Understanding Huntington's disease using iPSC-derived models: insights into personalized medicine

Magdalena Czeredys

Mossakowski Medical Research Institute, Polish Academy of Sciences, Department of Stem Cell Bioengineering, Huntington's disease Group, Warsaw, Poland

Induced pluripotent stem cells (iPSCs) are cells originally taken from the skin or blood of adult subjects that have been reprogrammed back into an embryonic-like pluripotent state. Therefore, iPSCs are capable of differentiating into any type of cell in the body. Since iPSCs keep the genetic material of the donor, it is possible to obtain patient-derived stem cells that can recapitulate a disease by showing how different cell types or tissues behave in a given pathology, as opposed to those cells or tissues obtained from a healthy individual.

In our lab, we have obtained iPSC lines from healthy individuals and Huntington's disease (HD) patients with adult and juvenile onsets. HD is known as a neurodegenerative disease and recently has also been considered as a neurodevelopmental disorder. We use these cell lines to generate and characterize striatal neurons called medium spiny neurons (MSNs) and three-dimensional structures called organoids that resemble the brain and internal structures being affected in HD, such as the striatum. We also model interactions between different brain regions involved in HD using iPSC-derived assembloids and enrich them with microglia differentiated from iPSCs to study neuroinflammation.

All of these models are *in vitro* cultures that allow us to model HD and identify pathological mechanisms using patient-derived cells. Our data show that iPSC models differ between both HD onsets compared to controls. Moreover, the identified pathological features may have clinical relevance, including applications in personalized medicine.

The therapeutic potential of iPSCs has been radically increasing over the last years, as they are being used in drug discovery, including screening and toxicology. In addition, they provide a solid platform to develop patient-specific cell therapy products that have no risk of rejection. Moreover, the patient-derived neural cells that can be obtained by iPSC differentiation can undergo genetic modifications to correct the causing mutation of a disease. These approaches have been successfully performed in iPSC-derived models of HD, holding promise for future clinical trials on cell replacement therapy.

This work was supported by the NCN OPUS grant 2023/49/B/NZ3/04131.

References:

Piechota M, Latoszek E, Liszewska E, Hansíková H, Klempíř J, Mühlbäck A, Landwehrmeyer GB, Kuźnicki J, Czeredys M*. Generation of two human iPSC lines from dermal fibroblasts of adult- and juvenile-onset

Huntington's disease patients and two healthy donors. Stem Cell Res. 2023 Sep;71:103194. doi: 10.1016/j.scr.2023.103194.

Latoszek E, Piechota M, Liszewska E, Hansíková H, Klempíř J, Mühlbäck A, Landwehrmeyer GB, Kuznicki J, Czeredys M*. Generation of three human iPSC lines from patients with Huntington's disease with different CAG lengths and human control iPSC line from a healthy donor. Stem Cell Res. 2022 Oct;64:102931. doi: 10.1016/j.scr.2022.102931.