

By Using Different Methods of Gene Transfer In Gene Therapy - New Advancement As Antineoplastic

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Abstract—Because of its high recurrence rate following radical surgery and traditional therapies, as well as its lack of early symptoms and early diagnosis, cancer is the second leading cause of death globally, after cardiovascular diseases. Thus, there is hope that new methods like gene therapy will greatly increase the survival rate of cancer patients. The goal of this review is to present current information on gene therapy, including oncolytic virotherapy, gene-editing, suicide genes, anti-tumour angiogenesis, and gene silencing. Here, we highlight the potential of gene therapy in cancer treatment, even though there are still certain obstacles to overcome before it can fully cure cancers. We also anticipate ongoing advancements in gene therapy techniques and methodologies. Lastly, this review provides a detailed summary of gene therapy medications that have been approved to treat cancer, including Names, gene therapy methods, vectors, and indications. Gene therapy emerges as a substitute. To an existing disease management system. Consequently, gene products using secure vectors.

Index Terms—Gene therapy, Oncolytic virotherapy, Gene silencing, Suicide gene therapy, Anti-tumor angiogenesis, CRISPR-Cas9, Small interfering RNA (siRNA).

I. INTRODUCTION

GENE- • Since Gregor Mendel's inheritance experiments, the idea of a gene has changed. These days, DNA sequences that code for functional products, primarily proteins, are referred to as genes. Our knowledge of genetic mechanisms, disease pathology, and drug response has been completely

transformed by the Human Genome Project and developments in sequencing technologies Watson JD et al;2017[44].

The basic building blocks of heredity are genes, which contain the instructions required to synthesize proteins and useful RNA molecules. They are in charge of passing down genetic information from one generation to the next and are made of deoxyribonucleic acid (DNA). Specific nucleotide sequences found in each gene dictate the traits and biological processes of living things. Since the classical Mendelian model, the idea of a gene has undergone significant change. A significant turning point in molecular biology was reached in 1953 when Watson and Crick discovered the DNA double helix structure Watson & Crick et al;1953[44].

Since genetic variations among people affect drug metabolism, efficacy, and toxicity, the expanding field of pharmacogenomics has further brought attention to the significance of genes in personalized medicine Relling &Evan et, al;2015[38].

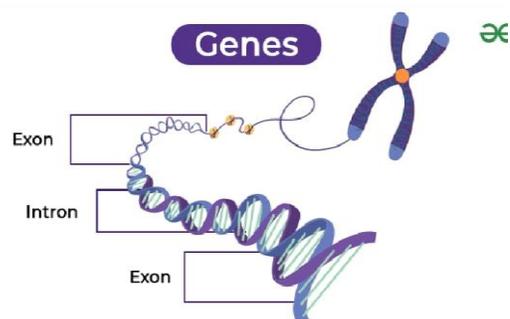


Fig.No.1 Gene

II. GENE THERAPY

Gene therapy is a cutting-edge biomedical strategy that treats or prevents diseases at the molecular level by replacing or modifying damaged genes. Gene therapy seeks to address the underlying genetic cause of disease rather than just treating its symptoms. Recombinant DNA technology was discovered in the 1970s, and the first authorized clinical trial for gene therapy was carried out in 1990 to treat adenosine deaminase deficiency (ADA -SCID) Friedmann & Roblin et al;1972[19], Blaese et al;1995[8].

Depending on whether genetic alterations are heritable or only impact the treated individual, gene therapy approaches can be broadly classified as somatic or germline Gene replacement, RNA interference-based gene silencing, and genome editing tools like CRISPRCas9 are some of the methods used in modern gene therapy Naldini et al;2015[35], Doudna & Charpentier et al;2014[16]. DNA (Deoxyribonucleic Acid) – • Nucleotides with a deoxyribose sugar, phosphate group, and nitrogenous bases—adenine (A), thymine (T), cytosine (C), and guanine (G)—make up DNA, a doublestranded helical molecule. Accurate genetic information replication and transmission are made possible by the complementary base pairings of A–T and C–G Alberts et al;2015[3].

