Molecular Therapy
Nucleic Acids
Commentary

Precision genome editing offers hope for treatment of β-thalassemia and other genetic disorders

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β-Thalassemia is a hereditary blood disorder,[1] characterized by a lack of functional β-globin, a crucial component of hemoglobin. In its most severe forms, β-thalassemia necessitates regular blood transfusions and iron chelation therapy, impacting the quality of life and lifespan of affected individuals.[2] However, recent advancements in genome editing technology, particularly the development of base editors (BEs), offer promising avenues for curative therapies. Traditional genome editing techniques, like CRISPR-Cas9, rely on creating double-strand breaks (DSBs), which can lead to unintended consequences, such as large insertions or deletions, chromosomal rearrangements, or off-target effects.[3] On the other hand, BEs catalyze precise base transitions without inducing DSBs, a potentially safer alternative, enabling researchers to correct disease-causing mutations with greater precision.[4]

A recent study explores an innovative approach to address a specific mutation, $HBB^{IVSI-110(G>A)}$, responsible for aberrant splicing in β-thalassemia.[5] The authors utilized two recently published adenine BEs (ABEs; SpRY and SpG), which feature relaxed protospacer adjacent motif requirements, granting them a wider range of DNA targets. This flexibility is crucial when addressing specific mutations, such as $HBB^{IVSI-110(G>A)}$, which disrupts the normal splicing of the β-globin gene. The nucleofection of ABE components as RNA into patient-derived CD34+ cells achieved up to 90% editing of upstream sequence elements, which is critical for correcting aberrant splicing.

One of the notable outcomes of this study is the comprehensive characterization of the on-target base editing profiles of each ABE. The authors observed potentially context-dependent differences in on-target insertions and deletions, suggesting that the surrounding DNA sequence could influence editing outcomes. This finding underscores the complexity of base editing and the importance of understanding the broader genomic context when implementing such techniques.

The study also revealed opposing effects on splice correction for two neighboring context bases, further highlighting the need for precision in base editing. The frequency distribution of multiple base editing events within the editing window was established, providing insights into the likelihood of various outcomes based on the specific context of the DNA sequence. This level of detail is critical for ensuring that base editing remains a safe and effective therapeutic strategy.

Functionally, the study demonstrated high-efficiency correction of the $HBB^{IVSI-110(G>A)}$ mutation at multiple levels, including RNA, protein, and erythroid differentiation. This achievement represents a significant step toward curative therapy for β-thalassemia, as it indicates a restoration of hemoglobin function and, consequently, a normalization of the affected phenotype.

The methodology employed by the authors involves virus- and DNA-free, highly transient delivery of the BEs to restore HbA and the normal phenotype, further mitigating potential risks associated with gene therapy. By avoiding permanent genomic alterations or the integration of viral vectors, this approach enhances the safety profile of the treatment, addressing common concerns associated with advanced therapies.

One of the key takeaways from this study is the tailored approach to correcting the $HBB^{IVSI-110(G>A)}$ mutation. By focusing on this specific mutation, the authors offer a potentially more effective alternative to universal therapeutic approaches, providing greater flexibility in the choice of DNA editors. This approach could serve as a model for other genetic disorders, particularly those involving abnormal splicing, where direct editing of the causative mutation might not be feasible.

In conclusion, this study represents a significant advancement in the field of gene therapy, demonstrating the potential of BEs to correct complex genetic mutations with high precision and safety. By harnessing the power of BEs, researchers are inching closer to realizing the dream of personalized, gene-based therapies for a myriad of genetic disorders, including β-thalassemia. As we continue to unravel the complexities of the human genome, the journey toward precision medicine marches forward, offering hope and healing to those affected by genetic diseases.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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