DOI: 10.7860/JCDR/2013/5412.3071

Review Article

Dentistry Section

Gene Therapy in Oral Cancer: A Review

M. SATHISH KUMAR, K.M.K. MASTHAN, N. ARAVINDHA BABU, KAILASH CHANDRA DASH

ABSTRACT

Gene therapy is the use of DNA as an agent to treat disease. Gene therapy aims at the insertion of a functional gene into the cells of a patient for the correction of an inborn error of metabolism, to alter or repair an acquired genetic abnormality, and to provide new function to the cell. Many experiments have been done with respect to its application in various diseases.Today, most of the gene therapy studies are aimed at cancer and hereditary diseases which are linked to genetic defects. Cancer usually occurs due to the production of multiple mutations in a single cell which cause it to proliferate out of control. Several methods such as surgery, radiation therapy and chemotherapy have been used widely to treat cancers. But, the cancer patients who are not helped by these therapies can be treated by gene therapy. The purpose of this article is to review the use and purpose of gene therapy in oral cancer.

Key Words: Gene therapy, Gene, Mutations, Cancer

INTRODUCTION

Cancer, as today, is projected as one of the fatal diseases amongst all the dreadful diseases of this modern world. Cancer cells are different from other neighbouring cells in having phenotypic changes in the manner of a rapid division rate, a high metabolic rate, and alteration in their shapes. Some of the mutations may get transmitted from parents through the germ line, while others may arise de novo in the somatic cell lineage of a particular cell. Oral cancer, namely, Oral Squamous Cell Carcinoma (OSCC) is one of the commonly seen malignant lesions in the oral cavity, which is seen globally [1] and it is about the 6th most common cancer world-wide [2]. Oral cancer is associated with genetic mutations which occur due to the exposure to tobacco, alcohol, betel quid, etc [3]. 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 [4,5]. It is a malignant disorder in which the genes that control cell growth and apoptosis are mutated and this results in an uncontrolled proliferation of the cells in the tumour [1]. With an increase in the total cell mass in the tumour, it has the ability to invade and undergo metastasis. 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 [6]. The applications of gene therapy in cancer are associated with bio-engineering and clinical development [7]. In the dental field, it is also applied in bone repair, auto immune diseases, pain, caries and periodontal diseases [8].

THE HISTORY OF GENE THERAPY

Gene amplification, which is used in the treatment of various human diseases, was put forward by Cusack and Tanabe in 1998 [9]. Gene therapy is defined as gene transfer for the purpose of treating human diseases effectively (Cusack and Tanabe, 1998) [9,10], which includes both the transfer of new genetic material and manipulation of the existing genetic material [9]. The first successful treatment was of X-linked Severe Combined Immunodeficiency (X-SCID) by *ex vivo* gene replacement therapy [11].

The Types of Gene Therapies

i. Somatic gene therapy
ii. Germ line gene therapy

In somatic gene therapy, the therapeutic genes are introduced into somatic cells, which restricts the effects of the individual and are not passed on to the next generation. In germ line gene therapy, either the sperm or egg can be altered by introducing the therapeutic gene, which gets integrated into the genome [1].

The other various gene therapies are suicide gene therapy, immunologic gene therapy, excision gene therapy, etc. Suicide gene therapy is the introduction of a gene into the cell, which converts a non-toxic pro-drug into a toxic substance [9,12] and it is also called genetic pro-drug activation therapy [9,13]. Immunologic gene therapy aims at increasing the immunologic potential of the tumour cells, thereby increasing the patient's immune response to the tumour. Excision gene therapy is the removal of oncogenes, which inhibits the growth of the tumour cells [9].

The Vectors in Gene Therapy

Genetic material is delivered into the host cells through viruses or bacteria [14]. Gene therapy is concerned with DNA which can be delivered into cells by various methods. All viruses such as retroviruses, adenoviruses, lentiviruses, herpes simplex virus, vaccinia, pox virus, and adeno-associated virus bind to their hosts by introducing their genetic materials into the host cells. In gene therapy, the viral DNA can be removed, while the viruses can act as vehicles to deliver the therapeutic DNA into the host cells. The viruses which are used as vectors in gene therapy

include retroviruses, adenoviruses, adenoassociated viruses and Herpes simplex virus [1]. The methods of non-viral gene therapy include the injection of naked DNA, electroporation, the gene gun and the use of oligonucleotides, dendrimers and inorganic nanoparticles. However, the non-viral vectors which are inhibited by the serum components, limit the efficiency of the gene delivery in vivo [15]. Despite the use of several non-viral methods, viruses provide a more efficient mode in gene therapy [16].

The 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 [6]. According to the results of animal studies which were done in mice, combination gene therapy which uses several genes, showed significant tumour regression in mice [17,18].

Gene Addition Therapy

Genetic alterations include mutations of p53, the Retinoblastoma Gene (RB1), p16 and p21. Among which, the tumour suppressor gene which is commonly used in gene therapy is the p53 gene [19] and about 60% of the human tumours are associated with mutations at the p53 locus [20]. In this technique, the tumour growth is controlled by the introduction of tumour suppressor genes which inactivate the carcinogenic cells [6].

