Gene Therapy for Cancer : What Have We Done and Where Are We Going?

Research plan:

INTRODUCTION

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What is biological therapy?

What is the immune system and what role does it have in biological therapy for cancer?

What are cancer treatment vaccines?

What is oncolytic virus therapy?

What is gene therapy?

Second

What are the side effects of biological therapies?

Third

How can people obtain information about clinical trials of biological therapies for cancer?

CONCLUSIONS

INTRODUCTION :

The broad field of gene therapy promises a number of innovative treatments that are likely to become important in preventing deaths from cancer.in this research, we discuss the future of three different gene therapy treatment approaches: immunotherapy, oncolytic virotherapy and gene transfer. Immunotherapy uses genetically modified cells and viral particles to stimulate the immune system to destroy cancer cells. Recent clinical trials of second and third generation vaccines have shown encouraging results with a wide range of cancers, including lung cancer, pancreatic cancer, prostate cancer and malignant melanoma. Oncolytic virotherapy, which uses viral particles that replicate within the cancer cell to cause cell death, is an emerging treatment modality that shows great promise, particularly with metastatic cancers.. Gene transfer is a new treatment modality that introduces new genes into a cancerous cell or the surrounding tissue to cause cell death or slow the growth of the cancer. This treatment technique is very flexible, and a wide range of genes and vectors are being used in clinical trials with successful outcomes. As these therapies mature, they may be used alone or in combination with current treatments to help make cancer a manageable disease.

So….

- What is biological therapy?
- What is the immune system and what role does it have in biological therapy for cancer?
- What are cancer treatment vaccines?
- What is oncolytic virus therapy?
- What is gene therapy?
- What are the side effects of biological therapies?
- How can people obtain information about clinical trials of biological therapies for cancer?

First :

What is biological therapy?

Biological therapy involves the use of living organisms, substances derived from living organisms, or laboratory-produced versions of such substances to treat disease. Some biological therapies for cancer use vaccines or bacteria to stimulate the body's immune system to act against cancer cells. These types of biological therapy, which are sometimes referred to collectively as "immunotherapy" or "biological response modifier therapy," do not target cancer cells directly. Other biological therapies, such as antibodies or segments of genetic material (RNA or DNA), do target cancer cells directly. Biological therapies that interfere with specific molecules involved in tumor growth and progression are also referred to as targeted therapies.

For patients with cancer, biological therapies may be used to treat the cancer itself or the side effects of other cancer treatments. Although many forms of biological therapy have been approved by the U.S. Food and Drug Administration (FDA), others remain experimental and are available to cancer patients principally through participation in clinical trials.

What is the immune system and what role does it have in biological therapy for cancer?

The immune system is a complex network of organs, tissues, and specialized cells. It recognizes and destroys foreign invaders, such as bacteria or viruses, as well as some damaged, diseased, or abnormal cells in the body, including cancer cells. An immune response is triggered when the immune system encounters a substance, called an antigen, it recognizes as "foreign."

White blood cells are the primary players in immune system responses. Some white blood cells, including macrophages and natural killer cells, patrol the body, seeking out foreign invaders and diseased, damaged, or dead cells. These white blood cells provide a general—or nonspecific—level of immune protection.

Other white blood cells, including cytotoxic T cells and B cells, act against specific targets. Cytotoxic T cells release chemicals that can directly destroy microbes or abnormal cells. B cells make antibodies that latch onto foreign intruders or abnormal cells and tag them for destruction by another component of the immune system. Still other white blood cells, including dendritic cells, play supporting roles to ensure that cytotoxic T cells and B cells do their jobs effectively.

It is generally believed that the immune system's natural capacity to detect and destroy abnormal cells prevents the development of many cancers. Nevertheless, some cancer cells are able to evade detection by using one or more strategies. For example, cancer cells can undergo genetic changes that lead to the loss of cancer-associated antigens, making them less "visible" to the immune system. They may also use several different mechanisms to suppress immune responses or to avoid being killed by cytotoxic T cells.

The goal of immunotherapy for cancer is to overcome these barriers to an effective anticancer immune response. These biological therapies restore or increase the activities of specific immune-system components or counteract immunosuppressive signals produced by cancer cells.[1]

What are cancer treatment vaccines?

Cancer treatment vaccines are designed to treat cancers that have already developed rather than to prevent them in the first place. Cancer treatment vaccines contain cancer-associated antigens to enhance the immune system's response to a patient's tumor cells. The cancer-associated antigens can be proteins or another type of molecule found on the surface of or inside cancer cells that can stimulate B cells or killer T cells to attack them.

