REVIEW

Gene Therapy: A Novel Promising Tool for Oral Cancer

Palak H. Shah[1], Rashmi Venkatesh[2]

Abstract

Introduction: Oral cancer is among the most formidable disease for mankind. It has significant morbidity and mortality. The treatment for oral cancer is mainly aimed to cure the disease, prevent recurrence and improve the quality of life of the patient.

Materials and Methods: The traditional treatment modalities have certain disadvantages like lack of conservativeness and chances of recurrence. In the present era, Gene therapy is a newer promising treatment modality which has shown very encouraging results. As genetic mutations play a key role in pathogenesis of Oral cancer, modulation of the genes can be one newer and attractive therapeutic as well as preventive treatment modality.

Conclusion: The present review is summarizing the various aspects of gene therapy in context with oral cancer.

Keywords: Gene therapy, Oral Cancer, Oral Precancer, Vectors

Oral and Maxillofacial Pathology Journal (2023): ***https://www.ompj.org/archives***

Introduction

Oral cancer is one of the major health problems in the Indian subcontinent. It ranks among three most common types of cancer in the country.[1] Oral cancer accounts for over 30% of all cancers in India and it has significant morbidity and mortality.[2] The traditional treatment options include surgery with or without combined with radiotherapy or chemotherapy. These conventional treatment approaches are very invasive and have significant effect on patient's quality of life. In spite of newer advancements and attempts for organ preservation, the treatment outcomes and its debilitating effects are not improved significantly.[3] In a view of improving the treatment effectiveness and also the quality of life of patients, newer conservative treatment modalities such as gene therapy is anticipated to be a useful tool for oral and systemic cancer treatment.

Tobacco, alcohol and betel quid are considered as major etiological factors for Oral Cancer.[4] The ingredients of these cause genetic mutations in the body cells. Mutation of the genes controlling cell mitosis and apoptosis results in uncontrolled proliferation of the cells leading to cancer.[5] As gene mutation is associated with the pathogenesis of cancer, gene therapy, a new emerging technique of biomedicine, has been thought to be a potential treatment modality for cancer. Due to its frequent genetic mutations, oral squamous cell carcinoma is one of the attractive tumor-target for gene therapy.[6]

Gene Therapy

Gene therapy is basically a procedure directed at replacement or manipulation of nonfunctional or malfunctional gene with a healthy gene. The objective of gene therapy is to introduce genetic modification into the cells in order to treat the disease.[7,8] Gene therapy can be successfully used for the treatment of cystic fibrosis, hemophilia, muscular dystrophy, immune deficiency disorders and many tumors. In dental conditions, gene therapy can be used in periodontics, pain and dental caries.[7,9]

Types of Gene Therapy

There are two types of gene therapy:[7,10]

Somatic gene therapy

It is characterized by transfer of genetic material into somatic target cell in order to cure the disease. In this, the individual may be cured from the disease but their off-springs cannot be prevented from the same disease. It is the most common type of gene therapy practiced in various centers.

Germ line gene therapy

It involves introduction of foreign gene into a sperm or egg which will pass genetic changes in the future generations. This is primarily indicated to prevent inherited diseases.

Vectors of Gene Therapy

Vectors in the gene therapy are the vehicles that facilitate

[1]Department of Oral Medicine and Radiology, Manubhai Patel Dental College and Hospital, Vadodara, Gujarat, India; [2]Department of Oral Medicine and Radiology, K. M. Shah Dental College and Hospital, Sumandeep Vidyapeeth Deemed to be University, Piparia, Vadodara, Gujarat, India.

Corresponding Author: Palak H. Shah, Department of Oral Medicine and Radiology, Manubhai Patel Dental College and Hospital, Vadodara, Gujarat, India. Email: shahpalak98@gmail.com

How to cite the article: Shah PH, Venkatesh R. Gene Therapy: A Novel Promising Tool for Oral Cancer Oral Maxillofac Pathol J 2023; 14(2). Page number 214-216

Source of Support: Nil

Conflict of Interest: None

the transfer of genetic material into target cells. The vectors are broadly classified into two types: Viral vectors and non-viral vectors. The vectors for gene therapy are enlisted in Table 1.

