MicroRNA profiling in cellular models of Huntington's disease generated using iPSC technology

MicroRNA (miRNA) are large group of small non-coding RNAs that fine-tune gene expression. They interact with mRNA of target genes and modulate translational efficiency by inhibiting translation, with or without transcript degradation. A enormous regulatory potential of miRNA is associated with the fact that one miRNA can regulate many genes as well as sequence heterogeneity of individual miRNAs. It is known more than two thousand mature human miRNA sequences. Moreover, during miRNA biogenesis from the precursor can be released not only the canonical miRNA but heterogeneous pool of sequences called isomiRs, which additionally increase regulatory potential of miRNAs.
miRNAs are involved in many physiological and pathological processes. In case of the neurodegenerative diseases, like Huntington's disease (HD), there are observed changes in miRNA expression profiles. Deregulation of miRNAs can be both cause and effect of disturbances in cell homeostasis caused by the presence of altered huntingtin (HTT) gene products: the mutated transcript and protein. Particular sensitivity to neurodegeneration caused by the mutant form of HTT show striatal and cortex neuronals.
Due to the difficulties with modeling neurological diseases we will use induced pluripotent stem cells (iPSCs) technology to obtain material derived from patients and exhibiting the properties of neuronal cells. iPSCs are generated by the process of reprogramming which means dedifferentiation of somatic cells derived from patients and healthy individuals (most often fibroblasts- cells obtained by skin biopsy). Generated iPSC colonies exhibiting pluripotency may then be used to generate any type of cells by an stimulated differentiation. Using this technology it is possible obtaining in vitro neuronal cells with a mutations in any gene, including HTT, for disease modeling and drug screening in variants therapeutic strategies (Figure).

The aim of the project is to find connection between miRNAs deregulation and pathogenesis of HD by using latest technologies: next-generation sequencing and iPSC technology. Significant changes in miRNA levels in patients cells can indicate their direct involvement in pathological processes. Further analysis will precede with a detailed bioinformatics predictions, which will allow us to link miRNA deregulation with a reduced or increased expression of certain genes involved in the pathogenesis of HD. Global analysis of miRNA and isomiRs in human neuronal cells will also help to identify new biomarkers of HD.

Additionally, miRNA has been shown to participate in the process of reprogramming, but considerably less is known about the involvement of miRNAs in neuronal differentiation processes. Comparison of miRNA expression profiles of iPSCs and iPSC-derived neuronal stem cells will help to better understand role of miRNAs in neurogenesis process.
The research conducted under this project will therefore deepen the knowledge about the possibilities of using iPSC technology in the study of neurodegenerative diseases, and the roles of miRNAs in the pathogenesis of one of the most common diseases of the group- Huntington's disease.