Some vaccines that are under development target antigens that are found on or in many types of cancer cells. These types of cancer vaccines are being tested in clinical trials in patients with a variety of cancers,

1. Rivoltini L, Canese P, Huber V, et al. Escape strategies and reasons for failure in the interaction between tumour cells and the immune system: how can we tilt the balance towards immune-mediated cancer control? *Expert Opinion on Biological Therapy* 2005,463-476.

including prostate, colorectal, lung, breast, and thyroid cancers. Other cancer vaccines target antigens that are unique to a specific cancer type. Still other vaccines are designed against an antigen specific to one patient's tumor and need to be customized for each patient. The one cancer treatment vaccine that has received FDA approval, sipuleucel-T, is this type of vaccine.

Because of the limited toxicity seen with cancer vaccines, they are also being tested in clinical trials in combination with other forms of therapy, such as hormonal therapy, chemotherapy, radiation therapy, and targeted therapies.[2]

What is oncolytic virus therapy?

Oncolytic virus therapy is an experimental form of biological therapy that involves the direct destruction of cancer cells. Oncolytic viruses infect both cancer and normal cells, but they have little effect on normal cells. In contrast, they readily replicate, or reproduce, inside cancer cells and ultimately cause the cancer cells to die. Some viruses, such as reovirus, Newcastle disease virus, and mumps virus, are naturally oncolytic, whereas others, including measles virus, adenovirus, and vaccinia virus, can be adapted or modified to replicate efficiently only in cancer cells. In addition, oncolytic viruses can be genetically engineered to preferentially infect and replicate in cancer cells that produce a specific cancer-associated antigen, such as EGFR or HER-2.[3]

One of the challenges in using oncolytic viruses is that they may themselves be destroyed by the patient's immune system before they have a chance to attack the cancer. Researchers have developed several strategies to overcome this challenge, such as administering a combination of immune-suppressing chemotherapy drugs like cyclophosphamide along with the virus or "cloaking" the virus within a protective envelope. But an immune reaction in the patient may actually have benefits: although it may hamper oncolytic virus therapy at the

[2] Finn OJ. Cancer immunology. *New England Journal of Medicine* 2008:p 2704-2715.

[3] Russell SJ, Peng KW, Bell JC. Oncolytic virotherapy. *Nature Biotechnology* 2012: p 658-670.

time of viral delivery, it may enhance cancer cell destruction after the virus has infected the tumor cells.

No oncolytic virus has been approved for use in the United States, although H101, a modified form of adenovirus, was approved in China in 2006 for the treatment of patients with head and neck cancer. Several oncolytic viruses are currently being tested in clinical trials. Researchers are also investigating whether oncolytic viruses can be combined with other types of cancer therapies or can be used to sensitize patients' tumors to additional therapy.[4]

What is gene therapy?

Still an experimental form of treatment, gene therapy attempts to introduce genetic material (DNA or RNA) into living cells. Gene therapy is being studied in clinical trials for many types of cancer.

In general, genetic material cannot be inserted directly into a person's cells. Instead, it is delivered to the cells using a carrier, or "vector." The vectors most commonly used in gene therapy are viruses, because they have the unique ability to recognize certain cells and insert genetic material into them. Scientists alter these viruses to make them more safe for humans (e.g., by inactivating genes that enable them to reproduce or cause disease) and/or to improve their ability to recognize and enter the target cell. A variety of liposomes (fatty particles) and nanoparticles are also being used as gene therapy vectors, and scientists are investigating methods of targeting these vectors to specific cell types.

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[4] Alemany R, Cascallo M. Oncolytic viruses from the perspective of the immune system. *Future Microbiology* 2009:p 527-536.

Liu TC, Kirn D. Gene therapy progress and prospects cancer: oncolytic viruses. *Gene Therapy* 2008:p 877-884.

Researchers are studying several methods for treating cancer with gene therapy. Some approaches target cancer cells, to destroy them or prevent their growth. Others target healthy cells to enhance their ability to fight cancer. In some cases, researchers remove cells from the patient, treat the cells with the vector in the laboratory, and return the cells to the patient. In others, the vector is given directly to the patient. Some gene therapy approaches being studied are described below.

- Replacing an altered tumor suppressor gene that produces a nonfunctional protein (or no protein) with a normal version of the gene. Because tumor suppressor genes (e.g., *TP53*) play a role in preventing cancer, restoring the normal function of these genes may inhibit cancer growth or promote cancer regression.
- Introducing genetic material to block the expression of an oncogene whose product promotes tumor growth. Short RNA or DNA molecules with sequences complementary to the gene's messenger RNA (mRNA) can be packaged into vectors or given to cells directly. These short molecules, called oligonucleotides, can bind to the target mRNA, preventing its translation into protein or even causing its degradation.
- Improving a patient's immune response to cancer. In one approach, gene therapy is used to introduce cytokine-producing genes into cancer cells to stimulate the immune response to the tumor.
- Inserting genes into cancer cells to make them more sensitive to chemotherapy, radiation therapy, or other treatments
- Inserting genes into healthy blood-forming stem cells to make them more resistant to the side effects of cancer treatments, such as high doses of anticancer drugs
- Introducing "suicide genes" into a patient's cancer cells. A suicide gene is a gene whose product is able to activate a "pro-drug" (an inactive form of a toxic drug), causing the toxic drug to be produced only in cancer cells in patients given the pro-drug. Normal cells, which do not express the suicide genes, are not affected by the pro-drug.
- Inserting genes to prevent cancer cells from developing new blood vessels (angiogenesis)

