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A Brief Review on Gene Therapy

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ABSTRACT

Gene therapy is modern technique for treatment and control of diseases which cannot be treated by conventional drug compounds. Through this technique disease like haemophilia, Glaucoma can be treated. Gene therapy includes the incorporation of foreign genes into body to treat genetic defects. Somatic cell gene therapy is better than the germ line gene therapy because of less problems in term of ethics and easiest in terms of technology. This review includes brief introduction of Gene therapy including history, types, approaches and recent advancement in the field of Gene therapy.

Keywords: Gene therapy, gene expression.

1.INTRODUCTION

Gene therapy is defined as a transfer of genetic material for treatment of a disease or to improve the clinical status of a patient (1). This technique is widely used to treat those defective genes which takes part in disease development. Gene therapy include the incorporation one or more foreign genes into an organism to treat acquired or hereditary genetic defects. In gene therapy, DNA encoding a therapeutic protein is packaged within a "vector", which brings the DNA inside cells within the body (1).

Gene therapy is a technology that aims to produce a therapeutic effect through modification of gene expression or through altering the biological properties of living cell. In Gene Therapy genetic material is used for treatment or prevention of disease. Material used in Gene therapy is generally DNA or RNA, which are strings of molecules with the information to instruct cells to produce proteins. Gene therapy could treat diseases that cannot be treated with conventional medicine. It is applied by transferring one or more nucleic acids into a patient's cells or by manipulating a defective gene. The main factors of investment in gene therapy for human diseases involve the development of gene therapy vectors, optimization of gene delivery under in vivo and in vitro conditions, and enhancement of clinical experience. Gene therapy, as an advanced technology, goes beyond the alteration of genetic disorders and has spread to a wide range of applications.

