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Professional paper

GENE THERAPY FOR CANCER TREATMENT: CONTEMPORARY APPROACHES AND PRINCIPLES

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Abstract

Cancer is a complicated illness in which certain cells in the body proliferate uncontrollably, encroaching on neighboring tissues. It is a significant global public health concern. Despite extensive preclinical research on achieving tumor-selective effects, various challenges hinder its effective clinical application, such as nonspecific effects, poor delivery efficiency, and biosecurity concerns. Various novel genetic methods are being developed to modify vectors or transgenes to enhance their safety and efficacy. With the newest delivery technologies, gene activity can now be precisely targeted to specific tissues and organs. With these developments, gene therapy is set to be poised for standard cancer treatment, potentially elevating this approach to a primary therapy for malignant diseases. Numerous clinical trials carried out in the USA, Europe, Canada, and China with sanctioned protocols, have demonstrated positive outcomes. Nevertheless, as our understanding of cancer mechanisms improves, innovative approaches like gene therapy will be favored over conventional treatment methods for identifying suitable treatments and targets. Gene therapy aimed at treating cancer has advanced significantly over the years, ; numerous medications have been approved, while others remain under investigation. Gene therapy offers enhanced safety and more manageable side effects than chemotherapy for treating cancer.

Keywords: cancer, biological drugs, gene therapy, gene modification, genetic engineering

1. Introduction

These biological therapies, currently used to treat cancer, have significantly advanced and represent targeted therapies that align with the trend of precision oncology. Precision oncology uses next-generation sequencing (NGS) to identify new and rare mutations in cancer cells, enabling tailored treatment for each patient (Monica, et al., 2021).

Rogers et al. were the first scientists to conduct a preliminary demonstration of virus-mediated gene transfer. They demonstrated that genetic material taken from another organism could be transferred to cells of interest using viruses (Roger, et al., 1968). Motivated by the results, he dared to perform an unprecedented action. He decided to apply this method on humans. He became the first scientist to perform gene modification therapy on humans. In this case, he used a papillomavirus to introduce the gene for arginase synthesis into two girls who suffered from urea cycle disorders (Roger, et al., 1973 & Terheggen et al., 1975).

He predicted that the papillomavirus could encode the gene responsible for arginase activity and that introducing the virus into the human body could transfer this gene. Unfortunately, the results obtained from this study were negative. There was no change in the clinical condition of the patients or in their arginine levels. Although Rogers' idea and action were quite intriguing at the time, it was later proven that this experiment was doomed to failure because the genome of the virus in question does not encode the arginase gene (Roger, et al., 1973).

Later, precisely in 1989, first gene therapy protocol was approved. At that time, neoplasm-infiltrating lymphocytes taken from cases with late melanoma were transduced ex vivo with a marker gene (i.e., not an amendatory gene), and after in vitro treatment were reinfused into the patients (Rosenberg, et al., 1990). Another notable event in this field is the study conducted by Cline and co-authors, who treated patients with thalassemia with gene therapy. Cline took cells

from the patients' bone marrow and transfected them with plasmids carrying the globulin gene. Before processing, these cells were returned to the patients' bodies (MacMillan et al., 1982; Beutler et al., 2001). This study was conducted without the approval from the Institutional Review Board of the University of California, Los Angeles (UCLA), This case revealed that knowledge about this new area of genetics was significantly restricted, and that natural gene therapy would be technically and conceptually far more complex than anticipated (Monica et al., 2021).

2. Materials and methods

This narrative review of the literature includes many of the most recent articles published over the past two decades, reports and clinical studies dealing with the most current therapy for the treatment of cancer diseases. For comparison purposes, much older publications have also been used, ; they were of particular importance in showing the chronological development of events.

3. Results and discussion

This narrative review provides a global and comprehensive overview of the latest, progressive, and regularly approved therapies against cancer. In addition to these issues, new strategies currently in the research phase were also addressed, aiming to prove that these therapies do not have the shortcomings of conventional therapies. The greatest challenge in cancer treatment is resistance to therapy and its delivery systems. The efficacy of conventional cancer treatment is significantly reduced due to various tumor pathologies and angiogenesis (El-Readi, et al., 2019). Advanced and innovative types of cancer treatments are presented below, along with their advantages, disadvantages and difficulties.

Cancer stem cells

Stem cells are undifferentiated cells that reside in the bone marrow. A characteristic of these cells is their ability to differentiate into any type of cell in the body. Considering the newest options for treating cancer and the mechanism of action of these cells, this therapy is considered safe and effective. The use of stem cells is still in the clinical study phase, and recently their potential for use in the regeneration of damaged tissues is being studied. Mesenchymal stem cells (MSCs) are currently being used in trials administered from BM, adipose tissue, and connective tissue (Naji A, et al., 2019).