Gene Therapy Techniques

The therapeutic gene can be delivered to the target cells by two techniques:

In vivo – Inoculation of therapeutic gene directly to the target site locally or systematically

Ex vivo – Cells from the target are genetically modified outside the body and then reinserted

This can be accomplished by Physical, Chemical and Electrical methods enlisted in Table 2.

Gene Therapy Approaches for Oral Cancer

Oral Cancer, being easily approachable due to superficial locations of the lesion, is a good tumor target for gene therapy. The following are the approaches that can be opted for treatment of Oral Cancer:

Gene Addition Therapy

In this technique, a tumor suppressor gene is introduced to inactivate the carcinogenic cells in order to control the growth of the tumor. The mutation of p53 gene is most commonly associated with Oral Cancer and hence is the most commonly used gene for gene therapy. Adenovirus is the most preferred vector for this gene.[13,14] A phase III clinical trial has demonstrated positive treatment outcome using adenovirus vector and p53 gene for head and neck cancers.[15] The other genes involved in Oral Cancer are the retinoblastoma gene, p16 and p21.[16]

Gene Excision Therapy

This technique is aimed at elimination of defective oncogene leading to suppression of tumor cell growth.[13,17] Genes that encode for cell cycle and cell growth as well as the ones encoding for tissue factors TGF-β1, PDGF-A and PTEN are regulated by expression of Egr-1 (Early growth regulation factor – 1). Hence, inhibition of Egr-1 is a good approach for gene therapy. Okadaic acid, a highly toxic polyether, is used for inhibition of Egr-1.[18] Another approach demonstrated by certain studies is inhibition of protein kinase C to reduce expression of this gene, thereby increasing the tumor sensitivity for radiotherapy.[19]

Antisense RNA Therapy

In this technique, expression of specific defective gene is prevented by introduction of are medial gene. Gene expression can be suppressed by an RNA which is complementary to the strand of DNA responsible for expression of the gene. Antisense RNA prevents expression of oncogenes such as myc, fos and ras and also inhibits certain viruses including HSV-1, HPV and HTLV-1.13,17 Preclinical studies have shown effective anti-tumor activity using antisenseRNA.[17,20]

Immunotherapy

Patients with oral cancer demonstrate deficient function of certain immune cells such as Natural Killar cells, T lymphocytes and cytokines.[21] The aim of immunotherapy is to enhance the patient's immune response to malignancy. Researches have demonstrated successful decrease in cancer by combined use of mIL-2 and mIL-12 causing increased activation of cytotoxic T lymphocytes and natural killer cells.[22] Suppression of NF-kB activity has shown to help increasing radiosensitivity to ◎radiation and chemosensitivity to 5-fluoracil (5-FU) in oral squamous cell carcinoma. Inhibition of NF-kB also helps to prevent progression and metastasis of oral cancer.[23] Administration of anti-ICAM-2 systemically has been found to introduce complete regression of oral cancers.[24] Other studies have shown transduction of IL-2 gene and intra-tumoral injection of Adv-F/RGD is apparent to have anti-tumor effect.[17]

Suicide Gene Therapy

It is the most commonly used gene therapy. It involves introduction of certain genes/enzymes that covert non-toxic drug into active cytotoxic substance. Most frequently performed suicide gene therapy involves use of thymidine kinase gene of herpes simplex virus which converts non-toxic ganciclovir into cytotoxic ganciclovir phosphatase which induces cell death by bystander effect.[25]

