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Applications and Challenges of Genome Engineering Technologies in the Treatment of Cystic Fibrosis

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Abstract. Cystic fibrosis is an autosomal recessive genetic disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, leading to CFTR dysfunction and impaired ion transport, which subsequently results in progressive dysfunction of the digestive and respiratory systems and reduced life expectancy. Although current therapies, including airway clearance techniques, antibiotics, pancreatic enzyme replacement therapy, CFTR modulators, and RNA-based approaches, have significantly improved survival and the quality of life, most of these therapies primarily focus on symptom management and are limited by genotype specificity, transient efficacy, and the inability to permanently correct the underlying genetic defect. As a result, patients may require lifelong treatment. Genome engineering technologies appeared as promising causative therapeutic strategies to address cystic fibrosis by directly repairing or replacing defective CFTR alleles. Recently, the latest progress in base editing, prime editing, and gene addition technology has successfully repaired the CFTR function of common and rare mutations in patient-derived airway epithelial cells and organoids, highlighting the potential for long-lasting and mutation-specific repair. However, significant challenges remain, including the effective delivery to airway stem cells and progenitor cells, achieving sufficient in vivo editing efficiency, minimizing the off-target effects, as well as solving ethical, regulatory, and manufacturing barriers. Overall, genome editing provides a potentially transformative method for the treatment of cystic fibrosis, which is expected to achieve long-term disease correction and surpass lifelong symptomatic treatment.

Keywords: Cystic fibrosis, CFTR gene mutation, Genome engineering, CFTR modulators

1. Introduction

Cystic fibrosis is the most common life-shortening autosomal recessive disorder in Caucasians. More than 70,000 people worldwide are living with cystic fibrosis [1]. Cystic fibrosis is an autosomal recessive genetic disorder caused by mutations in the CFTR gene. It has a significant impact on both life expectancy and life quality. CFTR gene provides instructions for making CFTR protein which is a chloride and bicarbonate ions channel located on the surface of the epithelial cells. When the CFTR gene is defective or absent, ion transport across epithelial membranes is disrupted, affecting the digestive, respiratory, and reproductive systems.

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Currently, treatments for cystic fibrosis help patients manage symptoms and improve quality of life instead of addressing the root cause of disease. Therapies like airway clearance therapies, antibiotics treatments to combat chronic infections, and CFTR modulators are designed for restoring the function of the defective CFTR protein. These reduce the symptoms of cystic fibrosis by improving lung function and reducing infection rates. Pancreatic enzyme replacement therapy (PERT) is used for those with pancreatic insufficiency and aids the digestion and absorption of nutrients [2]. RNA-based therapies including microRNA modulation could also be used in managing the symptoms. Inhibiting miRNAs can increase CFTR production, while other miRNA such as miR-255 and miR-126 can help in reducing excessive airway inflammation [3,4].

Although these treatments have significantly relieved the symptoms, they still fall short in several important ways. Many CFTR modulators are mutation specific which means they are effective on patients with specific mutations; however, they are ineffective for rare or complex mutations [5]. Besides, using antibiotics to treat chronic lung infections often leads to antibiotic resistance and side effects may appear. mRNA therapies have a short duration of effect, and it also limits lung delivery [6,7].

Therefore, although the current therapy plays a crucial role in controlling the symptoms of cystic fibrosis and improving the quality of life of patients, its effectiveness is still limited due to the inability to correct potential CFTR gene defects. This limitation emphasises the need for more transformative approaches that correct the underlying genetic defect rather than mitigating their consequences. In view of this, this paper aims to explore how to apply genome editing techniques to the treatment of cystic fibrosis, and to evaluate its therapeutic potential and the main challenges that currently hinder its clinical transformation. By exploring existing research, evaluating technological progress and identifying residual obstacles, this article will comprehensively explain whether genome editing represents a feasible and realistic method to ultimately achieve long-term and curative treatment of cystic fibrosis.

2. Current treatment for cystic fibrosis

Current treatments mainly aim at managing symptoms rather than addressing the underlying genetic defect, setting the stage for exploring the mechanisms of targeted drug therapies. Symptoms of cystic fibrosis can be managed by a combination of treatments which target symptoms and improve patients' quality of life. The use of mucolytics, for instance, dornase alfa and hypertonic saline, helps reduce the thickness of the mucus that accumulates in the lungs caused by defective CFTR function, thereby improving airflow [2]. Chest physiotherapy, high-frequency chest wall oscillation, and positive expiratory pressure devices are routinely used to mobilize mucus and maintain lung function [5]. PERT is significant for individuals with pancreatic insufficiency which affects digestion and growth. Nevertheless, these therapies fail to modify the underlying CFTR genetic abnormality and thus provide only symptomatic benefit without achieving curative outcomes [2].

