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AN OVERVIEW OF GENE THERAPY USED IN CANCER TREATMENT

[1] Md. Salman Farsi, [2] Ms Tanya Sharma

[1] Student of B Pharma, [2] Assistant Professor
College of Pharmacy, Mewar University, Gangrar, Chittorgarh, Rajasthan 312901.

ABSTRACT :

Cancer has, from the outset, been the most widely studied disease for gene output : - therapy approaches. More than 60 percent of all currently ongoing clinical gene therapy, worldwide are aiming at cancer. This is particularly so because conventional cancer therapies frequently limited by toxicities. Despite advances in traditional therapies such as surgery, radiation, and chemotherapy, cancer treatment continues to be a major medical challenge due to the disease's complexity, heterogeneity, and ability to develop resistance. In recent years, gene therapy has emerged as a promising and innovative approach to cancer treatment, harnessing the body's genetic machinery to treat or even cure various types of cancer. This article provides an overview of gene therapy as it applies to oncology, highlighting its mechanisms, types, applications, challenges, and future prospects.

Keywords: - cancer; glioma; gene therapy; gene transfer; viral vectors; non-viral vectors; safety; clinical trials

1.Introduction:

Cancer is a major cause of mortality worldwide accounting, annually, for more than eight millions death. Gene therapy refers to the technique of altering the genetic material of a person's cells to treat or prevent disease. In the context of cancer, gene therapy aims to modify the genes within cancer cells or immune cells to enhance the body's natural ability to fight cancer. The idea is to either fix faulty genes, introduce new genes that can attack cancer cells, or strengthen the immune system's capacity to recognize and destroy cancerous cells. [1]
Gene therapy for cancer can be classified into mainly two categories:

Somatic Gene Therapy:

This involves modifying the genes of non-reproductive (somatic) cells to treat diseases like cancer. These modifications are confined to the patient and are not passed on to offspring.

Germline Gene Therapy:

This involves altering the genes in reproductive sperms or cells (eggs, embryos) which can be inherited by future generations. However, this approach is still largely experimental and controversial in the context of cancer treatment.
Gene therapy involves the introduction, alteration, or removal of genetic material within a patient's cells to treat disease. Unlike traditional drugs that act on the symptoms of a disease, gene therapies seeks to modify the root cause at the molecular or genetic level.
Correct genetic defects that may lead to cancerous growths.
Introduce therapeutic genes that can directly kill cancer cells.
Reprogram cancer cells to make them more responsive to other treatments.
Given the intricate nature of cancer's genetic basis, gene therapy offers the potential to specifically target and treat cancer cells while sparing healthy tissue, a significant advantage over traditional methods like chemotherapy. [2]

2. Gene Therapy for Cancer: An Overview:

Cancer is characterized by uncontrolled cell growth and genetic instability. Advances in molecular biology have revealed that most cancers are driven by genetic and epigenetic alterations. Gene therapy aims to modify or manipulate gene expression to restore normal cell function or eliminate cancer cells. This review aims to provide an accessible yet detailed overview of gene therapy in cancer, including the key mechanisms, tools, and clinical progress to date. [3]

