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REVIEW
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Genetic engineering as a novel approach in tooth regeneration: CRISPR technologies, regenerative strategies, and clinical translation in dentistry

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Abstract

The relevance of the study is due to the rapid development of regenerative dentistry, which is gradually moving from traditional restoration methods to biological restoration of dental tissues based on genetic engineering, cell technologies and precision medicine.

***The purpose** of this review was to summarize and critically analyze modern literary sources on the role of genetic engineering in stimulating tooth growth and restoration, as well as to determine the prospects for its implementation in clinical dental practice.*

***Materials and methods** included a systematic search and analysis of scientific publications in international databases using keywords covering gene engineering, CRISPR/Cas, stem cells, tooth regeneration and oncological aspects of dentistry. The selected sources were analyzed taking into account their scientific novelty, relevance and level of evidence. The results were summarized by thematic areas, which included genome editing, cell therapy, dental bioengineering and the use of CRISPR in tumor research.*

***Results.** The analysis of results of published studies indicates that genome editing technologies, in particular CRISPR/Cas, significantly expand the capabilities of regenerative dentistry. It has been established that genetically modified dental stem cells demonstrate an increased ability to odontogenic differentiation and dentin formation. Separate studies confirm the possibility of creating tooth-like structures in vitro using cell cultures, biomaterials and 3D technologies. It has also been shown that CRISPR screenings allow the identification of new molecular targets and mechanisms of tumor resistance, which is important for the development of precision dentistry and oncology. At the same time, most of the research is at the preclinical stage, and the implementation of these technologies in practice is limited by technical, biological and ethical factors.*

***Conclusions.** An analysis of modern literary sources showed that genetic engineering is a promising direction in the development of modern dentistry, capable of changing approaches to the treatment of tooth loss and oral diseases. Further research should be aimed at improving methods for delivering genetic material, increasing the accuracy of genome editing, and ensuring the safety of clinical application.*

***Keywords:** regenerative dentistry; genetic engineering; CRISPR/Cas; stem cells; enamel remineralization; dentin regeneration; oral cancer*

Introduction

The modern development of dentistry is characterized by a gradual transition from conventional restorative approaches toward biologically oriented strategies aimed at the regeneration of dental and periodontal tissues [1, 2]. Despite significant progress in prosthetic and implant rehabilitation, artificial replacements are unable to fully replicate the structural, functional, and biological properties of natural teeth. This limitation has stimulated growing interest in regenerative approaches based on molecular biology and tissue engineering.

Recent advances in gene engineering have opened new perspectives for controlling cellular behavior and tissue development. Genome editing technologies, including zinc finger nucleases (ZFN), transcription activator-like effector nucleases (TALEN), and CRISPR/Cas systems, enable targeted modification of genetic material with high precision [3, 4]. Among these, CRISPR/Cas has emerged as the most versatile and efficient tool, significantly expanding research opportunities in regenerative medicine and dentistry.

One of the promising directions in modern dentistry is the application of gene engineering in combination with stem cell technologies. Dental stem cells, particularly dental pulp stem cells, are considered a key component of regenerative strategies due to their capacity for self-renewal and differentiation into odontogenic lineages [5]. These approaches form the basis for developing biologically driven methods aimed at restoring dental tissues.

In addition, molecular regulation of odontogenesis plays a critical role in tooth development and regeneration. Various signaling pathways are involved in these processes, highlighting the complexity of genetic control over tooth formation. Understanding these mechanisms provides a theoretical foundation for future regenerative interventions.

Beyond regenerative applications, gene editing technologies are also being explored in dental oncology and other areas of maxillofacial medicine, further emphasizing their broad biomedical potential. Despite these advances, the clinical implementation of gene engineering in dentistry remains limited due to technical, biological, and ethical challenges. Most studies are still at the experimental or preclinical stage, which necessitates further research to ensure safety and effectiveness.

Thus, the systematization of current knowledge on gene engineering technologies in dentistry is an important scientific task that contributes to the development of regenerative and personalized treatment approaches.

The purpose of this review is to summarize and critically analyze modern literary sources on the role of genetic engineering in stimulating tooth growth and restoration, as well as to determine the prospects for its implementation in clinical dental practice.