Elexacaftor/tezacaftor/ivacaftor (ETI) is one of the most effective CFTR modulator therapies for cystic fibrosis. It combines two correctors (elexacaftor and tezacaftor) to improve the folding, stability, and trafficking of CFTR protein such as F508del CFTR protein, and ivacaftor, the potentiator, enhances the gating activity of CFTR channels at the cell surface. Clinical studies have shown that ETI leads to substantial improvements in lung function. It also improves the nutritional status, life quality, and disease trajectory. Despite these advances, the effectiveness of ETI is highly dependent on CFTR genotype. Nonsense mutations in the CFTR gene cause translation to stop early, resulting in the production of a truncated CFTR protein that lacks essential functional domains. As CFTR modulators require the presence of rescuable CFTR protein to function, ETI is ineffective

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against nonsense mutations, highlighting a major limitation of current modulator-based therapies [8-10].. Moreover, ETI does not correct the underlying CFTR gene mutation, patients require lifelong therapy as the efficacy of ETI depends on continuous daily administration, discontinuation will lead to the loss of therapeutic benefits which emphasise the importance for alternative strategies that intervene at the RNA level, offering the potential to overcome genotype-specific constraints and move closer to disease-modifying treatment [5,8].

RNA-based therapies primarily regulate gene expression or correct common mRNA splicing defects, instead of directly repairing the underlying gene mutation. RNA-based therapies have also emerged as an important tool for cystic fibrosis, offering strategies to modulate CFTR expression or correct downstream molecular defects without altering genomic DNA. Antisense oligonucleotides (ASOs), which are one of the major approaches, can restore normal CFTR splicing or reduce aberrant transcripts. These molecules correct common splicing mutations and restore chloride transport in airway epithelial cells [11]. miRNA- and siRNA-based therapies aim to reduce inflammation or restore CFTR expression by silencing harmful RNA pathways and modifying the molecular environment underlying cystic fibrosis. miRNA-based therapies target miRNAs that inhibit CFTR expression or enhance airway inflammation. Inhibition of miR-145 and miR-223 has been shown to increase CFTR protein levels, while blocking miR-155 can reduce excessive inflammatory signaling [2,4]. Additionally, siRNA-based therapies use synthetic siRNAs to suppress specific mRNAs involved in inflammation or pathways that indirectly inhibit CFTR function, thereby, improving the epithelial cell environment and enhancing CFTR activity [12]. However, these therapies are short-lived because RNA molecules are rapidly degraded in cells. As a result, the therapeutic effects are temporary and require frequent repeated dosing [13]. Moreover, thickened mucus, chronic inflammation and airway remodeling limit the ability of RNA molecules to reach epithelial cells, reducing therapeutic efficiency [14].

In conclusion, cystic fibrosis therapies have improved from symptom management to genotype-targeted treatments, with CFTR modulators improving lung function, nutrition, and quality of life significantly. However, current therapies remain genotype-dependent, do not permanently correct CFTR mutations, and RNA-based approaches are still facing delivery or stability challenges. These limitations show the importance for genome-editing strategies, which could offer durable, mutation-specific correction.

3. Genome editing technologies for CF

Genome editing technologies can correct CF as its molecular origin by repairing or replacing the CFTR gene that is defective. Therapeutic efforts have used programmable nucleases such as zinc-finger nucleases (ZFNs), TALENs, and CRISPR/Cas9 to introduce targeted double-strand breaks (DSBs) at the CFTR locus. DSB-based correction is based on cellular homology-directed repair (HDR) to install a correct sequence from a donor template. However, HDR is inefficient in non-dividing airway epithelia, and DSBs raise the risk of unwanted insertions, deletions or chromosomal rearrangements, both of these limits the appeal of classical nuclease approaches for direct in-vivo lung editing [15].

To resolve these safety and efficiency limitations, base and prime editing have emerged as promising alternatives for CF, around 30% of pathogenic CFTR mutations could be correct by base editors, while prime editing could potentially target up to around 95% of pathogenic CFTR mutation [16]. Base editors chemically convert single bases without creating DSBs, making them well suited to repair many single nucleotide CFTR defects. Cytosine base editors (CBEs) and adenine base editors (ABEs) have been used to correct nonsense and splice-site mutations in airway cells and

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have demonstrated functional restoration of chloride transport in vivo [17,18]. Ultimately, analysis of large organoid biobanks suggests that a non-trivial proportion of CF patients carry base-editable alleles, emphasising the clinical relevance of this modality [18]. Prime editing enables precise small insertions, deletions and all 12 base substitutions without DSBs or donor templates [19]. Prime editing has been applied to patient-derived airway epithelial cells and organoids and has functionally corrected both rare and common CFTR alleles that cannot be treated with modulators or simple base editing [20]. These data provide the most compelling principle-based proof to date that DSB-free genome editing can restore CFTR activity across a broader range of mutations.

