Content available at: https://www.ipinnovative.com/open-access-journals

Archives of Dental Research

Journal homepage: https://www.adr.org.in/

Review Article

Gene therapy in oral cancer: A review

Joseph Johny[1]*, Sinitha Sreedhar[1], Rohini S Nair[1], Liz Megha I J[1], Vidya Sankar V B[1]

[1]*Dept. of Oral Medicine and Radiology, Sree Anjaneya Institute of Dental Sciences, Calicut, Kerala, India*

ARTICLE INFO

Article history:
Received 25-06-2022
Accepted 09-07-2022
Available online 28-07-2022

Keywords:
Gene therapy
Oral cancer
Vectors
Gene gun

ABSTRACT

Gene therapy is the utilization of DNA as a specialist to treat illness. Gene therapy focuses on the inclusion of a functional gene into the cells of a patient for the rectification of an inborn error of metabolism, to change or fix a procured hereditary irregularity, and to give new capacity to the cell. Today, vast majority of the gene therapy studies are focused on malignant growth and inherited diseases which are connected to hereditary deformities. Malignant growth typically happens because of the creation of various mutations in a solitary cell which makes it proliferate wildly. A few techniques like surgery, radiation treatment, and chemotherapy have been utilized generally to treat tumors, yet recurrence is normal in roughly 33% of patients. To further develop the therapy methodology and to expand the endurance rate, gene therapy can be utilized as an aid to different treatments for malignant growth in patients. The reason for this article is to audit the ideas and strategy, with a knowledge into the ebb and flow research on its applications in oral squamous cell carcinoma (OSCC).

1. Introduction

OSCC is the well-known malignancy in the oral cavity and is the 6th most common cancer world-wide.[1] Oral malignancy is related with hereditary changes resulting from openness to tobacco, alcohol, betel quid, etc.[2] The patients with disease usually stay impervious to the standard treatments which are utilized promptly. Thus, to further develop the treatment methodology and the general endurance rates, gene therapy has arisen in the field of bio-medicine, which replaces the defective gene and this is fixed by a remedial gene.[3] This alternate treatment choice has been demonstrated to expand endurance paces of OSCC patients. In the dental field, it is additionally applied in bone repair, auto immune diseases, pain, caries and periodontal diseases.[4]

* *Corresponding author*.
E-mail address: joseph_kjr@rediffmail.com (J. Johny).

2. The History of Gene Therapy

Gene amplification, which is utilized in the therapy of different human illness, was put forward by Cusack and Tanabe in 1998.[5] Gene therapy is characterized as gene exchange to treat human sickness effectively (Cusack and Tanabe, 1998)[5,6] which incorporates both the exchange of new hereditary material and control of the current hereditary material.[5]

2.1. Idea of gene therapy

Gene therapy includes the exchange of a remedial gene into explicit cells of a person to fix a defective gene. The goal of gene therapy is to bring new hereditary material into target cells without making any harm to the encompassing tissues and furthermore treatment-related morbidity is diminished with gene therapy when compared with other methods.[7]

https://doi.org/10.18231/j.adr.2022.002

2.2. Types of gene therapies

1. Somatic gene therapy
2. Germ line gene therapy

In somatic gene therapy

The therapeutic genes are brought into somatic cells, which confines the impacts of the individual and are not given to the offspring.[8]

In germ line gene therapy

Either the sperm or egg can be altered by introducing the therapeutic gene, which gets integrated into the genome.[9]

2.3. Techniques to deliver therapeutic genes

Therapeutic gene can be conveyed to the target cells in two ways.

Ex vivo—Therapeutic gene can be embedded into cells from the impacted tissue outside the body and afterward brought back to the body.

In vivo—Therapeutic gene is embedded straight forwardly into the impacted site.