Materials and methods

This study was designed as a narrative literature review with elements of a structured search conducted according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) 2020 recommendations for transparent reporting of evidence identification and selection [6]. The flowchart for selecting publications is formed and depicted in Figure 1.

The search for literary sources was carried out in leading international scientometric databases, in particular PubMed/MEDLINE, PubMed Central, Scopus, Web of Science Core Collection, ScienceDirect, Wiley Online Library and Google Scholar. In addition, a manual search for relevant sources was carried out in the reference lists of selected articles. To expand the coverage of the studies, publications from different countries of the world and in different languages were analyzed, with the exception of Russian-language sources, which were not included in the analysis.

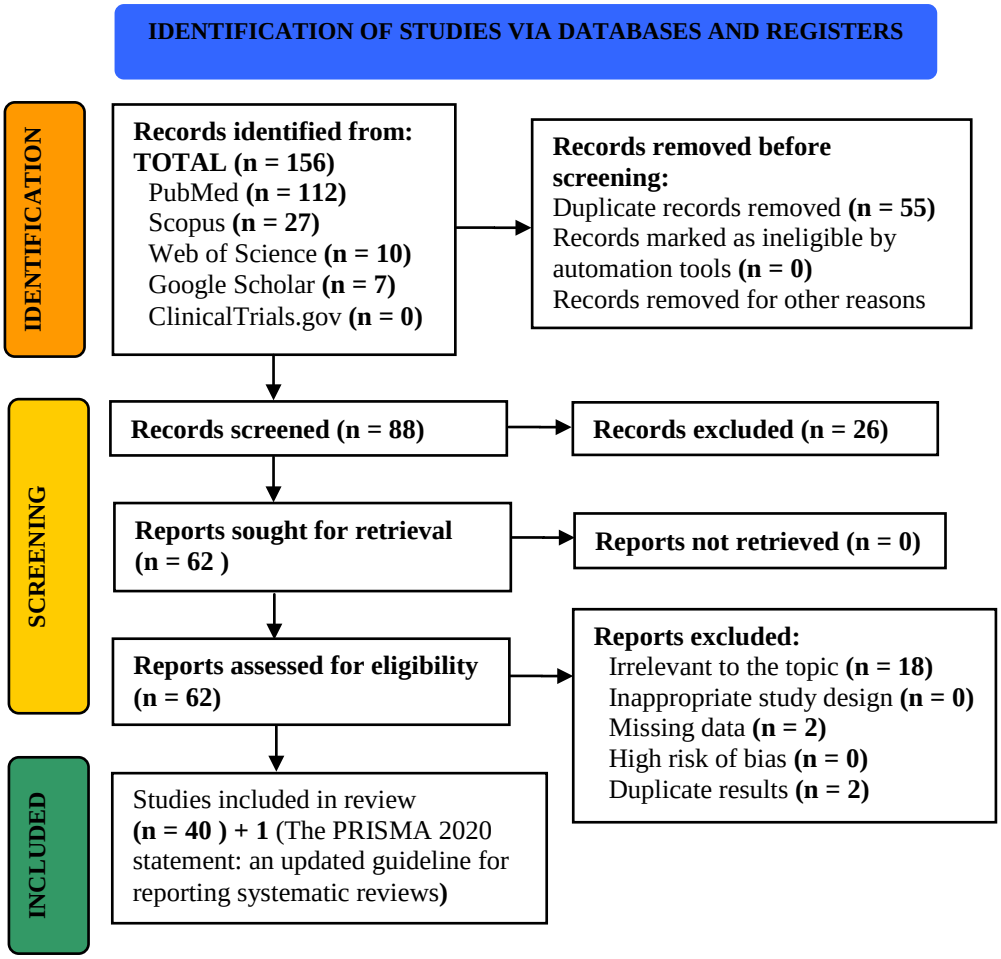

Fig. 1. Flowchart of publication selection according to the PRISMA 2020 reporting guidelines for systematic reviews and meta-analyses

The search strategy was based on the use of combinations of keywords and their synonyms in English, in particular: “genetic engineering”, “genome editing”, “CRISPR/Cas9”, “TALEN”, “ZFN”, “tooth regeneration”, “dental stem cells”, “odontogenesis”, “dentin regeneration”, “enamel regeneration”, “regenerative dentistry”, “biomaterials”, “nanocomposites”, “enamel remineralization”, “pulp revitalization”, “platelet concentrates”, “growth factors”, “3D bioprinting”, “exosome therapy”, “biomarkers”, “oral cancer”, “oral squamous cell cancer”, as well as relevant MeSH terms.