RNA (Ribonucleic Acid) – • In contrast, RNA is usually single-stranded and contains uracil (U) in place of thymine along with ribose sugar. It comes in different forms, each with a unique biological function: ribosomal RNA (rRNA) forms the structural and catalytic core of ribosomes, messenger RNA (mRNA) transports genetic instructions from DNA to ribosomes, and transfer RNA (tRNA) transports amino acids during translation. Furthermore, non-coding

RNAs like small interfering RNA (siRNA) and microRNA (miRNA) regulate the expression and silencing of genes Cech & Steitz et al;2014[11].

HISTORY

Gregor Mendel (1866) laid the groundwork for genetic theory by proposing that traits are inherited through distinct factors, now known as genes, based on his experiments with pea plants. Until it was rediscovered in 1900 by de Varies, Correns, and von Tschermak, Mendel's work went mostly unnoticed, signalling the start of modern genetics Mendel G. et al;1866[31].

In the decades that followed, developments like the Human Genome Project (1990–2003), recombinant DNA technology (1970s), and genetic code deciphering (1960s) transformed our knowledge of genes and gave rise to disciplines like genetic engineering, gene therapy, and genomics. In order to reflect the complexity of genomic regulation in living things, the idea of a gene has evolved beyond simple coding sequences to include regulatory regions, non-coding RNAs and epigenetic elements Watson JD & Crick et al;1953[44].

IMMUNITY

The body's capacity to fend off or eradicate potentially dangerous foreign substances or aberrant cells is known as immunity. It is an essential defence system that keeps the body healthy by shielding it from pathogens like parasites, fungi, viruses, and bacteria. The different organs, cells, and molecules that make up the immune system cooperate to identify and eliminate foreign substances

Abbas & A.K. et al;2023[1]

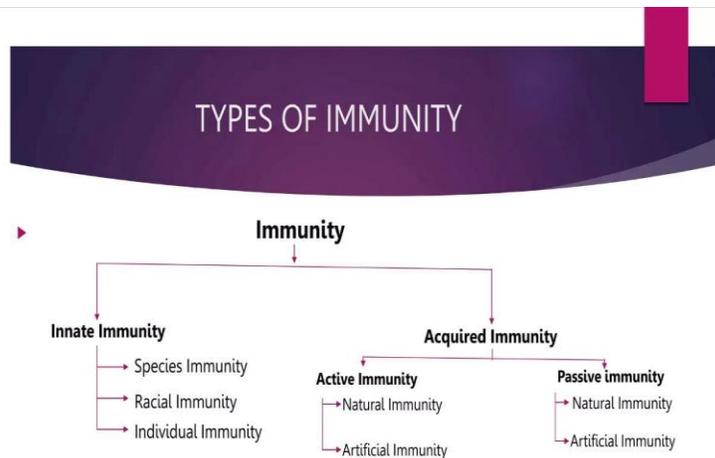


Fig.No. 2-Types of Immunity

Description of the Main Types 1. Natural Immunity, or Innate Immunity: present from birth. offers defence right away. Comprises defences such as phagocytic cells, mucous membranes, skin, and inflammatory reactions.

2.Acquired immunity, or adaptive immunity arises following exposure to a particular pathogen or antigen. Possesses both immunological specificity and memory. Separated into:

- Active immunity is created by the person's immune system (e.g., infection or vaccination).
- Passive immunity: Acquired from an outside source, such as antiserum or maternal antibodies.

III. METHOD OF GENE TRANSFER

Methods of Gene Transfer:

- 1)Physical Mediated
- 2)Chemical Mediated
- 3)Bacterial Mediated
- 4)Viral Mediated

1.Physical mediated gene transfer

- Non-biological, non-chemical techniques that use mechanical, electrical, or physical forces to introduce exogenous genetic material (DNA, RNA, or oligonucleotides) into target cells are referred to as physically mediated gene transfer.

