ISSN: 3107-6513

An Overview of Gene Therapy in Chronic Diseases

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Abstract:
Chronic diseases represent a major global health burden due to their long duration, complex pathophysiology, and requirement for lifelong management. Conventional treatment strategies for chronic conditions often focus on symptomatic relief rather than addressing the underlying genetic or molecular causes, leading to limited efficacy. Gene therapy involves the modification, replacement, or regulation of defective genes to restore normal cellular function. Advances in molecular biology and biotechnology have enabled the development of efficient gene delivery systems, including viral vectors such as adeno-associated viruses and lentiviruses, as well as non-viral delivery platforms like nanoparticles and liposomes. These technologies have significantly improved the safety, specificity, and effectiveness of gene transfer.

Keywords: Global health, Pathophysiology, gene therapy, mechanism of action.

Introduction:
Chronic diseases are long-lasting conditions that pose a significant burden on healthcare systems worldwide due to their progressive nature and need for continuous treatment. Conventional therapies often focus on managing symptoms rather than correcting the underlying molecular defects responsible for disease progression. Gene therapy has emerged as an innovative therapeutic strategy that aims to treat chronic diseases at their genetic root by introducing, modifying, or silencing specific genes. Advances in gene delivery systems and gene-editing technologies have expanded the potential applications of gene therapy across a wide range of chronic conditions, offering prospects for long-term disease control or permanent cure.

An overview of chronic diseases:
Chronic diseases are long-term conditions that tend to be persistent, often lasting for months or years, and usually require ongoing management rather than a one-time treatment. They can affect daily life, quality of life, and overall health.

Key Characteristics
- **Long duration:** Often lifelong or long-lasting
- **Slow progression:** Symptoms may worsen gradually
- **Require continuous care:** Medications, lifestyle changes, and regular monitoring
- **Not usually contagious:** Most are non-communicable

Common Types of Chronic Diseases
1. **Cardiovascular diseases**
   - Hypertension (high blood pressure)
   - Heart disease
   - Stroke
2. **Metabolic disorders**
   - Diabetes mellitus (Type 1 and Type 2)
   - Obesity
3. **Respiratory diseases**
   - Asthma
   - Chronic Obstructive Pulmonary Disease (COPD)
4. **Musculoskeletal disorders**
   - Arthritis
   - Osteoporosis
5. **Neurological disorders**
   - Epilepsy
   - Parkinson’s disease
   - Alzheimer’s disease
6. **Autoimmune diseases**
   - Rheumatoid arthritis
   - Lupus
   - Multiple sclerosis

ISSN: 3107-6513

7. **Chronic kidney and liver diseases**

Causes and Risk Factors

- Genetic predisposition
- Unhealthy lifestyle (poor diet, physical inactivity, smoking, alcohol use)
- Environmental factors
- Aging
- Infections or untreated acute illnesses

Emergence of Gene Therapy:

Gene therapy is an advanced medical approach that aims to treat or prevent diseases by modifying or correcting defective genes responsible for disease development. Its emergence marks a major milestone in modern medicine, offering potential cures rather than symptomatic treatment.

First Clinical Applications

- The first successful human gene therapy was performed in 1990 on a child with Adenosine Deaminase (ADA) deficiency, a form of severe combined immunodeficiency (SCID).
- This success proved that gene transfer could be safe and therapeutically effective.

Technological Advances

- Development of viral vectors (adenovirus, retrovirus, lentivirus, adeno-associated virus) enabled efficient gene delivery.
- Non-viral methods such as liposomes and nanoparticles improved safety.
- Advances in genome sequencing enhanced identification of disease-causing genes.

Current Status and Future Prospects

- Gene therapy is now a rapidly expanding field with several FDA- and EMA-approved therapies.
- Ongoing research aims to improve safety, affordability, and accessibility.
- Future potential includes personalized medicine and permanent cures for genetic and chronic diseases.

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 (i.e., a protein or RNA molecule). 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. They also determine things like whether the child will be male or female, the amount of oxygen the blood can carry, and what the IQ will be2.

GENE THERAPY

n experimental procedure aimed at replacing, manipulating, or supplementing nonfunctional or malfunctioning genes with healthy genes. Genes are specific sequences of bases that encode instructions on how to make proteins. Although genes get a lot of attention, it's the proteins that perform most life functions and even make up 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 result.

