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Derleme / Review

Is Genie Having a Cure for Oral Cancer? – Genetic Dentistry

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ÖZET

Genin oral kanser için bir tedavisi var mı? Genetik diş hekimliği

Dünyada en yaygın görülen kanser türleri arasında olan oral karsinom, global olarak en sık görülen altıncı kanserdir. Oral kanser, tütün ve alkol kullanımına bağlı olarak ortaya çıkan genetik mutasyonlarla ilişkilidir. Son yıllarda oral kanser hastalarının cerrahi, radyoterapik ve kemoterapik tedavilerindeki gelişmeler hasta sağkalımında anlamlı gelişmeler yaratmamıştır. İmmunoterapi, gen terapisi ve hedeflenmiş terapideki son gelişmeler oral kanser tedavisinde umut verici sonuçlar ortaya koymaktadır. Gen terapisi çevre dokuda toksik etkiler oluşturmadan hedef hücrelere spesifik genetik materyalin sunulmasını içerir. Günümüzde gen terapisi çalışmalarının çoğu kanser ve genetik bozukluklarla ilişkili kalıtsal hastalıkları hedeflemiştir. Bu derleme oral kanser türlerinde gen terapisi ile yapılmış çalışmaların temel kavram ve çeşitlerine açıklık getirmektedir. Gen terapisi oral kanser tedavisinde öne çıkan yeni çalışma alanlarından biridir.
Anahtar sözcükler: Gen terapisi, oral kanser

ABSTRACT

Is genie having a cure for oral cancer? – genetic dentistry

Worldwide, oral carcinoma is one of the most prevalent cancers and it is the sixth most common cancer globally. Oral cancer is associated with genetic mutations which occur due to the exposure to tobacco, alcohol, betel quid. Advances over recent decades in the surgical, radiotherapeutic and chemotherapeutic treatment of oral cancer patients did not produced a significant improvement in patient survival. Recent advances like immunotherapy, gene therapy, and targeted therapy are showing promising results in the management of oral cancer. Gene therapy essentially consists of introducing specific genetic material into target cells without producing toxic effects on surrounding tissue. Today, most of the gene therapy studies are aimed at cancer and hereditary diseases which are linked to genetic defects. This article highlights the basic concept, types and various studies done on oral cancer using gene therapy. Gene therapy has becoming one of the emerging fields in the management of oral cancer.
Key words: Gene therapy, oral cancer

INTRODUCTION

In this modern world, cancer is projected as one of the fatal diseases amongst all the dreadful diseases nowadays. Cancer cells are different from its neighboring cells in having phenotypic changes like a rapid division rate, a high metabolic rate, and alteration in their shapes. Few 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 (1). Oral cancer is a genetic disease in which the genes that control cell growth and apoptosis are mutated, allowing cells to acquire the ability to invade and metastasize. Despite of all these research efforts and new therapies, the five-year survival rate has not shown any improvement over the past 4-5 decades. Patients with recurrent oral cancer that is refractory to chemotherapy or radiotherapy have a life expectancy of only months and the response rate to second- and third-line treatments is only

15% (2). Oral cancer accounts for 2% of cancer deaths in males and 1% of cancer deaths in females (3).

History of gene therapy

The fundamental tenets of gene therapy were led by Joshua Lederberg and Edward Tatum (4). Micheal et al. in 1977 succeeded in transferring a gene TK gene coding for thymidine kinase into mammalian cells took a large step in the field of gene therapy (5,6). The first approved clinical trial on gene therapy took place on September 14, 1990, on a 4 year-old girl, Ashanthi De Silva with Adenosine Deaminase (ADA)-deficiency / Severe Combined Immunodeficiency (SCID) syndrome. She was given her own T cells engineered with a retroviral vector carrying a normal ADA gene by the NIH (National Institutes of Health) team of Anderson, Blaese and Rosenberg (7). Gene amplification, which is used in the treatment of various human diseases, was put forward by Cusack and Tanabe in 1998 (8). The first successful treatment of X-linked Severe Combined Immunodeficiency (X-SCID) was done by ex vivo gene replacement therapy (9). As of March 2004, 619 gene therapy / transfer clinical protocols have been submitted to the NIH / FDA (Food and Drug Administration) for approval: cancer-405 (65%), monogenic diseases (17 different genetic diseases including SCID, haemophilia and cystic fibrosis) -58 (9%), infectious diseases (primarily human immunodeficiency virus, HIV) -40 (6%), other diseases primarily peripheral artery disease and coronary artery disease 69 (11%) and marker or nontherapeutic trials-47 (9%) (10).

Molecular basis of oral cancer

Oral squamous cell cancer (SCC) is the result of a multistage process from normal to dysplastic lesions and ultimately to SCC. Carcinogenesis is a genetic process that leads to a change in morphology and in cellular behavior (11). Major genes involved in head and neck squamous cell carcinoma (HNSCC) include proto-oncogenes and tumor suppressor genes (TSGs). Other factors that play a role in the progression of disease may include allelic loss at other chromosome regions, mutations to proto-oncogenes and TSGs, or epigenetic changes such as deoxyribonucleic acid (DNA) methylation or histone deacetylation (11). Mutations of the p53 tumour suppressor gene result either in the production of structurally altered protein or complete loss of the protein. p53 has been shown to be functionally inactivated in oral tumours and restoration of p53 in oral cancer lines and tumours induced in animal models has been shown to reverse the malignant phenotype (12). Cytokine growth factors, angiogenesis, cell adhesion molecules, immune function, and homeostatic regulation of surrounding normal cells could also play a role. Certain viruses have also been found to be associated with oral cancer (11).

What is gene therapy?

