Revolutionizing Treatment: Gene Therapy Offers Hope for Hurler Syndrome

Krisha Agarwal

Abstract

Hurler Syndrome, also known as mucopolysaccharidosis type I (MPS I), is a rare lysosomal disorder wherein genetic mutations prevent the synthesis of enzyme IDUA, disrupting the breakdown of sugar molecules. This autosomal recessive condition targets newborns and causes physical and cognitive abnormalities, potentially resulting in brain damage (Cleveland Clinic, 2022). Current treatments include bone marrow transplants, which are not only dangerous but also an unfavorable solution for progressive brain damage. Recently, a new form of gene therapy, Proprietary System (PS) gene editing, has shown promising results in mice as a treatment method, as concluded by researchers at the University of Minnesota. Using high-resolution resting-state functional MRI (rs-fMRI) technology, researchers could support normal neural connections using liver enzymes. This advanced approach also helps monitor brain connectivity in other lysosomal disorders affecting brain function (University of Minnesota, 2023).

Lysosomal Storage Diseases

Lysosomes, integral to cellular function, are specialized membrane-bound organelles that house digestive enzymes. These organelles consist of luminal proteins, membrane-integral proteins, and associated proteins, which all play a crucial role in cellular processes. However, when these components are affected by congenital metabolic single-gene errors, known as lysosomal storage diseases (LSDs), the intricate balance within lysosomes is disrupted. This disruption arises from mutations in lysosome-encoding genes located on a specific chromosome locus, leading to the transcription of defective lysosomes.

The consequences of these disorders extend beyond the molecular level, manifesting as cell swelling and eventual organ dysfunction at the sites of substrate accumulation. This, in turn, significantly contributes to morbidity and mortality. Notably, the impact is more pronounced in infants and children, as their developing brains exhibit heightened vulnerability to dysfunction (Rajkumar, Dumpa, 2023).

Hurler Syndrome

Hurler Syndrome (MPS I), discovered by German pediatrician Gertrud Hurler in 1919, stands among the 11 disorders of mucopolysaccharidoses (MPS), impacting roughly 1 in 100,000 births. This neurodegenerative condition arises from a mutation in a gene on chromosome 4, tasked with encoding the lysosomal enzyme α-L-iduronidase (IDUA). IDUA plays a pivotal role in breaking down glycosaminoglycans (GAG), such as dermatan sulfate and heparin sulfate. The overaccumulation of GAG leads to the enlargement and thickening of organs like the heart, spleen, and muscles, while also impairing synapses within the central nervous system.

Typically, symptoms of Hurler Syndrome manifest in the first year of a child's life. Unfortunately, the average age of mortality is five years, with the majority of patients not surviving beyond ten years. Indications of the disorder progressive developmental delay, respiratory infections, and cardiac manifestations. Diagnosis involves clinical examinations of urinary GAG levels and DNA analysis. To expand upon the latter point, gene sequencing aids in identifying inheritable mutations and facilitates improved family planning. In contrast, treatments primarily target symptoms of the disorder rather than their underlying abnormalities. Options like enzyme replacement therapy (ERT) through intravenous injections of recombinant IDUA and hematopoietic stem cell transplants (HSCT) offer some relief. HSCT gradually substitutes donor-derived, enzyme-competent cells for hematopoietic cells lacking enzymes (Sakuru, Bollu, 2023). However, it is important to note that ERT cannot cross the blood-brain barrier, limiting its efficacy in curing the central nervous system, a critical concern for severe MPS I patients (Concolino et al., 2018). Additional interventions may include surgical procedures such as cardiac valve replacement and spinal decompression to address specific symptoms (Sakuru, Bollu, 2023). Therefore, it is imperative to seek alternative therapies that are less risky.

Gene Therapy

Gene therapy is a dynamic field in biomedical science, orchestrating the modulation of gene expression to reshape the biological function of living cells. This versatile approach offers the capacity to replace defective genes with healthy counterparts, inactivate disease-causing genes, or introduce modified genes to treat specific diseases. Therefore, it presents effective applications in conditions like cancer, cystic fibrosis, and diabetes.

The procedural aspect involves the introduction of genes into the body via carriers known as vectors, with viruses being the primary vehicles due to their ability to recognize target cells and facilitate genetic transfer. Figure 1 portrays a simplified diagram of the method. However, amidst the promises of gene therapy lie inherent risks.

As the body encounters the introduced viral vectors, an undesired immune response may ensue, potentially resulting in inflammation and, in severe cases, organ failure. Precision errors with the vectors may lead to unintended targeting, affecting healthy cells, or causing infections. Missteps in gene insertions hold the potential for tumor formation (Mayo Clinic, 2017).