The search covered publications issued between January 2021 and March 2026. Only peer-reviewed full-text articles indexed in international scientific databases were considered. Inclusion criteria: original experimental studies; clinical studies; systematic or narrative reviews relevant to the topic; publications focused on gene engineering in dentistry, tooth regeneration, stem cells, odontogenesis, or oral oncology. Exclusion criteria: duplicate records; conference abstracts without peer review; non-full-text publications; irrelevant studies not related to the review topic; studies with insufficient methodological quality.

After database searching, 156 records were identified. Following duplicate removal, 88 publications remained for title and abstract screening. After preliminary assessment, 62 full-text articles were reviewed for eligibility. Finally, 40 studies were included in the qualitative synthesis and used for preparation of this review.

Data extraction and synthesis were performed using methods of comparison, critical analysis, and thematic systematization. Particular attention was paid to the following analytical domains: genome editing technologies, stem cell-based regeneration, molecular

regulation of odontogenesis, tooth bioengineering, oral oncology applications, and barriers to clinical translation.

Results and discussion

A review of current literature has shown that genetic engineering in dentistry is developing within a multidisciplinary approach that combines molecular biology, tissue engineering, cell technologies, and bioinformatics [7]. The main research results can be grouped into several key areas: regulation of odontogenesis, application of genome editing, cell engineering approaches, tooth bioengineering, oncological aspects, and barriers to clinical translation [8]. Analysis of contemporary scientific literature demonstrates that gene engineering represents a fundamentally new phase in the evolution of dentistry, marking a shift from conventional restorative strategies toward regenerative medicine. Whereas traditional treatment modalities primarily focus on the replacement of lost tissues, current strategies aim to restore their inherent biological architecture and functionality [9]. Overall, contemporary research provides a strong foundation for the evolution of dentistry toward a biologically driven paradigm, where the primary goal shifts from artificial replacement to the restoration of natural structures and functions of the dentofacial system.

Molecular regulation of odontogenesis

The first fundamental result is a significant deepening of the understanding of the molecular mechanisms of tooth development. Thanks to the use of modern methods, such as single-cell RNA sequencing and spatial transcriptomics, a complex interaction of signaling pathways that coordinate the formation of the tooth germ and cell differentiation has been established. In particular, the central role of the Wnt, BMP, FGF, and SHH pathways in the regulation of odontogenesis has been confirmed, which opens up the possibility of their targeted modification for the induction of tooth regeneration [10].

Along with cell-oriented approaches, considerable attention is being paid to the molecular mechanisms of odontogenesis regulation, in particular the Wnt and BMP signaling pathways, which play a crucial role in the formation of tooth buds, cell differentiation, and tooth morphogenesis [11]. One of the most promising research targets is the USAG-1 protein (SOSTDC1), which acts as an antagonist of these signaling cascades and limits the development of tooth structures. Among the molecular targets, the USAG-1 protein is of particular importance, acting as a negative regulator of tooth development. Its inhibition leads to the activation of BMP and Wnt signaling and stimulates the formation of additional teeth in animal models [12].

Experimental data indicate that inhibition of USAG-1 activity can reactivate latent tooth buds and induce the formation of new teeth, which opens up prospects for the creation of fundamentally new methods for the treatment of adentia and other dentition defects [13]. Experimental studies have shown that the use of neutralizing antibodies to USAG-1 is capable of inducing the so-called third generation of teeth, which is considered a fundamentally new approach to the treatment of adentia. Further work confirms the possibility of clinical translation of this approach, in particular by developing humanized antibodies and preparing for clinical trials [14].

A pivotal transformation is observed in the approach to managing adentia. Previously, clinical practice relied predominantly on prosthetic rehabilitation and dental implants; however, recent research highlights the potential for stimulating the formation of a patient's own tooth [15]. In this context, modulation of the USAG-1 pathway appears particularly promising, as it enables the activation of endogenous mechanisms responsible for tooth development. This paradigm shift suggests that future therapeutic concepts may emphasize

the stimulation of intrinsic regenerative capacity rather than artificial substitution of dental structures [16].

