Credit: KTSDESIGN/SCIENCE PHOTO LIBRARY/Getty

NEURODEGENERATIVE DISEASE

Delivering gene therapy

> Unlike untreated knockout mice, knockout animals receiving this gene therapy showed no signs of paralysis or dyskinesia and indeed could not be differentiated phenotypically from wild-type littermates up to P35

Neuronopathic Gaucher disease (nGD) is a lysosomal storage disorder that is caused by mutations in the gene encoding glucocerebrosidase (GBA), a lysosomal enzyme. Individuals with the less severe form of nGD show visceral and neurological symptoms and may live into adulthood, whereas those with the more severe form exhibit symptoms associated with hindbrain neurodegeneration and die in early childhood. GBA replacement therapies offer some management of visceral symptoms, but the enzyme cannot cross the blood–brain barrier, meaning there are no approved, effective treatment options for the neurological manifestations. Now, Massaro et al. show in a mouse model of nGD that intracranial injection of a viral vector expressing GBA into fetal animals prevents neurodegeneration, ameliorates associated neuroinflammation and promotes survival, and demonstrate delivery of a viral vector into fetal non-human primate brains.

The authors used a previously generated nGD mouse model in which *Gba* is knocked out in all tissues except the skin. Although skin expression of GBA prevents fatal dehydration in neonatal animals, these animals still have a short lifespan (of up to approximately 2 weeks) owing to neurodegeneration. The authors first characterized the neuropathology of these mice, revealing that knockout animals exhibited marked microglial and astrocytic activation from birth, and developed marked neuronal loss in cortical and thalamic areas and the brainstem. In line with the loss of GBA, these mice showed a build-up of various glycosphingolipids in the brain, with some being elevated by postnatal day 1 (P1).

Given the early-life changes in the knockout mice, the authors hypothesized that such animals may benefit from in utero replacement of GBA, so they delivered a human GBA-expressing adeno-associated virus 9 (AAV9) vector via intracranial injection into fetal mice. Unlike untreated knockout mice, knockout animals receiving this gene therapy showed no signs of paralysis or dyskinesia and indeed could not be differentiated phenotypically from wild-type littermates up to P35, the end of the assessment period. Treated knockout mice also showed decreased levels of glial activation in various brain regions compared with untreated knockout mice at P12, and no neurodegeneration in the thalamus or the gigantocellular reticular formation of the brainstem. Thus, intracranial delivery of GBA-expressing AAV9 in utero prevented or ameliorated the effects of GBA loss in the short term.

The authors next examined the longer-term effects of this treatment strategy. Unlike untreated knockout mice, which predictably developed severe neurological symptoms within 2 weeks of birth, all 5 treated mice appeared to be phenotypically normal and fertile, lived for at least 18 weeks and showed wild-type levels of brain GBA activity. Despite the positive effects of gene therapy, the treated mice exhibited deficits in two different motor tasks, some signs of glial activation and elevated levels of certain lipids, and, in most cases, developed ventriculomegaly, indicating that the gene therapy only partly corrects the effects of GBA loss.

Nevertheless, given the promising effects of fetal GBA therapy in the mouse model of nGD, the authors examined whether they could widely express a protein in the fetal primate brain by delivering similar AAV9 vectors in utero. They injected, via ultrasound guidance, a green fluorescent protein (GFP)-expressing AAV9 vector into the brains of two mid-gestation macaques. Immunohistochemistry revealed GFP-positive cells in nearly all brain regions assessed for both animals, suggesting this method may allow the delivery of potential gene therapies to fetal human brains.

Overall, these findings support further investigation of fetal gene therapy approaches to treat inherited early-onset neurodegenerative brain disorders.

Darran Yates

ORIGINAL ARTICLE Massaro, G. et al. Fetal gene therapy for neurodegenerative disease of infants. *Nat. Med.* https://doi.org/10.1038/s41591-018-0106-7 (2018)