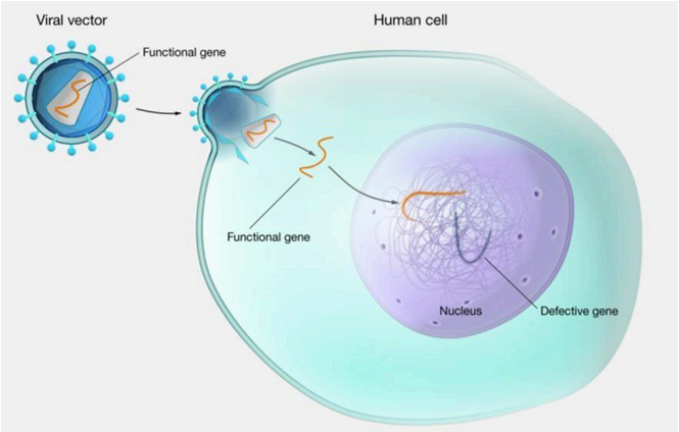

Figure 1. Diagrammatic representation of gene therapy technique (National Human Genome Research Institute, 2024)

Proprietary System Gene Editing to Treat Hurler Syndrome

Researchers at the University of Minnesota have pioneered a Proprietary System (PS) for gene editing aimed at treating Hurler Syndrome in neonatal mice. This innovative technique, represented in Figure 2, involves the action of Cas9, which induces a double-stranded break at the intron 1 locus of liver protein albumin. Simultaneously, the guide RNA (gRNA) synthesizes therapeutic transgene promoterless IDUA cDNA.

The method employs homology-directed repair to introduce the splicing acceptor, IDUA cDNA, and poly(A) sequence into the target, forming a cohesive genetic structure. Alternatively, nonhomologous end-joining pathways come into play, incorporating the donor template at the double-stranded break. This results in the creation of a hybrid sequence of albumin exon 1 and IDUA sequence. Therefore, PS gene editing is versatile, seamlessly functioning in both dividing and nondividing pathways.

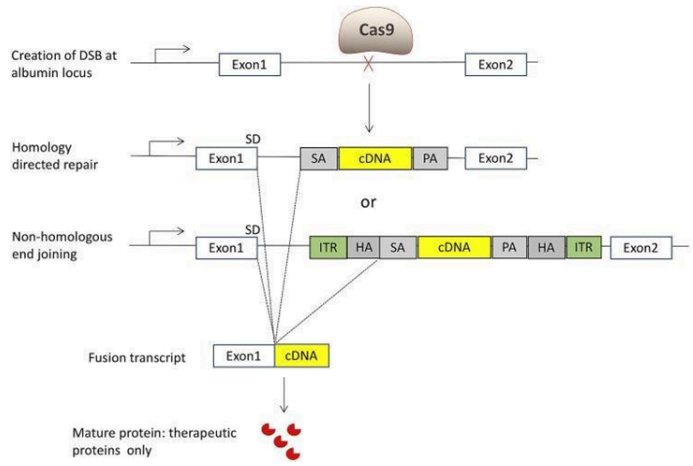

Figure 2. A diagrammatic representation of the molecular mechanism of PS gene editing (Ou et al. 2020)

The highly expressed endogenous albumin promoter assumes a pivotal role in governing the transgene's expression, with its benefits harnessed through a mechanism known as cross-correction. In this process, a lysosomal enzyme produced by one cell is released and subsequently internalized by another cell. This facilitates the degradation of stored materials, culminating in metabolic correction. To prevent transgene expression in the central nervous system, the researchers strategically employed liver-specific human IDUA.

The technique showed positive results, as evidenced by elevated IDUA activity and reduced GAG levels in both the liver and brain. The findings suggest that maintaining a consistently elevated level of IDUA in the bloodstream leads to a modest yet sufficient entry of IDUA into the brain. Notably, a particular gRNA,5′-GTATCTTTGATGACAATAATGGGGGAT-3′, demonstrated the highest efficiency in driving therapeutic effects.

The inherent advantage of PS gene editing lies in its potential to yield elevated enzyme levels with a single administration. This efficiency arises from the increased likelihood of successfully edited hepatocytes. Consequently, the application of PS gene editing opens avenues for administering reduced doses of the adeno-associated virus (AAV) vector for the treatment of LSDs. This not only mitigates toxicity but also streamlines vector production, thereby reducing overall costs.

The significance of this approach becomes pronounced in the context of LSD patients, particularly children, where uninterrupted cell division is essential for normal growth. Traditional AAV gene therapy encounters a significant hurdle in the form of vector dilution as children undergo growth and maturation. The primary merit of PS lies in its potential to confer sustained therapeutic benefits throughout an individual's life, ensuring ongoing efficacy beyond the initial post-treatment years (Ou et al., 2020).

Using resting state functional MRI (rs-fMRI) to Map MPS I

High-resolution resting state functional MRI (rs-fMRI) emerges as a non-invasive and whole-brain activity imaging technique for the diagnosis and post-treatment evaluation of MPS I. This tool examines the spontaneous blood oxygenation level-dependent fluctuations across various brain regions without stimulation. Clinically, rs-fMRI has successfully identified multiple resting state networks (RSNs) in conditions such as Alzheimer's disease, major depression, and schizophrenia. These results emphasize the foundational role of neural network deficits and interconnectivity in certain neurological disorders.