Additionally, unlike mutation-specific editing, gene addition does not depend on the specific CFTR genotype. It is particularly valuable for patients whose mutations are not amenable to precise editing or modulators. However, its clinical utility depends on achieving durable expression in airway stem or progenitor cells so as to provide persistent physiological benefit [15,21]. To summarise, improvements in delivery approaches which have historically been a major barrier to CF gene editing, are helping bring these strategies closer to clinical translation. These developments highlight the rapidly evolving landscape of genome editing, which supports the feasibility of correcting various CFTR mutations.

4. Limitations and challenges of genome editing

Although genome editing strategies can correct or replace defective CFTR alleles, converting these techniques into practical therapies poses significant challenges. The most immediate barrier is efficient delivery to airway stem and progenitor cells, echoing the challenges seen with RNA based approaches, which is essential for achieving lasting correction, especially for base editing, prime editing, and genome addition approaches. The pathological CF airway environment is characterised by viscous mucus, chronic bacterial infection, inflammation, and epithelial remodelling, which significantly limit the penetration and distribution of delivery vectors [14].

Beyond delivery, editing efficiency and genomic precision are the critical obstacles. Although base and prime editing avoid double-strand breaks associated with ZFNs, TALENs, and CRISPR/Cas9, achieving sufficient levels of correction remains challenging. Modelling indicates that restoring CFTR function in just 10-30% of airway epithelial cells may provide clinical benefits, but the efficiency of in vivo genome editing in large animal models remains far below this threshold [18]. However, even advanced genome editing tools that avoid double-strand DNA breaks can still generate off-target DNA or RNA modifications [19,22]. Rare off target events could persist long term, making rigorous genomic safety screening essential, since airway basal stem cells are long-lived and self-renewing.

Finally, although genome editing appears promising for curing cystic fibrosis, its irreversible nature raises profound practical and ethical issues that remain before these therapies can be applied to patients, including substantial regulatory, manufacturing and challenges. Producing high-purity editors and delivery systems at scale remains complex. For safety and regulatory approval, it is essential to ensure batch-to-batch consistency [21]. Furthermore, because irreversible somatic genome editing demands careful assessment of potential delayed or rare adverse effects, long-term monitoring is required. Ethical considerations have arisen regarding the risks associated with permanent genetic modification and the responsibility of communicating uncertainties to patients. Social and economic factors have added further complexity, including the expected high cost of genome editing therapies, concerns about unequal access, and the need to manage patients' expectations regarding treatment outcomes [23].

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5. Conclusion

Genome engineering is a transformative approach for treating cystic fibrosis by directly targeting underlying genetic defects directly instead of managing the symptoms of cystic fibrosis. Unlike current therapies, including CFTR modulators, RNA based therapies, and other treatments that mainly aim to relieve the symptoms of cystic fibrosis, genome editing approaches such as base editing, prime editing, and gene addition have the potential to restore or replace defective CFTR alleles and enable CFTR proteins to function permanently and act in a mutation-specific manner. Importantly, genome editing is not limited by CFTR genotype, which is crucial and valuable for patients with rare, complex, or currently untreatable mutations. Furthermore, preclinical studies have demonstrated functional restoration of CFTR activity across both common and rare mutations using patient-derived airway cells and organoids, providing compelling evidence and underlining the feasibility of mutation targeted and long-lasting therapies. Despite this promise, several challenges must be addressed before the implementation of genome editing technologies. Challenges including efficient and targeted delivery to airway stem and progenitor cells, achieving sufficient editing efficiency, minimizing off-target effects, and overcoming ethical, regulatory, and manufactory constriction associated with irreversible genetic modification. In conclusion, although significant technical and clinical obstacles remain, genome editing technologies represent a promising therapeutic strategy for cystic fibrosis by improving the durability and mutation-specific correction of CFTR defects and progressing current therapeutic strategies beyond lifelong symptomatic management toward durable restoration of CFTR function. Genome editing technologies have shown huge potential on restoring CFTR function permanently, however the current research remains mostly in preclinical stage. Long-term stability and safety still have not been clinically validated and while having promising prospects, further studies are essential to confirm sustain therapeutic efficacy.

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