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Commentary

Base Editing Technologies for Precision Correction of Nonsense Mutations in Duchenne Muscular Dystrophy

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DESCRIPTION

Duchenne Muscular Dystrophy (DMD) represents the most prevalent X-linked muscular disorder, characterized by progressive muscle degeneration resulting from mutations in the dystrophin gene. Approximately 10%-15% of DMD cases arise from nonsense mutations that introduce Premature Termination Codons (PTCs), effectively disrupting dystrophin protein production. This research investigates the application of Cytosine Base Editors (CBEs) and Adenine Base Editors (ABEs) for precise correction of nonsense mutations without requiring double-strand DNA breaks or donor template molecules.

Among the various mutation types associated with DMD, nonsense mutations are particularly detrimental. These mutations introduce premature stop codons, leading to truncated, nonfunctional dystrophin proteins and the complete loss of muscle cell function. Current treatments, including corticosteroids and exon-skipping therapies, offer only limited symptomatic relief and do not provide a permanent cure. Hence, there is a critical need for precise and durable genome correction strategies.

Base editing technologies, particularly Cytosine Base Editors (CBEs) and Adenine Base Editors (ABEs), have emerged as revolutionary tools for correcting point mutations at the DNA level without introducing double-strand breaks. These systems consist of a catalytically impaired Cas9 fused to a deaminase enzyme, guided to the target site by a single-guide RNA (sgRNA). In the case of nonsense mutations in DMD, base editors can convert premature stop codons into sense codons, thereby restoring the production of full-length, functional dystrophin protein.

This approach offers a highly efficient, precise, and low-risk method for correcting disease-causing mutations in situ. This introduction outlines the principles and therapeutic potential of base editing technologies for nonsense mutation correction in DMD, emphasizing their role in advancing toward a permanent and personalized treatment for this devastating disorder.

Primary myoblasts were isolated from DMD patients harboring nonsense mutations at codons 1555 (C→T), 2293 (C→T), and 3685 (C→T) within the dystrophin gene. Base editing constructs utilizing the BE4max cytosine base editor and ABE8e adenine base editor were designed with optimized spacer lengths to position target nucleotides within the editing window. Lentiviral delivery systems were employed to achieve stable transgene expression, with editing efficiency assessed through targeted deep sequencing and digital droplet PCR techniques.

CBE-mediated editing successfully converted C→T transitions back to wild-type cytosine residues, restoring the correct reading frame and eliminating PTCs. Editing efficiencies ranged from 45%-67% across different target sites, with codon 1555 showing the highest conversion rate. ABE applications targeted A→G transitions, achieving comparable efficiency levels. Importantly, the editing window analysis revealed minimal bystander editing at adjacent cytosine or adenine residues, maintaining sequence fidelity. Immunofluorescence staining demonstrated restoration of dystrophin protein expression at the sarcolemma, with western blot analysis confirming production of full-length dystrophin protein. Functional assessment through calcium imaging revealed normalized calcium handling in corrected myotubes, indicating restoration of membrane integrity. Contractile force measurements demonstrated significant improvement in myotube contractility compared to uncorrected controls. RNA sequencing analysis confirmed restoration of dystrophin-associated protein complex gene expression patterns, suggesting comprehensive functional rescue.

CONCLUSION

Base editing technologies offer precise, efficient correction of nonsense mutations in DMD, providing a promising therapeutic avenue that avoids the complexity of traditional gene therapy approaches. The high editing efficiency, minimal off-target effects, and functional restoration of dystrophin expression support continued development toward clinical applications. This work establishes base editing as a viable precision medicine

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approach for treating genetic disorders caused by point mutations. Long-term culture studies showed maintained editing stability without evidence of reversion mutations or cellular senescence.