aspects, one gene in our bodies may code several protein isoforms as a result of a process called alternative splicing. In this process, the precursor mRNA, following enzymatic reactions, is remodeled distinctly depending on tissue-specificity as well as presence and concentration of regulatory factors. The family of MBNL (Muscleblind-like) proteins constitutes such tissue-specific regulators of RNA metabolism including alternative splicing and plays an essential role in proper transition from fetal to adult splicing isoforms leading to the expression of adult-like isoforms of proteins. MBNL proteins deserve special attention since their functional depletion in cells underlies a relatively frequent and severe genetic disease – myotonic dystrophy (DM), associated with pathological alterations in multiple organs and manifests as for example the muscle myotony, myopathy of skeletal muscles and heart or development of cataract. The pathomechanism of DM is associated with a mutation in a single gene, which expression leads to the accumulation of the so called toxic RNA sequestering MBNL proteins in the nucleus. MBNL1 deficiency in cells results in the expression of fetal protein isoforms in the adult body.

MBNL proteins recognize and bind specific RNA sequence motifs within regulated transcripts through a binding domain. The aim of the project is to define the mechanism of structural and functional interaction of MBNL with RNA and consequently alternative splicing regulation. The objects of my research are the structural aspects of MBNL domains, as well as structural conformation of targeted RNAs as predominant determinants of effective binding and splicing activity as well as other protein factors which assist in MBNL:RNA complex formation.

The MBNL family consists of three paralogs MBNL1, MBNL2 and MBNL3 which, as our results show, interact with the same RNA sequence motifs and regulate the same transcripts but with different activity. Their expression is rather a dynamic and specific process occurring with different intensity in distinct tissues. MBNL1 and MBNL2 are predominantly responsible for the muscle cell differentiation, contrarily to MBNL3 which is remarkably significant during initial stages of fetal development and muscle regeneration. In this project, I would like to focus on shedding more light on a mechanism underlying different paralogs' activity, as well as the functional implications of this phenomenon mainly in reference to muscle cells during regeneration.

Gained knowledge will be a valuable piece to better understand DM pathomechanism, as well as develop potential experimental therapies against DM.