GENE THERAPY IN ORAL CANCER: AN OVERVIEW

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ABSTRACT:

The treatment and prevention of oral cancer is one of the major hurdles in the field of cancer. Gene therapy is one of the recent advances in this field to tackle this hurdle with promising prospects. This overview introduces the reader into the basic idea of gene therapy, types of gene therapy and the various modes of introduction of therapeutic gene into the cancer affected cell.

KEY WORDS: Gene therapy, Vector

INTRODUCTION:

A eukaryotic gene is a combination of DNA segments that together constitute an expressible unit, the expression leading to the formation of one or more specific functional gene product. Genes are specific bases that encode instruction on how to make proteins. The gene product may either be RNA molecule or polypeptide.

Oral squamous cell carcinoma is a malignant disorder in which genes that control cell growth and apoptosis are mutated. Their mutation results in uncontrolled cell proliferation in a tumor. Apoptosis or programmed cell death is a mechanism by which cell population in a tumor is controlled. As the gene controlling apoptosis is mutated, the process of natural cell suicide does not take place in a tumor,

thereby increasing the total cell mass in a tumor. Cells in a tumor acquire the ability to invade and metastasis. Cancer cells demonstrate impaired cell cycle progression, mutation and over expression of cell cycle regulators.

Cell cycle regulators act at various levels during a cell cycle resulting in impaired cell cycle and division. Cell cycle is an orderly process which is governed by protein complexes composed of cyclins and cyclin-dependent kinases. Mutations and over expression of cyclin and cyclin-dependent kinases chiefly cyclin D1 and Cdk4 are proposed to be oncogenic events. Recently Cdk-inhibitory molecules have been identified which may function as tumor suppressor genes. These tumor suppressor genes and their complexes may have a regulatory function on two important cell cycle regulators, viz p53 and pRII. There seems to be potential link between p53 and pRB in cell cycle control, apoptosis and tumor progression.

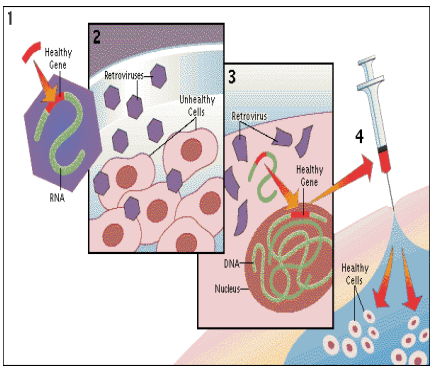
GENE THERAPY:

Gene therapy is a technique for correcting defective genes which are responsible for genetic abnormalities and diseases. The idea of gene transfer for treating human diseases was put forward by CUSACK and TARNER in 1998. The idea envisages the transfer of a therapeutic gene into cancer cells via a vector. These processes delete the mutant alleles' and are replaced by the therapeutic or functional gene. The process though sounds simple requires a complex multistep machinery which includes identification of the mutant allele, a vector which accept the therapeutic gene and a careful swapping of the mutant alleles with the functional gene through a vector. Inactivation of tumor suppressor gene p161NK4A is the most common genetic alteration in head and neck squamous cell carcinomas.

Types of gene therapy: - There are two primary modes of gene therapy.

They are:-

1. Germ line therapy
2. Somatic gene therapy



Schematic diagram of gene transfer therapy

In germ line therapy the germ cell, either sperm or egg is altered by the introduction of the therapeutic gene which gets integrated into their genome. Since the genetic change engineered is on the germ cells the consequent changes are inheritable. The ethical considerations of this therapy are manifold and prohibitory.

Whereas in somatic gene therapy, the therapeutic genes are incorporated in to the somatic cells of the patient and hence the effects are restricted to the individual only and will not be passed on to the next generation.

There are several approaches to correct defective genes.

1. A normal gene is inserted into a nonspecific location in the genome replacing a nonfunctional or defective gene.
2. An abnormal gene is exchanged for a normal gene through homologous recombination.
3. The abnormal gene may be repaired through selective reverse mutation there by abnormal genes returns to its normal function.

VECTOR:

The transfer of a therapeutic gene in to the recipient cells is possible only via a vector or a carrier. All viruses replicate by binding to the host cell and the viral genome is integrated into the host cell. Thereafter the host cell

multiplies and the viral genome is replicated and more and more copies of virus infected cell are produced. Viruses can thus be manipulated to carry the functional gene in to the diseased cell where in the abnormal gene is replaced by the functional gene. The different types of viruses used as a vector in gene therapy are-

1. Retrovirus
2. Adenoviruses
3. Adenoassociated virus
4. Herpes simplex virus

Besides viruses non viral insertion techniques are also used. Use of chemicals like Ca (PO4), liposomes and protein complexes are also employed. Lipid vectors are generated by a combination of plasmid DNA and a lipid solution that result in the formation of a liposome. Many carcinoma cells, including oral squamous cancer cells, express high levels of folate receptor. Linkage of DNA or DNA-lipid complexes to folate can specifically target cancer cells.

Physical methods like electroporation, microinjection and ballistic particles are used for the transfer of therapeutic genes into the affected cells. The technique of electroporation causes a transient increase in cell membrane permeability. This causes the penetration of cytotoxic agents into the cells causing progressive necrosis. Hence it is a technique which could be useful in destroying large bulky tumors.

Research on gene therapy in oral cancer is increasing in the laboratory and in the clinical settings. In future, it may contribute to a definitive treatment for oral cancer and precancer that offers greater effectiveness when compared with current therapies and markedly reduces the high mortality associated with these lesions. Phase I trials have established the safety of gene therapy in squamous cell carcinoma of the head and neck, and Phase II studies have

demonstrated clinical efficacy of gene therapy when combined with chemotherapy or radiation therapy. Phase III clinical trials and studies of the use of gene therapy in the adjuvant setting are presently under way. Further investigation is warranted to establish safe and effective approaches that utilize gene therapy for the prevention and treatment of oral cancer.

CONCLUSION:

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 approach to the management of oral cancer and precancer. Other techniques such as suicide gene therapy, use of oncolytic viruses or the use of antisense RNA have shown positive although very preliminary results. Therefore, further research into these promising gene therapy techniques is required to assess their true efficacy and safety in the management of other lesions.

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