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Project: Deciphering the role of m6A RNA methylation as a new layer of gene expression regulation in Huntington´s disease pathology (MetHD)

Summary of the project:

Huntingtons disease is a devasting disorder that cause irreversible decline in control of mood, memory, and movement. The main cause of HD is a mutation in the huntingtin gene that leads to generation of toxic fragments by proteolytic processing as well as by incomplete splicing of mHTT pre-mRNA. In the last years it has been shown that mutant huntingtin toxicity disrupts the normal signalling of many intracellular pathways that lead to synaptic dysfunction and death of striatal neurons. Some of these alterations are attributed to perturbations in cellular transcriptional programmes that induce changes in the pattern of gene expression. So far, the posttranscriptional mechanisms regulating the HD transcriptome and importantly the expression of the causative gene, are not completely understood. Recently, several studies have revealed a new dimension of posttranscriptional regulation of gene expression relying on RNA modifications, known as epitranscriptomics. Among them m6A has been shown to play a crucial role in orchestrating the gene expression patterns needed for the development and activity of the nervous system in health and disease. Interestingly, our previous findings showing alterations in the hippocampal epitranscriptome of HD mice suggest that aberrant methylation in mRNA could play a critical role in HD. We hypothesize that m6A is involved in the regulation of the gene expression programmes in HD as well as in the expression of the toxic form of mHTT which is the causative factor in this disease. To validate this hypothesis, we propose in this project to determine the contribution of m6A mRNA modifications in the control of gene expression in the HD striatum. To accomplish this aim we will map these modifications in HD mice with a well-established transcriptome-wide study of m6A and characterize expression of m6A-associated enzymes. The study of the m6A landscape in the HD striatum and its function on the posttranscriptional control of gene expression could contribute to design new therapeutic modalities that target specific epitranscriptomic processes.

We are seeking for highly motiovated **master students** (Master of Neurosciences, Master of Molecular Biotechnology or Master of Genetics and Genomics) to work in our project and carry out their final thesis of master. Interest in RNA Biology and Neuroscience is required.