Gene Excision Therapy

In this technique, the defective oncogenes are removed, as a result of which, there is an inhibition in the growth of the tumour cells [6].

Antisense RNA Therapy

The Antisense RNA checks the tumour growth by inhibiting the RNA which is complementary to the strands of the DNA which expresses that particular gene [6].

Immunotherapy

Oral cancer patients usually show defects or deficient immune cell functions of the natural killer cells, lymphocytes, cytokines, etc. This technique increases the immune response of the patients to the tumour [6].

Suicide Gene Therapy

Many studies have been done on the gene delivery system with retrovirusor adenovirus vectors [21-24]. This therapy involves enzymes, the expression of which transforms the non-toxic producing drug into an active cytotoxic substance [6]. It is the most commonly used gene therapy which uses thimidine kinase or other chemosensitizing genes [25].

Gene Therapy with the Use of Oncolytic Viruses

In this therapy, a vector (virus) is genetically modified, which replicates and lyses the tumour cells [6]. For example, adenovirus-mediated gene therapy is used for advanced cancers than traditional therapies [26].

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. The other drug resistance genes include the bacterial nitroreductase gene and the dihydrofolatereductase mutants which protect against methotrexate [6].

Some Disadvantages of Gene Therapy

i. Even after the therapeutic DNA is integrated into the genome, some cells prevent the gene therapy for long-term effects, for which patients may undergo multiple rounds of the gene therapy.
ii. There is a possibility that the host's immune system and its response may reduce the effectiveness of the gene therapy.
iii. The viral vectors can present a variety of potential problems to the patient, such as toxicity and immune and inflammatory responses.
iv. Single gene disorders are the best candidates for gene therapy. But, some of the most commonly occurring diseases, such as heart disease, high blood pressure, Alzheimer's disease, arthritis, and diabetes are multi-gene or multi-factorial disorders which are difficult to treat effectively with the use of gene therapy.
v. If the DNA is introduced into a wrong place in the genome, for example, into a tumour suppressor gene, it can induce a tumour.

Advantages

Despite of the disadvantages of gene therapy, it has advantages as well;

i. A functional gene has the ability to replace a defective gene.
ii. Gene therapy aids in the prevention against the potentially toxic effects in the body, which can be caused by other therapies.
iii. It decreases the cost of various therapies and improves the patient's life style for a longer period [27].

CONCLUSION

Gene therapy is an attractive tool in the treatment of oral squamous cell carcinoma and pre-cancer, because it targets cancer cells only. Today, the research on gene therapy in oral cancer is increasing day by day, both in the laboratory and the clinical settings. 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. At present, the use of adenoviruses altered gene therapy technique with chemotherapy or immunotherapy appears to be the most promising approach in the management of oral cancer and pre-cancer.

REFERENCES

[1] Heera R, Beena VT, Rency Simon, Kanaram Choudhary. Gene therapy in oral cancer: an overview. *Oral and Maxillofacial Pathology Journal*. 2010; 1(2).
[2] PM Sunil, CR Ramachandran, Arulmoli, Santha Devy, Soma Susan Varghese. Cytogenetic alterations in oral squamous cell carcinoma detected by karyotyping (g-banding). *Oral and Maxillofacial Pathology Journal*. 2011; 2(1): 89-95.
[3] Philip B Sugerman, Neil W Savage. Current concepts in oral cancer. *Australian Dental Journal*. 1999; 44(3):147-56.
[4] Crispian Scully. Oral cancer aetiopathogenesis; past, present and