2.4. Vectors in gene therapy

The vector or carrier is used for the transfer of a therapeutic gene in to the recipient cells.[10]

Vectors are broadly comprised of two types:

3. Viral Vectors

3.1. Non-viral vectors

Genetic material is conveyed into the host cells through viruses or bacteria.[11] Gene therapy deals with DNA which can be incorporated into cells by various means. All viruses such as retroviruses, adenoviruses, lentiviruses, herpes simplex virus, vaccinia, pox virus, and adeno-associated virus bind to their hosts by bringing their hereditary materials into the host cells. In gene therapy, the viral DNA can be eliminated, while the viruses can go about as vehicles to introduce the remedial DNA into the host cells. The viruses which are utilized as vectors in gene therapy incorporate retroviruses, adenoviruses, adeno associated viruses and Herpes simplex virus.[12]

The methods of non-viral gene therapy incorporate the infusion of bare DNA, electroporation, the gene gun and the use of oligonucleotides, dendrimers and inorganic nanoparticles. Nonetheless, the non-viral vectors which are restrained by the serum components, limit the effectiveness of the gene transfer in vivo.[13] Despite the use of a few non-viral strategies, viruses give a more productive mode in gene therapy.[14]

3.2. Approaches of gene therapy

The therapies that, results in the death of cancer cells, include,

1. Gene addition therapy.
2. Gene excision therapy.
3. Antisense RNA therapy.
4. Immunotherapy.
5. Suicide gene therapy.
6. Gene therapy with inclusion of oncolytic viruses.

3.3. Gene addition therapy

Genetic alterations incorporate mutations of p53, the Retinoblastoma Gene, p16 and p21. P53 is the most widely involved tumor suppressor gene in gene therapy and around 60% of tumors are related with mutation of the p53 gene. In this strategy, the cancer development is constrained by the presentation of tumor suppressor genes which inactivates the carcinogenic cells.[15] p53 is the most widely involved gene with adenovirus as viral vectors

3.4. Gene excision therapy

This therapy suppresses tumor growth by evacuation of oncogenes. The genes that control development and cell cycle progression, including a few variables like- TGF-α1, PDGF-α and PTEN are controlled by the expression of the protein EGR-1. Along these, suppressing this protein represents great remedial methodology for the cancer cells. A few studies exhibited that hindrance of the protein kinase C diminishes the expression of this gene, setting of higher sensitivity of the tumor to radiotherapy (Okamura et al., 2002).[16]

3.5. Antisense RNA therapy

In this method, remedial gene is presented that inhibits the expression of a specific defective gene is called as “Antisense therapy.” Gene expression can be restrained by RNA complementary to DNA strand expressing the gene. This method can be directed towards cancer cells whose malignant phenotype is subject to the expression of specific oncogenes like Myc, Fos, and Ras. Inhibition of expression of these oncogenes might change the phenotype, thus prevents the tumor growth.[17]

3.6. Immunologic gene therapy

Immunotherapy acts either by increasing the immunogenic potential of tumor cells or the immune response of patient to tumor. Patients with OSCC show diminished function of a few types of immune cells which include natural killer cells, T-lymphocytes and cytokines. The combined use of mIL – 2 (murine interleukin 2) and mIL -12 (murine interleukin -12) gene therapy resulted in considerable reduction in the tumor due to increased activation of cytolytic T lymphocyte and natural killer cells. Radiosensitivity to γ radiation and chemosensitivity to 5-fluoracil (5-FU) in oral squamous cell carcinoma can be enhanced after suppression of NF-

κB activity, which activates the antiapoptotic proteins TNF, TRAF-1, TRAF-2 and cIAP-1. The activation of NF-κB can increase expression of proinflammatory cytokines, e.g., IL-1α, IL-6, and IL-8, and of enzymes that degrade matrix metalloproteinase -9 (MMP-9). The progression and metastasis of OSCC can be prevented by inhibiting NF-κB activity which may be a useful co adjuvant treatment in oral cancer therapy. Systemic administration of Anti-ICAM-2 induced the complete regression of OSCC. ICAM-2 is a glycosylated protein with surface adhesion that is expressed in endothelial cells and activated lymphocytes.[18]

