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The applications of gene therapy in Oral Cancer: A Review

Sruthy Davis, Junior Resident, Department of Oral Medicine and Radiology Calicut Govt. Dental College

Jyothi H Senior Resident, Department of Oral Pathology, Alapuzha Govt. Dental College

Corresponding Author: Sruthy Davis, Junior Resident, Department of Oral Medicine and Radiology Calicut Govt. Dental College

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Abstract

In gene therapy genes or short oligonucleotide sequences are used as therapeutic molecules.it has been used to treat defective genes. DNA encoding a with therapeutic vector main machinery of gene therapy.In this therapy adverse effect of drug is decreasd. Many diseases such as ADA-SCID, X-linked SCID, Leber's congenital amaurosis (a retinal disease), Parkinson's disease, multiple myeloma, chronic and acute lymphocytic leukemia, adrenoleukodystrophy have reported of successful clinical trials. Cancer occurs due to mutations, defective gene. Surgery ,radiation and chemotherapy are the treatment modalities.gene therapy are under clinical trials for oral cancer.the aim of this article to review use of gene therapy in oral cancer.

Introduction

Oral cancer (OSCC, for Oral Squamous Cell Carcinoma) is a genetic disease in which the genes that control cell growth and apoptosis are mutated, allowing cells to acquire the ability to invade and metastasize. Despite research efforts and new therapies, five-year survival has not improved over the past 4-5 decades. Patients with recurrent oral cancer that is refractory to chemotherapy or radiotherapy have a life expectancy of only months and the response rate to second- and third-line treatments is only 15% .[1]. The patients with cancer usually remain resistant to the standard therapies which are used readily. But, there may be chances of acute and chronic toxicities, as well as secondary malignancies. Hence, to improve the treatment modality and the over- all survival rates, gene therapy has emerged in the field of bio-medicine, which replaces the defective gene and this is repaired by a therapeutic gene.[2]

Theory of Gene Therapy

The objective of gene therapy is to introduce new genetic material into target (cancerous) cells while causing no damage to surrounding healthy cells and tissue. It has been defined as the “genetic modification of cells of a patient in order to fight a disease”[3]. Gene therapy includes both the transfer of new genetic material and the manipulation of existing genetic material. At the present time, the most widely used gene therapy transfer of the therapeutic gene into these cells via a vector, using a gene that contains a promoting sequence to enable its expression .

Types of gene therapy in oral cancer

There are several approaches for correcting faulty genes; the most common being the insertion of a normal gene into a specific location within the genome to replace a non functional gene. Gene therapy is classified into the following two types: [4]

1. Somatic gene therapy
2. Germ line gene therapy

In somatic gene therapy, the somatic cells of a patient are targeted for foreign gene transfer. In this case the effects

caused by the foreign gene is restricted to the individual patient only, and not inherited by the patient's offspring or later generations. In germ line gene therapy the functional genes, which are to be integrated into the genomes, are inserted in the germ cells, i.e., sperm or eggs. Targeting of germ cells makes the therapy heritable.

Gene Therapy Strategies of oral cancer

1. Gene Augmentation Therapy (GAT)

Simple addition of functional alleles is used to treat inherited disorders caused by genetic deficiency of a gene product.[5]

2. Targeted Killing of Specific Cells

It involves utilizing genes encoding toxic compounds (**suicide genes**), or **prodrugs** (reagents which confer sensitivity to subsequent treatment with a drug) to kill the transfected/ transformed cells. This general approach is popular in cancer gene therapies.[6]

3. Targeted Inhibition of Gene Expression

This is to block the expression of any diseased gene or a new gene expressing a protein which is harmful for a cell. This is particularly suitable for treating infectious diseases and some cancers.[7]

4. Targeted Gene Mutation Correction

It is used to correct a defective gene to restore its function which can be done at genetic level by homologous recombination or at mRNA level by using therapeutic ribozymes or therapeutic RNA editing.[8]

Gene Therapy Approaches in oral cancer

Classical Gene Therapy

It involves therapeutic gene delivery and their optimum expression once inside the target cell.

Non-classical gene therapy

It involves the inhibition of expression of genes associated with the pathogenesis, or to correct a genetic defect and restore the normal gene expression.[9]

Methods of gene therapy in oral cancer

1**.** Transfer of genes into patient cells outside the body (*ex vivo gene therapy*)

2. Transfer of genes directly to cells inside the body (*in vivo*).[10]

Brief Review of Methods of Gene Therapy in Clinical Trails of Oral Cancer

Immunotherapy

In this technique increases the immune response of the patients to the tumour.[11]

Suicide Gene Therapy

Many studies have been done on the gene delivery system with retrovirusor adenovirus vectors [12,13,14.] It is the most commonly used gene therapy which uses thimidine kinase or other chemosensitizing genes[15.]

Gene Therapy with the Use of Oncolytic Viruses

In this therapy, a vector (virus) is genetically modified, which replicates and lyses the tumour cells .[16]

The Delivery of Drug Resistance Gene(s) to Normal Tissues for Protection from Chemotherapy

The drug resistance genes protect the normal tissues which are vulnerable to destruction. The drug resistance gene in humans is the Multidrug Resistance-1 (MDR-1) gene. [17]

Conclusion

Research on gene therapy in oral cancer is increasing in the laboratory and in the clinical settings. In the medium- and long-term, it may contribute a definitive treatment for oral cancer and precancer that offers greater effectiveness compared with current thera-pies and markedly reduces the high mortality associated with these lesions. At present, the use of adenoviruses to act at altered gene level and the combination of this technique with chemotherapy or immunotherapy appear to be the most promising approaches to the management of oral cancer and precancer.

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