Study verifies human gene therapy in model of rare metabolic disorder

28 July 2016

Researchers are closer to finding a better way to treat children with a rare metabolic disorder called MPS I. It is caused by a deficiency of the key enzyme IDUA needed to break down complex sugars in cells. MPS I eventually leads to the abnormal accumulation of sugar debris and cell death. The two main treatments are bone marrow transplantation and intravenous enzyme replacement therapy; however, both are only marginally effective or clinically impractical, especially when the disease enters the central nervous system (CNS).

In an ongoing preclinical program using gene therapy to help cells restore normal levels of IDUA, researchers from the Perelman School of Medicine at the University of Pennsylvania have shown that exposure to the human IDUA protein early in the life of an MPS I canine model increased immune tolerance to the foreign gene. Normally the dogs elicit a strong immune response to the human IDUA protein, making it difficult to test whether gene therapy is effective. The team published their findings this month in *Molecular Genetics and Metabolism*.

In the dogs that were exposed to the human IDUA protein early in life, the gene therapy could be tested without interference from an immune response. When the gene was delivered to the brain in these immune-tolerant dogs, the researchers observed widespread expression of the enzyme and resolution of the brain lesions that typically occur in MPS I patients.

"Our approach can test new human gene therapies in relevant animal models and may also have clinical applications for the prevention of immune responses to gene and protein replacement therapies," said first author Christian Hinderer, PhD, a senior research investigator working to complete his medical degree in the MD-PhD program at Penn. Hinderer, senior author James M. Wilson, MD, PhD, a professor of Medicine and Pediatrics and director of the Penn Orphan Disease Center, and Penn coauthor Mark Haskin, PhD, VMD, worked with Plott hounds, in which MPS I naturally occurs. These dogs were originally used to develop Aldurazyme, a substance used in enzyme replacement therapy that breaks down the protein fragments left in cells.

MPS I is part of a family of about 50 rare inherited disorders marked by defects in the lysosomes, compartments within cells filled with enzymes to digest large molecules. If one of these enzymes is mutated, molecules that would normally be degraded by the lysosome accumulate within the cell and their fragments are not recycled. Many of the individual MPS disorders share symptoms, such as vision and hearing problems, hernias, and heart problems. Patient groups estimate that in the United States 1 in 25,000 births will result in some form of MPS. Life expectancy varies significantly for people with MPS I, but individuals with the most severe form rarely live more than 10 years.

MPS I dogs have similar CNS, heart, and brain features as humans with MPS I. The dog model is better than mouse models for delivering the IDUA gene to the brain because the canine brain is closer in size to humans and better recapitulates human disease.

Animal models that closely mimic human disease are essential for preclinical evaluation of gene and protein therapeutics. However, these studies can be complicated by exaggerated immune responses against the human genes. In this paper, the team demonstrated that dogs with a genetic deficiency of IDUA were rendered immunologically tolerant to human IDUA through early exposure to the enzyme.

The team used an adeno-associated viral (AAV) vector to introduce normal human IDUA to glial and neuronal cells of the brain and spinal cord in dogs. Their aim was to treat the CNS manifestations of

MPS I at the source. After a single injection of the AAV9 vector expressing a human IDUA gene sequence into the spinal fluid, they saw enzyme expression exceeding normal levels in spinal fluid, and complete reversal of the characteristic brain lesions of MPS I.

These studies may help inform the planning and design of first-in-human trials. REGENXBIO Inc., which has exclusively licensed certain key AAV-related technologies from Penn, is involved in planning studies to test treatments for MPS I.

Provided by Perelman School of Medicine at the University of Pennsylvania