Gene Therapy for Cancer Treatment

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How to cite this paper: Ms. Chetana D. Patil | Ms. Siddhi Chavan | Mr. Ritesh Kadam "Gene Therapy for Cancer Treatment" Published in International Journal of Trend in Scientific Research and Development (IJTSRD), ISSN: 2456-6470, Volume-3 | Issue-5, August 2019, pp.2488-2491, https://doi.org/10.31142/ijtsrd26537

ABSTRACT

Gene therapy is a new tool used in combating different diseases. The majority of gene therapy clinical trials are focused on cancer and so it was no coincidence that the first commercial treatment in 2003 was for neoplasia. Currently there are a wide variety of gene therapy proposals involving a large number of anti tumour molecular mechanisms that will conceivably pave the way for highly effective a treatment options. Despite the significant advances that how been made in gene therapy in the fight against cancer, its efficacy, safety and commercial availability are still limited.

INTRODUCTION

Cancer is a disease characterized by an accelerated and uncontrolled growth of cells that have capacity to spread throughout the body and effect vital organ function. When detected at a late stage, cancer is generally fatal therefore intensifying the search of new medication to help patience. Gene therapy appears to be an adequate antineoplastic strategy that currently plays an important role in research projects and has a promising future in clinical oncolgical practice.

What is gene therapy?

One of the most amazing genetic applications in medicines is gene therapy. Also known as somatic gene therapy, this procedure involves inserting portion of the genes in diseases patients so that they can be cured and live healthier lives.

- An abnormal gene could be swapped for a normal gene through homologous recombination.
- The abnormal gene could be repaired through selective reverse mutation, which returns the gene to its normal function.
- The regulation (the degree to which a gene is turned on or off) of a particular gene could be alter.

How does gene therapy works?

In most gene therapy studies, a "normal" gene is inserted into the genome to replace an "abnormal", disease causing gene. A carrier molecule called a vector must be used to deliver the therapeutic gene to the patients target cells. The most common vector is a virus. Scientists have try to take advantage of capability and manipulate the virus genome to remove disease causing genes and insert therapeutic genes.

Methods of inserting genetic material into human chromosomes

Two methods exist for inserting genetic material into human chromosomes.

- The first method called, involves surgically removing cells from the affected tissue area, injecting or splicing the DNA (the DNA that will correct the disease) into the cells and letting them divide in culture. The new tissues are placed back into the affected area of the patient.

Genes, which are carried on chromosomes, are the basic physical functional units of heredity. Genes are Specific sequences of bases that encode instructions on how to make proteins. It's the proteins that perform most life functions an even makeup the majority of cellular structures. When genes are altered so that the encoded proteins are unable to carry out their normal functions, genetic disorders can results. Gene therapy is a technique for correcting defective genes responsible for disease development. Researchers may use one of several approaches for correcting faulty genes:

- A normal gene may be inserted into a non-specific location within the genome to replace a non-functional gene. This approach is most common.

Who is a gene and how is it function?

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The second method called the in vivo technique requires no surgery. In this process the therapeutic DNA is injected directly into body cells, usually via one of two types of viruses (retro virus).

What is cancer?
Cancer is a cellular tumour that, unlike benign tumour cells, can metastasize and invade like surrounding and distend tissues. Cancer has been a major cause of death in the USA for the past few decades. Approximately 20% of all deaths in America are due to cancer. There are at least fifty different types of malignant tumours being identified. More than 50% of the newly diagnosed cancers occur in five major organs: lungs, colon/rectum, breast, prostate and uterus.

Properties of cancer cells
Cancer cells are characterized by three important properties:
- Diminished or unrestricted control of growth
- Capability of invasion of local tissues
- Capable of spreading to distant parts of body by metastasis

Etiology of cancer (carcinogenesis)
A. Predisposing Factors:
1. Age: cancer can develop in any age, though it is most common in those over 55 years of age. Certain cancers are particularly common in children below 15 years of age, viz.
   - Retinoblastomas
   - Neuroblastomas

- Wilm's tumours
- Certain tumours of haemopoietic tissues as lymphomas and leukaemias.
- Sarcomas of bones and skeletal muscles.

2. Heredity: heredity plays and important role in carcinogenesis

3. Environmental factors: 80% of human cancers are caused by environmental factor
- Lifestyle: Cigarette smoking, tobacco chewing
- Dietary: Groundnuts and other foodstuffs infected with fungus like Aspergillus produce aflatoxin B1, which is Carcinogenic.
- Occupational: Asbestos, Benzene, naphthylamines, beryllium.
- Iatrogenic: Certain therapeutic drugs may be carcinogenic.