CRISPR technologies in dentistry

The second important direction is the application of genome editing technologies, primarily CRISPR/Cas. Compared with ZFN and TALEN, this system provides simpler and more efficient editing of genetic material, which significantly expands the possibilities of its use in dentistry. CRISPR technologies are used to model diseases, study gene functions, and create new therapeutic strategies [17].

Thus, genetic engineering, in particular genome editing technologies, forms a new paradigm for the development of dentistry, aimed at restoring the natural structures of the tooth and periodontal tissues [18]. Systematization of modern literature data on the possibilities, limitations and prospects for the use of these technologies is an urgent scientific task, which is of great importance for the further development of regenerative and personalized dentistry.

Another promising direction involves the modulation of the oral microbiome using CRISPR technology. Evidence indicates that CRISPR/Cas systems can selectively eliminate cariogenic bacteria, including *Streptococcus mutans*, thereby offering innovative opportunities for caries prevention and the advancement of personalized dental care [19]. Persistent microbial colonization within periodontal tissues is recognized as a key contributor to chronic inflammation, which supports the rationale for applying targeted genetic and molecular interventions to influence disease pathogenesis [20, 21].

Stem cell-based regeneration

A significant achievement is the introduction of CRISPR into cell therapy. In particular, it has been shown that genetically modified dental pulp stem cells are able to differentiate more efficiently into odontoblasts and form dentin [22]. Modern experimental studies demonstrate that genetic modification of these cells using CRISPR technology can enhance their odontogenic differentiation, stimulate dentin formation, and improve tissue regeneration under inflammatory conditions [23]. This suggests the possibility of creating guided cell therapies aimed at restoring the functional integrity of the tooth. Immune mechanisms also play a key role in the regulation of inflammatory processes in periodontal tissues, influencing cell proliferation, differentiation, and tissue remodeling, which is of fundamental importance for understanding the potential of genetically controlled regenerative approaches [24].

Studies using CRISPR-activated BDNF expression have demonstrated a significant increase in the volume of newly formed dentin and an improvement in its organization, which confirms the high potential of genetically modified cells for tooth regeneration. Similarly, CRISPR-knockout of individual genes, such as C5L2, enhances mineralization and regenerative properties of cells under inflammatory conditions [25].

Alterations in the biochemical characteristics of oral fluid, particularly changes in pH levels and trace element composition following orthopedic interventions, reflect modifications in the local microenvironment. These changes may significantly influence the course of regenerative processes and determine the effectiveness of bioengineering-based therapeutic approaches in dental practice [26].

Tooth bioengineering and organoids

A separate area of research is related to tooth bioengineering. Current work demonstrates the possibility of forming tooth-like structures *in vitro* using stem cells and biomaterials, including hydrogels and 3D scaffolds [27]. In particular, enamel-like tissues have

been obtained by inducing ameloblast differentiation, and tooth rudiments capable of further development after implantation have been formed. However, these structures do not yet achieve full functional compliance with a natural tooth [28].

A notable advancement is the convergence of gene-editing technologies with other domains of regenerative medicine, particularly through the incorporation of biomaterials, bioactive molecules, and exosome-based systems. Contemporary strategies focus on designing multifunctional constructs that integrate cells, signaling factors, and extracellular matrices, thereby enabling a more precise simulation of physiological tissue development and regeneration processes [29].

At the same time, existing evidence underscores the inherent complexity of achieving complete tooth regeneration. Unlike many other tissues, the tooth is a highly organized biological unit composed of multiple tissue types with distinct embryological origins. Consequently, successful regeneration requires precise orchestration of spatial and temporal interactions between various cell populations and signaling pathways, which remains a considerable challenge for modern biomedical science [30, 31].

Applications in oncology

In addition to regenerative aspects, gene editing technologies are actively studied in the context of oncological dentistry. In particular, the CRISPR/Cas system is used to study the molecular mechanisms of oral cancer development, identify key genes involved in carcinogenesis, and develop new targeted therapeutic strategies. Previous studies have demonstrated the ability to suppress tumor cell proliferation by correcting oncogenic mutations or inactivating genes that ensure tumor survival, which indicates the potential of CRISPR technologies in the personalized treatment of malignant neoplasms of the maxillofacial region [32].