TARGET CELLS FOR GENE THERAPY

- Peripheral blood lymphocytes
- Haemopoietic stem cells
- fibroblasts
- Keratinocytes
- Skeletal muscle myoblasts
- Airwayepithelialcells
- Vascular endothelial cells

TWO TYPES OF GENE THERAPY

1) Somatic gene therapy, involves introducing a "good" gene into targeted cells with the end result of treating the patient - but not the patient's future children because these genes do not get passed along to offspring. In other words, even though some of the patient's genes may be altered to treat a disease, the likelihood remains that the same disease will affect the patient's children. This is the form of gene therapy that is being done at most genetics laboratories throughout the world

Principle of gene therapy; homologous An abnormal gene could be swapped for a normal gene through recombination.

The abnormal gene could be repaired through selective re verse 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 altered

Approaches of gene therapy

1.Gene modification

- Replacement therapy
- Corrective Gene therapy

2.Gene transfer

- Physical
- Chemical
- Biological

3.Gene transfer in specific cell line

ISSN: 3107-6513

- Somatic gene therapy
- Germ line gene therapy

4.Vectors in gene therapy : Some of the different types of viruses used as gene therapy vectors:

- **Retroviruses- A** class of viruses that can create double-stranded DNA copies of their RNA genomes. Human immunodeficiency virus (HIV) is a retrovirus. eg:-can insert the genetic material of the virus into any arbitrary position in the genome of the host; it randomly inserts the genetic material into a chromosome occur.
- **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.

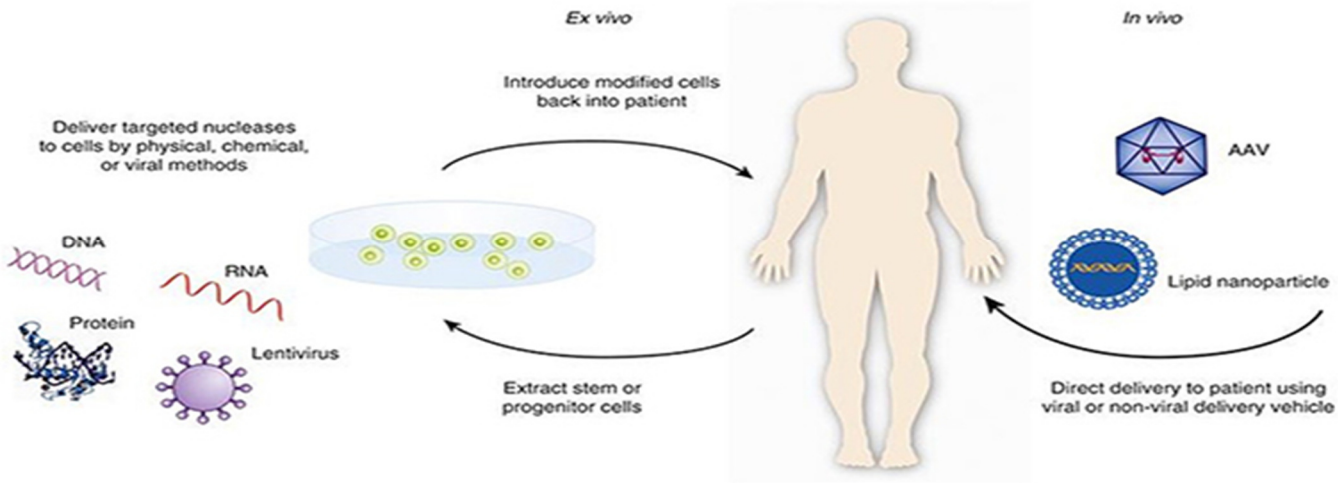

Fig:1 Vectors in gene therapy

Non-viral methods

- Non-viral methods present certain advantages over viral meth ods,
- with simple large scale production and low host immunogenicity being just two. Previously, low levels of transfection and expression of the gene held non-viral methods at a disadvantage; however, recent advances in vector technology have yielded molecules and techniques with transfection efficiencies similar to those of viruses.

Injection of Naked DNA This is the simplest method of non-viral transfection. Clinical trials carried out of intramuscular injection of a naked DNA plasmid have occurred with some success; however, the expression has been very low in comparison of method of transfection.