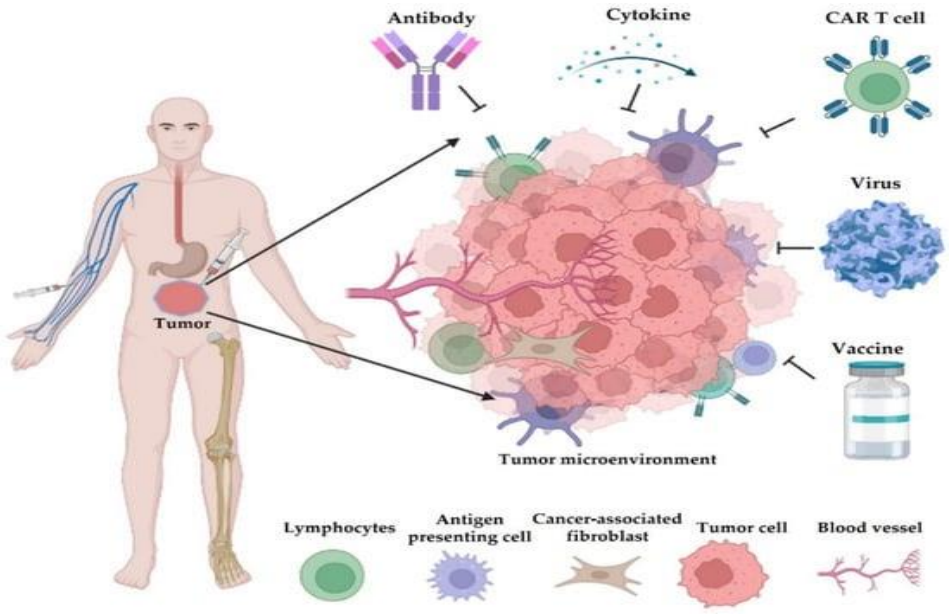

Figure: - *Different types of cancer immunotherapy*

Reference: - www.mdpi.com/1999-4923/14/8/1630

3. Principles of Gene Therapy in cancer:

Gene therapy in cancer involves:

- **Gene replacement**: Restoring tumor suppressor genes.
- **Gene silencing**: Inhibiting oncogenes using RNA interference.
- **Suicide gene therapy**: Converting prodrugs into toxic agents inside cancer cells.
- **Immunogene therapy**: Enhancing the immune system's ability to recognize and destroy tumor cells. [4]

4. Vectors for Gene Delivery:

Efficient gene delivery is essential for successful therapy. Two broad categories exist:

4.1. Physical Vectors:

Physical strategies such as electroporation, ultrasound and quality weapon conveyances have. As the title as of now proposes, with viral vectors an organic (i. e., infection) vector is utilized as a vehicle to provide the hereditary fabric into the cells, while with non-viral quality exchange strategies a engineered carrier (liposomes or nanoparticles) Diverse vectors have diverse properties in relation to their transduction proficiency and their viability to express the presented genes. Depending on the request, distinctive vectors are utilized for distinctive restorative purposes.Viral vectors are as of now the most solid of all quality conveyance modalities for in vivo. [5]

4.2Viral Vectors:

Viral vectors most commonly utilized viral vectors for quality exchange are Adenoviruses, lentiviruse and Retroviruses (counting the human immunodeficiency infection (HIV)), vaccinia infections, adeno related infections (AAV), and baculoviruse. [6]

- **Adenoviruses**: High transduction efficiency, used for non-integrating applications.
- **Retroviruses and Lentiviruses**: Integrate into host genome, suitable for long-term expression.
- **AAV (Adeno-associated Virus)**: Low immunogenicity, limited cargo capacity.

4.3. Non-viral Vectors:

Non-viral Vectors have been appeared to be productive quality exchange devices. All things considered, downsides such as fast clearing of viral vectors from the circulatory system (when infused systemically), their immunogenic and provocative potential, has encouraged the improvement of unused manufactured quality conveyance vectors. In reality, non-viral quality conveyance frameworks are a subject that is as of now being examined broadly as choices for viral conveyance frameworks. The least complex frame of a non-viral framework is exposed plasmid DNA. The advantage of exposed plasmid is that it postures the most reduced shape of harmfulness or other undesirable responses. In expansion, it is simple to define and cheap to deliver. Be that as it may, its impediment is the moo transfection productivity compared to viral-mediated quality exchange. The victory of the non-viral quality treatment

is subordinate on the different additional- and intracellular boundaries that influence the adequacy of all quality conveyance frameworks, counting cellular take-up, endosomal elude, atomic take-up, and quality expression. [7]

- **Liposomes and nanoparticles**: Lower immunogenicity, easier to produce.
- **Electroporation**: Physical method using electric pulses.
- **Direct injection of naked DNA or RNA**

5. Strategies in Gene Therapy for Cancer:

5.1. Gene Replacement Therapy

Involves inserting normal genes to replace mutated ones. An example includes restoring p53 function in cancer cells.

- Targets tumor suppressor genes (e.g., p53, RB1).
- Example: Advexin, a p53 gene therapy vector tested in head and neck cancer. [8]

5.2. Gene Silencing

Targets oncogenes using siRNA or antisense oligonucleotides to reduce gene expression.

- Uses siRNA, shRNA, or antisense oligonucleotides.
- Targets mutated oncogenes like RAS or MYC.

5.3. Suicide Gene Therapy

Cancer cells are genetically modified to convert non-toxic prodrugs into toxic drugs, killing the cells.

