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CRISPR/Cas9: A Promising Approach for Alopecia

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ABSTRACT

Alopecia, characterized by abnormal hair loss, is more than an aesthetic problem; it is a major psychosocial challenge affecting millions of people worldwide. Traditional treatments, such as finasteride and minoxidil, often offer limited solutions and come with side effects. As an alternative, CRISPR/Cas9, an advanced technique for targeted gene modification, is emerging as a powerful tool to tackle alopecia at its genetic roots. The use of CRISPR/Cas9 to stimulate hair growth has shown efficacy in several experimental models and holds promise for manipulating key genes at different phases of the hair cycle and influencing molecular pathways related to hair growth. Therefore, the objective of our research was to deepen and summarize the use of CRISPR/Cas9 technology in editing genes involved in hair growth. This work provides a deeper understanding of the underlying genetic mechanisms and paves the way for personalized and effective therapy.

Keywords: CRISPR/Cas9; Gene Editing; Alopecia; Hair Growth, Hair Cycle, Hair Follicle; Therapeutic Potential

Introduction

The hair cycle comprises four stages: anagen (growth), catagen (regression), telogen (rest), and exogen (shedding) [1]. Alopecia, characterized by abnormal hair loss, stems from an imbalance in these phases. This imbalance is triggered by factors such as genetic predispositions, stress, nutritional deficiencies, hormonal changes, infections, and lifestyle habits [2]. According to the American Academy of Dermatology (AAD), androgenetic alopecia affects approximately 50% of men and 30% of women. In contrast, alopecia areata affects about 2% of the population of the world [3]. Currently, the drugs finasteride and minoxidil, approved by the Food and Drug Administration (FDA), serve as primary treatments for alopecia. However, the use of these drugs can lead to adverse side effects [4]. Despite advancements in pharmacological treatments and topical therapies, the efficacy of these solutions is often limited. In this context, the CRISPR/Cas9 genetic editing technology (Clustered Regularly Interspaced Short Palindromic Repeats/CRISPR-associated protein 9) emerges as a promising tool. It provides a novel approach to understanding and potentially treating alopecia at the molecular level [5]. The CRISPR/Cas9 offers high-precision genetic editing, which opens possibilities for innovative approaches in understanding and addressing alopecia. Its potential application in this field could revolutionize the management of hair growth by editing fundamental genes, thereby enabling the reversal or prevention of hair loss [6]. This study discusses recent developments and perspectives on the use of CRISPR/Cas9 in hair research and the treatment of alopecia [7-15].

Molecular Mechanism of CRISPR/Cas9

The CRISPR/Cas9 represents a novel and highly sophisticated technology, facilitating targeted gene editing through a precise molecular mechanism, as illustrated in Figure 1.

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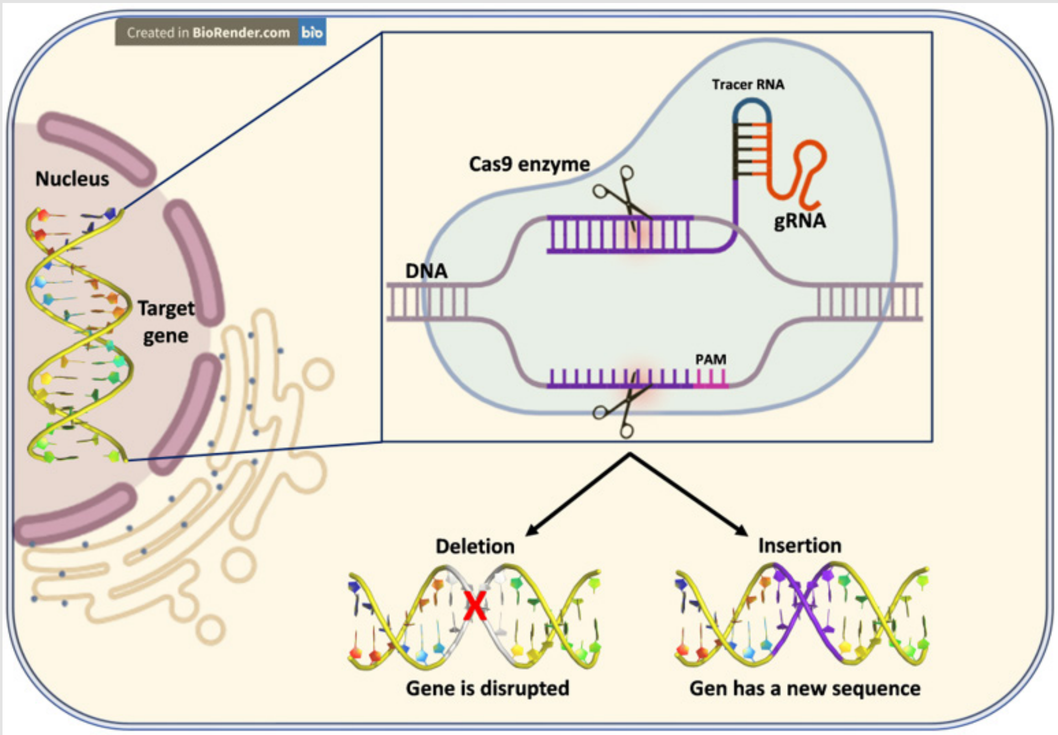

Figure 1: Molecular mechanism of gene editing by CRISPR/Cas9. The Cas9 enzyme, guided by a specifically designed guide RNA (gRNA), navigates the genome to locate a target DNA sequence, identifying it by the essential Protospacer Adjacent Motif (PAM), which is crucial for Cas9 recognition and activation. After locating the target gene, Cas9 executes a high-precision incision in the DNA strand, as indicated by the scissors symbol. This molecular intervention can have two outcomes: it can suppress the function of the gene by deleting it, or it can serve as a platform for integrating new genetic sequences at the site of the incision, thus modifying the original gene.