It is an undeniable fact that chemotherapy destroys a large number of tumor cells, but in some cases, stem cells can eliminate chemotherapeutic agents. This mechanism creates resistance to some treatments, like the overexpression of ATP-binding cassette transporters such as ABCB1, which encodes P-glycoproteinresistant to mitoxantrone (Naji A, et al., 2019).

Cancer stem cells possess normal stem cell traits that confer longevity, including relative quiescence, resistance to drugs and toxins through the expression of drug efflux transporters, active DNA repair capacity and resistance to apoptosis, vascular localization, quiescence, hypoxic stability, and increased activity of repair enzymes (Pal B, et al., 2016; Dean M et al., 2005). By closely observing cancer cells and their aforementioned properties, it is observed that even in cured patients these cells continue to be present and can cause cancer recurrence. Therefore, identifying and eliminating these cells is very important. (Pal B, et al., 2016).

Targeted drug therapy

Targeted cancer treatments are medicines or other substances frequently referred to as "molecularly targeted medicines," “molecularly targeted therapeutics,” and "ultraprecision medicines." These drugs work by interfering with growth molecules, blocking cancer growth and spread. The growth phase of these cells occurs in an atypical cell layer including endothelial cells, smooth muscle cells, fibroblasts, and nerve cells (Yadav P. et al., 2017).
These cells interact with cancer cells dynamically through various mechanisms and pathways, ensuring high cell distribution (Valter K, et al., 2017). Therefore, using the conditions of the TM to mediate effective targeted measures is an area of investigative interest (Adjej IM, et al., 2015). The careful treatment of cancer cells with conventional chemotherapy is delicate because cancer cells are analogous to normal cells. Thus, these problems are mediated by cellular mechanisms similar to cell cycle arrest, apoptosis induction, proliferation inhibition, and interference with metabolic reprogramming by targeted medicine agents (Valter K, et al., 2017). TM revision and TM targeting for drug delivery for effective treatment are two strategies that can be used to treat cancer (Bailey KM, et al., 2012). Targeted drugs work in different ways than standard chemotherapy medicine treatment, such as by attacking cancer cells while causing less damage to normal cells, a characteristic that distinguishes them from common and healthy cells (Yadav P. et al., 2017). The most modern and advanced methods used for discovering new drugs allow these studies to be carried out rapidly, especially in the field of targeted drug therapy where, with the help of very small molecules such as protein kinases, anticancer therapy can be directed to a specific site (Yadav P. et al., 2017).

Oncologic Viruses

Several decades ago, the idea of using viruses to fight cancer emerged. However, this only became possible after advances in genetic engineering. Oncolytic viruses are designed to selectively attack and destroy only cancer cells or to enhance anti-cancer immunity (Muik, et al., 2014). Neoplastic cells infected with an oncolytic virus are processed under immunological surveillance, as they begin to express major histocompatibility complex class I (MHC I) molecules on their surface (Murphy, J et al., 2019). Research on oncolytic viruses uses naturally occurring oncolytic viruses or viruses genetically modified in such a way that they have an affinity only for neoplastic cells (Gong, J 2016 and Liu, 2003). Modified oncolytic viruses are altered so that they can selectively bind only to mutant tumor cell receptors, or a portion is removed that allows the virus to replicate selectively only in tumor cells (HU, J, et al., 2006).
Their ability to replicate in neoplastic cells is an advantage, allowing them to infect other cells (Roberts et al., 2006). Moreover, if they infect normal cells, they exhibit reduced pathogenicity in those cells (Chen, N, et al., 2009). The most modified viruses for anticancer therapy are adenoviruses, vaccinia virus, and HSV (Andtbacka, et al., 2016). Expectations for the response of the human body affected by cancer and injected with oncolytic virus therapy were very high; however, in practice, the human body's response to this type of therapy is often ineffective. Initially, it is inhibited by the human immune system, which responds to the virus, apparently preventing its replication. Then, obstacles appear that are activated by the tumor's own defense mechanisms (Murphy, J et al., 2019).
However, combined therapies with immunotherapy seem to be more effective, and have multiple goals. In some cases, an oncological virus can be introduced into the body of a patient undergoing surgery for a tumor; this may increase the effects of subsequent treatment. Combination therapies are the focus, and they seem very promising in treating cancer (NCI, 2020).

