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Review Article

The Role of Gene Therapy in Modern Cancer Treatment

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ABSTRACT

Gene therapy is an emerging treatment approach that introduces new genetic material into host tissues to modify gene expression or alter cellular properties for therapeutic benefit. Cancer, a leading global cause of death, remains challenging to treat due to late diagnosis and high relapse rates following conventional therapies like chemotherapy, which also damages healthy, fast-dividing cells. Gene therapy offers a promising alternative by delivering therapeutic genes to cancer cells to produce beneficial biological effects. However, early strategies using viral promoters such as the CMV promoter caused non-specific toxicity in both cancerous and normal tissues, limiting clinical success. To enhance specificity, tumor-specific promoters have been developed, allowing targeted gene expression exclusively within tumor cells. These innovations, combined with advanced delivery methods, improve the safety and efficacy of gene therapy. As research progresses, gene therapy holds the potential to revolutionize cancer treatment, significantly improving survival rates and the quality of life for cancer patients.

INTRODUCTION

Cancer is a medical condition in which certain cells in the body grow uncontrollably, forming abnormal tissue masses known as tumors. If left untreated, these tumors can invade nearby tissues and spread to other parts of the body through the bloodstream or lymphatic system (1). Cancer is a broad term that encompasses a group of diseases that can develop in various organs and tissues. It is a serious health concern affecting people of all ages, genders, and ethnicities. Globally, cancer is one of the leading causes of death, responsible for approximately 9.6 million deaths in 2018—equating to about one in every six deaths (2). Due to its complex nature, cancer is often difficult to treat and manage, making early detection and prevention crucial. A tumor refers to the abnormal mass formed by cancerous cells. Depending on the site of origin, there are over 200 types of cancer,

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including breast cancer, lung cancer, and brain cancer. Cancers can also be classified based on the type of cells from which they originate. The five major categories are:

1. **Carcinoma:** Cancer that begins in the skin or the tissues lining internal organs, such as the lungs, liver, and intestines. Common subtypes include adenocarcinoma, basal cell carcinoma, squamous cell carcinoma, and transitional cell carcinoma.

2. **Sarcoma:** A rare type of cancer that originates in supportive or connective tissues, including bone, cartilage, fat, muscle, and blood vessels. Sarcomas account for less than 1% of all cancers.

3. **Leukemia:** Cancer of the blood-forming tissues, particularly the white blood cells responsible for fighting infection. It originates in the bone marrow and includes types such as acute lymphoblastic leukemia, chronic lymphocytic leukemia, acute myeloid leukemia, and chronic myeloid leukemia.

4. **Lymphoma and Myeloma:** These cancers arise from the cells of the immune system. Lymphoma affects the lymphatic system, while myeloma targets plasma cells that produce antibodies.

5. **Brain and Spinal Cord Cancers:** Collectively known as central nervous system (CNS) cancers, these affect the brain, spinal cord, and other parts of the nervous system. Symptoms often include headaches, seizures, and motor or coordination difficulties (3).

Types of Cancer Treatment (4)

1. Chemotherapy: Uses drugs to kill or stop the growth of cancer cells, specific to the cancer type.

2. Radiotherapy: Uses high doses of radiation to destroy cancer cells.

3. Surgery: Involves physically removing the cancer from the body.

4. Hormone Therapy: Slows or stops tumor growth by targeting hormone-sensitive cancer cells.

5. Immunotherapy: Boosts the immune system to help it recognize and fight cancer cells.

6. Stem Cell Transplant: Restores healthy blood-forming stem cells after intensive chemotherapy or radiation.

7. Targeted Therapy: Uses drugs or substances to specifically target cancer cell proteins, reducing harm to normal cells. It can be used alone or with other treatments depending on the cancer type and stage.

Gene Therapy

Gene therapy is an emerging approach used to combat cancer by correcting or modifying genetic mutations responsible for uncontrolled cell growth and tumor formation. Such mutations may result from environmental factors like smoking, exposure to harmful substances, or inherited genes. By addressing these genetic defects, gene therapy holds the potential to prevent cancer development. A significant advancement in this field is suicide gene therapy, where a therapeutic gene is introduced into cancer cells, prompting them to self-destruct. This targeted strategy minimizes harm to healthy cells while enhancing treatment safety and effectiveness. The success of suicide gene therapy marks a key milestone, offering new hope for the treatment of cancer and other genetic disorders.

Techniques Used in Gene Therapy

Gene therapy involves the following three main steps:

1. **Gene Identification:** The process begins by identifying the gene of interest responsible for the disease.
2. **Gene Duplication:** The selected gene is duplicated to generate sufficient copies for therapeutic use.
3. **Gene Insertion:** The duplicated gene is inserted into the recipient's cells to restore or modify genetic function.

