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Opinion Article

High Fidelity Gene Correction *via* Emerging Editing Technologies: Beyond Conventional Methods

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DESCRIPTION

The ability to change single DNA letters without cutting both strands of the double helix has emerged as a powerful advance. Traditional nucleases like CRISPR/Cas9 often produce double strand breaks that the cell must repair, which may lead to insertions, deletions, or rearrangements. Newer methods such as base editing and prime editing sidestep many of those risks, enabling more controlled and precise alterations. These newer strategies refine how small mutations may be corrected or programmed, with implications for research, diagnostics, and potentially therapeutic applications.

Base editors combine a catalytically disabled or nickase form of Cas9 with deaminase enzymes that convert one base into another in a DNA strand. For example, Cytosine Base Editors (CBEs) may change C to U (which then becomes T), effectively converting a C-G pair into T-A. Adenine Base Editors (ABEs) perform A to I (inosine, interpreted as G) changes, thus converting A-T pairs to G-C. Because these editors do not cut both DNA strands, the risk of large disruptive errors is reduced. However, their editing window is limited, and off target deamination or "bystander" edits on nearby bases can occur if the deaminase is too active or poorly localized. Improvements in base editor design now include more precise targeting windows, engineered deaminases with reduced off target activity, and modular recruiting systems that restrict editing only to intended contexts.

Yet base editing is limited in its capacity: Tt cannot handle all possible base substitutions, nor can it reliably insert or delete segments. That is where prime editing presents a more flexible approach. Prime editing uses a fusion of Cas9 nickase and a reverse transcriptase enzyme, guided by a prime editing guide RNA (pegRNA). The pegRNA both directs the complex to the target and encodes the desired edit, including substitutions, insertions, or deletions. Once the nickase cuts one strand, a new flap containing the edited sequence is generated via reverse transcription; downstream DNA repair can resolve integration of the change. This "search and replace" style editing allows correction of all twelve possible base conversions and small insertions or deletions, without full double strand breaks.

Because prime editing involves multiple steps (guiding, nicking, flap generation, strand resolution), its specificity is high: mismatches in the pegRNA pairing, flap annealing, or hybridization steps may cause the system to abort rather than introduce incorrect edits. This layered specificity reduces unintended edits at non target sites. Compared to base editing, prime editing minimally produces bystander edits and is immune to some types of off target deamination independent of Cas activity.

Still, prime editing faces challenges. Its efficiency varies widely depending on the cell type, target locus, chromatin context, DNA accessibility, sequence context of the pegRNA, and the design of flaps. In some cases, editing efficiencies remain fairly low for therapeutic use. Some edits still provoke unintended double strand breaks or indels when the cellular repair machinery responds unexpectedly. The larger size and complexity of the prime editing machinery (Cas9 nickase+ reverse transcriptase+pegRNA) complicates delivery into cells, especially *in vivo*. AAV vectors, lipid nanoparticles, or nonviral nanoparticles are under exploration, but cargo size and cellular uptake remain obstacles.

To improve performance, variant engineering is underway. Modified pegRNAs (epegRNAs) include stabilizing motifs or structured RNA elements that resist degradation and maintain correct hybridization. Some systems include nicking guide RNAs on the opposite strand to stimulate repair in favor of edited sequences. Coexpression of repair modulators (e.g. mismatch repair inhibitors) or chromatin remodeling peptides fused to Cas9 or reverse transcriptase has improved edit rates. In addition, combining prime editing with site specific recombinases has enabled larger fragment insertions or swaps beyond a few base pairs, expanding possible edits.

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One particularly interesting direction is combining prime editing with machine learning to predict the best pegRNA designs or anticipate locus accessibility. Recent models use attention based multi task learning to forecast editing outcomes across base editor variants, which may similarly guide prime editing designs. Such predictive tools can reduce trial iterations and accelerate optimization.