IDENTIFICATION OF NOVEL DISEASE MODIFIERS IN HUNTINGTON'S DISEASE: NEURO-GLIA INTERACTIONS IN THE PATIENT-DERIVED MULTIDIMENSIONAL MODEL

Neurodegenerative diseases (NDDs), including Alzheimer's disease, Parkinson's disease, Huntington's disease (HD) and amyotrophic lateral sclerosis are devastating, age-related disorders resulting from the neuronal cell death. The incidence of NDDs cases rises continuously in the aging population, which represents an increasing socioeconomic burden. Despite substantial efforts and extensive studies in the field, no effective therapies have been proposed and NDDs are largely uncurable. This drawback is in part due to the lack of reliable models that would provide good translatability to the clinic. Therefore, implementation of models that better introduce the human context is essential for the identification of strategies that will benefit the human condition. Such approaches are particularly difficult in case of NDDs, as cellular phenotypes are the results of cumulative effect of genetic predisposition and aging. Recently introduced models of direct reprogramming of somatic cells obtained from patients to cells of neural lineage offer unprecedented possibility to explore molecular mechanisms of NDDs *in vitro*.

The deposition of misfolding-prone proteins is one of the major hallmarks and a common feature of NDDs. Cells evolved a sophisticated protein quality control (PQC) system that protects them from the accumulation of harmful proteins. Multiple evidence points to the deregulation of this system in NDDs. We have previously shown that prolonging the first line of defense against cellular stress, protects cells from the deleterious consequences of misfolded proteins accumulation. In turn, prolonging this first line of defense pharmacologically prevented the development of different protein misfolding diseases in mice. Importantly, applied strategy was effective to prevent unrelated NDDs, which points to the broad application of general approaches that target the PQC.

In my team, we focus on the Huntington's disease, the most common monogenic NDDs. Recent studies led to the identification of novel genetic factors that correlate with the pathology of HD, revealing also genes implicated in PQC. Specific changes were observed also in cells accompanying neurons, namely astrocytes, whose role in the HD pathology remains largely unexplored. We consider these genes as potential disease modifiers, i.e. such genes which either aggravate or ameliorate the pathological features. In this project, we will investigate the effect of genetic manipulation of candidate genes in neurons and astrocytes reprogrammed from patient-derived somatic cells to identify novel, effective modulators of HD pathology. We will further explore the relevance of selected genes in the context a neuro-glia dialogue in co-culture as well as *in vivo*. Finally, we will investigate the downstream mechanism engaged in the function of selected hits.

In summary, accomplishment of this study will improve our understanding of the molecular mechanisms underlying the HD pathology both in neurons and astrocytes. We expect to discover factors with therapeutic potential in the therapy of HD and other NDDs.