- Common system: HSV-tk/Ganciclovir.
- Cancer cells convert prodrug into toxic form, leading to selective killing. [9]

5.4. Immunogene Therapy

Enhancing the immune system to target cancer cells. This includes CAR-T cell therapy and cytokine gene transfer.

- CAR-T cells: T cells genetically engineered to recognize specific tumor antigens.
- Cytokine gene therapy: IL-2, GM-CSF to boost immune activation. [10]

6. Clinical Efficacy of Gene Therapy in Cancer Treatment:

The clinical efficacy of gene therapy in cancer has gained significant attention over the past two decades, as both monotherapy and adjunctive approaches have demonstrated tangible benefits in various cancers. The outcomes of several clinical trials, coupled with regulatory approvals, underscore the potential of gene therapy in improving survival, reducing tumor burden, and enhancing the quality of life for cancer patients. [11]

Distinctive quality treatment approaches, based on distinctive quality exchange vectors have been explored for cancer quality treatment For illustration, acceptance of apoptosis, oncolytic virotherapy, resistant balance, anti-angiogenic quality treatment, adjustment of quality surrenders, hindrance of tumor intrusion, quality treatment to improve chemo- and radiotherapy; myeloprotective quality treatment; antisense and RNA impedances (RNAi) based methodologies, and pro-drug activation/suicide quality treatment. Shockingly, as it were few of these methodologies have made it really to the clinic. One common procedure in cancer quality treatment has been the utilize of a commonly happening change in the p53 protein. [12]

Since of the ponder plan, tumor reaction was not conceivable, but ponder appeared negligible harmfulness. No systemic viral yield: no dispersal was watched and a most extreme endured measurements was not come to in this think about. In expansion, investigation of tumor examples appeared nearby confinement of transgene expression near to the infusion site.

Another consider, and one that is comparative to the infection utilized by Lang et al. is GendicineTM. [13]

The cancellation of this quality anticipates the Infection ties and inactivates wild-type p53, a fundamental cell self-defence component they have against infection contamination.

In arrange to make strides adequacy of oncolytic infections, extra restorative proteins have been included to the infections.

6.1. Quality Restorative Approaches to Fortify the Safe Framework Immunotherapy is a theme that has picked up much consideration as of late. Ordinarily, in immunotherapy the objective is to upgrade either the acknowledgment or introduction of tumor-associated antigens (TAA's). Shockingly, there are common challenges that have been confronted by immunotherapies, counting the normal resistance towards TAAs and the emphatically immunosuppressive tumor microenvironment. Especially, the hereditary designing of T cells has been of seriously investigate. [14]

7. Safety of Gene Therapy in Cancer Treatment:

While gene therapy holds significant therapeutic promise, safety remains a critical concern that influences its clinical development, regulatory approval, and patient acceptance. Gene therapy involves manipulating genetic material, which introduces potential risks including immune responses, insertional mutagenesis, and off-target effects. Over the years, advancements in vector design and delivery systems have improved safety profiles, but challenges

remain. In spite of the appalling case of Jesse Gelsinger who kicked the bucket as a result of quality treatment utilizing adenoviral vectors, the security information collected amid diverse human quality treatment trials have been consistently palatable. It ought to be famous that viral vectors utilized in quality treatment are by and large Pre-existing antibodies against the viral vector may be display, and in this way, the viability- activating an undesired safe response. For case, infusion of adenoviral vectors will Result in a starting non-specific resistant reaction in the have, i. e., discharge of an assortment of cytokines taken after by a particular counter acting agent and cell-mediated resistant reaction coordinated against transduced cells. [14,15]

However, the reaction to adenoviruses depends on the serotype. For illustration, a consider by Thoma et al. 18 appeared that the intense cytokine reaction of macrophages after adenovirus stimulation varies between adenovirus serotypes. [15]

Generally, there is still small long-term security information utilizing viral vectors in people. All things considered, a few meta-analysis as of now exist for adenoviruses illustrating a satisfactory security profile into people. The tolerability to adenoviral vectors has been satisfactory and the side impacts have been mellow and no genuine antagonistic occasions related to quality treatment have been reported. [16,17]

Different implies pointing at upgrading the security of quality treatment have been introduced.