CRISPR/Cas9 in Hair Growth Modulation

Currently, the efficacy of CRISPR/Cas9 in editing specific genes and assessing their impact on hair growth and hair cycle regulation is being extensively studied. This includes exploring how these genes modulate molecular pathways and understanding their significance. These assessments have been conducted across various murine models, as detailed in Table 1. Experimental advances with CRISPR/Cas9 open a promising horizon in the understanding and activation of the hair cycle at a molecular level. This technology represents an innovative alternative for hair regeneration and the treatment of alopecia, marking a significant advance in the field of dermatology and regenerative medicine.

Table 1: CRISPR/Cas9 in editing genes involved in hair growth.

Edited gene	Biological model	Molecular pathways involved	Biological effect	References
SRD5A2	C57BL/6 Mice	Suppression of apoptosis and increased VEGF expression	Increase in the number and thickness of hair follicles	[5]
FGF5	C57BL/6 Mice	Activation of the WNT/β-catenin signaling pathway	Increase in the number of follicles, hair length, and thickness of hair follicles	[7]
FGF5	Rabbit	Suppression of BMP2/4 and VERSICAN signaling pathway	Prolongation of the anagen phase and shortening of other phases, increased fiber diameter, and increased number of follicles per area	[8]
FGF5	Cashmere Goats	Promotion of hair cycle activation	Increased number of secondary hair follicles and fiber length	[9]
FGF21	BALB/c Mice	Suppression of PI3K/AKT and MAPK/ERK signaling pathway	Reduction in hair regeneration speed and number of hairs per area	[10]
Tβ4	Cashmere Goat	Increased vasoconstriction, angiogenesis, and vascular permeability around secondary hair follicles	Increase in the number of follicles and hair length	[11]

VDR	Cashmere Goat	Suppression of WNT and BMP4 pathways, and expression of genes like VGF, Noggin, LEF1, and β-catenin	Affected hair formation and significantly lower growth rate, inactivation of hair growth cycle	[12]
LAMA3	C57BL/6 and BALB/c Mice	Suppression of the PI3K/AKT signaling pathway	Hair loss starting from day 80 after birth, enlargement of sebaceous glands in the dermis, and absence of normal hair follicle structure	[13]
PLCD1	C57BL/6 Mice	Effect on genes involved in hair follicle differentiation and FOXN1 signaling pathway	Development of baldness on the abdomen, sparse hair on the back, histological abnormalities, reduced number of hair follicles, and altered epidermal differentiation	[14]
CCHCR1	C57BL/6 Mice	Alteration in keratinization signaling pathway and hair development	Hair loss and morphological abnormalities	[15]

Note: SRD5A2: Steroid 5 Alpha-Reductase 2, FGF5: Fibroblast Growth Factor 5, FGF21: Fibroblast Growth Factor 21, Tβ4: Thymosin Beta-4, VDR: Vitamin D Receptor, LAMA3: Laminin Subunit Alpha 3, PLCD1: Phospholipase C Delta 1, CCHCR1: Coiled-Coil α-Helical Rod Protein 1, VEGF: Vascular Endothelial Growth Factor, BMP2/4: Bone Morphogenetic Protein 2/4, Pi3k/Akt: Phosphoinositide 3-Kinase/Protein Kinase B, Mapk/Erk: Mitogen-Activated Protein Kinase/Extracellular Signal-Regulated Kinase, VGF: VGF Nerve Growth Factor, Lef1: Lymphoid Enhancer-Binding Factor 1, and, Foxn1: Forkhead Box N1.

Perspectives

The role of CRISPR/Cas9 in editing critical genes to induce hair growth presents enormous opportunities, spanning from enhancing our understanding of genetic causes to developing personalized therapies. This technology holds the potential to prevent hair loss in individuals with a high genetic risk and aid in hair regeneration in advanced cases. However, there are challenges in clinical implementation, such as the need for precise genetic editing, effective delivery systems, and the minimization of adverse immune responses. Additionally, ethical, and regulatory considerations, public acceptance, and accessibility to these therapies must be considered. It is essential to conduct further research on the long-term effects of CRISPR/Cas9 and undertake clinical trials to ensure its safe application in humans.

Conclusion

CRISPR/Cas9 has revolutionized the approach to tackling alopecia, providing a deeper molecular understanding and the ability to induce hair growth through the editing or insertion of specific genes. These remarkable advances underscore the transformative potential of this molecular tool in hair gene therapy.

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Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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