

Searching for new therapeutic targets in polyglutamine diseases

Expansion of the CAG/CTG motif in functionally unrelated genes is a causative factor in at least 16 hereditary neurological and neuromuscular disorders, including Huntington's disease (HD) and myotonic dystrophy type 1. Currently these diseases are incurable. The CAG repeats are unstable and, upon reaching a certain length threshold, may elongate out of control, leading to the formation of mutant proteins. The mechanism of repeat instability is not yet fully understood. It has been proposed that CAG long repeats have the ability to form DNA structures that can interfere with cellular processes.

While shortening the repeat tract would be a very promising therapeutic strategy for all repeat expansion diseases, we still do not know how to induce repeat contractions and control expansions. Generation of double-stranded or single-stranded DNA breaks within expanded repeats using genome editing technology may result in unexpected mutations and chromosomal rearrangements. In order to develop more specific therapeutic approaches that do not induce DNA damage, it is essential to understand the mechanisms of repeat instability. Of special importance are mechanisms and factors responsible for specific shortening of repeats in non-dividing cells, such as neurons which are the main site of pathogenesis in neurodegenerative disorders.

Therefore, the aim of this project is to better understand the mechanisms of CAG repeat instability, and to identify new therapeutic targets that can be used for safe and controlled repeat contraction. We plan to achieve these objectives by implementing the following tasks: (1) identification of genes and cellular processes involved in CAG repeat instability, (2) validation of the contribution of selected candidate genes/pathways to repeat instability, (3) analysis of factors influencing the instability of CAG repeats (genetic context and cell type), (4) controlled contraction of CAG repeats in mouse model of HD.

New methods, such as CRISPR interference screens and next-generation sequencing allow for analysis of complex biological processes in a precise and high-throughput manner. These tools will be used for large scale analysis of genes and pathways involved in CAG repeat instability. In addition, we will use human cellular models of neurodegenerative disorders, such as patient-derived fibroblasts, neuronal cells and hepatocytes derived from iPSCs with identical genetic background.

Currently, there are no treatment methods for diseases caused by repeat expansion, and several advanced and promising clinical trials for HD have failed this year. The development of a method for controlled "shortening" of the expanded repeats could solve the problem of treating many human genetic diseases. Our experience in large-scale analysis of repeated sequences, gained during the project implementation, along with bioinformatics algorithms and research protocols, will be very helpful for the scientific community.