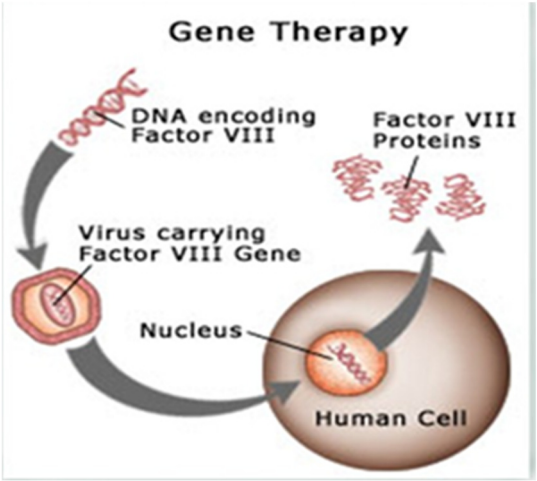

Fig 2: Gene Therapy encoding

Mechanism of Action

Gene Replacement in Chronic Diseases

Gene replacement therapy is a form of gene therapy in which a defective or missing gene is replaced with a functional copy to restore normal cellular function. This approach is especially valuable in chronic diseases caused by inherited or acquired genetic defects.

ISSN: 3107-6513

Concept of Gene Replacement

- Many chronic diseases arise due to mutations in a single gene.
- Gene replacement introduces a normal (wild-type) gene into patient cells.
- The new gene produces the correct protein, reducing or eliminating disease symptoms.
- The faulty gene is usually not removed; instead, a healthy gene is added.

Gene Replacement in Selected Chronic Diseases

1. Severe Combined Immunodeficiency (SCID)
   - Replacement of the ADA gene restores immune function.
   - One of the earliest successes of gene therapy.
2. Hemophilia A and B
   - Functional clotting factor genes (Factor VIII or IX) are introduced.
   - Reduces bleeding episodes and dependency on factor injections.
3. Cystic Fibrosis
   - Replacement of the CFTR gene improves chloride ion transport.
   - Research ongoing to improve gene delivery to lung cells.
4. Muscular Dystrophy
   - Introduction of dystrophin or micro-dystrophin genes.
   - Helps slow disease progression.
5. Inherited Retinal Diseases
   - RPE65 gene replacement restores vision in certain forms of blindness.
   - One of the first approved gene therapies.

Gene Silencing: RNA Interference (RNAi)

Gene silencing is a biological process in which the expression of a specific gene is reduced or completely turned off. One of the most important mechanisms of gene silencing is RNA interference (RNAi), a naturally occurring, sequence-specific regulatory pathway.

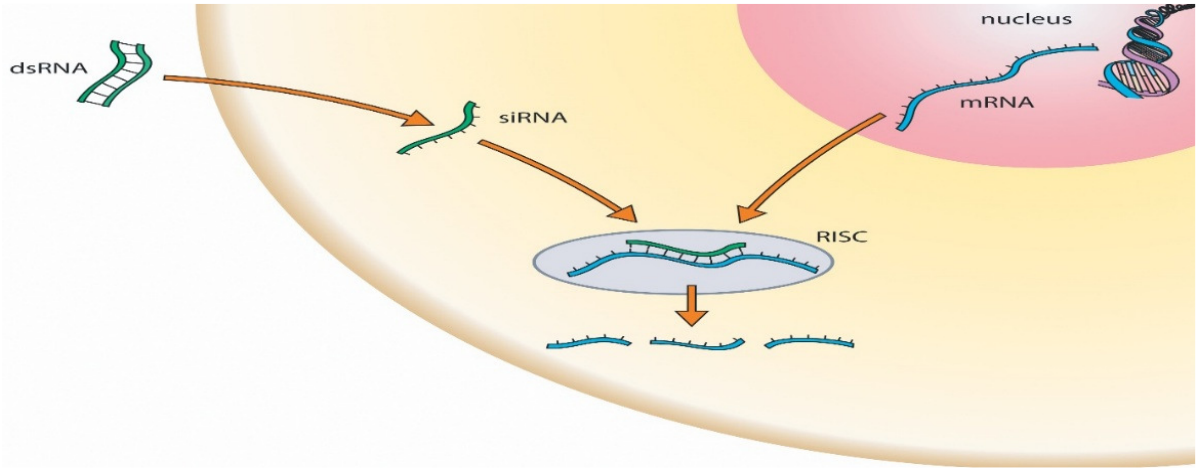

Fig:3 Gene Silencing

What is RNA Interference?