Proposed gene therapy clinical trials, or protocols, must be approved by at least two review boards at the researchers' institution before they can be conducted. Gene therapy protocols must also be approved by the

FDA, which regulates all gene therapy products. In addition, gene therapy trials that are funded by the National Institutes of Health must be registered with the NIH Recombinant DNA Advisory Committee.[5]

Second:

What are the side effects of biological therapies?

The side effects associated with various biological therapies can differ by treatment type. However, pain, swelling, soreness, redness, itchiness, and rash at the site of infusion or injection are fairly common with these treatments.

Less common but more serious side effects tend to be more specific to one or a few types of biological therapy. For example, therapies intended to prompt an immune response against cancer can cause an array of flu-like symptoms, including fever, chills, weakness, dizziness, nausea or vomiting, muscle or joint aches, fatigue, headache, occasional breathing difficulties, and lowered or heightened blood pressure. Biological therapies that provoke an immune system response also pose a risk of severe or even fatal hypersensitivity (allergic) reactions.

Potential serious side effects of specific biological therapies are as follows:

MAbs

- Flu-like symptoms
- Severe allergic reaction
- Lowered blood counts
- Changes in blood chemistry
- Organ damage (usually to heart, lungs, kidneys, liver or brain)

Cytokines (interferons, interleukins, hematopoietic growth factors)

- Flu-like symptoms

[5] 1Morgan RA, Dudley ME, Wunderlich JR, et al. Cancer regression in patients after transfer of genetically engineered lymphocytes. *Science* 2006:p 126-129.

- Severe allergic reaction
- Lowered blood counts
- Changes in blood chemistry
- Organ damage (usually to heart, lungs, kidneys, liver or brain)

Treatment vaccines

- Flu-like symptoms
- Severe allergic reaction

BCG

- Flu-like symptoms
- Severe allergic reaction
- Urinary side effects
    - Pain or burning sensation during urination
    - Increased urgency or frequency of urination
    - Blood in the urine

Oncolytic viruses

- Flu-like symptoms
- Tumor lysis syndrome: severe, sometimes life-threatening alterations in blood chemistry following the release of materials formerly contained within cancer cells into the bloodstream

Gene therapy

- Flu-like symptoms
- Secondary cancer: techniques that insert DNA into a host cell chromosome can cause cancer to develop if the insertion inhibits expression of a tumor suppressor gene or activates an oncogene; researchers are working to minimize this possibility
- Mistaken introduction of a gene into healthy cells, including reproductive cells
- Overexpression of the introduced gene may harm healthy tissues
- Virus vector transmission to other individuals or into the environment[6]

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[6] Rosenberg SA, Restifo NP, Yang JC, et al. Adoptive cell transfer: a clinical path to effective cancer immunotherapy. *Nature Reviews Cancer* 2008:p 299-308.

Third:

How can people obtain information about clinical trials of biological therapies for cancer?

Both FDA-approved and experimental biological therapies for specific types of cancer are being studied in clinical trials. The names of the biological therapy types listed below are links to descriptions of ongoing in clinical trials that are testing those types of biological therapies in cancer patients. These trial descriptions can also be accessed by searching NCI's list of cancer clinical trials on the NCI website. NCI's list of cancer clinical trials includes all NCI-funded clinical trials as well as studies conducted by investigators at hospitals and medical centers throughout the United States and around the world.[7]

Monoclonal antibodies

Cytokine therapy

Vaccine therapy

Adoptive T-cell therapy

Oncolytic virus therapy

Gene therapy

DNA oligonucleotide therapy

RNA oligonucleotide therapy

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[7] Grupp SA, Kalos M, Barrett D, et al. Chimeric Antigen Receptor-Modified T Cells for Acute Lymphoid Leukemia. *New England Journal of Medicine* 2013:p 1509-1518.

CONCLUSIONS :

The field of cancer gene therapy is rapidly maturing and will no doubt be part of the future of cancer therapeutics. Several very exciting cancer vaccine treatments are in late stage trials, thanks to the advent of genetic engineering. In addition, gene transfer technology for cancer treatment holds great promise for increasing the effectiveness of current chemotherapeutic treatment regimens. Significant advances have been made in the field of oncolytic virotherapy, and trials are in progress that incorporate this technique for precancerous, as well as cancerous treatment. Many of the past obstacles to treatment are being actively overcome and current second and third generation therapeutics are being tested. While not all the current trials will lead to a viable therapeutic agent, there is great hope that these advances will help relegate cancer to a manage able chronic disease without severe suffering and death.

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Index: