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A Review on Gene Therapy for Cancer

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A B S T R A C T

Gene transfer is a new treatment modality that introduce new genes into cancerous cell or surrounding the tissue to cause cell death or slow the growth of cancer. Gene therapy is treatment that become important in preventing deaths from cancer. It is intensely used in research projects in 1989. First commercial gene treatment in 2003 was for neoplasia. Some examples of cancer that are treated with gene therapy are Brain cancer, Lung cancer, Breast cancer, Pancreatic cancer, Liver cancer, Bladder, Head and neck, Skin, Ovarian cancers etc. There are different gene therapy strategies for cancer Such as pro-drug activation suicide gene therapy, Anti-angiogenic gene therapy, Oncolytic viro-therapy, Immunotherapy, Gene therapy-based immune modulation.

Keywords: Gene therapy, Cancer, Treatment of Cancer, History of gene therapy, Therapies in gene therapy for cancer, Safety, Challenges, etc.

Introduction & History

Cancers are a group of diseases characterized by uncontrolled growth and spread of abnormal cells. If the spread of cancer cells this stage is known as metastasis is not controlled, it can result in death. Cancer is caused by many external factors (tobacco, chemicals, radiation and infectious organisms) as well as some internal factors (inherited mutations, hormones, immune conditions and random mutations).Cancer has become one of the causes of death in India. It is estimated that there are nearly 2 to 2.5 million cancer cases at any given point of time. Over 7 lakhs new cases and 3 lakhs Deaths occur annually due to cancer. Nearly 15 lakh patients require facilities for diagnosis treatment and follow up at a given time [1].

In men, the highest percentages of cancer types occur in the prostate, lung and bronchus, colon and rectum, and urinary bladder, respectively. In women, cancer prevalence is highest in the breast, lung and bronchus, colon and rectum, uterine corpus and thyroid, respectively. This data indicates that prostate and breast cancer constitute a major portion of cancer in men and women, respectively.

occurs by a series of successive mutations in genes so that these mutations change cell functions. Chemical compounds have an obvious role of forming gene mutations and cancer cells. In addition, smoking involves several carcinogenic chemical compounds that lead to lung cancer [2].

Gene therapy aims at delivering genetic material into target cells or tissue and to express it with the intention to gain a therapeutic effect. It has the advantage over conventional therapies due to the fact that it can be administered locally, thereby delivering, locally, a high therapeutic dose without risking systemic adverse effects. Furthermore, since most gene therapies are single time applications, they can be cost effective in the long run [3].

The purpose of this transference of genetic material or of genes is to re-establish a cellular function that had been abolished or become defective, to introduce a new function or to interfere in an existing function. A simple example would be the use of gene therapy in treating a disease caused by a defective gene in a patient's cells. This defective gene would produce a defective protein incapable of carrying out a certain function. With gene therapy, a normal gene could be introduced into the patient's cells that would produce the adequate protein and thus cure the disease. However, it is presently very difficult to substitute the function of a defective gene by replacing it with a new gene. Very few projects have successfully achieved this and there have been adverse effects that can be very serious [4].

History

- Advances in 1990s

Four-year-old Ashanti DeSilva received treatment for a genetic defect that left her with adenosine deaminase deficiency (ADA-SCID), a severe immune system deficiency. The defective gene of the patient's blood cells was replaced by the functional variant. Ashanti's immune system was partially restored by the therapy [5]

- Advances in 2013

In July researchers reported promising results for six children with two severe hereditary diseases had been treated with a partially deactivated lentivirus to replace a faulty gene and after 7–32 months. Three of the children had metachromatic leukodystrophy, which causes children to lose cognitive and motor skills [6].

❖ Advances in 2016

A 2016 Cochrane systematic review looking at data from four trials on topical cystic fibrosis transmembrane conductance regulator (CFTR) gene therapy does not support its clinical use as a mist inhaled into the lungs to treat cystic fibrosis patients with lung infections [7].

❖ Advances in 2021

In May, a new method using an altered version of the HIV virus as a lentivirus vector was reported in the treatment of 50 children with ADA-SCID obtaining positive results in 48 of them [8].

In June a clinical trial on six patients affected with transthyretin amyloidosis reported a reduction the concentration of misfolded transthretin (TTR) protein in serum through CRISPR-based inactivation of the TTR gene in liver cells observing mean reductions of 52% and 87% among the lower and higher dose groups. This was done in vivo without taking cells out of the patient to edit them and reinfuse them later [9].

❖ Advances in 2022

In February, the first ever gene therapy for Tay–Sachs disease was announced, it uses an adeno-associated virus to deliver the correct instruction for the HEXA gene on brain cells which causes the disease. Only two children were part of a compassionate trial presenting improvements over the natural course of the disease and no vector-related adverse events [10].

Types of Cancer

1. Carcinoma-

It starts in the tissue or the skin, which covers the glands and internal organ surface. It forms a solid tumor. Breast cancer, prostate cancer, colorectal cancer, lung cancer.

2. Sarcoma-

It starts in the tissues which connect and support the body. It can be formed in nerves, tendons, joints, fat, blood vessels, bone, lymph vessels, muscles, or cartilage.

3. Lymphoma-

Lymphoma is cancer that begins in the lymphatic system and it is a network of glands and vessels that helps to fight with infection. Hodgkin lymphoma and Non-Hodgkin lymphoma.

4. Leukemia's:

Leukemia is a cancer of the blood. It begins when healthy blood cells grow uncontrollably and change. It is divided into 4 types, that are acute myeloid leukemia, acute lymphocytic leukemia, chronic myeloid leukemia, and chronic lymphocytic leukemia.

5. Multiple Myeloma:

Multiple myeloma is cancer that begins in plasma cells, another type of immune cell. The myeloma cells which are plasma cells, are build up in bone marrow and make tumors in bones. It is called plasma cell myeloma and Kahler disease [11].

Symptoms of Cancer

- Chills
- Fatigue
- Fever
- Loss of appetite
- Night sweats
- Weight loss
- Changes in bowel or bladder habits
- Any sore that does not heal

- Unusual upset stomach or difficulty Swallowing. [1]

Types of treatment

1. Surgery

To prevent or reduce the disease's spread and remove cancer from the body, the surgeon may remove lymph nodes. Small thin knives called scalpels are used by the surgeons and other sharp tools also used to cut through muscle, skin and sometimes bones during surgery.

Surgery can be used to:

- Remove the entire tumor
- Remove some but not all tumor. De-bulking is used when removing an entire tumor might damage an organ or the body.
- Remove tumor that causing pressure or pain.

2. Radiation Therapy: -

In this therapy high doses of radiation are used to treat cancer by shrinking tumors, killing cancer cells, and slow the growth of cancer cells by damaging their DNA because the damaged DNA does not repair and the cell die which is removed by the body. The treatment takes weeks or months and prevents from returning.

3. Chemotherapy: -

In this therapy, chemicals are used to treat cancer by stopping or slowing the growth of cancer cells or by killing cancer cells or also by shrink tumors that causing pain and other problems but have severe side effects. Chemotherapy is given only and also given with other cancer treatments that depend upon the cancer type.

4. Immunotherapy: -

In this therapy, the immune system is boost by medication or other treatments. Example, adoptive cell and checkpoint inhibitors treatment, etc. The immune system is made up of WBC and tissues of lymph nodes help to provide the strength to the body to fight against the disease and infection. It is also called biological therapy, which means the substances used in the treatment made from living organisms to treat cancer.[11]

Etiology of cancer

As in younger patients, little is known about the causes of cancer in adolescents and young adults. It is likely that environmental agents contribute to the great majority of cancers in older age groups following chronic exposures over many years but in the young, there is no opportunity for such long-term exposures.

