



Review Article

GENE THERAPY FOR ORAL SQUAMOUS CELL CARCINOMA-A PROMISING FUTURE

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ABSTRACT

Gene therapy is commonly used in reference to any clinical application of the transfer of a foreign gene. Initially, gene therapy was associated with either the correction of inherited genetic disorders or the treatment of life threatening conditions. Now the procedure has been extended to the level of treating malignant conditions such as cancer of the lungs, breast, colon etc. Clinical applications of gene transfer can be accomplished in two ways in vivo or ex vivo. This review highlights various types of gene therapy procedures with respect to squamous cell carcinoma.

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INTRODUCTION

Cancer, as today, is projected as one of the fatal diseases amongst all the diseases of this modern world. Oral cancer, namely, Oral Squamous Cell Carcinoma (OSCC) is one of the commonly seen malignant lesions in the oral cavity, which is seen globally (Heera and Beena, 2010). And it is about the 6th most common cancer world-wide (Sunil *et al.*, 2011). Oral cancer is associated with genetic mutations which occur due to the exposure to tobacco, alcohol, betel quid, etc (Philip *et al.*, 1999). It occurs in people who are aged 50 years or over. However, about 6% of the cases occur in young people who are under the age of 45 years (Crispian, 2011 and Llewellyn *et al.*, 2001). The current treatment strategies for oral squamous cell carcinoma (OSCC) include a combination of surgery, radiation therapy and chemotherapy. Surgical resection of tumors frequently causes profound defects in oral functions such as speech and swallowing as well as in cosmetic aspects (Wakasa *et al.*, 2002). Chemotherapy is associated with well-known toxicity and has demonstrated no clear impact on the survival of patients. Recurrence develops in approximately one third of the patients despite definitive treatment (Schrijvers *et al.*, 1998).

Hence, to improve the treatment modality and the overall survival rates, gene therapy has emerged in the field of biomedicine, which replaces the defective gene and this is repaired by a therapeutic gene (Sunil and Isaac Joseph, 2011). This review highlights various gene therapy methods that are available for combating OSCC.

History

Joshua Lederberg and Edward Tatum laid out the fundamental tenets for gene therapy (Tatum, 1966). Gene amplification, which is used in the treatment of various human diseases, was put forward by Cusack and Tanabe in 1998 (Arun Singh *et al.*, 2012). The first successful treatment was of X-linked Severe Combined Immunodeficiency (X-SCID) by *ex vivo* gene replacement therapy (Kevin and Scanlon, 2004).

Concept of gene therapy

Gene therapy, refers to replacing or repairing a defective gene in the diseased cells genome in order to restore normal cell function and tissue integrity. Therapeutic material can be delivered to the target cells in two main ways. First, it can be inserted into cells from the affected tissue outside the body and

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these cells then returned to the body (ex vivo). Second, it can be delivered directly into the body at the required site (in vivo). The ex vivo approach has not been utilized in oral cancer because superficial lesions usually lend themselves to the direct injection of genetic material. Either way, a delivery vehicle called a vector is used to introduce the therapeutic material into the patient's target cells (Blau and Springer, 1995).

Vectors for Gene therapy

Genetic material is delivered into the host cells through viruses or bacteria (Susy *et al.*, 2003). Majority of viral-mediated gene therapy trials in patients with oral cancer have used adenoviruses. These particles are either administered through intraperitoneal, intrahepatic arterial, intratumoral or intravenous routes (Norris *et al.*, 2005). Among the nonviral vectors are electroporation, (Toneguzzo and Keating, 1986) microinjection and use of ballistic particles which are physical methods, whereas liposomes, proteins and calcium phosphate are biochemical methods employed to deliver DNA into the host cells (Wagner *et al.*, 1994).

Technique of gene therapy

The main objective of gene therapy is to introduce new genetic material into the target cells without causing any sort of damage to the surrounding normal cells. The therapies that express gene products, which result in the death of cancer cells, include, gene addition therapy, gene excision therapy, antisense RNA therapy, immunotherapy, suicide gene therapy, gene therapy with the use of oncolytic viruses, the introduction of genes to inhibit tumour angiogenesis and the delivery of drug resistance genes into normal tissues for protection against chemotherapy (Sunil *et al.*, 2011).

Gene Addition Therapy

In this technique the tumor growth is controlled by the introduction of tumor suppressor genes which inactivates the carcinogenic cells [17]. Since the protein p53 plays a role in cell-cycle regulation and apoptosis, p53 gene transfer was initially tested in squamous cell carcinoma patients by injecting the primary or regional tumor with an adenoviral vector expressing wild-type p53 (Clayman *et al.*, 1998).

Gene excision therapy

This therapy involves the removal of oncogenes, thereby inhibiting the growth of the tumour cells. The genes that control growth and cell cycle progression, including some factors like-TGF- β 1, PDGF-A and PTEN are regulated by the expression of the protein Egr-1. Thus, inhibiting this protein represents good therapeutic approach for the tumour cells. Some studies demonstrated that inhibition of the protein kinase C reduces the expression of this gene, triggering higher sensitivity of the tumour to radiotherapy (Okamura *et al.*, 2002).

Antisense RNA therapy

The treatment of genetic disorders by introducing a remedial gene that prevents the expression of a specific defective gene is called as Antisense therapy. Specific types of HPV are associated with oral cancers. Certain genes of the human

papillomavirus (HPV) such as E6 and E7 show continuous expression in growing tumours. Although there have been no clinical trials of gene therapy for HPV-associated oral cancers, in vitro studies show that expression of these genes (Shillitoe, 2006).

Immunologic gene therapy

The immunologic gene therapy approach to oral cancer involves either increasing the immunogenic potential of tumor cells or augmenting the patient's immune response to a tumour. Biological molecules produced by tumour cells are found to elicit strong immune response. T-cells are the major immune cells involved in antitumour immunity (Ferris, 2004).

Suicide gene therapy

This therapy involves enzymes, the expression of which transforms the non-toxic producing drug into an active cytotoxic substance. It is the most commonly used gene therapy which uses thymidine kinase or other chemosensitizing genes (Gardlik *et al.*, 2011).

Conclusion

Gene therapy is an attractive tool in the treatment of oral squamous cell carcinoma and pre-cancer, because it targets cancer cells only. In future, it can be a forerunner as a definitive treatment option for oral cancer and pre-cancer, which can offer better effectiveness as compared to that of the current therapies, by reducing the high mortality which is associated with these lesions.

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