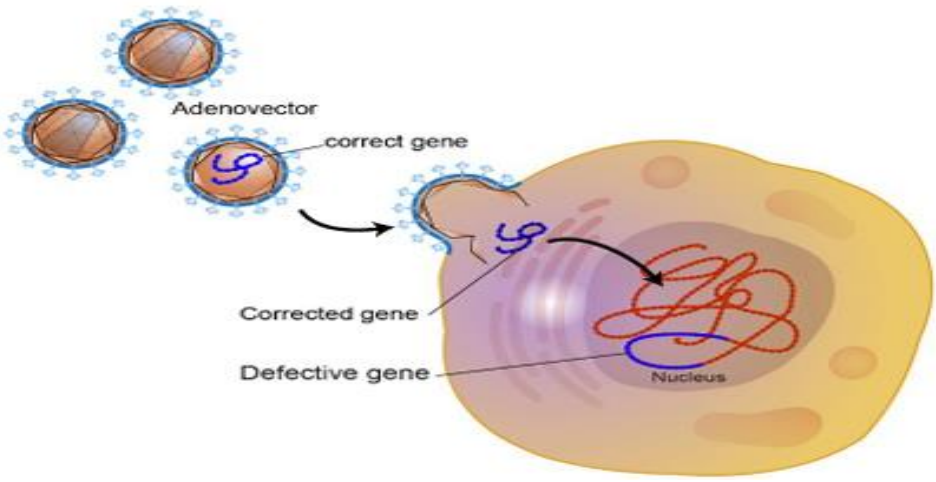


Fig. 1. The Concept of Gene therapy

2. HISTORY

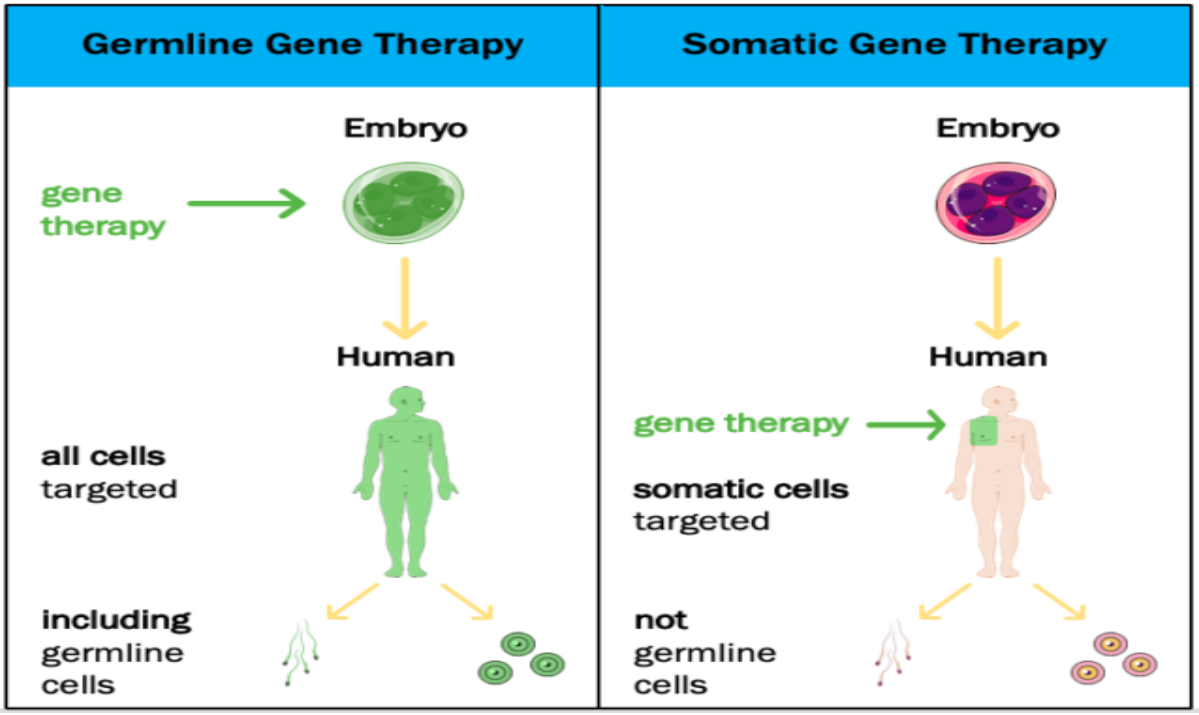
Genetic studies started in the early 1850s when Gregor Mendel performed a series of experiments with green peas and described the inheritance pattern by observing the traces that were inherited as separate units known as genes. The physical nature of genes was known after the revolutionary model of the double strand DNA by James Watson and Crick (1). In the mid-1960s, researchers estimated that DNA groupings can be embedded into patients' cells to treat hereditary diseases. In 1980 Martin Cline initially endeavored to adjust human DNA, anyway the first fruitful result of atomic quality was seen after a long stretch finally in May 1989 (2). In September 1990 by French Anderson the main helpful use and furthermore the initial direct addition of human DNA into atomic genome was accomplished. Four-year-old Ashanthi de Silva turned into the principal quality treatment example of overcoming adversity in the year 1990. She was brought into the world with an extreme joined immunodeficiency (SCID) because of the absence of protein adenosine deaminase (ADA). In absence of ADA, her T cells died off, making her inadequate to battle infections. Infusions of an engineered ADA compound aided, however just immediately. Specialists chose to convey a relatively solid ADA quality into her platelets, by the utilization of an impaired infection that can't spread in the body. The success they accomplished empowered more preliminaries for a similar type of SCID during the 1990s. Presently in her 30s, de Silva is loaded with life even after having an uncommon sickness. From1989 to December 2018, more than 2,900 clinical preliminaries were led, with the more significant part of them in stage 1. Principal quality treatments to enter the market endorsed by the FDA Starting at Spark Therapeutics' Luxturna in 2017(for visual deficiency prompted by RPE65 Mutation) and Novartis' Kymriah (antigen T cell treatment of chimeric receptor) (2). Most of these techniques use Adeno Associated Virus (AAVs) and lentivirus for executing quality inclusions, ex-vivo and in-vivo individually [5].

3. TYPES OF GENE THERAPY

3.1. Germ-line Gene Therapy: It involves insertion of corrective genes into cells of the germ line, eggs, or sperm cells, which will then also pass on any genetic modifications to future generations. However, this method of gene therapy has the potential to prevent inherited diseases, it is highly controversial and less research is currently being done in this field, due to technological and moral issues.

