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Review Article

GENE TECHNOLOGY: A NEW WAY TO TREAT CANCER

Prajapati P M.[1]*, Solanki A S.[1], Sen D J.[2]
[1]I K Patel College of Pharmaceutical Education and Research, "Samarth Campus", Opp. Sabar Dairy, Hajipur, Himatnagar - 383120, Gujarat, & Research Scholar of JJTUniversity, Rajasthan, India
[2] Shri Sarvajanik Pharmacy College, Gujarat Technological University, Arvind Baug, Mehsana-384001, Gujarat, India

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*E-mail: swami.parimal@gmail.com

ABSTRACT:
Gene therapy is the process of introducing genetic material RNA or DNA into a person's cells to fight disease. Gene therapy treats disease by either replacing damaged or missing genes with normal ones, or by providing new genes. The concept of gene therapy was born more than thirty years ago; however, new technology is opening the door to dramatically new possibilities in the treatment of cancers of all kinds. The long-term goal of cancer gene therapy is to develop treatments that attack only cancer cells, thereby eliminating adverse effects on the body and improving the possibility to cure disease. Gene therapy may someday soon make cancer a manageable disease with nominal side effects to the patients. Furthermore, since gene therapy has potential for other diseases such as cystic fibrosis, hemophilia, sickle-cell anemia, muscular dystrophy and Parkinson's, the value of research and discovery has broad applications.
KEYWORD: ATM, BRCA1, BRCA2, CHEK2

INTRODUCTION

WHAT ARE GENES?

Genes are the biological units of heredity. Genes determine obvious traits, such as hair and eye color, as well as more subtle characteristics, such as the ability of the blood to carry oxygen. Complex characteristics, such as physical strength, may be shaped by the interaction of a number of different genes along with environmental in Genes are working subunits of DNA. DNA is a vast chemical information database that carries the complete set of instructions for making all the proteins a cell will ever need. Each gene contains a particular set of instructions, usually coding for a particular protein. DNA exists as two long, paired strands spiraled into the famous double helix. Each strand is made up of millions of chemical building blocks called bases. While there are only four different chemical bases in DNA (adenine, thymine, cytosine, and guanine), the order in which the bases occur determines the information available, much as specific letters of the alphabet combine to form words and sentences. DNA resides in the core, or nucleus, of each of the body's trillions of cells. Every human cell (with the exception of mature red blood cells, which have no nucleus) contains the same DNA. Each cell has 46 molecules of double-stranded DNA. Each molecule is made up of 50 to 250 million bases housed in a chromosome. The DNA in each chromosome constitutes many genes (as well as vast stretches of noncoding DNA, the function of which is unknown). A gene is any given segment along the DNA that encodes instructions that allow a cell to produce a specific product - typically, a protein such as an enzyme - that initiates one specific action. There are between 50,000 and 100,000 genes, and every gene is made up of thousands, even hundreds of thousands, of chemical bases. The genes lie in long strands of DNA (deoxyribonucleic acid) called chromosomes. Humans have 23 pairs of chromosomes - or a total of 46. A donkey has 31 pairs of chromosomes, a hedgehog has 44, and a fruit fly has just 4. A gene consists of a long combination of four different nucleotide bases (chemicals). There are many possible combinations. The four nucleotides are: A(adenine),C(cytosine),G(guanine),T(thymine).

Different combinations of the letters ACGT give people different characteristics. For example, a person with the following combination - AAACCGGTTTTT - may have green eyes, while somebody whose combination is - AAACCGGTTTAA - may have blue eyes. If fact, the last two letters - TT - and - AA - mean the color, and the first ten letters - AAACCGGTTT - mean the eye. (this gene formula is a simplification; in reality they would be much longer).[1-2]

WHAT IS GENE THERAPY?