Beyond regenerative applications, CRISPR-based approaches are increasingly being explored in dental oncology. Experimental studies have demonstrated that targeted gene editing in oral squamous cell carcinoma can inhibit tumor cell proliferation and enhance responsiveness to anticancer therapies [33]. In addition, CRISPR-driven genomic screening has emerged as a powerful tool for uncovering novel therapeutic targets and elucidating mechanisms underlying tumor resistance [34].

Within dental oncology, CRISPR technology offers promising opportunities for the advancement of personalized medicine. Precise gene-editing capabilities enable the development of tailored therapeutic approaches targeting specific molecular pathways involved in tumor progression [35]. However, similar to regenerative dentistry, these strategies remain largely experimental and require further validation to establish their safety and clinical efficacy.

Limitations and future prospects

At the same time, despite significant progress in this field, the clinical implementation of genetic engineering in dental practice remains limited. The main limiting factors are the risk of off-target effects, the complexity of delivering genetic constructs to target cells, the need for precise spatiotemporal control of gene expression, as well as the ethical and regulatory aspects of the use of genome editing in humans. Most of the existing studies are at the stage of preclinical experiments, which requires further large-scale studies to confirm the safety and efficacy of the proposed approaches [36].

At the same time, current literature indicates that the majority of these developments remain at the preclinical stage. Despite substantial progress in fundamental research, the clinical implementation of genetic engineering in dentistry is still limited. This is largely due

to technical, biological, and ethical challenges that require further investigation before widespread clinical adoption can be achieved [37].

A critical consideration involves the inherent limitations of CRISPR-based technologies. Although these systems demonstrate remarkable efficiency, they are still associated with the possibility of off-target modifications, which may result in unintended genetic alterations. Furthermore, the effective delivery of gene-editing components to specific target cells remains a significant challenge, particularly under *in vivo* conditions. These constraints hinder the immediate translation of CRISPR into routine clinical practice and highlight the need for improved delivery platforms, including advanced nanoparticle systems and viral vectors [38].

Equally important are the ethical and regulatory challenges. The application of genome editing in humans requires rigorous oversight and comprehensive safety evaluation, which inevitably delays the clinical adoption of such innovations. Current literature consistently emphasizes a pronounced gap between experimental research and its practical implementation, largely due to the high cost of these technologies, difficulties in standardization, and insufficient clinical training in this emerging field [39].

In general, the analyzed evidence suggests that genetic engineering holds substantial potential to reshape modern dentistry. Nevertheless, its successful clinical integration depends on overcoming a range of fundamental and translational challenges [40]. Among the most promising directions are the combination of gene-editing technologies with cell-based therapies, the advancement of bioengineering solutions, and the implementation of personalized treatment strategies [41].

Prospects for further research

Prospects for the development of genetic engineering in dentistry are associated with the improvement of CRISPR/Cas technologies, increasing their safety and creating effective systems for delivering genetic material. An important direction is the integration of genetic technologies with cell therapy, biomaterials and 3D bioprinting for the formation of functionally complete dental structures. The use of cell-free approaches, in particular monoclonal antibodies to USAG-1 and signaling molecules, as well as the development of personalized treatment methods in dental oncology, is also promising.

Conclusions

Current literature data indicate that genetic engineering is one of the key areas of development of regenerative dentistry, aimed at restoring natural tooth structures. It has been established that the Wnt and BMP signaling pathways play a leading role in the regulation of odontogenesis, and their targeted modulation, in particular through inhibition of USAG-1, can initiate the formation of new teeth. Genome editing technologies, primarily CRISPR/Cas, significantly expand the capabilities of cell therapy, contributing to an increase in the regenerative potential of stem cells and the restoration of dentin.

At the same time, full-fledged tooth regeneration remains a difficult task, and the clinical implementation of these technologies is limited by technical, biological and ethical factors. Thus, genetic engineering forms the basis of future biologically oriented dentistry, but requires further research for widespread clinical application.

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