By temporarily rupturing the cell membrane, these techniques let nucleic acids enter the nucleus or cytoplasm.

Physical approaches use direct physical energy to increase permeability, which makes them broadly applicable across species and cell types, in contrast to biological (like *Agrobacterium*-mediated) or chemical (like liposome-mediated) approaches. Brown, T.A et al;2016[10].

2.Chemical mediated gene transfer • Chemically mediated gene transfer is the process of introducing foreign DNA or RNA into host cells by means of chemical agents or carriers. These techniques increase uptake and make it easier for nucleic acids to enter the cytoplasm or nucleus by utilizing chemical interactions between the genetic material and the cell membrane.

Due to their affordability, ease of use, and compatibility with a wide variety of cell types—particularly for in vitro transfection in mammalian cells these methods are frequently employed. Brown, T.A et al;2016[10]. 3. Bacterial mediated gene transfer

- The process of introducing foreign genes into plant, animal, or bacterial cells by means of bacteria or bacterial processes is known as "bacterial-mediated gene transfer."

It can be artificially engineered (as in *Agrobacterium*-mediated transformation) or occur naturally (as in conjugation, transformation, and transduction).

This technique is among the most popular and effective in biotechnology for genetic modification, particularly in plants Griffith,F.et al;1928[23] 4. Viral mediated gene transfer

Using altered viruses as vehicles to introduce foreign genes (transgenes) into host cells is known as viral-mediated gene transfer, or viral vector-mediated transduction

Scientists use viruses' innate ability to infect cells and transfer their genetic material into the host genome to effectively deliver experimental or therapeutic genes.

This technique creates a viral vector that can effectively introduce genes into target cells by removing or deactivating the virus's harmful genes and replacing them with the desired gene Miller,A.D. et al;1990[32]

IV. ADVANCEMENT

1. Oncolytic virotherapy: OV, or oncolytic virotherapy, is the most efficacious strategy for immunotherapy of tumors. Replication competent viruses, which can multiply selectively, are used by OV. attacking the tumour cells. Natu-Oncolytic viruses are classified as genetically modified viruses or naturally occurring viruses. Organic occurring viruses such as Newcastle disease and parvoviruses viruses that only reproduce in tumor cells with ease without genetic alteration. The second group of viruses, such as adenoviruses, vesicular stomatitis viruses, HSV, vaccinia, and measles viruses, genetically altered to enhance the tumorspecificity, safety, and reduce the pathogenicity of viruses. The application of Using oncolytic viruses to treat cancer is an immune-associated alternative to treatment. Oncolytic viruses function by lyses tumor cells directly and introduce wild-type tumour suppressor genes into -free cells suppressor gene Tafere Mulaw Belete et al; 2021[43].

2. Gene silencing: RNA interference (RNAi) is a method of gene silencing. Mediated suppression of particular genes in cancerous cells. Single or double-stranded noncoding RNAs are known as RNAi (21 Ribonucleotides) that cause degradation specific to a sequence of complementary messenger RNAs through the internal Equipment.siRNA is essential since the majority of genes do not lack ligand binding sites, which results in inhibitors. And homology between amino acid sequences and other proteins that restrict

the target's selectivity. RNAi is made up of microRNA. Short hair (miRNA), small interfering RNA (siRNA), and RNA pin (shRNA). Twenty years following the discovery ONPATRO™

(patisiran), RNAi, was authorized for the first Time for the treatment of hereditary polyneuropathy Amyloidosis mediated by tary transthyretin (hATTR). Oncogenes, tumor suppressor genes, and genes implicated in DNA resistance and the advancement of cancer are encouraging trends. receives -based cancer treatment for gene silencing because it selectively silences genes and has comparatively fewer side effects than traditional chemotherapy Tafere Mulaw Belete et al; 2021[43].