Gene therapy is an experimental technique that uses genes to treat or prevent disease. In the future, this technique may allow doctors to treat a disorder by inserting a gene into a patient's cells instead of using drugs or surgery. Researchers are testing several approaches to gene therapy, including:

- Replacing a mutated gene that causes disease with a healthy copy of the gene.
- Inactivating, or "knocking out," a mutated gene that is functioning improperly.
- Introducing a new gene into the body to help fight a disease.

Although gene therapy is a promising treatment option for a number of diseases (including inherited disorders, some types of cancer, and certain viral infections), the technique remains risky and is still under study to make sure that it will be safe and effective. Gene therapy is currently only being tested for the treatment of diseases that have no other cures. Gene therapy is an experimental treatment that involves introducing genetic material (DNA or RNA) into a person's cells to fight disease.[3-4]

TYPES OF GENE THERAPY :

There are two forms of gene therapy – Somatic gene therapy and Germ line gene therapy.

- ✓ Somatic gene therapy involves the manipulation of gene expression in cells that will be corrective to the patient but not inherited to the next generation. Somatic cell gene therapy is at an early stage of development.
- ✓ Germ line gene therapy involves the genetic modification of germ cells (sperms and eggs) in order to prevent a genetic defect from being transmitted to future generations.[5]

GENE MAINLY DECIDES….

- ✓ Whether you are tall or not
- ✓ The color of your hair
- ✓ The color of your skin
- ✓ Whether you are more likely to develop certain diseases
- ✓ Whether you are good at sports
- ✓ How you respond to environmental triggers
- ✓ What you look like inside and out[6]

WHAT IS CANCER?

Cancer starts with one cell that has lost control over its growth. Normal cells divide in a highly controlled manner to form new cells. Cancer cells also divide and form new cells, but at a more rapid rate. Furthermore cancer cells do not know when to stop dividing. They keep on dividing and multiplying until they have displaced or damaged the affected body tissue or organ. Yet these cells still continue their excessive growth and, because cancer cells do not grow within an enclosing capsule, some break away and are carried to the next organ by the lymph or the bloodstream, and there they multiply further. This is called metastasis.[7]

BRCA1 AND BRCA2 GENES:

Most inherited cases of breast cancer are associated with two abnormal genes: BRCA1 (BReast CAncer gene one) and BRCA2 (BReast CAncer gene two). Everyone has BRCA1 and BRCA2 genes. The function of the BRCA genes is to repair cell damage and keep breast cells growing normally. But when these genes contain abnormalities or mutations that are passed from generation to generation, the genes don't function normally and breast cancer risk increases. Abnormal BRCA1 and BRCA2 genes may account for up to 10% of all breast cancers, or 1 out of every 10 cases. Having an abnormal BRCA1 or BRCA2 gene doesn't mean you will be diagnosed with breast cancer. Researchers are learning that other mutations in pieces of chromosomes called SNPs (single nucleotide polymorphisms) may be linked to higher breast cancer risk in women with an abnormal BRCA1 gene as well as women who didn't inherit an abnormal breast cancer gene. Women who are diagnosed with breast cancer and have an abnormal BRCA1 or BRCA2 gene often have a family history of breast cancer, ovarian cancer, and other cancers. Still, most people who develop breast cancer did not inherit an abnormal breast cancer gene and have no family history of the disease. If one family member has an abnormal breast cancer gene, it does not mean that all family members will have it. The average woman in the United States has about a 1 in 8, or a 12-13%, risk of developing breast cancer in her lifetime. Women who have an abnormal BRCA1 or BRCA2 gene (or both) can have up to an 80% risk of being diagnosed with breast cancer during their lifetimes. Breast cancers associated with an abnormal BRCA1 or BRCA2 gene tend to develop in younger women and occur more often in both breasts than cancers in women without these abnormal genes. Women with an abnormal BRCA1 or BRCA2 gene also have an increased risk of developing ovarian, colon, pancreatic, and thyroid cancers, as well as melanoma. Men who have an abnormal BRCA2 gene have a higher risk for breast cancer than men who don't -- about 8% by the time they're 80 years old. This is about 80 times greater than average. Men with an abnormal BRCA1 gene have a slightly higher risk of prostate cancer. Men with an abnormal BRCA2 gene are 7 times more likely than men without the abnormal gene to develop prostate cancer. Other cancer risks, such as cancer of the skin or digestive tract, also may be slightly higher in men with abnormal BRCA1 or BRCA2 genes.[8-10]