future aspects. *Med Oral Patol Oral Cir Bucal*. 2011;16 (3):e306-11.
[5] Llewellyn CD, Johnson NW, Warnakulasuriya KA. Risk factors for squamous cell carcinoma of the oral cavity in young people-A comprehensive literature review. *Oral Oncol*. 2001;37:401-18.
[6] PM Sunil, Isaac Joseph, Soma Susan Varghese. Gene therapy in oral squamous cell carcinoma – a short review. *Oral and Maxillofacial Pathology Journal*. 2011; 2(2): 142-47.
[7] Frank McCormick. Cancer gene therapy:Fringe or cutting edge? *Nature Reviews Cancer*. 2001; 1: 130-41.
[8] Paramel Mohan Sunil, Ramachandran CR, Jaisanghar N, Santhosh Kumar C. Dental Surgeons as Gene Therapist. *International Journal of Oral and Maxillofacial Pathology*. 2012;3(3): 65-67.
[9] Arun Singh, Manjunath Badni, Anil Singh, Fahad M Samadi, Arpita Kabiraj. Gene therapy for oral cancer – journey to a new horizon. *Oral and Maxillofacial Pathology Journal*. 2012; 3(1): 203-10.
[10] Xi S, Grandis JR. Gene Therapy for the treatment of oral squamous cell Carcinoma. *J Dent Res*. 2003; 82(1): 11-16.
[11] Kevin J Scanlon. Cancer Gene Therapy: Challenges and Opportunities. *Anticancer Research*. 2004; 24: 3-7.
[12] Saraswathi TR, Kavitha B, Priyadarshini JV. Gene therapy for oral squamous cell carcinoma: An overview. *IJDR*. 2007; 18(3): 120-23.
[13] Gleich LL. Gene therapy for head and neck cancer. *Laryngoscope*. 2000; 110: 708-26.
[14] Susy M Scholl, Silke Michaelis, Ray McDermott. Gene Therapy Applications to Cancer Treatment. *Journal of Biomedicine and Biotechnology*. 2003; 1: 35–47.
[15] Mark Young, Nathan Overlid, Krystyna Konopka, Nejat Düzgünes. Gene Therapy for Oral Cancer: Efficient Delivery of a 'Suicide Gene' to Murine Oral Cancer Cells in Physiological Milieu. *CDA Journal*, 2005; 33(12): 967-71.
[16] Edward J Shillitoe. Gene therapy: the end of the rainbow? *Head and Neck Oncology*. 2009; 1(7): 1-5.
[17] KR Spencer, JW Ferguson, D Wiesenfeld. Current concepts in the management of oral squamous cell carcinoma. *Australian Dental Journal*. 2002; 47(4):284-89.
[18] O'Malley BW, Cope KA, Chen SH, Li D, Schwarta MR, Woo SL. Combination gene therapy for oral cancer in a murine model. *Cancer Res*. 1996;56:1737-41.
[19] Sonia Ayllón Barbellido, Julián Campo Trapero, Jorge Cano Sánchez, Miguel A Perea García, Nayra Escudero Castaño, Antonio Bascones Martínez. Gene therapy in the management of oral cancer: Review of the literature. *Med Oral Patol Oral Cir Bucal* 2008;13(1):E15-21.
[20] Gary L Clayman, Douglas K Frank, Patricia A Bruso. Adenovirus-Mediated Wild-Type p53 Gene Transfer into Head and Neck Cancers. *Gene Therapy of CancerMethods in Molecular Medicine*™, 2000; 35: 537-44.
[21] Noriyuki Yamamotoa, Yasushi Hayashia, Hideaki Kagamia, Takafumi Fukuia Hirokazu Fukuharaa, Iwai Tohnaia, Minoru Uedaa Masaaki Mizunob, et al. Suicide Gene Therapy Using Adenovirus Vector for Human Oral Squamous Carcinoma Cell Line *in vitro*. *Nagoya J. Med. Sci*. 2005; 67: 83-91.
[22] Moolten FL, Wells JM: Curability of tumors bearing herpes thymidine kinase gene transferred byretroviral vectors. *J. Natl. Cancer Inst.*1990; 82: 297–300.
[23] O'Malley BW Jr, Chen SH, Schwartz MR and Woo SLC. Adenovirus-mediated gene therapy for human head and neck squamous cell cancer in a nude mouse model. *Cancer Res*.1995; 55: 1080–85.
[24] Sewell DA, Li D, Duan L, Westra WH, O'Malley BW Jr. Safety of in vivo adenovirus-mediated thymidine kinase treatment of oral cancer. Otolaryngol. *Head Neck Surg*., 1997; 123: 1298–1302.
[25] Gardlik R, Celec P, Bernadic M. Targeting angiogenesis for cancer (gene) therapy. *Bratisl LekListy*. 2011; 112(8): 428-34.
[26] Anna Kanerval, Akselihemminki. Modified Adenoviruses For Cancer Gene Therapy. *Int. J. Cancer*. 2004; 110: 475–80.
[27] Rashmi Sharma, Ruchi Khajuria, CL Sharma, B Kapoor, KC Goswami, K Kohli. Gene Therapy: Current Concepts. *JK Science*. 2004; 6(2): 62-66.

AUTHOR(S):
1. Dr. M. Sathish Kumar
2. Dr. K.M.K Masthan
3. Dr. N. Aravindha Babu
4. Dr. Kailash Chandra Dash

PARTICULARS OF CONTRIBUTORS:
1. Professor and Head of the Department, Department of Oral Pathology and Microbiology, Karpaga Vinayaga Institute of Dental Science, Chennai, Tamil Nadu, India.
2. Professor and Head of the Department, Department of Oral Pathology and Microbiology, Sree Balaji Dental College & Hospital, Bharath University, Chennai, Tamil Nadu,India.
3. Associate Professor, Department of Oral Pathology and Microbiology, Sree Balaji Dental College & Hospital, Bharath University, Chennai, Tamil Nadu, India.
4. Post Graduate Student. Department of Oral Pathology and Microbiology, Sree Balaji Dental College & Hospital, Bharath University, Chennai, Tamil Nadu, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Kailash Chandra Dash,
Post graduate student, Department of Oral Pathology and Microbiology, Sree Balaji Dental College & Hospital, Bharath University, Chennai-600100, Tamil Nadu, India.
Phone: +919789914796/+919444238645
E-mail: dash.rajaji.kailash@gmail.com

FINANCIAL OR OTHER COMPETING INTERESTS:
None.

Date of Submission: **Dec 04, 2012**
Date of Peer Review: **Jan 14, 2013**
Date of Acceptance: **Mar 16, 2013**
Date of Publishing: **Jun 01, 2013**