3. Suicide gene therapy; Viral or bacterial genes are used in suicide gene therapy to cancerous cells that convert nontoxic prodrugs into. A poisonous substance. A number of suicide gene systems were discovered, including the gene for HSVthymidine kinase (HSV-TK) in conjunction with cytosine deaminase and ganciclovir (GCV) 5fluorocytosine (5-FC) gene (CD) Gene-based One tactic is cytotoxic immunotherapy, in which an adeno-viral vector with thymidine kinase from the herpes virus AdV-TK gene is delivered locally to the tumor site.that results in the HSV-TK gene being expressed locally to the production of the viral thymidine kinase, which changes GCV into monophosphate of GCV. The administration comes next of GCV, which is phosphorylated and an HSV-TK substrate to generate monophosphate of GCV. Cellular kinases next convert GVCmonophosphate to GVC triphosphate through metabolism. A deoxyguanosine triphosphate analog is GCV triphosphate.log, added to the chain of DNA, resulting in chain termi- nation and death of tumor cells. Suicide gene therapy A number of growth factors are involved in tumor-driven angiogenesis Tafere Mulaw Belete et al; 2021[43].

4. Anti -Tumor Angiogenesis: A number of growth factors are involved in tumor-driven angiogenesis. Vascular endothelial growth factor, for example (VEGF), angiopoietins, and fibroblast growth factor-2 (FGF-2) Or IL-8, to ensure the supply of nutrients and oxygen. There are two main Strategies to prevent tumor angiogenesis are being investigated.The first strategy is to suppress proangiogenic Expression of factors like VEGF, and the second Strategy is to increase the expression of antiAngiostatin, endostatin, and other angiogenic factors Human soluble receptor

for FMS-like tyrosine kinase. Despite the effective therapeutic application of mAb such as Bevacizumab for cancer targeted treatment, the product Therapeutic mAb administration and tion are restricted because To expensive manufacturing. Consequently, gene-based research was Carried out to create a cancer that targets angiogenesis Therapy Tafere Mulaw Belete et al; 2021[43].

Classification:



Fig.No.3-Classification of Antineoplastics

V. CONCLUSION

Gene therapy is an innovative substitute for the man. Aging of illnesses for which there is no effective treatment. Gene Cancer treatment therapy has advanced well in recent years. Few medications have been approved in thirty years, and others are still in Trials. Gene therapy is comparatively safer and more tolerable. More detrimental effects than chemotherapy when used to treat cancer. In summary, gene therapy offers the advantage of directly repairing or even replacing harmful genes as well as correcting aberrant gene expression at the molecular level, which allows for precise and individualized disease treatment when compared to other therapeutic approaches. However, there are still unanswered questions regarding gene therapy’s safety and effectiveness. Furthermore, germ-cell gene therapy has generated ethical controversy and is currently not allowed in human trials. Nowadays, it is believed that tumors are complicated diseases with multiple genes, stages, and contributing factors. A future direction for cancer treatment where a cure is achievable is projected by combining gene therapy—a crucial component—with immunotherapy, chemotherapy, radiotherapy, and stem cell therapy.

VI. FUTURE SCOPE

Correcting or deactivating genes that cause cancer is known as precision gene editing.

Immune cell engineering, which includes immunogene therapies such as TCR-T and CAR T.

Oncolytic Viruses: These viruses increase immunity while specifically killing cancer cells.

Gene Silencing/RNA Therapies: These involve blocking genes that promote tumor growth using siRNA, shRNA, or miRNA.

Personalized Therapy: Interventions based on the genetic makeup of the patient's tumor.

Combination Therapy: Combining immunotherapy, radiation, chemotherapy, or gene therapy.

Advanced Delivery Systems: Better vectors, both viral and non-viral, for focused treatment.

Improved Safety: Lowering immunological responses and off-target effects.

Cost reduction and accessibility through the creation of scalable and off-the-shelf treatments.

Solid Tumor Treatment: Gene therapy's success is being extended beyond blood cancers.

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