Researchers decode a puzzling movement disorder

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Neurodegenerative diseases represent one of the greatest challenges of our aging society. However, investigation into these diseases is made particularly difficult due to the limited availability of human brain tissue. Scientists from the Life & Brain Research Center and Neurology Clinic of Bonn University have now taken a roundabout path: They reprogrammed skin cells from patients with a hereditary movement disorder into so-called induced pluripotent stem cells (iPS cells) and obtained functional nerve cells from them. They subsequently decoded how the disease arises. Their results have now been published in the specialist periodical *Nature*.

The so-called Machado-Joseph disease is at the center of the current Bonn study. This is a disorder of movement coordination which was originally described in inhabitants of the Azores of Portuguese descent and which represents the most frequent dominantly inherited cerebellar ataxia in Germany today. The majority of patients develop gait abnormalities and a series of other neurological symptoms between the ages of 20 and 40. The cause of the disease is a recurring genetic sequence in the ataxin-3 gene which leads to agglutination of the corresponding protein and as a result, the nerve cells in the brain become damaged eventually. Until now, it was not clear why the disease only affects nerve cells and how the abnormal protein agglutination is triggered.

"Jack-of-all-trades" from skin specimens of patients

In order to study the disease process on a molecular level, scientists working with the stem cell researcher Prof. Dr. Oliver Brüstle at the Institute for Reconstructive Neurobiology at Bonn University initially produced so-called induced pluripotent stem cells (iPS cells) from small skin specimens from patients. These induced pluripotent stem cells are cells which are returned to a very early, undifferentiated stage. These „jacks-of-all-trades“ – once obtained – can be multiplied to a nearly unlimited degree and they mature in all cells of the body. In the next step, the team working with Prof. Brüstle converted the iPS cells into brain stem cells from which the scientists were able to develop as many nerve cells needed for their investigations.

In particular: Since the nerve cells come from the patients themselves, they have the same genetic changes and can therefore serve as a cellular model of the disease. ”This method allows us to research the disease in the cells that are actually affected and which we otherwise could not access - almost as if we had placed the patient’s brain into the cell culture dish,“ says Dr. Philipp Koch, a long-time colleague of Prof. Brüstle and one of the lead authors of the study. Together with his colleague Dr. Peter Breuer from the Neurology Clinic and Polyclinic of the Bonn University Medical Center, Koch electrically stimulated the artificially created nerve cells. In doing so, the researchers were able to show that the formation of the protein aggregates is directly correlated with the electrical activity of the nerve cells. ”The enzyme calpain plays a key role in this; calpain is activated by the increased calcium content of stimulated nerve cells,“ says the biochemist Breuer. ”This newly identified mechanism explains why the disease only affects nerve cells,“ Prof. Brüstle points out.

Reprogrammed nerve cells as a study objective for drugs

”The study illustrates the potential that this special type of stem cells has for neurological disease research,“ says Prof. Dr. Thomas Klockgether, Clinical Director of the German Center for Neurodegenerative Diseases (DZNE) and Director of the Bonn University Clinic for Neurology, whose team closely collaborated in this study with the scientists working with Prof. Brüstle. For Prof. Brüstle, this is reason enough to contemplate new configurations: ”We need interdisciplinary departments in which scientists from stem cell biology and molecular disease research work together side by side.“ Prof. Dr. Dr. Pierluigi Nicotera, scientific chairman and chief executive of the DZNE, concurs: “The DZNE is very interested in cooperative arrangements. Because reprogrammed stem cells have enormous potential for understanding the pathology of neurodegenerative diseases.“

As a next step, Prof. Brüstle and his colleagues from Life & Brain want to use reprogrammed nerve cells for the development of active substances to treat neurological diseases.

More information: Koch, P., Breuer, P., Peitz, M., Jungverdorben, J., Kesavan, J., Poppe, D., Doerr, J., Ladewig, J., Mertens, J., Tüting, T., Hoffmann, P., Klockgether, T., Evert, B.O., Wüllner, U., Brüstle, O. (2011) Excitation-induced ataxin-3 aggregation in neurons from patients with Machado-Joseph disease. *Nature* doi:10.1038/nature10671

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