Scientists at the University of Minnesota hypothesized that the observed deficits in learning memory and spatial navigation in MPS I are influenced by alterations in limbic network connectivity. Hence, rs-fMRI is proposed as a sensitive imaging tool to assess compromised RSNs in the

MPS I brain and track their restoration following gene treatment.

As seen in Figure 3, in the realm of rs-fMRI, the examination of wild-type mice highlighted robust functional connectivity throughout the brain. Conversely, MPS I mice exhibited weakened and altered connections in crucial cortical and subcortical regions associated with learning, memory, and sensorimotor behavior. Notably, researchers observed a significant loss of functional connectivity in default mode networks, including the retrosplenial cortex, thalamus, and hippocampus. However, MPS I mice treated with gene therapy displayed a restoration of functional connections between the anterior cingulate and motor cortex, dorsal striatum, and hippocampus.

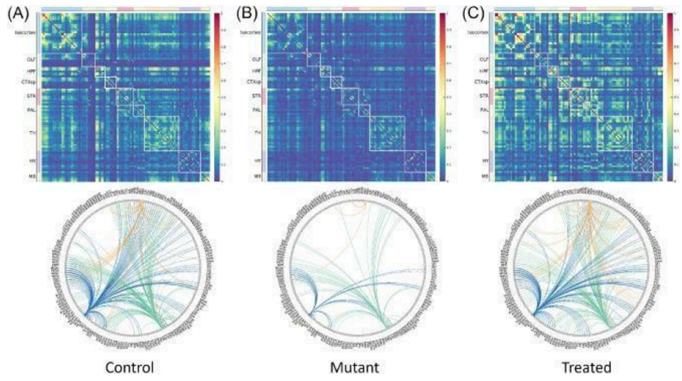

Figure 3. Correlation matrices and circular graphs of functional brain connections between (**A**) control, (**B**) MPS I, and (**C**) MPS I treated mice. Blue-connectome with connections at anterior cingulate area, green-connectome with connections at Ammon's horn, and yellow-connectome with connections at mediodorsal nucleus of thalamus. Brain connectome is sporadic for mutant but recovers after treatment. (Zhu et al., 2023)

The rs-fMRI findings reinforce the notion that Hurler Syndrome impacts synapse formation, leading to diminished neural connectivity. The observed dysfunction in hippocampal connectivity with the retrosplenial cortex holds implications for spatial navigation performance. These results bear clinical relevance for the diagnosis, monitoring, and treatment of Hurler Syndrome.

Furthermore, rs-fMRI's translational potential extends to the clinical analysis of other human neurological disorders and gene therapy outcomes (Zhu et al., 2023).

Conclusion

This comprehensive exploration provides valuable insights into Hurler Syndrome and underscores the promising avenues offered by gene therapy, particularly through PS gene editing. Traditional treatments for Hurler Syndrome emphasize the necessity for more targeted interventions addressing the root cause, and gene therapy, a burgeoning field with transformative potential, emerges as a beacon of hope.

PS gene editing marks a significant stride in pursuing effective and sustainable treatments for Hurler Syndrome. The insights gained from rs-fMRI not only enhance our understanding of the neurological deficits associated with Hurler Syndrome but position rs-fMRI as a promising diagnostic and therapeutic imaging technique. As scientists navigate this frontier of knowledge, the potential for transformative breakthroughs in treating Hurler Syndrome and related disorders becomes increasingly tangible.

References

1. Concolino, D., Deodato, F., & Parini, R. (2018). Enzyme replacement therapy: efficacy and lmitations. Italian journal of pediatrics, 44(Supply, 120. https://doi.org/10.1186/s13052018-0562-1 Gene therapy. Genome.gov. (n.d.-a). https://www.genome.gov/genetics-glossary/Gene-Therapy

2. Mayo Foundation for Medical Education and Research. (2017, December . Gene therapy. Mayo-Clinic. https://www.mayoclinic.org/tests-procedures/genet herapy/about/pac20384619

3. Ou, L., Przybilla, M. J., Ahlat, O., Kim, S., Overn, P., Jarnes, J., O'Sullivan, M. G., & Whitley, C. B. (2020, June 3). A highly efficacious PS gene editing system corrects metabolic and neurological complications of mucopolysaccharidosis type I. Molecular therapy : the journal of the American Society of Gene Therapy. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7264433/

4. Rajkumar, V., & Dumpa, V. (2023, July 24). Lysosomal storage disease - statpearls - NCBI Bookshelf. National Library of Medicine- National Center for Biotechnology Information. https://www.ncbi.nlm.nih.gov/books/NBK563270/

5. Sakuru, R., & Bollu, P. C. (2023, July 10). Hurler Syndrome – statpearls – NCBI bookshelf. National Library of Medicine- National Center for Biotechnology Information. https://www.ncbi.nlm.nih.gov/books/NBK532261/

6. Zhu, W., Ou, L., Zhang, L., Clark, I. H., Zhang, Y., Zhu, X. H., Whitley, C. B., Hackett, P. B.,Low, W. C., & Chen, W. (2023). Mapping brain networks in MPS I mice and their restoration following gene therapy. Scientific reports, 13(1), 12716. https://doi.org/10.1038/s41598-023-39939-0