CRISPR

CRISPR/Cas is a revolutionary gene-editing technology originally discovered in bacteria as part of their immune defense. The system consists of two main components: the CRISPR sequence, which acts as a molecular memory bank, and the Cas enzyme, which functions as molecular scissors to cut DNA at specific sites. By combining these elements, scientists can program the system to target and edit specific genes (8). CRISPR technology alters the DNA sequence of cells, changing their genetic information. It has made gene editing more affordable and accessible. The most commonly used system, CRISPR-Cas9, allows for precise targeting and editing of DNA sequences by guiding the Cas9 enzyme with RNA segments to cut the DNA and introduce desired genetic changes (9).

Steps involved in CRISPR gene editing:

1. Identification of the problematic gene sequence.
2. Programming of an RNA molecule to locate the faulty DNA sequence.
3. Use of the Cas9 protein to cut the DNA at the specific location.
4. Insertion of the correct genetic sequence during natural DNA repair.

There are two main approaches for CRISPR-based therapy:

- **Ex vivo gene editing:** Cells are modified outside the body and then reintroduced.
- **In vivo gene editing:** The CRISPR system is delivered directly into the patient's body (10).

CAR T-Cell Therapy

CAR T-cell therapy involves modifying a patient's T cells in a laboratory to enable them to recognize and destroy cancer cells. This therapy enhances the immune system's capacity to target cancer more effectively (11). T cells are equipped with Chimeric Antigen Receptors (CARs) designed to bind to specific antigens on cancer cells. CARs consist of three proteins: one for recognizing antigens and two for activating the T cell. Each CAR T-cell therapy is tailored to the antigen profile of the patient's cancer, such as CD19 in leukemia or lymphoma. Upon encountering cancer cells, CAR T cells activate, multiply, and release cytokines that trigger an immune response, potentially eliminating cancer (12).

Process:

1. Collection of T cells via leukapheresis.
2. Genetic modification to express CAR receptors.
3. Expansion of modified cells.
4. Reinfusion into the patient after preconditioning chemotherapy.
5. Monitoring for immune response and side effects (14).

Suicide Gene Therapy

Suicide gene therapy involves introducing genes that trigger tumor cell death. This can be achieved directly, by expressing toxic proteins, or indirectly through gene-directed enzyme prodrug therapy (GDEPT), where a gene converts a non-toxic prodrug into a toxic compound (15, 16, 17). One well-studied example is the HSV thymidine kinase gene with ganciclovir. Despite promising results in animal models, clinical success has been limited, often requiring combination with radiation therapy (18). GDEPT leverages the "bystander effect"—where toxic products diffuse to neighboring cancer cells—offering a more targeted, less harmful treatment option (19, 20).

Immunotherapy

Immunotherapy harnesses the immune system to fight cancer by boosting its ability to recognize and attack cancer cells. This approach offers a less toxic alternative to chemotherapy and has been enhanced by gene therapy advancements (31, 32).

While immunotherapy can be effective, it does not work for all patients, with response rates around 15–20% (33).

Examples include:

- Stem cell transplants and CAR T-cell therapy
- Precision medicine: Tailoring treatment based on genetic analysis
- Hormone therapy: Targeting hormone-dependent cancers
- Biosimilar drugs: Affordable alternatives to biologics
- Tumor-agnostic drugs: Targeting specific mutations across cancer types
- Hyperthermia: Using heat to kill cancer cells, often combined with immunotherapy
- Cell therapy: Genetically modified immune cells reintroduced to the patient

Cancer-Specific Promoters

Cancer-specific promoters drive gene expression selectively in cancer cells, sparing normal tissues. The telomerase promoter (hTERT) is a prime example, as telomerase is highly active in most cancers but not in normal cells (21, 22, 23, 24). Other promoters include COX, cytokeratin 18/19, survivin, and CAR genes, which can enhance the specificity of gene therapies by targeting gene expression to cancer cells (25, 26). Tumor-specific promoters such as AFP, TTF-1, GPC3, MUC1, COX2, BRCA1, and BRCA2 further refine this approach by activating gene expression only in limited tumor types, reducing off-target effects (27, 28, 29, 30).

CONCLUSION

Gene therapy offers a promising new frontier for the treatment of cancer and other diseases with limited therapeutic options. Its application in cancer has advanced significantly over the past three decades, with multiple approved therapies and ongoing clinical trials. Compared to traditional chemotherapy, gene therapy shows better safety profiles and fewer adverse effects. The use of cancer- and tumor-specific promoters enhances the precision of gene therapies, potentially leading to more effective and less toxic treatments. Continued progress in tumor genomics and immunology will be essential to refine gene therapy strategies, ensuring that more patients can benefit from personalized, targeted approaches in the future.

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