GENE THERAPY

In vivo glia-to-neuron conversion corrects Huntington's disease in mice

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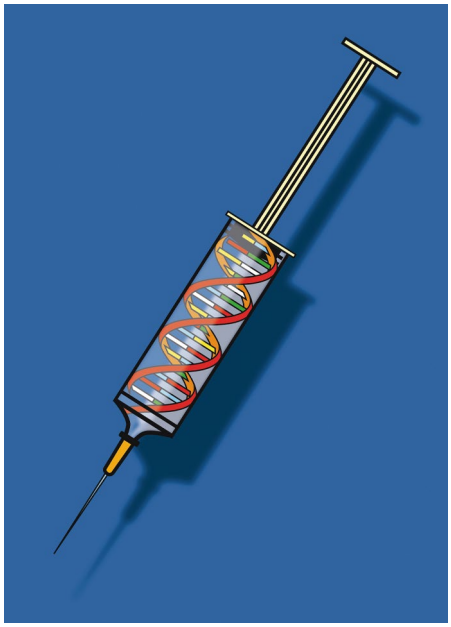
Huntington's disease (HD) is an inherited neurodegenerative disorder caused by intracellular aggregation and accumulation of mutant huntingtin proteins in brain cells, resulting in gradual and progressive loss of neurons. No cure is available for this disease, but preclinical studies have reported successful results, offering the hope of a future therapy. In rodent models for example, decreasing the level of mutant protein with antisense oligonucleotides or CRISPR/cas9 gene editing technology can improve HD features. In light of these results, human studies were initiated, notably a phase I/II trial to evaluate the safety of antisense microRNAs therapeutics for HD. Cell transplantation has emerged as a potential strategy to replace lost neurons in HD, despite a risk of immune rejection by the host.

In a study published in *Nature Communications*, a team of investigators from Pennsylvania State University describes a new gene therapy approach to convert astrocytes—a type of glial cells—into neurons in the brain of mice with HD. By showing that the therapy improved pathological features of HD, this study demonstrates that in vivo glia-to-neuron conversion might be a viable strategy to treat HD.

"In comparison to transplantation of external cells, the astrocyte-converted neurons are in the right place from the very beginning," explain the investigators in their report. In this case, the right place refers to the striatum, an area of the brain particularly vulnerable in HD. GABAergic medium spiny neurons (MSNs) are the most abundant neurons within the striatum and show early degeneration in the striatum of patients with HD. The study was designed to replace this specific type of neurons using glial cells as a cell source. Although studies had previously reported the successful conversion of astrocytes or NG2 cells—another type of glia—into neurons in mouse brains, in vivo conversion of glial cell into MSN had not yet been achieved.



Gene therapy. Credit: Thisisnotme / Alamy Stock Photo

Glial cells were reprogrammed via adeno-associated virus (AAV)-mediated introduction of two transcription factors—NeuroD1, which mainly generates glutamatergic neurons, and Dlx2, which is critical for generating GABAergic neurons—in the striatum of the mice. The gene therapy efficiently converted astrocytes into GABAergic neurons when administered in 2 months old R6/2 mice, a well characterized and widely used model of HD that shows early signs of degeneration, and in 15 months old YAC128 mice, a more slowly developing HD model, indicating that the strategy also worked in very old mice.

The functional properties of astrocyte-converted neurons were assessed in acute striatal slices from R6/2 mice using whole-cell recording at 30–32 dpi following AAV infection. The results show that converted cells had similar firing pattern and electrical properties to those of native striatal neurons. Further analysis indicated that the converted cells were also able to integrate local synaptic circuits and to restore the axonal projections to the basal ganglia, which are severely disrupted in HD brains.

At 38 dpi (viral injection at 2 months old), 93.9% of the R6/2 mice that were injected with NeuroD1 and Dlx2 were still alive, whereas only 55.2% of the R6/2 mice that received control AAV injection survived. In addition to extended lifespan, treated R6/2 mice showed reduced weight loss and improved locomotion compared with control mice, indicating that in vivo cell conversion could alleviate the abnormal phenotypes in the R6/2 mice.

In the discussion of the article, the investigators acknowledge the limitations of the proposed gene therapy. First, glial cells need to be present in the brain for cell conversion to occur. However, in patients with severe degeneration, glial cells are also damaged, and the deficit of glial source might limit the efficiency of cell conversion. Second, converting astrocytes into neurons does not directly address the gene mutation problem. The converted neurons might still develop pathological inclusions and degenerate again. Additional interventions such as tissue transplantation to compensate for glia loss and CRISPR gene editing techniques to correct gene mutations might therefore be necessary to complement the gene therapy.

This proof-of-principle study confirms that striatal astrocytes can be converted in vivo into GABAergic neurons and improve the phenotype of HD mice. "The significant extension of life span in the R6/2 HD mouse model after our NeuroD1+ Dlx2 gene therapy treatment suggests that a potential disease-modifying therapy is now on the horizon for HD and other neurodegenerative disorders," conclude the investigators.

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