3.2. Somatic Cell Gene Therapy: It involves the insertion of a target gene into targeted cells with the result of curing the patient, but not the potential children of the patient, since these genes are not transmitted to the offspring. In other ways, while some of

the genes of the patient can be changed to treat a disease, the possibility remains that the children of the patient may be affected by the same illness. This is the most preferred technique of gene therapy. (3)



4. GENE THERAPY APPROACHES

There are so many ways to point a disease or genetic variation, so there are different gene and cell therapy approaches that can be considered. There are various Gene Therapy Approaches are- Gene addition, Gene Editing, cell Therapy, RNA Therapy, Cell Silencing.

4.1 Gene addition: In this type of gene therapy that targets a specific gene in the body cells. In this gene addition process has the administration cell to make more of the specific protein needed. Gene Vectors, those are most often viruses, are used to deliver the working gene to the cell's nucleus, where the DNA is stored. This gene will now live in the nucleus which gives a greater chance of being permanent and is only given one time. This technique is used for the treatment of sickle cell disease. (4)

4.2 Gene Editing: corrects pieces of DNA by altering or deleting the information within the affected individual's gene. In Gene editing process Genetic material is sent directly to edit or change the pieces of DNA already exist within a cell to correct the protein being made by that DNA. Gene editing technology provides the accurate correction of gene sequence. (5)

4.3 Cell therapy: Cell therapy is a process in which the transfer of a specific type of cell into a patient to treat or prevent a disease. According to the cell therapy, the cells can come from the affected individual. Some cell therapies are more common, like a hematopoietic stem cell (blood forming cells) transplant. Based on the treatment, prepare the body to accept the biological material is done to decrease the risk of an immune response and help the body successfully accept the cells.

Cell therapy is of two types, stem cell based, and non-stem cell based. (6)

4.4 RNA Therapy: is the use of shorter sequences of genetic material in RNA format to treat or prevent a disease. There are so many types of RNA therapy that can us for the treatment of diseases like Cystic fibrosis, Cancer etc. (7)

4.5 Gene silencing: It is gene therapy approach in which suppression of genes. It is post-transcriptional gene silencing method. (8)

5.VECTORS USED IN GENE DELIVERY

Vectors for gene therapy are classified into two types:

5.1 Viral Vectors

5.2 Non-viral vectors

5.3 Hybrid (Combination of Viral Vectors and Non-Viral Vectors)

5.1 Viral vectors: These are better system of gene delivery as compared to non-viral vectors. Adenoviral vectors, Retrovirus, Adeno associated viruses, Poxviruses and other viruses are the commonly used vectors.

5.1.1 Adenoviruses: Adenoviruses has a double-stranded DNA genome that causes intestinal, ocular and respiratory infections in humans. When these viruses infect a cell, they incorporate their DNA molecules into the host's. Adenovirus genetic material does not replicate into the genetic material of the host cell. Instead, the DNA molecule remains inside the host cell's nucleus, and this foreign DNA is transcribed like any other gene in the cell. (9)

Advantages:

1. Target cell proliferation is not required
2. High efficacy

Disadvantages:

1. Due to neutralizing anti-body formation does not be repeated
2. Integration is unstable.

5.1.2 Retroviruses: This class of viruses that can create double-stranded DNA copies of their RNA genomes which can be integrated into the chromosomes of host cells. Retrovirus is a human immunodeficiency virus (HIV). (10)

Advantages:

1. Have stable integration and lack of immunogenicity.
2. Having 8 kilobases capacity which is sufficient for most of the gene therapy applications.

Disadvantages:

1. Work only on the dividing cells
2. In case of Insertional metagenesis risk of malignancy.

5.1.3 Adeno-Associated Viruses: AAVs comprise a small class of viruses with single-stranded and non-coated DNA from the family of Parvovirus. It can infect both dividing cells and non-dividing cells with constitutive expression. (11) The capacity of these viruses to be present in cells, in both lysogenic and lytic forms, has made them a suitable candidate for gene therapy.