Gene therapy with the use of Oncolytic Viruses

In this approach, a virus(vector) is genetically modified in order to induce lysis of tumor cells. These genetically modified viruses characteristically replicate into tumor cells but remain attenuated in normal host cells.[13,17] Genetically modified adenovirus ONYX-015 has been successfully used in treatment of oral cancer both alone and in combination with chemotherapy.[26,27] The oncolytic herpesvirus have shown to reduce tumor metastasis significantly.[17,28] ONYX-015 incorporated into mouthwash Advexin can be successfully used for prevention of progression oral precancerous lesions into oral cancer. The dysplastic changes have been found to resolve in 37% of cases in previous clinical trials.[17,29]

Conclusion

The various techniques in gene therapy have shown overall positive effect in treatment of oral cancer and prevention of invasion, metastasis and recurrence. Also, it has been found that gene therapy potentiates effects of other treatment modalities such as radiotherapy and chemotherapy. The research on gene therapy for the treatment is progressing both in vivo and in

Table 1: Vectors of Gene Therapy[9,11]

ViralVectors	Non-viralVectors
• Retrovirus	• Naked DNA delivery
• Adenovirus	• Cationiclipids
• Adenoassociated virus	• Protein–DNAcomplex
• Herpesvirus	

Table 2: Techniques of Gene Therapy[9,12]

Physical	Chemical	Electrical
• Electroporation	• Oligonucleotides	• Electrotransfer of geneticmaterial
• Genegun	• Lipoplexes and polyplexes	
• Sonoporation	• Dendrimers	
• Magnetoporation	• Hybridmethods	

vitro settings. In upcoming time, gene therapy can become definitive treatment modality either alone or in combination with other treatment modalities.

