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Cancer Vaccines: A Promising Role in Cancer Therapy

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Abstract: Cancer became a big question for scientific community as no existing treatments could solve the problems related to this dreadful disease. Research is in well progress since half century but it failed to give a right solution to fight against it. However the developments in science and technology facilitated scientists to develop new methods of treatment. One such mile stone treatment for cancer that is giving good hope to the people is cancer vaccines. The aim of cancer vaccines is to stimulate the immune system to be able to recognise cancer cells as abnormal and destroy them. Majorly, cancer vaccine research is in progress to develop universal as well as specific cancer vaccines. In the present paper the developments in cancer thearapy especially by empahising vaccine development against cancer was discussed.

Key words: Cancer Vaccines · Cancer Therapy · DNA Vaccines · Universal Cancer Vaccines

INTRODUCTION

Cancer is the name given for these diseases in which the body cells become abnormal and divide without control. Cancer cells may invade nearby tissues. And they may spread through the bloodstream and lymphatic system to other parts of the body. Its two main characteristics are uncontrolled proliferation of the cells in the human body and ability of these cells to migrate from the original site and spread to distant sites (metastasis). If the spread is not controlled, cancer can result in death.

Cancer, by definition, is a disease of the genes. A *gene* is a functional unit of DNA, which is the master molecule of the cell. Genes make "proteins," which are the ultimate workhorses of the cells that allow our bodies to carry out all the processes that permit us to breathe, think, move, etc. Throughout people's lives, the cells in their bodies are growing, dividing and replacing themselves. Many genes produce proteins that are involved in controlling the processes of cell growth and division. An alteration (mutation) to the DNA molecule can disrupt the genes and produce faulty proteins. This causes the cell to become abnormal and lose its restraints on growth. The abnormal cell begins to divide uncontrollably and eventually forms a new growth known as a "tumor" or neoplasm (medical term for cancer meaning "new growth"). In a healthy individual, the immune system can recognize the neoplastic cells and destroy them before they get a chance to divide. However, some mutant cells may escape immune detection and survive to become tumors or cancers.

Causes of Cancer: Cancer may arise both from genetic or environmental factors that lead to aberrant growth regulation of a stem cell population, or by the dedifferentiation of more mature cell types. Normally, cells proliferate only in response to injury, immune responses, or, in a few cases, to replace cells that have undergone apoptotic cell death. Mutations in DNA that lead to cancer appear to disrupt this orderly process. A majority of cancers are caused by changes in the cell's DNA because of damage due to the environment. Environmental factors that are responsible for causing the initial mutation in the DNA are called carcinogens and there are many types, for eg: UV rays, industrial pollutants etc.

There are some cancers that have a genetic basis. In other words, an individual could inherit faulty DNA from his parents, which could predispose him to getting cancer. While there is scientific evidence that both factors (environmental and genetic) play a role, less than 10% of all cancers are purely hereditary. Cancers that are known to have a hereditary link are breast cancer, colon cancer, ovarian cancer and uterine cancer.

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Types of Cancers: Cancers are of different types based on their site of origin,

Carcinomas: are cancers that arise in the epithelium (the layers of cells covering the body's surface and lining the internal organs and various glands). Ninety percent of human cancers fall into this category. Carcinomas can be further divided into two subtypes: Adenocarcinomas, cancers that develop in an organ/gland. Squamous cell carcinomas refer to cancers that originate in the skin. Eg: prostrate cancer, cervical cancer, lung cancer, liver cancer, colon cancer, kidney cancer, thyroid cancer, pancreatic cancer.

Melanomas: originate in the skin, usually in the pigment cells. Eg: Melanoma Cancer.

Sarcomas: are cancers of the supporting tissues of the body, such as bone, muscle and blood vessels. Eg: Bone cancer, breast cancer and soft tissue cancer.

Leukemias and Lymphomas: are the cancers of the blood and lymph glands respectively. Eg: ALL, AML, CLL, CML, Hodgkins and Non Hodgkins.

Gliomas: are cancers of the nerve tissue. Eg: Brain cancer.

Trends in Cancer Treatment: Cancer is a nearly invincible disease that has plagued humankind for centuries. Only in recent decades have doctors found effective ways to treat it and also found better methods for early detection of this devastating disease. But there are still years away from any possible cure for cancer, something that many scientists think is impossible. While early detection is the best form of prevention, there are several techniques that are used to treat cancer. These techniques include:

- Surgery
- Radiation therapy
- Chemotherapy
- Hormone therapy
- Immuno therapy

Surgery: is the oldest and most widely used treatment available for cancer patients. If a growth is found early there is a good chance to remove an entire tumor before it spreads. Surgery is rarely used as a stand-alone treatment. Usually, it is combined with radiation therapy and /or chemotherapy.