Advantages:

1. These viruses are non-pathogenic for humans.
2. Integrated only into non-dividing cells.

Disadvantages:

1. It may produce genetic damage.
2. Less capacity

5.1.4 Herpes Simplex Viruses: HSV contain double-stranded DNA that infects a specific type of neural cells. Type 1 herpesvirus infection is a common human pathogen that causes cold sore syndrom.14 Herpes Simplex Virus is a human neurotropic virus which is used for gene transfer in the nervous system. (3)

Advantages:

1. It has broad genome.
2. Prolonged expression of transgene.

Disadvantages:

1. Toxic to cells
2. May cause herpes infection.

5.2 Non-viral Vectors:

Non-viral methods are more beneficial than viral ones because of ease of production in a high scale and lower immune responses by the host (host immune system responses). The level of transfection and low expression of the gene were considered as two main disadvantages of this method. (9)

Non-viral methods are of two types:

5.2.1 Physical Methods:

i) Electroporation

In this method high-voltage short pulses used to transfer DNA from cell membranes. Due to electrical shock small pores are formed temporarily on the surface of the membrane, which makes it permeable to nucleic acid. (9)

Advantage:

1. Simple and have low cost.
2. Applicable to different types of cells.

Disadvantage:

1. Have high rates of cell death
2. Invasiveness

ii) Gene Gun

The use of gene gun or particle bombardment is another physical method for DNA transfer. In gene gun method, the DNA is coated with gold particles and then placed inside a device which gives the required force to enter the cell. (9)

Advantages:

1. Simple and safe

Disadvantage:

1. On repeated injection may cause damage in proliferating cells

iii) Magnetofection

In this method nucleic acid is delivered into the cell under the influence of magnetic field. To form a biomolecule/magnetic reagent complex exogenous nucleic acid are mixed with magnetofection reagent after that by the force of magnetic field complex incorporated into the cell.

Advantages:

1. Useful to transfect the difficult to transfect cells
2. Non-invasive

Disadvantages:

1. After removal of magnetic field may cause agglomeration of magnetofection reagents.
2. With naked DNA has lower efficiency

5.2.2 Chemical Methods:

i) Cationic lipids

Cationic lipids are a significant class of compounds appropriate for transporting negatively charged DNA cationic liposomes. Some of commercial cationic lipid-based recombinant reagents are as Lipofectin, Neophectin and Transfectam. The head groups are positively charged, and tail groups are hydrophobic with linker structure that connect both. The positive charge containing head group binds with negative charge containing phosphate group in nucleic acid and form compacted structure known as Lipoplexes. (13)

ii) Solid lipid Nanoparticles: These are the particles made up of lipids which are solid at room and body temperature. The properties of cationic lipid and lipid nanoparticles protect the nucleic acid from nuclease degradation. (14)

5.3 Hybrid Methods

It is method of gene transfer which includes combination of several techniques. For ex. Virosome is combination of inactive virus and liposome.

6. ADVANTAGES OF GENE THERAPY

1. Gene therapy is used to treat and prevent hereditary diseases such as; heart disease, AIDS, cystic fibrosis and cancer. (9)
2. Gene therapy can trat genetic disease by addition and deletion of gene or by replacing a mutated gene with corrected gene.

7. DISADVANTAGES OF GENE THERAPY

1. **Short-lived Nature:** Before gene therapy can become a permanent cure for any condition, the therapeutic DNA introduced into target cells must remain functional and cells containing the therapeutic DNA must be long-lived and stable.
2. **Immune Response:** The gene injected by a virus into human tissues, the immune system has evolved to attack the invader. The risk of stimulating the immune system in a way that decreases the potential of gene therapy. (9)
3. **Multigenic Disorders:** The combined effects of variations in many genes causes disorders, such as heart disease,

high blood pressure, Alzheimer's disease, arthritis and diabetes. (9)

4. **Ethical Considerations:** Deciding what is normal and what abnormal; deciding whether disabilities are diseases and whether they should be treated; deciding whether searching for a treatment demeans the lives of people who have infirmities are some of the ethical issues associated with it. (12)

8. APPLICATIONS OF GENE THERAPY:

8.1 Cancer:

Gene therapy-related research and its clinical application have been mostly used in the field of malignancy. Research related to gene therapy and its clinical presentation have been generally applied in the concept of malignancy. Cancer amounts to nearly two-third of all gene therapy-related research being conducted. The first permitted anticancer drug which was created on this principle of gene therapy was Gendicine. Suicide gene therapy is one more effort to cure cancer by delivering of gene coding for enzyme that metabolizes prodrugs into locally active chemotherapeutic drug moiety. (2)

8.2 Eye Diseases:

Eye is a small organ, hence there is possibility of transfecting a great number of ocular cells. Leber's hereditary optic neuropathy, glaucoma, macular degeneration and red- green colour-blindness are clinical ophthalmologic conditions for gene therapy. colour vision in adult red-green colour-blind monkeys. (2)