References

1. Sankaranarayanan R, Ramadas K, Thomas G, Muwonge R, Thara S, Mathew B, et al. Effect of screening on oral cancer mortality in Kerala, India: A cluster-randomised controlled trial. Lancet. 2005;365:1927–33.
2. Coelho KR. Challenges of the Oral Cancer burden in India. Journal of Cancer Epidemiology. 2012: 1-17.
3. Jensen SB, Pedersen AM, Vissink A, Andersen E, Brown CG, Davies AN, et al. A systematic review of salivary gland hypofunction and xerostomia induced by cancer therapies: prevalence, severity and impact on quality of life. Support Care Cancer. 2010; 18:1039–1060.
4. Sugerman PB, Savage NW. Current concepts in oral cancer. Australian Dental Journal. 1999; 44(3):147-56.
5. Heera R, Beena VT, Rency Simon, Kanaram Choudhary. Gene therapy in oral cancer: an overview. Oral and Maxillofacial Pathology Journal. 2010; 1(2).
6. XiS, Grandis JR. Gene therapy for the treatment of oral squamous cell carcinoma. J Dent Res. 2003 ;82(1):11-6.
7. Patil S, Al-Zoubi I, Raghuram PH, Misra N, Yadav N, Alam MK. Gene therapy: A comprehensive review. International Medical Journal 2018; 25(6): 361-64
8. Cusack JC Jr, Tanabe KK. Cancer gene therapy. Surg Oncol Clin N Am 1998; 7: 421-69.
9. Verma G, Mishra MK. A review on gene therapy: History, vectors, technologies and application. World journal of pharmacy and pharmaceutical sciences 2016; 5(10): 1334-55
10. Kumar MS, Masthan KMK, Babu NA, Dash KC. Gene therapy in oral cancer: A review. J Clin Diag Res 2013; 7(6): 1261-63
11. Weichselbaum RR, Kufe D. Gene therapy of cancer. Lancet 1997; 349 (suppl II): 10-12
12. Sai Lakshmi LJ, Radhika T, Jeddy N. Gene therapy in oral cancer – An update. J NTR Univ Health Sci 2020;9:1-5.
13. Sunil PM, Joseph I, Varghese SS. Gene therapy in oral squamous cell carcinoma: A short review. Oral & Maxillofacial Pathology Journal 2011; 2(2): 142-7
14. Lopez-Martinez M, Anzola M, Cuevas N, Aguirre JM, De-Pancorbo M. Clinical applications of the diagnosis of p53 alterations in squamous cell carcinoma of the head and neck. Med Oral 2002;7:108–20.
15. Liu TJ, Zhang WW, Taylor DL, Roth JA, Goepfert H, Clayman GL. Growth suppression of human head and neck cancer cells by the introduction of a wild-type p53 gene via a recombinant adenovirus. Cancer Res. 1994 Jul 15;54(14):3662-7.
16. Johny J, Sreedhar S, Nair RS, Liz Megha I J, Vidya Sankar V B. Gene therapy in oral cancer: A review. Arch Dent Res 2022;12(1):5-8.
17. Ayllón-Barbellido S, Campo-Trapero J, Cano-Sánchez J, Perea-García MA, Escudero-Castaño N, Bascones-Martínez A. Gene therapy in the management of oral cancer: Review of the literature. Med Oral Patol Oral Cir Bucal. 2008;13(1):E15-21.
18. Okamura H, Morimoto H, Fujita M, Nasu F, Sasakia E, Haneji T. Suppression of Egr-1 expression in human oralsquamous carcinoma cells by okadaicacid. OralOncol. 2002 Dec;38(8):779-84
19. Vijaylaxmi M, Shrinivas B, Sattr M, Burde A. Gene therapy for oral squamous cell carcinoma-A promising future. Int J Inf Res Rev 2014;1:220–2.
20. Bertrand JR, Pottier M, Vekris A, Opolon P, Maksimenko A, Malvy C. Comparison of antisense oligonucleotides and siRNAs in cell culture and in vivo. Biochem Biophys Res Commun. 2002;296(4):1000-4.
21. Gleich LL. Gene therapy forheadandneck cancer. Laryngoscope 2000;110:708-72
22. Li D, Shugert E, Guo M, Bishop JS, Bwjr O. Combination nonviralinterleukin 2 and interleukin 12 gene therapy for head and neck squamous cell carcinoma. Arch Otolaryngol Head Neck 2001;127:1319–24.
23. Tamatani T, Azuma M, Ashida Y, Motegi K, Takashima R, Harada K, et al. Enhanced radiosensitization and chemosensitization in NF-
24. kappa B - suppressed human oral cancer cells via the inhibition of gamma-irradiation- and5-FU-induced production of IL-6 and IL-8. Int J Cancer 2004;108(6):912-21.
25. Perez OD, Kinoshita S, Hitoshi Y, Payan DG, Kitamura T, Nolan GP, et al. Activation of the PKB/AKT pathway by ICAM-2. Immunity. 2002 ;16(1):51-65.
26. Faneca H, Düzgüne¸s N, de Lima MP. Suicide gene therapy for oral squamous cell carcinoma. Methods Mol Biol. 2019;1895:43–55.
27. Chahlavi A, Rabkin S, Todo T, Sundaresan P, Martuza R. Effect of prior exposure to herpes simplex virus 1 on viral vector-mediated tumor therapy in immunocompetent mice. Gene Ther. 1999 Oct;6(10):1751-8.
28. Heise C, Kirn DH. Replication-selective adenoviruses as oncolytic agents. J Clin Invest. 2000 Apr;105(7):847-51.
29. Galanis E, Okuno SH, Nascimento AG, Lewis BD, Lee RA, Oliveira AM, et al. Phase I-II trial of ONYX-015 in combination with MAP chemotherapy in patients with advanced sarcomas. Gene Ther. 2005 Mar;12(5):437-45.
30. Rudin CM, Cohen EE, Papadimitrakopoulou VA, Silverman S Jr, Recant W, ElNaggar AK, et al. An attenuated adenovirus, ONYX-015, as mouthwash therapy for premalignant oral dysplasia. J Clin Oncol. 2003;21(24):4546-52.