In Radiation Therapy: the specific part of the body containing a cancerous growth is exposed to radiation energy to attack reproducing cancer cells, to shrink a tumor so that it can be removed through surgery, or to prevent tumor growth following surgery. However radiation affects normal cells along with the cancer cells which leads to several unpleasant side effects, including fatigue, dryness and peeling of skin, nausea and vomiting.

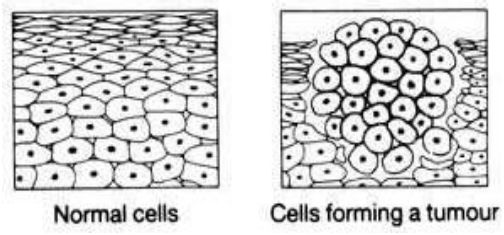
Chemotherapy: the treatment of cancer through drugs, is an effective treatment method for fighting cancerous cells that have spread to other parts of the body and that cannot be treated with any other method. Similar to radiation therapy, chemotherapy also can affect normal cells, causing the same kinds of side effects.

Two more recent treatments for cancer are hormone therapy and immunotherapy. Hormone therapy involves anything that deals with manipulating the body's hormones to treat the cancer, including administering hormones and drugs. It may also involve removal hormone glands to kill cancer cells or prevent further cancerous growth. Immunotherapy also manipulates the body's normal functions. During immunotherapy, patients are given medication to stimulate the body's immune system to fight cancerous cells. Many different compounds of biological origin that are used in the immune response can now be made in the laboratory; these are Interferons, Interleukin 2 (IL2) and Monoclonal antibodies. Interferon-alpha and Interleukin 2 might act by boosting the immune response to help the body kill off cancer cells.

Gene therapy encompasses a wide range of treatment types that all use genetic material to modify cells (either in vitro or in vivo). The original goal of gene therapy was to correct a genetic disorder by inserting a functional gene into an organism to replace a defective one. Numerous in vitro and preclinical animal models, testing a wide variety of gene therapy agents, have shown remarkable efficacy. Other than inherited diseases, single gene disorders have been treated with gene therapy.

Scientists are also trying to develop vaccinations against cancer cells. The immune system is trained to see cancer cells as being invaders and kill them.

Cancer and the Immune System: The human body is made up of tiny building blocks called cells. Cells look and function differently throughout the body, but reproduce and repair themselves in the same way. This process normally happens in an organised and controlled manner. If cells become cancerous they start to divide in an uncontrolled way.



The immune system sometimes has difficulty recognising cancer cells and does not destroy them. The cancer cells then continue to grow.

The Role of Immune System: The immune system protects the body against infections by bacteria, viruses and other parasites. The cancer can weaken the immune system by invading the bone marrow where the cells that help to fight infection are made, which happens mostly in leukaemia or lymphoma.

Chemotherapy and radiotherapy can weaken immunity by causing a drop in the number of white blood cells made in the bone marrow.Some cells of the immune system can recognise cancer cells as abnormal and kill them. Unfortunately, this is not enough to get rid of a cancer altogether. But some new treatments aim to use the immune system to fight cancer.

Vaccines: Vaccines have been used for many years as a way of preventing certain infectious illnesses: for example, 'flu, tuberculosis (TB), measles, mumps, typhoid and German measles. Vaccines stimulate the body's immune system to recognise and fight abnormal 'foreign' cells in the body, such as viruses and bacteria.

The Aim of Cancer Vaccines: The aim of cancer vaccines is to stimulate the immune system to be able to recognise cancer cells as abnormal and destroy them. Some vaccines for particular cancers have been developed and are being tested to see whether they can treat a cancer, or help to stop it from coming back after cancer treatment.

Types of Cancer Vaccines Probably the most promising form of cancer treatment is immunotherapy, where scientists are developing several experimental cancer vaccines that could lead to the eradication of cancer in this century. There are two major categories that cancer vaccines fit into:

- Specific cancer vaccine
- Universal cancer vaccine

As the name suggests, specific cancer vaccines are designed to treat specific types of cancers. In other words, a vaccine could be developed for lung cancer, another vaccine could be used to treat colon cancer and yet another vaccine could treat skin cancer and so on. A more appealing cancer vaccine would be one that could fight cancer cells regardless of cancer type. This type of vaccine is called a universal cancer vaccine.

