

CRISPR-Cas9 in Thyroid Research: Gene Editing for Future Therapies

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Introduction

CRISPR-Cas9 technology has revolutionized the landscape of biomedical research by offering an efficient, precise and cost-effective method for genome editing. In thyroid research, this tool is emerging as a powerful approach to dissect gene functions, model disease mechanisms and explore novel therapeutic strategies for both benign and malignant thyroid conditions. Thyroid disorders, particularly autoimmune thyroiditis and thyroid cancer, are influenced by genetic mutations, epigenetic changes and immune dysfunctions factors that can now be studied and potentially corrected using CRISPR-based platforms. Gene editing in thyroid cells and organoids allows researchers to reproduce disease-relevant mutations such as BRAF V600E and TERT promoter variants to better understand their oncogenic behavior. CRISPR also enables the development of animal models carrying human-like thyroid defects, providing valuable systems for drug testing and pathophysiological studies. Furthermore, innovations such as base editing and prime editing allow for refined modifications at the nucleotide level without causing double-strand breaks, minimizing off-target effects. These advancements open exciting avenues for correcting monogenic thyroid diseases like congenital hypothyroidism caused by mutations in TSHR or SLC5A5. Despite the promise, challenges remain, including delivery efficiency, immune responses to Cas9 and the ethical considerations of germline editing. This perspective highlights the growing role of CRISPR-Cas9 in thyroid research and its potential in shaping the future of endocrine therapeutics [1].

Description

CRISPR-Cas9's impact on thyroid research is anchored in its ability to model genetic mutations with high specificity. In thyroid cancer, key driver mutations such as BRAF V600E, RAS and RET/PTC rearrangements have been introduced into cell lines and mouse models using CRISPR systems to study their functional impact. These models replicate the aggressiveness and therapy resistance observed in human tumors, thereby enhancing the relevance of preclinical drug screening. The technology has enabled functional knockout of tumor suppressor genes like TP53 and PTEN, offering insight into synergistic mutations and tumor progression. CRISPR also supports lineage tracing in thyroid development, by tagging key transcription factors such as PAX8, NKX2-1 and FOXE1 to understand cell fate decisions. In addition to modeling malignancy, CRISPR tools are being used to replicate mutations causing congenital hypothyroidism, such as those in the TPO or DUOX2 genes, aiding in the understanding of thyroid hormone biosynthesis pathways. Single-guide RNAs (sgRNAs) can be designed to target virtually any gene, making CRISPR adaptable to different thyroid research goals. Multiplexing approaches now allow for simultaneous editing of multiple genes, which is useful for modeling complex disease interactions. These advances deepen our mechanistic understanding of thyroid biology and lay the

groundwork for therapeutic discovery [2].

Beyond disease modeling, CRISPR holds promise for therapeutic intervention in thyroid diseases. One major area of interest is the potential to correct pathogenic mutations in thyroid follicular cells using in vivo gene editing approaches. For monogenic conditions like Pendred syndrome or congenital dyshormonogenesis, CRISPR offers the potential for permanent correction at the DNA level. For thyroid cancers, CRISPR could be employed to inactivate oncogenes or re-sensitize tumors to radioactive iodine by reactivating Sodium-iodide Symporter (NIS) expression. Strategies include CRISPRa (CRISPR activation) systems that upregulate silenced genes or epigenetic editing to modify chromatin states that inhibit therapeutic gene expression. Ex vivo CRISPR editing of patient-derived thyroid organoids could allow for personalized screening of treatment regimens or eventual autologous transplantation. CRISPR-Cas9 has also contributed to immunotherapy development by enabling engineering of T cells for thyroid cancer applications, including the development of tumor-specific Chimeric Antigen Receptor (CAR) T cells. However, achieving efficient and tissue-specific delivery of the CRISPR components remains a critical bottleneck, particularly in the thyroid gland, which is relatively protected and less permeable than other organs. Ongoing efforts to develop viral and non-viral delivery systems tailored for thyroid tissue are crucial for translation to clinical use [3].

Despite its potential, the clinical application of CRISPR in thyroid therapy faces several technical and ethical challenges. Off-target effects remain a concern, especially in thyroid cancer patients where genomic instability may amplify unintended consequences. While newer CRISPR variants like high-fidelity Cas9, base editors and prime editors improve precision, their long-term safety profiles are not yet fully established. Immune responses to the Cas9 protein, especially from bacterial origins, can also limit its therapeutic viability. There are ethical debates surrounding the use of germline editing to prevent heritable thyroid conditions, particularly given the availability of less invasive management options. Regulatory frameworks globally are still evolving and many clinical trials are in early phases or limited to hematologic or retinal diseases. In thyroid disorders, therapeutic use remains largely experimental, though preclinical studies are rapidly expanding. Additionally, accessibility and cost remain barriers in lower-resource settings, potentially widening disparities in thyroid disease treatment if CRISPR-based therapies reach market. The balance between innovation and safety will be critical, as public perception and scientific responsibility shape the pace of adoption. Continued engagement with bioethicists, patients and policymakers will be vital to responsibly advance the clinical integration of gene editing [4].

Looking ahead, CRISPR is expected to significantly influence the future of thyroid research and care. Ongoing research focuses on integrating CRISPR with AI-driven gene target prediction, high-throughput screening and single-cell transcriptomics to refine target identification. In the diagnostic domain, CRISPR-based biosensors and SHERLOCK systems are being explored to detect thyroid cancer biomarkers in body fluids with high sensitivity and specificity. In regenerative medicine, CRISPR could support the generation of functional thyroid tissue from stem cells for patients with thyroid agenesis or extensive gland damage. There is also interest in using CRISPR tools to study environmental-gene interactions that may predispose individuals to thyroid

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autoimmunity. International collaborations are facilitating CRISPR resource sharing, standardizing protocols and creating open-source sgRNA libraries for thyroid-related targets. Educational outreach and responsible communication will play a key role in preparing the clinical community for the integration of gene editing into routine care. With the continued refinement of delivery systems and expansion of safety data, the application of CRISPR-Cas9 in thyroid disorders is poised to shift from bench to bedside. As the field matures, gene editing may become an essential tool in the arsenal against complex and inherited thyroid diseases [5].

Conclusion

In conclusion, CRISPR-Cas9 is emerging as a transformative tool in thyroid research, offering unprecedented opportunities for modeling disease, discovering targets and exploring gene-based therapies. While clinical application remains in its early stages, the pace of innovation, combined with advances in safety and delivery, is paving the way for potential use in correcting genetic thyroid conditions and improving cancer treatment outcomes. As ethical, technical and regulatory barriers are addressed, CRISPR is likely to redefine how we understand and treat thyroid disorders in the coming decade.

Acknowledgement

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Conflict of Interest

None.

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