RNA interference (RNAi) is a post-transcriptional gene silencing mechanism where double-stranded RNA (dsRNA) leads to the degradation or inhibition of target messenger RNA (mRNA), preventing protein synthesis.

Types of RNA Involved

1. Small interfering RNA (siRNA)
   - Synthetic or derived from long dsRNA
   - Perfectly complementary to target mRNA
   - Causes mRNA cleavage and degradation
2. MicroRNA (miRNA)
   - Endogenous, naturally produced
   - Partially complementary to target mRNA
   - Inhibits translation or destabilizes mRNA

Mechanism of RNA Interference

1. Introduction of dsRNA into the cell
2. Dicer enzyme cleaves dsRNA into small RNA fragments (siRNA/miRNA)
3. These fragments are incorporated into the RNA-Induced Silencing Complex (RISC)
4. The guide strand directs RISC to complementary mRNA
5. Target mRNA is cleaved or translationally repressed
6. Result: gene expression is silenced

Gene Editing in Gene Therapy for Chronic Diseases

Gene editing is an advanced form of gene therapy that involves precise modification of DNA

ISSN: 3107-6513

sequences to correct, disable, or replace faulty genes responsible for disease. Unlike traditional gene therapy, which adds a functional gene, gene editing directly alters the patient's genome, offering the possibility of long-term or permanent cures for chronic diseases.

What is Gene Editing?

Gene editing uses engineered molecular tools to:

- Correct mutations
- Knock out harmful genes
- Insert therapeutic genes at specific locations

The most widely used technology is CRISPR–Cas9, along with TALENs and Zinc Finger Nucleases (ZFNs).

Mechanism of Gene Editing (CRISPR–Cas9)

1. A guide RNA (gRNA) identifies the target DNA sequence
2. Cas9 enzyme creates a double-strand break in DNA
3. Cellular repair mechanisms act:
   - Non-homologous end joining (NHEJ): Gene disruption
   - Homology-directed repair (HDR): Precise gene correction
4. Corrected gene restores normal protein function

Application of gene therapy.

- **In case of Parkinson's diseases** Gene therapy has been proven to work for Parkinson's disease, The Independent has reported.A number of other newspapers also express the hope offered by the new procedure, which is intended to boost levels of a brain chemical called GABA, which is lacking in people with Parkinson's. In a small trial of the technique, 45 participants with severe disease had their brains implanted with tubes that led to areas of the brain that deal with movement. Half were injected with a virus carrying a gene that would increase GABA production. The other half were given a harmless saline solution. After six months, those treated with gene therapy showed a 23% improvement in movement, twice that seen among those given sham surgery.
- **In case of Alzheimer's disease** Scientists have successfully switched off a gene thought to cause Alzheimer's by using a new way to deliver drugs directly to the brain," reported the Daily Mirror. The newspaper said that re searchers have used "tiny particles called exosomes, cells, to administer drugs into the brains of mice"

  The laboratory study which are released by behind these headlines was carried out in mice. The findings are significant, demonstrating that exosomes could be used to carry gene therapy to particular genes in the brain. One of these genes is BACE1, which produces a protein associated with Alzheimer's disease.

- **In case of cyctic fibrosis** In therapy**,** treatment targets the cause of cystic fibrosis rather than just treating the symptoms. Although the first gene therapy experiments have involved lung cells, scientists hope that these technologies will be adapted to treat other organs affected by cystic fibrosis.

  Cystic Fibrosis
  Causes of Cystic Fibrosis
  Cystic Fibrosis Gene
  Early Symptoms of Cystic Fibrosis
  Cystic Fibrosis Symptoms
  Cystic Fibrosis Diagnosis
  Cystic Fibrosis Sweat Test
  Prenatal Testing for Cystic Fibrosis
  Cystic Fibrosis Genetic Testing
  Treatment for Cystic Fibrosis
  Living with Cystic Fibrosis
  Cystic Fibrosis and Who It Affects.