4. Acquired precancerous disorders: Certain clinical conditions are associated with increased risk of developing cancers – Leukoplasia, Cirrhosis of liver, ulcerative colitis.

B. Radiant Energy:
Damage to DNA brought about by radiations (x-rays, γ-rays or UV rays) may be as follows:
- Single or double strand breaks
- Elimination of purine/pyrimidine bases
- Cross-linking of strands
- Formation of pyrimidine dimers

Oncogenes:
"The genes capable of causing cancer are called oncogenes".

Proto-oncogenes:
- Proto-oncogenes produce specific proteins having specific role in the cell.
- They are located on specific chromosomes.
- Proto-oncogenes may become oncogenic by retro viral transduction or by influences that alter their behaviour in situ thereby converting them into cellular oncogenes.

Activation of proto-oncogenes to oncogenes
Mechanisms by which proto-oncogenes are transformed into oncogenes is brought about by two broad categories of changes:
1. Changes in the structure of the gene resulting in the synthesis of an abnormal gene product (oncoprotein)
2. Changes in regulation of gene expression, resulting in enhanced or inappropriate production of the structurally normal growth promoting protein

Growth inhibiting cancer suppressor genes or anti-oncogenes:
- These are genes which usually protect the individual from getting the cancer. When the gene is deleted or mutated, cancer develops.
- In fact, the products of these genes apply complete halt or breaks and thereby regulate proliferation of cells.
- Once these suppressor genes are lost, the cells growth control also goes off and thereby development of tumour.
Tumour markers:
- Tumour markers are "biochemical indicators" of the presence of a tumour.
- They include cell surface antigens, cytoplasmic proteins, enzymes and hormones.
- Tumour markers are also of value in determining the response to therapy and in indicating release during the follow-up period.
- Frequently used tumour markers: carcinoembryonic antigen (CEA), alpha – fetoprotein (AFP)

Gene therapy strategies for cancer:
Cancer is a leading cause of death throughout the world, despite the intensive treatment strategies. Gene therapy is the latest and a new approach for cancer treatment.

Suicide Gene Therapy
The gene encoding the enzyme thymidine kinase is often referred to as suicide gene. thymidine kinase phosphorylates nucleosides to form nucleotides which are used for the synthesis of DNA during cell division. The drug ganciclovir (GCV) bears a close structural resemblance to certain nucleoside. TK phosphorylates ganciclovir to form triphosphate – GCV, a false and unsuitable nucleotide for DNA synthesis.

Ganciclovir is frequently referred to as a prodrug and this type approach is called prodrug activation gene therapy.

Tumor Necrosis Factor Gene Therapy
TUMOR NECROSIS FACTOR (TNF) is a protein produced by human macrophages. TNF provides defense against cancer cells. This is brought out by enhancing the cancer fighting ability of Tumor – infiltrating lymphocytes (TILs) a special type of Immune cells. The TILs were transformed with a TNF gene (Along with a neomycin resistant gene) and used for the treatment of malignant melanoma. TNF as such is highly toxic, and fortunately no toxic side effects were detected in the melanoma patients injected with genetically altered TILs with TNF gene.

Gene Replacement Therapy
A gene named p53 codes for a protein with a molecular weight of 53 kilo Daltons (hence p53). p53 is considered to be a tumor-suppressor gene, since the protein it encodes binds with DNA and inhibits replication. The tumor cells of several tissues (breast, brain, lung, skin, bladder, colon, bone) were found to have altered genes of p53 (mutated p53), synthesizing different proteins from the original.

These altered proteins cannot inhibit DNA replication. It is believed that the damaged p53 gene may be a causative factor in tumor development. Some workers have tried to replace the damaged p53 gene by a normal gene by employing adenovirus vector systems. There are some encouraging results in the patients with liver cancer.

CONCLUSION
Gene therapy against cancer is a reality with a promising future. The hope for a miracle cure for cancer can be felt in the ideas that sustain gene therapy but not yet in its reality.Vectors are useful in specific cancers and patients and although they do not yet provide a cure they do improve patients quality of life and will continue to do so more and more. This type of therapy seems to be an adequate path to follow to successfully fight malignant tumours.
ACKNOWLEDGMENT
Authors are thankful to all who helped us for this study directly or indirectly.

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