NEURODEGENERATIVE DISEASE

ASO-mediated conversion of glial cells into neurons

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There is no effective treatment to prevent the clinical progression of neurodegenerative diseases. Cell reprogramming is a promising strategy to replace the neurons lost to disease and repair brain circuitry, and several studies in rodents have reported the successful conversion of glial cells into neurons using adeno-associated virus (AAV)-mediated delivery of reprogramming factors in the brain. However, major challenges such as safety concerns still need to be addressed before viral vectors are commonly used to treat neurological disorders in humans. By showing that a single-dose injection of an antisense oligonucleotide (ASO) against polypyrimidine tract binding protein 1 (PTB) converts glial cells into neurons in the mouse brain, a study might open new opportunities for the treatment of neurodegenerative diseases.

PTB is an RNA-binding protein that controls neuronal induction and maturation. Previous studies have shown that knocking down PTB by stereotactic injection of either an AAV encoding a short hairpin RNA to PTB mRNA, an AAV encoding a CRISPR–CasRx protein and a guide RNA targeting PTB mRNA or a PTB-targeting ASO triggers the conversion of GFAP-expressing cells into neurons in the mouse brain. ASOs are single-stranded deoxyribonucleotides that are designed to bind to the mRNA target and promote degradation of the bound RNA by endogenous nucleases such as RNase H1. Maimon, Chillon-Marinas and colleagues at the University of California at San Diego used an ASO-based approach to reduce PTB expression in neurons, selecting the best ASO candidates upon their ability to suppress PTB mRNA levels in cell culture.

The team introduced the selected PTB-ASO into the cerebrospinal fluid (CSF) of mice by single-dose intracerebroventricular injection. CSF circulates from the cerebral ventricles to all regions of the CNS, and studies in rodents and primates have demonstrated that ASOs infused intraventricularly distribute widely throughout the CNS.

Using a lineage tracing strategy (GFAP-CreERT2; CAG-lox-stop-lox-tdTomato), the investigators showed that PTB-ASO injection in the CSF is sufficient to reprogram glial cells into neurons in the adult and aged mouse brain and that the new neurons acquire mature neuronal features and functionally integrate into endogenous circuit over a 2-month period.

In the discussion, the investigators explain that although the approach is promising, the ASOs used in this study are not clinical candidates. "Optimization to identify ASOs with minimal toxicity and maximal efficacy is now essential. Nevertheless, our findings strongly support that a therapeutically feasible pharmacological intervention with ASOs to transiently suppress PTB can facilitate generation of replacement neurons within the aged mammalian nervous system," they conclude in their report.

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