In fact, many of the adolescent and young adult cancers that have been linked to etiologic factors are second malignant neoplasms in patients who were treated with chemotherapy and/or radiotherapy for a prior cancer. Given that the duration of exposure to potential environmental carcinogens is proportional to age, it is Epidemiology and Etiology of Cancer Chapter 3 53 not surprising that tobacco-, sunlight-, or diet-related cancers are more likely to occur in older adolescents and young adults than in younger persons [12].

What are genes

Genes are the fundamental physical and functional unit of heredity. A gene is an ordered sequence of nucleotides located in a particular position on a particular chromosome that encodes a specific functional product. Gene is termed as a "biological units of heredity". Inherited from the parents, determines the unique traits - like the color of the eyes and color and texture of the hair [13].

What is gene therapy

Gene therapy can be defined as the delivery of genetic elements to the cancer cell or to the cells of the immune response in order to correct the abnormalities in the cancer tissue or to induce an immune response against the cancer cells. The corrective strategies can involve replacing missing or defective genes.

The second step in gene therapy following the identification of a suitable gene is to introduce it into the target cell. Different vehicles (vectors) have been used to introduce the genes into the cells, such as viral vectors, nonviral vectors, and cell-based carriers. The mainly used viral vectors in cancer gene therapy are retroviruses, adenoviruses, and adeno-associated viruses [14].

Gene Transfer methods and vectors use for gene transfer

1. Viral vector

Retroviral vectors derived from retroviruses contain a linear single-stranded RNA of around 7– 10 kb and have a lipid envelope. The viral particles enter the mammalian cells expressing appropriate receptors for retroviruses.

After entering the cell, the viral reverse transcriptase transcribes the virus RNA into double-stranded DNA (dsDNS). The dsDNA transcribed in the cytoplasm forms a nucleoprotein preintegration complex (PIC) by binding cellular proteins.

2. Non-viral vector

Non-viral gene delivery systems are a topic that is currently being studied extensively as alternatives for viral delivery systems. The simplest form of a non-viral system is naked plasmid DNA. The advantage of naked plasmid is that it poses the lowest form of toxicity or other unwanted reactions. In addition, it is easy to formulate and inexpensive to produce. However, its disadvantage is the low transfection efficiency compared to viral-mediated gene transfer [3]. Cationic lipid DNA complexes (lipoplexes) (LPD/DNA) enter the target cell through an endosomal pathway. However, the transgene expression efficiency is very low with lipoplexes. It has been shown that only a very small portion of the systemically injected DNA could be reached to tumour tissue [14].

Gene targeting in cancer gene therapy

1. Physical targeting

The first one is physical targeting by means of some physical methods such as local injections, catheters, gene guns, and electroporation. This strategy is usually used for local delivery of gene therapy vectors and is therefore not suitable for most of the cancer patients who may have cancer spread throughout the body.

1. Biological targeting

In a second strategy, the viral or non-viral carriers of the genes are modified in such a way that they can only bind to tumor cells but not the normal cells. Because of the low transduction efficiency of the currently used gene therapy vectors in distant tissues when administered systemically, the specific transgene expression or viral replication in target tissues could provide an opportunity to achieve sufficient antitumor activity [14].

Targets for gene therapy of cancer

Gene-Directed Enzyme/Prodrug Therapy (GDEPT): -

The principle of pro drug activating suicide gene therapy is to introduce a transgene encoding for an enzyme that is either absent in mammalian cells or present in a very inactive form, into the tumor. The enzyme produced by the transduced cells will convert the subsequently administered inactive pro drug into its active form, evoking the death of cells expressing the therapeutic gene [3].

Conventional chemotherapeutic drugs are mainly directed to nonspecific direct cell killing. However, dose-limiting toxicities avoid the use of higher doses of those drugs to eradicate the disseminated cancer. However, if the drug was synthesized within the tumor tissue, then the toxicity level would only increase in tumor cells but not other parts of the body [14].

Dying tumor cells during suicide gene therapy could induce a tumor-specific immune response. Therefore, combining prodrug/enzyme systems with an immnuomodulating cytokine would further improve the efficacy. The addition of an IL-2 gene to the HSV-TK has yielded more potent antitumoral activity when compared each strategy alone [3].

