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Perspective

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Gene Therapy in the Treatment of Cancer

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Abstract

The expansive realm of gene therapy holds the potential for groundbreaking treatments that could play a crucial role in averting cancer-related fatalities. This opinion article delves into the history, notable achievements, and future prospects of three distinct approaches in gene therapy treatment: immunotherapy, oncolytic virotherapy, and gene transfer. Immunotherapy employs genetically modified cells and viral particles to activate the immune system, prompting it to eliminate cancer cells. Recent clinical trials of second and third-generation vaccines have demonstrated promising outcomes across various cancers, including lung cancer, pancreatic cancer, prostate cancer, and malignant melanoma. Oncolytic virotherapy, an emerging treatment modality, utilizes viral particles that replicate within cancer cells, inducing cell death. Particularly noteworthy is its potential efficacy against metastatic cancers, as evidenced by encouraging results from initial phase I trials involving several vectors, generating enthusiasm for the potency of this technique. Gene transfer, another innovative treatment approach, introduces new genes into cancerous cells or the surrounding tissue, leading to cell death or the deceleration of cancer growth. This method showcases remarkable flexibility, with a diverse array of genes and vectors undergoing successful clinical trials, marking a significant stride in the pursuit of effective cancer treatments.

Keywords: Gene therapy; Cancer; Immunotherapy; Oncolytic virotherapy; Clinical trials

Immunotherapy

Enhancing the immune system to identify and eliminate cancer cells, known as immunotherapy, has been a pursuit in cancer treatment for more than a century. Yet, conventional immunotherapy has faced challenges due to the ability of cancer cells to develop evasion mechanisms against immune detection. Various gene therapy approaches are currently being employed to overcome these limitation.

Gene therapy is currently employed in the development of recombinant cancer vaccines. Diverging from vaccines designed for infectious agents, these vaccines aim not to prevent disease but to treat or confine it. They achieve this by instructing the patient's immune system to recognize cancer cells through the presentation of highly antigenic and immunostimulatory cellular debris. The process begins with the harvesting of cancer cells from the patient (autologous cells) or established cancer cell lines (allogeneic), followed by in vitro cultivation. Subsequently, these cells undergo genetic engineering to enhance their recognition by the immune system. This often involves the addition of one or more genes, commonly cytokine genes producing pro-inflammatory, immune-stimulating molecules, or genes encoding highly antigenic proteins. After the genetic modification, these cells are cultured in vitro, killed, and their cellular contents are integrated into a vaccine. Immunotherapy is also explored through the in vivo delivery of immunostimulatory genes, predominantly cytokines, directly to the tumor. The method of introducing the gene to the tumor varies and is further detailed in the gene transfer section of this review. Once within the cancer cell, these genes induce the production of proteins that unveil the cells from immune evasion, fostering the development of antitumor antibodies.

Oncolytic Agents

Another expanding domain within gene therapy for cancer treatment involves the utilization of oncolytic vectors to eradicate cancer cells. Similar to immunotherapy, this concept has been in existence for almost a century and is experiencing a resurgence, propelled by advancements in gene therapy. Oncolytic gene therapy vectors typically consist of viruses that have been genetically modified to selectively target and destroy cancer cells while sparing the healthy tissues in the body.

These vectors are engineered to infect cancer cells, triggering cell death through viral propagation, expression of cytotoxic proteins, and cell lysis. Various viruses are employed for this purpose, including vaccinia, adenovirus, herpes simplex virus type I, reovirus, and Newcastle disease virus. The selection of these viruses is often based on their inherent ability to naturally target cancers and their amenability to genetic manipulation.

Initial trials of oncolytic therapies have underscored both their formidable efficacy and distinctive challenges in translating the treatment to practical implementation. Oncolytic gene therapy has demonstrated remarkable success in mammalian models. Murine models, in particular, have exhibited enhanced survival and reduced metastasis in cases of colon and bladder cancer when treated with oncolytic viral agents.

In a canine model focused on combating osteosarcoma, an oncolytic virus was designed to extend survival, even in immunocompetent dogs with syngenic osteosarcoma. Despite these encouraging results in animal models, the transition to oncolytic virotherapy in humans presents specific hurdles. A significant obstacle lies in the fact that many individuals possess antibodies against the common viruses used in therapy development, often triggering an immune response that clears the viral agent before it can effectively infect cells.

Gene Transfer

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One of the most captivating developments stemming from the gene therapy concept is the treatment approach known as gene transfer or insertion. This innovative treatment paradigm involves the introduction of an external gene into either the cancer cell or the adjacent tissue. Various genes with distinct functions have been proposed for this therapeutic approach, including suicide genes.

Clinical trials exploring this avenue of therapy have utilized a range of viral vectors, with replication incompetent adenovirus being the most frequently employed. Additionally, nonviral methods such as naked DNA transfer, oligodendromer DNA coatings, and electroporation are viable means of gene delivery. The choice of delivery vehicle depends on the desired specificity of the gene transfer therapy and the duration for which the gene must be expressed to achieve effectiveness. For instance, a replication incompetent adenoviral vector containing the *Herpes simplex virus thymidine kinase (HSVtk)* gene requires only transient expression for inducing cell death and is typically delivered through an adenoviral vector. On the other hand, antiangiogenesis genes like sFLT-1 and statin-AE necessitate continuous expression for therapeutic efficacy and have been delivered using plasmids containing a transposon for gene insertion into cellular DNA.

Conclusion

The domain of cancer gene therapy is advancing rapidly and is poised to become an integral component of future cancer therapeutics. Genetic engineering has ushered in a new era, enabling the development of highly promising cancer vaccine treatments currently undergoing late-stage trials. Additionally, gene transfer technology in cancer treatment holds tremendous potential for enhancing the efficacy of existing chemotherapeutic regimens. The field of oncolytic virotherapy has witnessed significant strides, with ongoing trials incorporating this technique for the treatment of both precancerous and cancerous conditions. Many past challenges in treatment are actively being addressed, and the current exploration of second and third-generation therapeutics is underway. While not all ongoing trials may yield viable therapeutic agents, there is substantial optimism that these advancements will contribute to transforming cancer into a manageable chronic disease, alleviating severe suffering and reducing mortality.

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