Gene therapy can be broadly defined as the transfer of genetic material to cure a disease or at least to improve the clinical status of a patient. One of the basic concepts of gene therapy is to transform viruses into genetic shuttles, which will deliver the gene of interest into the target cells (13).

Approaches of gene therapy (14)

1. Gene modification
• Replacement therapy
• Corrective gene therapy
2. Gene transfer
• Physical
• Chemical
• Biological
3. Gene transfer in specific cell line
• Somatic gene therapy
• Germ line gene therapy
4. Eugenic approach (gene insertion)

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 somatic gene therapy whereas in germ line gene therapy, either the sperm or egg can be altered by introducing the therapeutic gene, which gets integrated into the genome (13).

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 (8, 16) and it is also called genetic pro-drug activation therapy (8).

• 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 (8).

• Other forms of genetic engineering include gene targeting and knocking out specific genes via engineered nucleases such as zinc finger nucleases, engineered I-CreI homing endonucleases, or nucleases generated from TAL effectors. This approach is currently being used in several human clinical trials (17).

Vectors for gene therapy

Genetic material is delivered into the host cells through viruses/bacteria or non-viral vectors. The various viral agents include retroviruses, adenoviruses, lentiviruses, herpes simplex virus, vaccinia, pox virus, and adeno-associated virus whereas the non-viral agents consists of the injection of naked DNA, electroporation, the gene gun and the use of oligonucleotides, dendrimers and inorganic nanoparticles (13). However, the non-viral vectors are usually inhibited by the serum components resulting in its limited efficiency of the gene delivery in vivo (17). Despite of the uses of both the vectors, viruses provide a more efficient mode in gene therapy compared to the non-viral vectors (18).

Gene therapy in oral cancer

Several genetic alterations have been described in the pathogenesis of oral cancer consisting of mutations of p53, p16 and p21 (11). 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 tumour with an adenoviral vector expressing wild-type p53. Adenoviral p53 (Ad-p53) was demonstrated to be safe and well-tolerated. Twenty studies on Ad-p53 as a surgical adjuvant showed good results (21). The reconstitution of wild-type p53 function with p53-expressing adenovirus and combinational therapy using ionizing radiation and recombinant Ad-p53 has been reported to have a significant tumour-suppressant effect on various cells. The survival of SCC cell lines was inhibited after transfection with recombinant p53-expressing adenovirus (22).

Oral cancers are associated with specific types of human papillomavirus (HPV). Certain genes of the HPV such as E6

Table 1: Table showing the various studies done using gene therapy in oral precancer and cancer (26)

Gene	Vector used	Mechanism of action	Author and year
MnSoD gene	Addiction G.T	Suppresses tumour malignity by reducing peroxide flow and therefore cell mitosis	Liu et al, 1997
Mutated or altered P53	Adenovirus ONYX-015	Reduction of leukoplakias	Nemunaitis et al, 2000
tKHSV gene	Suicide G.T	Increases apoptosis	Fukui et al, 2001
Anti-ICAM-2	Immunotherapy	Complete regression of oral cavity tumours	Pérez et al, 2002
Intratumoural injection of Adv-F/RGD	Immunotherapy	Increases anti-tumour effect by local control of the disease	Dehari et al, 2003
MDR1, MRP1, DHFR	Suicide G.T	Reduces tumour angiogenesis, increases apoptosis, modifies immune system	Gottesman, 2003
Mutated or altered P53	Adenovirus ONYX-015	Increases replication in cells with altered p53 (OSCC) by using adenovirus or ONYX-015	Nemunaitis et al, 2003
Alteration of Rb protein	OAS403	Controls expression of gene E4 and decreases in vivo and in vitro toxicity	Ryan, 2004
4-1BB gene	Immunotherapy	Activation of T lymphocytes	Cheuck et al, 2004

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 could be inhibited by antisense therapy (23).

The immunologic gene therapy approach to oral cancer involves either increasing the immunogenic potential of tumour 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 (24). Studies in animal models have shown that administration of interleukin-2 (IL-2), tumour necrosis factor alpha (TNF-α), IL-4, interferon-gamma (IFN-γ), IFN-α, granulocyte macrophage colony-stimulating factor (GM-CSF) and IL-6 had enhanced killer cell-mediated cytotoxic effects. The feasibility and efficacy of a combination of nonviral, lipid-formulated murine interleukin-2 (mIL-2) and polymer-formulated, murine interleukin-12 (mIL-12) gene therapy for squamous cell carcinoma have been investigated in preclinical models. The use of combined mIL-2 and mIL-12 gene therapy resulted in significant anti-tumour effects, most likely due to increased activation of cytolytic T lymphocyte and natural killer cells (25).

Advantages and disadvantages of gene therapy (14)

Advantages of gene therapy

• In case of 'silence' a gene. In the case of someone with HIV, which had not yet developed into AIDS, scientists could save them the pain and suffering of the disease by using gene therapy to 'silence' the disease before its onset.

• Gene therapy has the potential to eliminate and prevent hereditary diseases such as cystic fibrosis and is a possible cure for heart disease, AIDS and cancer.

• These sceptics would almost certainly choose gene therapy, especially if it was the last hope for them or one of their loved ones – as is the case for many gene therapy patients.

Disadvantages of gene therapy

• Short-lived nature of gene therapy.

• Immune response - Genes injected with a virus may trigger an immune response against the virus. Problems with viral vectors (once inside the patient, the viral vector could recover its ability to cause disease).

• Multigene disorders - The genetic material might not get into the right cell, or the right place in the cell's DNA.

CONCLUSIONS

Gene therapy is becoming a very attractive tool in the management of oral 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 as well as in the clinical settings. In future, it will become a forerunner as a definitive treatment option for oral 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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