Immunotherapy

Unlike conventional cancer treatments such as chemotherapy and radiotherapy, immunotherapy is a novel treatment that dynamically alters the immune system to attack cancer cells (J. Couzin, et al., 2013). Immunotherapy is substantially used to strengthen the vulnerable system by modifying the tumor microenvironment, so that immune cells can attack and clear growing tumor cells (Chevolet, et al., 2015). In combination with traditional antitumor therapy or multiple immunocheckpoint inhibitors (ICI), it has been observed that most of the effects are significantly improved, however there are specific situations that remain to be studied further. The exploration of related antitumor medicines is gradually increasing, and the demand and use of medicines are gradually increasing. Currently, the gap with the international research is gradually narrowing, which greatly promotes the development of experimental immunotherapy. Tumor-specific T lymphocytes exert their antitumor activity by producing interferons that recognize tumor cells and cellular antibodies that present the antigens. This action can be carried out in several ways: inducing apoptosis inhibiting the spread of tumor cells, activating and recruiting other immune system cells, and increasing the expression of antigen-presenting proteins. For example, major histocompatibility complex (MHC) molecules (J. Gao, et al., 2016). If the pathway is mutated, PD-L1 expression is exposed (H. Kronig, 2014). Increased anti-PD-L1 expression of cancer cells blocks PD-L1 or PD-1 immunotherapy, rendering it ineffective. In this case, tumor cells directly express PD-L1, bind to PD-1 on the T cell surface to inhibit activated cytotoxic T lymphocytes (CTL), inhibit cytotoxic T cell activation, suppress the immune response, and cause a decrease in T cell numbers, thus leading to primary drug resistance (T. Seto et al., 2019).

Cancer Vaccines

Many recent studies have begun testing the possibility of cancer vaccines, offering hope and promise for the future. This new wave of treatments may be linked to new technologies developed during the COVID-19 pandemic, specifically an innovative type of vaccine called mRNA. Thanks to this innovative technology, scientists are working to create vaccine treatments that can be used to target cancer cells already present in the body. This means that personalized cancer vaccines are potentially close; one day vaccines could be used to both prevent and treat cancer.

New cancer vaccines aim to stimulate a response against antigens upon administration to patients. These vaccines can contain purified strains of viruses, genetically modified viruses, or synthetically produced viruses.

To this end, different vaccine systems are used to expose the body to the relevant antigen. These types of vaccines include peptide antitumor vaccines, DNA or RNA-based vaccines, and dendritic cell vaccines. The genetically modified vaccine, created through genetic engineering with the help of a plasmid or a viral vector, is injected into the patient (Hollingsworth, R.E., et al., 2019).

The role of the peptides used in this case is very important; not only must the right peptide be chosen, but special attention must also be paid to the peptide's length, which is essential to trigger a response in the organism. To date, peptide vaccines have not shown significant efficacy. The cause of these failures is thought to be the intracellular processing of peptide particles because it affects their antigenic properties, and the culture environment promotes immunosuppressive effects. Another possible cause may be the combinations of these vaccines with adjuvants or cytostatics during formulation. (Osipov A, et al., 2019). A problem with DNA-based vaccines is the potential threat of insertional mutagenesis. In this regard, RNA vaccines may be reliable. In addition, they are only temporarily present in cells due to enzymatic

degradation. Currently, effective methods of mRNA stabilization have been developed, including the creation of mRNA analogue caps, which extend the duration in the body, increase protein expression in dendritic cells several or tens of times, and allows it to be used directly in vivo (Calvo T, et al., 2019).

4. Conclusion

As the effectiveness and toxicity of chemotherapy reached its limits, there was a need for new therapies and regimens that would minimize side effects on the human body on the one hand, while increasing their efficiency in destroying cancer cells. The latest advancements in medicine include gene therapy, combination therapy, and personalized therapy. The development of molecular biology has enabled us to gain a deeper understanding of cancer, making it possible to discover techniques that would enable the destruction of tumor cells. These genetic engineering techniques have enabled a revolution in cancer treatment. It is expected that gene therapy will play a key role in the treatment of neoplasms. Thanks to combining these methods with bioinformatics, achieving better therapeutic action at the target site will be possible.

Current best-practice protocols for gene therapy are largely limited to intravenous administration of genetically modified vectors or ex vivo gene transfer methods. However, research should focus not only on vectors, but also on their production routes. However, producing these viral vectors is very expensive because production is difficult, and purification is challenging. (Hollingsworth, R. E., et al., 2019). This makes this type of therapy quite expensive, causing a significant disparity between the economic classes that can afford this type of treatment. Because this type of therapy is not accessible to the most of patients, numerous issues related to medical ethics arise.

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