3.7. Suicide gene therapy

This treatment includes enzymes, the expression of which transforms the non-toxicity creating drug into a functional cytotoxic substance. It is the most widely utilized gene therapy which utilizes thymidine kinase or other chemo sensitizing genes (Gardlik et al., 2011). Thymidine kinase gene of Herpes Simplex Virus (HSV) transforms ganciclovir into ganciclovir phosphate. Gene transfer of HSVtk gene (Herpes simplex virus thymidine kinase gene) through adenovirus vector in blend with ganciclovir administration might be a better remedial choice for OSCC. HSV-tk/GCV therapy in cultured oral squamous cancer cells have shown that cancer cell demise happens basically by an apoptotic interaction and the noticed high cytotoxicity is because of the bystander effect, which is promoted by the dissemination of the toxic agent into adjoining cells by means of gap junctions. The examinations in syngeneic orthotopic and subcutaneous murine models for squamous cell carcinoma of the head and neck uncovered that intratumoral administration of the HSV-tk gene interceded by transferrin- or folate-associated lipoplexes, trailed by intraperitoneal injection of ganciclovir, results in an intense antitumor effect.[19]

3.8. Gene therapy with the use of oncolytic viruses

In this treatment, a vector (virus) is hereditarily altered, which replicates and lyses the cancer cells. For instance, adenovirus mediated gene therapy is utilized for advanced malignancies than traditional treatments.[20]

3.9. Advantages of gene therapy

1. Gene therapy supports avoidance against the potentially harmful impacts in the body, which can be brought about by other treatments.
2. It diminishes the expenses of different treatments and improves the patient's way of life for a more extended period.[21]

3.10. Disadvantages of gene therapy

1. Patients might need to go through multiple rounds of gene therapy.
2. There is a possibility that the host's immune system and its response may lessen the adequacy of the gene therapy.
3. The viral vectors can cause a variety of potential problems to the patient, like toxicity and immune and inflammatory responses.
4. Gene therapy is utilized to treat only single gene disorders.
5. Cancer can be initiated assuming that the DNA is brought into the wrong place in the genome, for example, into a tumor suppressor gene.[21]

4. Conclusion

Gene therapy is an arising field of biomedicine, with a possibility to frame a conclusive therapy for oral cancer and precancer by offering more effectiveness and perhaps decreasing the death rate related with these lesions. The research on gene therapy in oral cancer is expanding day by day, both in the laboratory and the clinical settings. The research on stem cells and genetic engineering, particularly those utilizing viral vectors are impressive, which guarantees the chance of new choices for therapies and cure in the face of the need of reestablishment of oral health. It is realized that more studies are yet required for gene therapy to be viewed as a first option treatment.s

Later on, combination of gene therapy with chemotherapy and immunotherapy might frame one of the most encouraging fields of research in the management of oral cancer.

5. Source of Funding

None.

6. Conflicts of Interest

None.

References

1. Sunil PM, Ramachandran CR, Devy S, Varghese SS. Cytogenetic alterations in oral squamous cell carcinoma detected by karyotyping (g-banding). *Oral Maxillofac Pathol J*. 2011;2(1):89–95.
2. Sugerman PB, Savage NW. Current concepts in oral cancer. *Aust Dent J*. 1999;44(3):147–56. doi:10.1111/j.1834-7819.1999.tb00216.x.
3. Sunil PM, Isaac J. Varghese Soma Susan. Gene therapy in oral squamous cell carcinoma - a short review. *Oral and Maxillofacial PatholJ*. 2011;2(2):142–7.
4. Mohan SP, Ramachandran CR, Jaisanghar N, and CSK. Dental Surgeons as Gene Therapist. *Int J Oral Maxillofacial Pathol*. 2012;3(3):65–7.
5. Singh A, Badni M, Singh A, Samadi F, Kabiraj A. Gene therapy for oral cancer - journey to a new horizon. *Oral Maxillofacial Pathol J*. 2012;3(1):203–10.
6. Xi S, Grandis JR. Gene Therapy for the treatment of oral squamous cell Carcinoma. *J Dent Res*. 2003;82(1):11–6.
7. Barbellido SA, Trapero JC, Sánchez JC, García M, Castaño NE, Martínez AB, et al. Gene therapy in the management of oral