One way is to create focusing on methodologies to move forward quality exchange output:

Vectors and, in this way, to move forward the length and adequacy of quality expression. For the most part, one of the major downsides with quality treatment is their destitute characteristic to theirs target cells and moo yield: - transduction productivity. Progressing specificity and/or transduction viability eventually would result moreover, way better security profile. As a result, the advancement of transduction viability of quality exchange vectors have moreover created along with vector innovations, counting re-engineering of viral yield: e.g. epitope addition, chemical adjustment and atomic advancement. The impediment was that diverse alterations driven to moo vector titers amid output:

lentivirus generation. In expansion, focusing on may moreover possibly yield: compromise the passage of the vectors into the cells. Ischemic myocardium, stroke and harmed spinal, but might too be utilized in cancer quality treatment By and large, these hypoxia-specific administrative frameworks have Connected to ischemic malady models counting. [18]

TABLE

Safety Concern	Cause	Management/Prevention
Immune response & CRS	Viral vectors, CAR-T cells	Immunosuppressants, improved vector design
Insertional mutagenesis	Retroviral integration	SIN vectors, targeted gene editing
Off-target gene editing	CRISPR/Cas9 imprecision	High-fidelity enzymes, thorough screening
Toxicity from gene expression	Cytokine overexpression	Tissue-specific promoters, gene switches
Vector shedding	Systemic delivery of viral vectors	Biosafety protocols, shedding studies
Long-term effects	Persistent gene expression	Post-treatment surveillance

8.Future Directions in Cancer Gene Therapy:

The field of cancer gene therapy is dynamic and rapidly evolving, with numerous promising avenues for future research and clinical application. Building upon the foundational principles and current advancements, several key directions are poised to shape the future of this therapeutic modality: [19,20]

8.1. Advancements in Gene Editing Technologies:

- *Enhanced Precision and Specificity:* While CRISPR-Cas9 has revolutionized gene editing, ongoing research focuses on improving its precision and minimizing off-target effects. This includes developing new Cas enzymes with higher fidelity, refining guide RNA design algorithms, and exploring alternative gene editing systems like base editing and prime editing for more targeted modifications.
- *In Vivo Gene Editing:* Current gene editing therapies primarily rely on ex vivo modification of cells. Future efforts will concentrate on developing safe and efficient methods for in vivo gene editing, directly targeting cancer cells or immune cells within the patient's body. This could involve novel delivery systems like nanoparticles or viral vectors with enhanced tissue specificity.
- *Multiplex Gene Editing:* The ability to edit multiple genes simultaneously holds immense potential for cancer therapy. For instance, engineering T-cells with enhanced anti-tumor activity by knocking out inhibitory receptors while introducing tumor-targeting CARs.
- *Epigenome Editing:* Beyond modifying the DNA sequence, future gene therapies may target epigenetic modifications that play a crucial role in cancer development and progression. Technologies that can precisely alter DNA methylation or histone modifications could offer new therapeutic strategies. [20]

9. Conclusions

Gene therapy represents a promising frontier in the fight against cancer, offering the potential to target the disease at its genetic roots. Over the past few decades, advancements in molecular biology and biotechnology have significantly improved the precision, safety, and efficacy of gene-based interventions. From correcting oncogenic mutations and enhancing tumor suppressor gene activity, to sensitizing tumors to chemotherapy and stimulating immune responses through genetically engineered cells, the applications of gene therapy are vast and rapidly evolving.

Quality treatment is a captivating to treat different illnesses, counting cancer. Right now most quality treatment conventions are constrained to the nearby organization of the quality exchange vectors or to ex vivo quality exchange approaches. Quality treatment is still the moo transduction proficiency and its negligible conveyance of the vector inside the tissue. In any case, it ought to be emphasized that center ought to not as it were be coordinated towards

vector advancement itself, but moreover towards the fabricating of these vectors. The tall taken a toll included in viral vector fabricating. In expansion, the concept of utilizing quality treatment as a single operator treatment has not been as effective as being trusted. Thus, combination treatment with existing ordinary modalities or other modern treatments ought to be extra advantage in cancer quality treatment.

As research progresses and gene therapy becomes increasingly integrated with immunotherapy and conventional treatments, its role in cancer management is expected to expand. With sustained investment and rigorous clinical validation, gene therapy holds the promise of transforming cancer from a terminal diagnosis to a manageable—and potentially curable condition.

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