- **In case of Diabetic Neuropathy** Gene therapy shows promise in treating diabetic polyneuropathy, a disorder that commonly affects diabetics who've had the disease for many years, a new study finds. Researchers in Boston found that intramuscular injections of vascular endothelial growth factor (VEGF) gene may help patients with diabetic polyneuropathy. The study included 39 patients who received three sets of injections of VEGF gene in one leg and 11 patients who received a placebo loss of sensation and pain in the legs and feet, weakness, and balance problems are among the symptoms associated with diabetic neuropathy. The loss of sensation means that ulcerations on the feet

ISSN: **3107-6513**

may go undetected, which can lead to amputation. "Most patients had fairly severe neuropathy, and the expectation for improvement was therefore not high.

Conclusion

Gene therapy represents a transformative approach in the management of chronic diseases by targeting their underlying genetic and molecular causes rather than merely alleviating symptoms. Advances in gene delivery systems, including viral and non-viral vectors, along with the development of precise gene-editing technologies such as CRISPR–Cas systems, have significantly enhanced the safety, specificity, and therapeutic potential of this strategy. Mechanisms such as gene replacement, gene silencing through RNA interference, and genome editing offer promising solutions for a wide range of chronic conditions, including genetic, neurological, metabolic, and autoimmune disorders.. Overall, gene therapy holds immense promise for achieving long-term disease control and potential cures, marking a significant advancement in personalized and precision medicine for chronic diseases.

References

1. Friedmann, T., & Roblin, R. (1972). Gene therapy for human genetic disease? *Science*, 175(4025), 949–955.
2. Cavazzana-Calvo, M., et al. (2000). Gene therapy of human severe combined immunodeficiency (SCID)-X1 disease. *Science*, 288(5466), 669–672.
3. Naldini, L. (2015). Gene therapy returns to centre stage. *Nature*, 526(7573), 351–360.
4. Ginn, S. L., et al. (2018). Gene therapy clinical trials worldwide to 2017: An update. *Journal of Gene Medicine*, 20(5), e3015.
5. Kay, M. A. (2011). State-of-the-art gene-based therapies: The road ahead. *Nature Reviews Genetics*, 12(5), 316–328.
6. High, K. A., & Roncarolo, M. G. (2019). Gene therapy. *New England Journal of Medicine*, 381, 455–464.
7. Dunbar, C. E., et al. (2018). Gene therapy comes of age. *Science*, 359(6372), eaan4672.
8. Crystal, R. G. (2014). Adenovirus: The first effective in vivo gene delivery vector. *Human Gene Therapy*, 25(1), 3–11.
9. Wang, D., Tai, P. W. L., & Gao, G. (2019). Adeno-associated virus vector as a platform for gene therapy delivery. *Nature Reviews Drug Discovery*, 18, 358–378.
10. Lundstrom, K. (2018). Viral vectors in gene therapy. *Diseases*, 6(2), 42.
11. Fire, A., et al. (1998). Potent and specific genetic interference by double-stranded RNA in Caenorhabditis elegans. *Nature*, 391, 806–811.
12. Hannon, G. J. (2002). RNA interference. *Nature*, 418, 244–251.
13. Setten, R. L., Rossi, J. J., & Han, S. (2019). The current state and future directions of RNAi-based therapeutics. *Nature Reviews Drug Discovery*, 18, 421–446.
14. Doudna, J. A., & Charpentier, E. (2014). The new frontier of genome engineering with CRISPR-Cas9. *Science*, 346(6213), 1258096.
15. Porteus, M. H. (2019). A new class of medicines through DNA editing. *New England Journal of Medicine*, 380, 947–959.
16. Collins, F. S., & Gottlieb, S. (2018). The next phase of human gene-therapy oversight. *New England Journal of Medicine*, 379, 1393–1395.
17. Romano, G., et al. (2019). Gene therapy for cancer: From vectors to strategies. *Journal of Experimental & Clinical Cancer Research*, 38, 55.
18. Mingozzi, F., & High, K. A. (2011). Immune responses to AAV vectors: Overcoming barriers to successful gene therapy. *Blood*, 122(1), 23–36.
19. Bulcha, J. T., et al. (2021). Viral vector platforms within the gene therapy landscape. *Signal Transduction and Targeted Therapy*, 6, 53.
20. Kumar, V., Abbas, A. K., & Aster, J. C. (2021). Robbins and Cotran Pathologic Basis of Disease (10th ed.). Elsevier.