In these two categories, there are more specific types of cancer vaccines. Each type of cancer vaccine works on the same basic idea that the vaccine, which contains tumor cells or antigens, stimulates the patient's immune system, which produces special cells that kill cancer cells and prevent relapses of the cancer. Unlike vaccines for other disease that prevent the occurrence of the disease, there isn't a vaccine in development that can prevent the onset of cancer. Cancer vaccines are used only as a treatment after the cancer has been found in a patient. Here is a list of five kinds of cancer vaccines being developed:

- Antigen vaccines
- Anti-idiotype vaccines
- Dendritic cell vaccines
- DNA vaccines
- Tumor cell vaccines

Antigen Vaccines: These use tumor-specific antigens - proteins displayed on a tumor cell - to stimulate the immune system. By injecting these antigens into the cancerous area of the patient, the immune system will produce an increased amount of antibodies or cytotoxic T lymphocytes, also known as killer T cells, to attack cancer cells that carry that specific antigen. Multiple antigens can be used in this type of vaccine to vary the immune system response.

Anti-idiotype Vaccines: In some instances, some antibodies, called idiotype antibodies, act as antigens, triggering an immune response similar to that described above. In this case, the immune system will produce anti-idiotype antibodies to attack the idiotypes. Anti-idiotype antibodies can be mass-produced to produce a vaccine that can be injected to treat cancer.

Dendritic Cell Vaccines: Dendritic cells break the antigens on the cancer cell surfaces into smaller pieces. The dendritic cells then act as most-wanted posters for the immune system, displaying those antigen pieces to

the killer T cells. In order to make dendritic cell vaccines some of the patient's dendritic cells are extracted and immune cell stimulants are used to reproduce large amounts of dendritic cells in the lab. These dendritic cells are then exposed to antigens from the patient's cancer cells. This combination of dendritic cells and antigens is then injected into the patient and the dendritic cells work to program the T cells.

Tumor Cell Vaccines (Autologous /Allogeneic Tumor Cells): Autologous and allogeneic tumor cells were one of the first types of tumor vaccines to be used. Theoretically, the main advantage of tumor cell vaccines is that they have all the relevant tumor antigens needed by the immune system to mount an effective antitumor response. This is particularly true if autologous tumor cells are used instead of allogeneic tumor cells. A second advantage is that tumor cell-based immunization allows the development of cancer vaccines without knowing the specific antigens.

The advantages of tumor cell-based cancer vaccines must be balanced against two major disadvantages: the potential for autoimmunity and the potential for increasing the anergic status of the T cells due to the lack of functional co stimulatory molecules on tumor cells. Initial attempts to immunize cancer patients with tumor cells were disappointing and temporarily decreased interest in the field.

Tumor-APC Hybrids: A novel development in cancer vaccines is the use of tumor-APC fusion technology. The vaccines produced by exposing tumor cells and APCs to polyethylene glycol (PEG) or electrical fields, which results in the generation of a tumor-APC hybrid. The rationale behind this approach is that the resulting hybrid will have the appropriate TAA derived from the tumor and the unparalleled co stimulatory capabilities of the APCs. Preclinical studies have provided the rationale for the use of cell hybrids in the cancer vaccine setting. More importantly, the tumor-APC strategy already has been associated with major clinical responses in patients with metastatic renal carcinoma.

DNA Vaccines: With recent DNA (deoxyribonucleic acid) research, scientists are finding ways to use the genetic code of proteins produced in cells to aid the immune systems fight against cancer. Bits of DNA from the patient's cells are injected into the patient, which instructs the other cells to continuously produce certain antigens. This DNA vaccine increases production of antigens, which forces the immune system to respond by producing more T cells.

Cancer Vaccine Preparation: Cancer vaccines are made from the person's own cancer cells or from cells that are grown in a laboratory. The cancer cells are treated with heat or radiation, then they become inactive and can be used for vaccine prepartion. Certain proteins may then be taken from the cancer cells and used to make a cancer vaccine. These include antigens (the proteins on the cell surface which can stimulate an immune response), in some cases, whole cells may be used to make the vaccine. Often a cancer vaccine will also contain substances that are already known to boost the immune system, such as BCG (the vaccine that protects against tuberculosis). As the cancer vaccine contains similar proteins to the cancer cells, it is hoped that the immune system will be stimulated to start to attack and destroy them.

