Gene Editing of Monogenic Disorders in Human Hematopoietic Stem Cells

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Technology description

Researchers at the UCLA Department of Microbiology, Immunology & Molecular Genetics have developed novel methods to achieve efficient, precise gene integration and effective expression of cDNA cassettes to express normal versions of genes in hematopoietic stem cells.

BACKGROUND

Hematopoietic stem cells (HSCs) have great therapeutic potential because of their ability to both self-renew and differentiate. A small number of genetically modified HSCs could achieve lifelong, corrective reconstitution of the entire hematopoietic system in patients with various hematologic disorders. Many severe primary immune deficiencies (PIDs) are due to defects in lymphoid or hematopoietic cells that can be reconstituted through hematopoietic stem cell transplantation (HSCT). Unlike allogeneic HSCT, gene therapy using autologous HSCs has potential advantages from the absence of graft-versus-host disease and the less intense conditioning and immune suppression needed. Lentiviruses were the most widely used viral vectors to safely and effectively deliver a transgene of interest into HSCs for gene therapy. However, even though lentiviruses have been improved with lower risk of genotoxicity and increased safety compared with gammaretroviruses, lentivirus-based HSC gene therapy can still theoretically result in toxicity due to dysregulated transgene expression or residual genotoxicity. HSC-targeted gene editing technologies using engineered nucleases such as CRISPR/Cas9, allow for the site-specific correction of disease-causing mutations and have shown promising clinical benefits in multiple diseases. The ability to correct specific disease-causing mutations, rather than simply deliver a normal gene, extends the potential applications of gene therapy to dominant disorders in addition to those resulting from simple loss-of-function mutations.

INNOVATION

Researchers at UCLA have defined optimal design features of homologous donors (cDNA expression cassettes and homology arms) and CRISPR/Cas9 target sites for more efficient, precise gene integration, and effective expression of cDNA cassettes to express normal versions of genes in hematopoietic stem cells. The optimization will help minimize both targeted-re-cutting by nuclease and illegitimate recombination, and allow precise control of transgene expression to the highest level.

RELATED MATERIALS

C. Y. Kuo and D. B. Kohn, Gene Therapy for Primary Immune Deficiency Diseases, Clinical Immunology (Fifth Edition), 2019.

D. B. Kohn and C. Y. Kuo, New frontiers in the therapy of primary immunodeficiency: From gene addition to gene editing, Journal of Allergy and Clinical Immunology, 2017.
C. Y. Kuo, J. D. Long, B. Campo-Fernandez, S. de Oliviera, A. R. Cooper, Z. Romero, M. D. Hoban, A. V. Joglekar, G. Lill, M. L. Kaufman, S. Fitz-Gibbon, X. Wang, R. P. Hollis, and D. B. Kohn, Targeted Gene Insertion for the Treatment of X-Linked Hyper-IgM Syndrome, Cell Reports, In Press.

Application area

Gene therapy of hemoglobinopathies (i.e., sickle cell disease, beta-thalassemia)
Gene therapy of immune deficiencies (i.e., different genetic forms of severe combined immunodeficiency, X-linked Hyper IgM Syndrome, X-linked agammaglobulinemia, common variable immune deficiency, chronic granulomatous disease, Wiskott–Aldrich syndrome, hemophagocytic lymphohistiocytosis, leukocyte adhesion deficiency)
Gene therapy of storage and metabolic diseases (i.e., Gaucher, Hurler’ s, Hunters, San Filipo, etc.)

Advantages

More efficient and effective gene editing
Better expression of inserted transgenes

Institution

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