OTHER GENES

Changes in other genes are also associated with breast cancer. These abnormal genes are much less common and don't seem to increase risk as much as abnormal BRCA1 and BRCA2 genes, which are considered rare. Still, because these genetic mutations are rarer, they haven't been studied as much as the BRCA genes.

- ATM: The official name of this gene is "ataxia telangiectasia mutated." The ATM gene helps repair damaged DNA. DNA carries genetic information in cells. Inheriting two abnormal copies of this gene causes the disease ataxia-telangiectasia, a rare disease that affects brain development. Inheriting one abnormal ATM gene has been linked to an increased rate of breast cancer in some families because the abnormal gene stops the cells from repairing damaged DNA.
- p53 : **p53** also known as **protein 53.** The p53 gene provides instructions to the body for making a protein that stops tumor growth. Inheriting an abnormal p53 gene causes Li-Fraumeni syndrome, a disorder that causes people to develop soft tissue cancers at a young age. People with this rare syndrome have a higher-than-average-risk of breast cancer and several other cancers, including leukemia, brain tumors, and sarcomas (cancer of the bones or connective tissue).
- CHEK2: The official name of this gene is "checkpoint kinase 2."The CHEK2 gene also provides instructions for making a protein that stops tumor growth. Li-Fraumeni syndrome also can be caused by an inherited abnormal CHEK2 gene. Even when an abnormal CHEK2 gene doesn't cause Li-Fraumeni syndrome, it can double breast cancer risk.
- PTEN: Phosphatase and tensin homolog (PTEN) is a protein that, in humans, is encoded by the *PTEN* gene. The PTEN gene helps regulate cell growth. An abnormal PTEN gene causes Cowden syndrome, a rare disorder in which people have a higher risk of both benign (not cancer) and cancerous breast tumors, as well as growths in the digestive tract, thyroid, uterus, and ovaries.
- CDH1: The official name of this gene is "cadherin 1, type 1, E-cadherin (epithelial)." The CDH1 gene makes a protein that helps cells bind together to form tissue. An abnormal CDH1 gene causes a rare type of stomach cancer at an early age. Women with an abnormal CDH1 gene also have an increased risk of invasive lobular breast cancer.[11]

FACTORS AFFECT ON GENE THERAPY TO MAKE EFFECTIVE TREATMENT:

- **Short-lived nature of gene therapy** - Before gene therapy can become a permanent cure for any condition, the therapeutic DNA introduced into target cells must remain functional and the cells containing the therapeutic DNA must be long-lived and stable. Problems with integrating therapeutic DNA into the genome and the rapidly dividing nature of many cells prevent gene therapy from achieving any long-term benefits. Patients will have to undergo multiple rounds of gene therapy.
- **Immune response** - Anytime a foreign object is introduced into human tissues, the immune system is designed to attack the invader. The risk of stimulating the immune system in a way that reduces gene therapy effectiveness is always a potential risk. Furthermore, the immune system's enhanced response to invaders it has

seen before makes it difficult for gene therapy to be repeated in patients.

- **Problems with viral vectors** - Viruses, while the carrier of choice in most gene therapy studies, present a variety of potential problems to the patient --toxicity, immune and inflammatory responses, and gene control and targeting issues. In addition, there is always the fear that the viral vector, once inside the patient, may recover its ability to cause disease.
- **Multigene disorders** - Conditions or disorders that arise from mutations in a single gene are the best candidates for gene therapy. Unfortunately, some the most commonly occurring disorders, such as heart disease, high blood pressure, Alzheimer's disease, arthritis, and diabetes, are caused by the combined effects of variations in many genes. Multigene or multifactorial disorders such as these would be especially difficult to treat effectively using gene therapy.[12]

HOW ARE GENES TRANSFERRED INTO CELLS?

A gene cannot be directly inserted into a person's cell. It must be delivered to the cell using a carrier, or "vector." The vectors most commonly used in gene therapy are viruses. Viruses have a unique ability to recognize certain cells and insert genetic material into them. In some gene therapy clinical trials, cells from the patient's blood or bone marrow are removed and grown in the laboratory. The cells are exposed to the virus that is carrying the desired gene. The virus enters the cells and inserts the desired gene into the cells' DNA. The cells grow in the laboratory and are then returned to the patient by injection into a vein. This type of gene therapy is called *ex vivo* because the cells are grown outside the body. The gene is transferred into the patient's cells while the cells are outside the patient's body. In other studies, vectors (often viruses) or liposomes (fatty particles) are used to deliver the desired gene to cells in the patient's body. This form of gene therapy is called *in vivo,* because the gene is transferred to cells inside the patient's body.

VIRUSES ARE USED IN GENE THERAPY:

Many gene therapy clinical trials rely on retroviruses to deliver the desired gene. Other viruses used as vectors include adenoviruses, adeno-associated viruses, lentiviruses, poxviruses, and herpes viruses. These viruses differ in how well they transfer genes to the cells they recognize and are able to infect, and whether they alter the cell's DNA permanently or temporarily. Thus, researchers may use different vectors, depending on the specific characteristics and requirements of the study. Scientists alter the viruses used in gene therapy to make them safe for humans and to increase their ability to deliver specific genes to a patient's cells. Depending on the type of virus and the goals of the research study, scientists may inactivate certain genes in the viruses to prevent them from reproducing or causing disease. Researchers may also alter the virus so that it better recognizes and enters the target cell.

There are six main types of viruses used as vectors in gene therapy (shown in table below):

1. **Retroviruses -** A class of viruses that can create double-stranded DNA copies of their RNA genomes. These copies of its genome can be integrated into the chromosomes of host cells. Human immunodeficiency virus (HIV) is a retrovirus.
2. **Adenoviruses -** A class of viruses with double-stranded DNA genomes that cause respiratory, intestinal, and eye infections in humans. The virus that causes the common cold is an adenovirus.
3. **Adeno-associated viruses -** A class of small, single-stranded DNA viruses that can insert their genetic material at a specific site on chromosome 19.
4. **Herpes simplex viruses -** A class of double-stranded DNA viruses that infect a particular cell type, neurons. Herpes simplex virus type 1 is a common human pathogen that causes cold sores.
5. **Alphaviruses-** a single stranded positive sense RNA, particularly used to develop viral vectors for the Ross-River virus, Sindbis virus, Semliki Forest virus and Venezuelan Equine Encephalitis virus.
6. **Vaccina or pox viruses-** a large, complex, enveloped virus belonging to the poxvirus family. It has a linear, double-stranded DNA genome of approximately 190 kb in length, which encodes for around 250 genes. Can accept as much as 25kb of foreign DNA making it especially useful in expressing a large gene in gene therapy.[13]

MESOTHELIOMA A 'GOOD TARGET' FOR GENE THERAPY:

Malignant mesothelioma is an especially good target for a novel cancer treatment called gene therapy. Mesothelioma is an aggressive cancer of the thin, membranous mesothelial tissue surrounding the lungs, heart or abdomen. Also known as the 'asbestos cancer', because of its link to asbestos exposure, mesothelioma is extremely difficult to treat. One mesothelioma characteristic is the tendency for the cancer to remain relatively localized until late in the course of the disease, making it easier to confine the gene-altering therapy to the tumor cells. Another key aspect of mesothelioma that lends itself to gene therapy. Mesothelioma cells offer 'a large surface area for efficient, rapid and diffuse gene transfer'. Gene therapy is the alteration of genetic material on the cellular level to affect how cancer cells behave. Viruses that have been altered so they do not cause disease are typically used as 'carriers' for the new genetic material. Some gene therapy is aimed at triggering the natural process of cellular death. Other types of gene therapy affect the ability of cells to replicate, which is how cancer spreads. Still other types are aimed at altering genes in a way that makes the cancer cells more susceptible to anti-cancer drugs.[14]

RISKS ARE ASSOCIATED WITH GENE THERAPY TRIALS:

Viruses can usually infect more than one type of cell. Thus, when viral vectors are used to carry genes into the body, they might infect healthy cells as well as cancer cells. Another danger is that the new gene might be inserted in the wrong location in the DNA, possibly causing harmful mutations to the DNA or even cancer. When viruses or liposomes are used to deliver DNA to cells inside the patient's body, there is a slight chance that this DNA could unintentionally be introduced into the patient's reproductive cells. If this happens, it could produce changes that may be passed on if a patient has children after treatment. Other concerns include the possibility that transferred genes could be "overexpressed," producing so much of the missing protein as to be harmful; that the viral vector could cause inflammation or an immune reaction; and that the virus could be transmitted from the patient to other individuals or into the environment. Scientists use animal testing and other precautions to identify and avoid these risks before any clinical trials are conducted in humans.[15]

CONCLUSION:

Gene therapy is the treatment of disease by replacing, altering, or supplementing a gene responsible for the disease. Insertion of normal DNA directly into cells to correct a

genetic defect. Many diseases seen today are the result of a defective gene in the DNA of the patient and can not be cured using the traditional methods such as antibiotics and antiviral medication. The victims are now looking to gene therapy as a potential cure for their problems

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Figure.1 Gene Structure

Figure.2 Gene Therapy

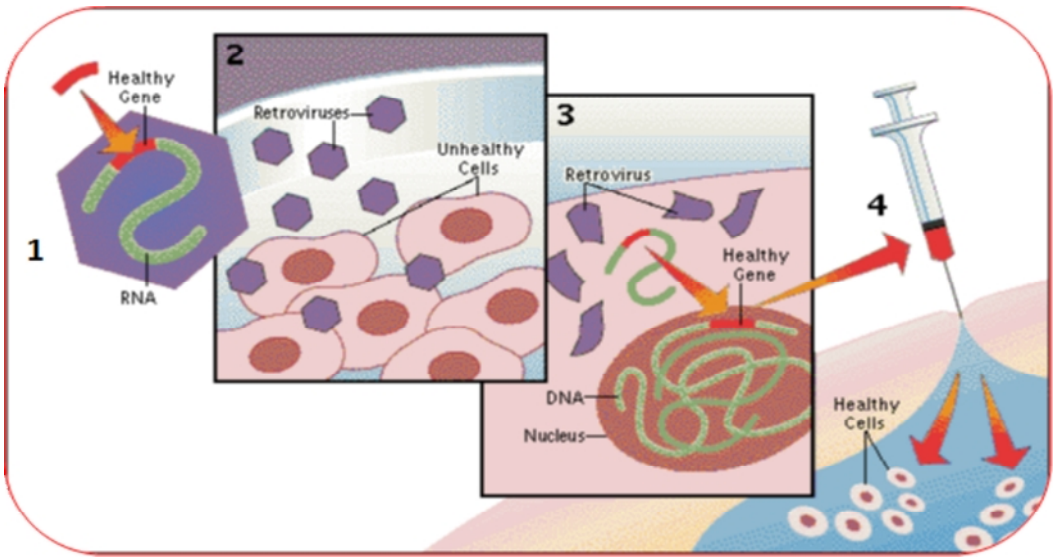

Figure.3 Gene Treatment To Tackle Cancer.