cancer: Review of the literature. *Med Oral Patol Oral Cir Bucal*. 2007;12(8):549–51.
8. Indu S, Ramesh V, Oza N, Prashad KV. Gene therapy: An overview. *J Orofacial Sci*. 2013;5(2):83–7. doi:10.4103/0975-8844.124249.
9. Kumar MS, Masthan KM, Babu NA, Dash KC. Gene therapy in oral cancer: A review. *J Clin Diagn Res*. 2013;7(6):1261–3. doi:10.7860/JCDR/2013/5412.3071.
10. Heera R, Beena VT, Simon R, Choudhary K. Gene therapy in oral cancer: An overview. *Oral Maxillofac Pathol J*. 2010;1:976–1225.
11. Susy MS, Silke M, Ray M. Gene Therapy Applications to Cancer Treatment. *J Biomed Biotechnol*. 2003;2003(1):35–47. doi:10.1155/S1110724303209037.
12. Heera R, Beena VT, Rency S, Kanaram C. Gene therapy in oral cancer: an overview. *Oral Maxillofacial Pathol J*. 2010;1(2).
13. Mark Y, Nathan O, Krystyna K. Düzgünes Nejat. Gene Therapy for Oral Cancer: Efficient Delivery of a 'Suicide Gene' to Murine Oral Cancer Cells in Physiological Milieu. *CDA J*. 2005;33(12):967–71.
14. Shillitoe EJ. Gene therapy: the end of the rainbow? *Head Neck Oncol*. 2009;doi:10.1186/1758-3284-1-7.
15. Singh R, Singh S, Kumar T, Kumar A, Kumar A, Nazeer J, et al. A novel approach in the treatment of oral cancer - Gene therapy an update. *World J Pharm Pharm Sci*. 2017;6:283–92. doi:10.20959/WJPPS20174-8855.
16. Madalli V, Shrinivas MB, Sattur A, Burde K. Gene therapy for oral squamous cell carcinoma-A promising future. *Int J Inf Res*. 2014;1:220–2.
17. Jacob KC, Yashoda R, Puranik MP. Gene therapy in the treatment and prevention of oral cancer: An overview. *Int J Adv Health Sci*. 2015;2:14–20.
18. Sunil PM, Joseph I. Susan Varghese S. Gene therapy in oral squamous cell Carcinoma - A short review. *Oral Maxillofac Pathol J*. 2011;2:976–1225.
19. Faneca H, Düzgüneş N, de Lima MP. Suicide gene therapy for oral squamous cell carcinoma. *Methods Mol Biol*. 2019;1895:43–55. doi:10.1007/978-1-4939-8922-5_4.
20. Blaese RM, Culver KW, Miller AD, Carter CS, Fleisher T, Clerici M, et al. T lymphocyte- directed gene therapy for ADA- SCID: Initial trial results after years. *Science*. 1995;270(5235):475–80. doi:10.1126/science.270.5235.475.
21. Sharma R, Khajuria R, Sharma CL, Kapoor B, Goswami KC, Kohli K, et al. Gene therapy: Current concepts. *JK Sci*. 2004;6(2):62–6.

Author biography

Joseph Johny, Associate Professor and HOD

Sinitha Sreedhar, Senior Lecturer

Rohini S Nair, Intern

Liz Megha I J, Intern

Vidya Sankar V B, Intern

Cite this article: 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.