Mode of Delivery: Cancer vaccines are usually a liquid which is given by an intradermal injection. The dosage will depend on the type of cancer being treated and the type of vaccine being used.

The Possible Side Effects: The possible side effects of cancer vaccines include a skin reaction at the injection site, a skin rash or mild flu-like symptoms. Certain cancer vaccines may cause more specific symptoms.

Cancer Vaccines Which Are Currently under Clinical Trials:

Onyvax: (a monoclonal antibody 105AD7 anti-idiotype vaccine) is used for the treatment of advanced colorectal adenocarcinoma. The vaccine is administered endemic together with the BCG vaccine orintramuscularly together with the alum adjuvant

Cancer VAX: (a polyvalent melanoma vaccine) is being used together with the surgical treatment in the treatment of melanoma III stage. In order to increase the cellular immune response, this vaccine is given together with the BCG-vaccine

- An autologous tumor cell vaccine is under clinical tests for the patients with II and III stage adenocarcinoma of colon to prevent relapses after surgical treatments.

NY-ESO-1 Peptide Vaccine: is used endermic in the treatment of II-IV stage sarcoma of soft tissues expressing NY-ESO-1,LAGE antigen NY-ESO-1 or LAGE antigen. Granulocyte-macrophage colony stimulating factor (GM-CSF) is to be injected, subcutaneous, in additional to this vaccine.

A Monoclonal Antibody 11D10 Anti-idiotype Vaccine and Monoclonal Antibody 3h1 Anti-idiotype Vaccine: are being used in the treatment of the patients with stage II or IIIA non-small cell lung cancer (T1-3, N1-2, M0) which is administered starting from the 14-45 days after operation.

- A vaccinotherapy using Tyrosinase, gp100 and MART-1 peptides together with the alum adjuvant is being used for the treatment of the patients with IIB, IIC, III, or IV cutaneous melanoma OR stage III or IV ocular or mucosal melanoma. Interleukin-12 and the granulocyte-macrophage colony-stimulating factor (GM-CSF) are also used beside the vaccine.

- ALVAC-CEA/B7.1, a deactivated strain of a virus, is being tested for the treatment of metastatic colorectal cancer. Virus antigens are identical to the antigens exhibited by colorectal tumors. Unlike its predecessors, this vaccine is being administered immediately upon diagnosis along with chemotherapy.
- VG-1000 Vaccine is a specialized vaccine, which undermines the cancer cells defense mechanisms. This vaccine is most beneficial in treating carcinomas and melanomas. Patients subjected to chemotherapy or radiation respond more slowly to VG-1000 as they have a depressed immune system, however, patients who have had neither radiation nor chemotherapy respond favorably indicating it as first-line treatment for persons with recently diagnosed cancers, as well as to help prevent recurrence.
- The name "Tricom" shorthand for a combination of three powerful co-stimulatory molecules - B7-1, ICAM and LFA-3 enhance T-cell response.
- The vaccine, called HSPPC-96, or Oncophage®, is a heat-shock protein, a class of compounds that has shown activity as autologous therapy, which means that the therapeutic agent is derived from and tailored to the tumors of individual patients. The HSPPC-96 vaccine contains antigens extracted from melanoma. Some of these antigens, like MART-1 and gp100, are unique to melanoma; others are found in many types of cancer.

Challenges to Be Addressed: Cancer vaccines have been researched for a number of years. Some studies in laboratory animals (such as mice) have shown promising results, in which vaccines have successfully stimulated the immune system. Research has not always been so successful in humans. However, recent studies have shown more encouraging results.

The main challenge is in the following areas:

- Many people with cancer have reduced immunity and so their immune systems are not able to react to the vaccines
- Some tumours produce proteins and chemicals that prevent the immune system from attacking them effectively, even when it has been stimulated by the vaccine
- Not all tumour cells are the same and some cells may be different to those in the vaccine. These 'different' cells will be resistant to and unaffected by, the vaccine

CONCLUSION

The vaccine development for Cancer is an exemplary approach of researchers to fight the most dread full disease around the globe. The various types of cancer vaccines and their clinical trails are most satisfactory and giving energy to the scientific community to concentrate more in this area. Future progress and development in this area surely provide the human kind beautiful weapons to fight with all kinds of cancer. In the present paper we highlighted the progress in cancer vaccine development and future perspective; it may be useful for researchers and student community to refresh their technical knowledge.

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