Oncolytic viral vectors: -

Oncolytic virotherapy (OV) is the most promising approach for tumor immunotherapy. OV uses plication-competent viruses that can proliferate selectively at tumor cells. Oncolytic viruses grouped as naturally occurring or genetically modified viruses. Natural occurring viruses like parvoviruses, and Newcastle disease viruses that selectively replicate in tumor cell without genetic modification. The therapeutic use of oncolytic viruses for cancer treatment is an immune related treatment alternative. Oncolytic viruses act by directly lyses tumor cells and by introducing wild-type tumor suppressor genes into cells that lack the tumor suppressor gene [15].

Viruses have long been recognized tumor cell lytic agents and tried to treat cancer patients. However, the use of unmodified oncolytic viruses usually failed in the clinic. The engineering of those viruses to increase their therapeutic index have been possible in the last two decades. Herpes simplex virus (HSV), adenoviruses, parvoviruses, Newcastle disease virus, and retroviruses have been modified as oncolytic viral vectors [14].

Tumor vascular targeting therapy:-

Unraveling the mechanisms of tumor-induced angiogenesis, which is a key event in tumor growth and metastasis, has opened a new therapeutic era in cancer treatment. The antiangiogenic gene therapy approaches have been reported to inhibit the tumor-induced angiogenesis and therefore tumor

growth. The main strategies in antiangiogenic gene therapy are targeting specifically the endothelial cells (direct antiangiogenic gene therapy) and interfering with a tumor-derived angiogenic factor or the receptor for it or delivery of genes that encode angiogenesis inhibitors (indirect antiangiogenic therapy).

there are conflicting results regarding the tumor inhibiting activity of antiangiogenic gene therapy modality in experimental models. The combination of antiangiogenic gene therapy with chemotherapy or radiation could be an efficient way of the inhibition of tumor growth [14].

Safety of Gene Therapy

Despite the tragic case of Jesse Gelsinger, who died as a result of gene therapy using adenoviral vectors, the safety data collected from different human gene therapy trials have been uniformly satisfactory. However, it should be pointed out that viral vectors used in gene therapy are typically human pathogens, and hence, pre-existing antibodies against the viral vector may be present, which might result in an unwanted immune response.

Different means with the intention of improving the safety of gene therapy have been implemented. One approach is to develop targeting strategies in order to enhance the delivery of gene transfer vectors, and hence, to improve the duration and efficacy of gene expression [3].

Challenges in Gene therapy

There are four problems to be solved before cancer gene therapy can be successful:

1. Identification of key target genes critical for disease pathology and progression.
2. Identification of the appropriate therapeutic gene to inhibit disease progression.
3. Optimal trans-gene expression for suppressing the target gene.
4. Delivery of therapeutic product to the target tissue at an efficacious dose

The optimal trans-gene expression requires two critical components: promoters and enhancers to define the duration of trans-gene expression in the cells. There are two types of promoters: constitutive or inducible. The constitutive promoters can be either of viral origin (cytomegalovirus) or tissue specific promoters [16].

Conclusion

Cancer is the most dangerous disease there is limited and painful treatment for cancer. Cancer is nothing but unlimited growth of cell that cause by carcinogenic factor. Cancer is treated with various treatments gene therapy is one of them. Recently India is approved the gene therapy for cancer. History of gene therapy is started from 1990s till up to date. In gene therapy delivery of genetic material and inhibit the growth of tumor cells and kills it. Gene therapy is fast, less toxic and effective compare to other treatment. There are viral and non-viral vectors used. Gene Vectors are used as vehicle to treat cancer. Gene therapy include various therapies such as: Gene-Directed Enzyme/Prodrug Therapy (GDEPT), Oncolytic viral vectors, Tumor vascular targeting therapy. There are many challenges in gene therapy for cancer. Currently study is going on gene therapy for cancer. Gene therapy for cancer is one step closer to treat cancer.

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