



GENE THERAPY IN DERMATOLOGY: CURRENT APPLICATIONS AND FUTURE POTENTIAL IN GENETIC SKIN DISEASES

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ABSTRACT

Gene therapy has revolutionized the approach to treating genetic skin disorders by targeting the root causes at the molecular level. Conditions such as epidermolysis bullosa (EB) and xeroderma pigmentosum have benefited from breakthroughs in gene-editing technologies, delivery systems, and regenerative medicine. This review highlights the advances in these areas, including the use of CRISPR-Cas9, RNA-based therapies, and emerging non-viral delivery mechanisms. Key challenges such as off-target effects, cost, and ethical issues are discussed, alongside the potential of future innovations like bioprinting and epigenetic therapies.

KEYWORDS: epidermolysis bullosa, xeroderma pigmentosum, CRISPR-Cas9, epigenetic therapy.

1. INTRODUCTION

Genetic disorders affecting the skin often result from inherited mutations in structural or regulatory genes. These conditions, such as epidermolysis bullosa (EB), lamellar ichthyosis, and xeroderma pigmentosum, significantly impair patients' quality of life. Gene therapy offers a unique opportunity to address these challenges by correcting genetic defects at their source.^[1,2] The skin, with its high accessibility and regenerative capacity, makes it a particularly promising target for gene-based interventions.^[3]

2. Current Applications of Gene Therapy in Dermatology

2.1 Epidermolysis Bullosa

Epidermolysis bullosa (EB) encompasses a group of disorders caused by mutations in genes encoding structural proteins of the skin. Current research focuses on *ex vivo* gene therapy, where patient-derived keratinocytes are genetically corrected and expanded in culture before transplantation. This approach has shown promise, particularly in dystrophic EB, where lentiviral vectors carrying the COL7A1 gene have demonstrated successful skin repair.^[4,5]

2.2 RNA Therapeutics

RNA-based therapies, including small interfering RNAs (siRNAs) and antisense oligonucleotides (ASOs), are emerging as effective tools for treating skin conditions. These molecules can target mutant alleles selectively, making them particularly useful for diseases caused by dominant-negative mutations.^[6] Recent advancements in

RNA stabilization and delivery have further enhanced their therapeutic potential.^[7]

2.3 CRISPR-Cas9 Technology

CRISPR-Cas9 gene-editing technology allows precise correction of genetic mutations and has been successfully applied in preclinical models of skin disorders. In diseases such as lamellar ichthyosis and xeroderma pigmentosum, CRISPR-based interventions have demonstrated the ability to restore normal skin function. Advanced versions like base editing and prime editing offer even greater accuracy, minimizing risks of off-target effects.^[8,9]

3. Delivery Systems for Gene Therapy

3.1 Viral Vectors

Adeno-associated viruses (AAVs) and lentiviruses are widely used for delivering therapeutic genes due to their efficiency and ability to target specific cell types. Recent studies have refined AAV serotypes to optimize their delivery to skin cells, improving their therapeutic potential for dermatological applications.^[10,11]

3.2 Non-Viral Systems

Non-viral delivery systems, such as lipid nanoparticles (LNPs), have gained attention for their safety profile and reduced immunogenicity. These systems can efficiently deliver nucleic acids, including siRNAs and CRISPR components, to epidermal cells. The use of non-viral carriers provides an alternative for patients at risk of immune reactions to viral vectors.^[12,13]

4. Future Innovations

4.1 Regenerative Medicine

The integration of gene therapy with regenerative techniques, such as bioprinting, offers a novel approach to treating skin diseases. This technology enables the creation of three-dimensional skin grafts using genetically corrected cells, providing a tailored solution for patients with severe conditions.^[14,15]

4.2 Epigenetic Modulation

Epigenetic therapies are being explored as complementary approaches to gene therapy. By targeting chromatin remodeling and DNA methylation, these therapies aim to modulate gene expression and provide long-term benefits for genetic skin diseases.^[16]

5. Challenges and Ethical Considerations

5.1 Off-Target Effects

Despite its precision, CRISPR technology is not immune to unintended edits. Off-target effects pose risks of introducing new mutations, necessitating the development of advanced editing tools like prime editors to enhance safety.^[17,18]

5.2 Accessibility and Cost

Gene therapy remains prohibitively expensive for many patients, largely due to the high costs associated with manufacturing and delivery. Developing scalable and cost-effective delivery systems is essential to make these therapies more accessible.^[19,20]

5.3 Ethical Concerns

The potential for misuse of gene-editing technologies raises ethical issues, particularly concerning germline editing. Regulatory frameworks must ensure that these technologies are used responsibly, with patient safety and societal implications carefully considered.^[21]

6. CONCLUSION

Gene therapy represents a paradigm shift in the treatment of genetic skin diseases, offering hope for conditions once deemed untreatable. Advances in delivery systems, gene-editing technologies, and regenerative medicine have brought significant progress, but challenges such as cost, ethical concerns, and technical limitations remain. Collaborative efforts between researchers, clinicians, and policymakers will be critical to unlocking the full potential of gene therapy in dermatology.

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