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GENE THERAPY STRATEGIES FOR ORAL CANCER: CURRENT PROGRESS, CHALLENGES, AND FUTURE PERSPECTIVES

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ABSTRACT

Gene therapy has emerged as a transformative approach in the treatment of a wide range of diseases by targeting underlying genetic defects. It involves the introduction, replacement, or modification of defective genes with functional counterparts to restore normal cellular function. This review provides an overview of the fundamental principles of gene therapy, various delivery systems, and their applications, with particular emphasis on oral cancer. Gene therapy is broadly classified into germline and somatic approaches, with somatic gene therapy being more clinically applicable. Both viral vectors—including retroviruses, adenoviruses, herpes simplex virus, and adeno-associated viruses—and non-viral delivery systems such as electroporation, gene gun, sonoporation, magnetofection, and chemical carriers are widely utilized. While viral vectors offer high transfection efficiency, they are associated with limitations such as immunogenicity, insertional mutagenesis, and restricted gene capacity. In contrast, non-viral methods are relatively safer and more scalable but often exhibit lower delivery efficiency. In the context of oral cancer, gene therapy has demonstrated promising therapeutic outcomes through strategies such as tumor suppressor gene replacement, oncolytic virotherapy, and immunomodulation. However, several

challenges persist, including immune responses to vectors, inefficient gene delivery to target cells, the complexity of polygenic disorders, and the need for repeated administration. Overall, gene therapy holds significant potential as a novel therapeutic modality for oral cancer and other chronic diseases, particularly when used in combination with conventional treatments such as chemotherapy and immunotherapy.

KEYWORDS: Gene therapy, oral cancer, electroporation, immune system, immunotherapy.

INTRODUCTION

Gene therapy involves identifying defective genes in cells or tissues and correcting them by inserting a functional copy, modifying the existing gene, or replacing it entirely. When successfully implemented, this approach has the potential to provide long-term or even permanent treatment for various diseases. Essentially, gene therapy aims to repair mutated genes by introducing functional genetic material at precise locations within the DNA. The concept of gene therapy was introduced in the late 20th century and has since evolved significantly.[1–3]

Gene therapy is broadly classified into two main types

1. Germline gene therapy
2. Somatic gene therapy

Germline Gene Therapy

Germline gene therapy involves modifying genetic material in reproductive cells such as sperm or ova. The two primary approaches include genetic modification prior to fertilization and intervention at the early embryonic (blastomere) stage. However, this approach remains largely experimental and is associated with ethical and technical challenges.[4–6]

Somatic Gene Therapy

Somatic gene therapy targets non-reproductive (somatic) cells to treat specific diseases without affecting future generations. It is comparatively safer and more practical than germline therapy. This approach has shown promising results in treating conditions such as oral cancer, haemophilia, and muscular dystrophy.[7–9]

VECTORS IN GENE THERAPY

Viruses are obligate intracellular parasites that can survive and replicate only within living cells. They possess a natural ability to deliver genetic material into host cells, making them

highly suitable as vectors in gene therapy. Recombinant viral vectors are engineered to carry therapeutic genes into diseased tissues. Gene transfer can be performed either in vivo (within the body) or in vitro (in cultured cells).[10–12]

Ideal Characteristics of Viral Vectors

- Minimal immunogenicity
- High stability and scalability
- Sustained gene expression

Viral Vectors

Common viral vectors used in gene therapy include:

- Retroviruses
- Adenoviruses
- Herpes simplex viruses (HSV)
- Adeno-associated viruses (AAV)

Retroviruses

Retroviruses contain RNA as their genetic material and utilize reverse transcriptase to convert RNA into DNA, which is then integrated into the host genome. This integration results in permanent genetic modification. However, random insertion can lead to insertional mutagenesis and potential oncogenesis.[13]

Adenoviruses

Adenoviruses carry double-stranded DNA and deliver it into the host nucleus without integrating into the genome. Although they allow high gene expression, the introduced gene is not replicated during cell division. Adenovirus-based therapies, such as p53 gene therapy, have been approved for cancer treatment.[11,14]

Herpes Simplex Virus (HSV)

HSV is a neurotropic virus with a natural affinity for nerve cells. Modified, replication-deficient HSV vectors are used for gene delivery to minimize cytotoxicity and immune responses.[12]

Adeno-Associated Virus (AAV)

AAV is a non-pathogenic virus capable of inserting genes at specific chromosomal sites. It has low immunogenicity but limited gene-carrying capacity and production challenges.[15–17]

NON-VIRAL VECTORS

Non-viral delivery systems offer advantages such as reduced immunogenicity and ease of large-scale production.

Physical Methods

- **Electroporation:** Uses electrical pulses to create temporary pores in cell membranes for gene entry.
- **Gene Gun:** Delivers DNA coated on microscopic particles into cells.
- **Sonoporation:** Utilizes ultrasound waves to facilitate gene transfer.
- **Magnetofection:** Employs magnetic fields to enhance gene delivery efficiency.

Chemical Methods

- Oligonucleotides
- Lipoplexes and polyplexes
- Dendrimers
- Inorganic nanoparticles

These methods are safer but often exhibit lower transfection efficiency compared to viral systems.[16–18]

GENE THERAPY IN THE MANAGEMENT OF ORAL CANCER

Oral squamous cell carcinoma is primarily a genetic disease characterized by mutations in genes regulating cell growth and apoptosis. Gene therapy offers a targeted approach to selectively eliminate cancer cells while sparing normal tissues.[19]

Gene Therapy Strategies

1. Addition Gene Therapy

This approach introduces tumor suppressor genes such as p53 to inhibit tumor growth. Adenoviral vectors delivering p53 have shown promising results in reducing precancerous lesions without significant toxicity.

2. Oncolytic Viral Therapy

Oncolytic viruses selectively infect and destroy tumor cells. Agents such as ONYX-015 have demonstrated tumor regression and improved survival, especially when combined with chemotherapy.

3. Suicide Gene Therapy

This method introduces genes encoding enzymes that convert non-toxic prodrugs into cytotoxic agents. However, uneven distribution of vectors remains a limitation.

4. Anti-Angiogenic Gene Therapy

Therapies targeting angiogenesis, such as angiostatin delivery and VEGFR-2 inhibition, aim to restrict tumor blood supply and growth.

5. Immunotherapy

Gene-based immunotherapy enhances the host immune response. Cytokines such as IL-2 activate immune cells, while inhibition of NF-κB increases sensitivity to chemotherapy and radiotherapy.

6. Excision Gene Therapy

This strategy removes oncogenes from cancer cells, thereby inhibiting tumor progression.

7. Antisense RNA Therapy

Antisense RNA molecules inhibit oncogene expression and viral replication. Clinical studies targeting the EGF receptor have demonstrated promising efficacy with low toxicity.

LIMITATIONS OF GENE THERAPY

- Polygenic Disorders: Complex diseases involving multiple genes are difficult to treat.
- Immune Responses: Host immune reactions may neutralize vectors.
- Vector Efficiency: Challenges in targeting specific tissues and maintaining safety.
- Repeated Administration: Temporary gene expression necessitates multiple treatments.

CONCLUSION

Gene therapy is an emerging and rapidly advancing field in biomedical science with significant potential for treating oral cancer and other chronic diseases. Despite existing challenges, advancements in vector design, delivery systems, and combination therapies are expected to enhance its clinical applicability. The integration of gene therapy with conventional treatments such as chemotherapy and immunotherapy represents a promising future direction in disease management.[1–19]

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