8.3 Cardiac Diseases:

Cardiac diseases are multigenic in origin hence, difficult to treat. Trials are being conducted in which scientists have developed methods to transport genes for different growth factors like Fibroblast Growth Factors (FGF), Vascular Endothelial Growth Factors (VEGF) to encourage vascular angiogenesis. However, their outcomes did not display remarkable enhancement in stress-induced myocardial perfusion but enhanced regional wall motion indicated a favourable anti-ischemic effect inspiring more research in this field. (2)

8.4 Immunodeficiency:

In early 90s first remarkable development seen in field of gene therapy. During the preliminary set back where two patients had died after being treated for X linked severe combined immunodeficiency (X SCID) using retroviral vectors due to leukaemia, even though there were clinical trials that showed strong therapeutic benefits of gene therapy in management of both X-SCID and SCID caused by the deficiency of adenosine deaminase (ADA). Secondary immunodeficiency states like Human Immunodeficiency Virus (HIV) in addition to primary immunodeficiency infection has likewise grown as a probable contestant for gene therapy. (2)

8.5 Single Gene Disorder:

There are various single gene disorders such as cystic fibrosis, muscular dystrophies, Huntington's disease, junctional epidermolysis bullosa, chronic granulomatous disease, haemophilia, lysosomal storage disease, ornithine transcarbamylase deficiency for their treatment gene therapy play an important role. (2)

8.6 Parkinson's Disease: The incidence is about 1% of population above 65 years of age, it is usually idiopathic in origin. In idiopathic Parkinson, there is degeneration of nigrostrial neuron in basal ganglia resulting in dopamine deficiency. In the research, genes produce some important chemical agent such as glutamic acid carboxylase (GAD) were transferred into the base ganglia cells, which are a set of cerebral areas controlling movement. The transferred glutamic acid carboxylase gene increased the level of a chemical messenger called GABA. The level of GABA in some parts of the basic ganglia is reduced in people with Parkinson's disease. (9)

8.7 Alzheimer's Disease: Alzheimer's disease (AD) is a neurodegenerative disorder, characterized by progressive impairment of memory and cognitive functions. In the Recent developments in the field of gene therapy-based approaches, recombinant AAVs (rAAVs) in particular, have provided new tools for the study of AD and other neurological disorders. (9)

8.8 Diabetic Neuropathy: In a study on a chronic diabetes, researchers found that gene therapy is promising in the treatment of diabetic polyneuropathy. Researchers in Boston found that diabetic neuropathy patients get some relieve by injecting vascular endothelial growth factor (VEGF) gene through intramuscular route. This study showed that this form of gene transfer process could be quite safe. (9)

9. RECENT ADVANCEMENT:

9.1 In Glaucoma:

Gene therapy is used in the treatment of glaucoma. There are three genes are associated with glaucoma have been identified are: myocilin/trabecular meshwork glucocorticoid response (TIGR) (GLC1A), optineurin (GLC1E), and WDR36 (GLC1G). Among these, the most extensively studied glaucoma gene is myocilin (a TM-inducible glucocorticoid response gene). There are several therapeutic strategies exist that modulate aqueous humour production and flow, thereby regulating intraocular pressure (IOP) and protecting retinal ganglion cells (RGCs) from apoptosis. With the emergence of gene therapy as a potentially viable approach to preserving vision, there are some new methods for managing glaucoma may soon become available. The most recent study in ocular gene therapy involves the treatment of retinitis pigmentosa (RP) through the insertion of a functional RPE65 gene using an AAV-based (adeno-associated virus) system to replace the non-functional gene. The RPE65 protein is essential for normal vision, and its replacement through gene therapy has shown promising results in restoring visual function. (15)

9.2 In Haemophilia: Haemophilia is a genetic disease due lack of a gene that encodes for coagulation factor IX or coagulation factor VIII. It is characterized by excessive bleeding. In Advanced Gene therapies consists of a various strategy such as cell therapy, gene therapy and regenerative medicine or tissue engineering. According to international medicine agencies, the products used in the context of advanced therapies are drugs for human use that are based on genes. According to international medicine agencies, the products used in the advanced therapies are drugs for human use that are based on genes, tissues or cells and that offer innovative solutions for the treatment of some diseases. (16)

Declaration by Authors

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