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TARGETING IMMUNITY TO TREAT CANCERS - A BRIEF REVIEW

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Abstract: Cancer cells have a multitude of mechanisms to avoid and suppress immunity. Normal cells when exposed to chemical carcinogens, irradiation and certain viruses get transformed to cancer cells which can grow indefinitely. These cells have decreased requirements for growth factors; do not undergo apoptosis resulting in malignancy. The tumor cells have various antigens which are responsible for the generation of immune responses towards that particular tumor. There are two types of tumor antigens; tumors specific transplantation antigens (TSTAs) and tumor associated transplantation antigens (TATAs). The TSTAs are specific to tumor, result from mutations which alter the cellular proteins while TATAs may be proteins present in or during some stages of fetal development but not expressed or expressed at low levels in normal adult cells. Adoptive T-cell therapy involves the ex vivo cultivation of T cells with activity against a specific target cancer antigen to increase the frequency of these T cells to achieve therapeutic levels and then infuse them back into the patient. Oncolytic viruses selectively infect, replicate in, and kill tumor cells with no or limited impact on normal tissues which means that tumor cells have surface receptors to bind the virus. Monoclonal antibodies (mAbs) are immunoglobulins derived from a single clone of B cells, act by targeting an antigen which acts a ligand of receptor involved in signal transduction within the cell.

Introduction

Cancer cells have a multitude of mechanisms to avoid and suppress immunity. Normal cells when exposed to chemical carcinogens, irradiation and certain viruses get transformed to cancer cells which can grow indefinitely. These cells have decreased requirements for growth factors; do not undergo apoptosis resulting in malignancy.

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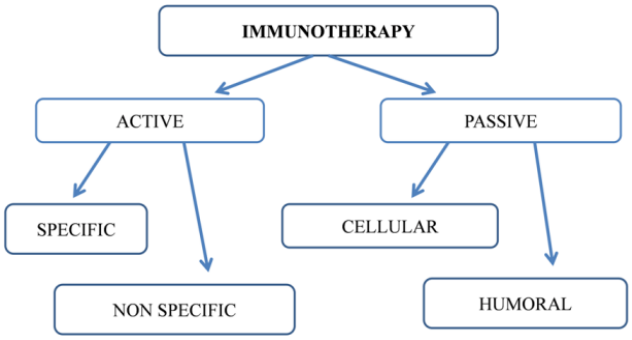
Cancer cells frequently arise in our body but are kept in check by immune surveillance which recognises them as foreign and eliminates these cells. Some T cells kill tumor cells while B cells secrete antibodies which mark certain antigens present on tumor cells making them more susceptible to killing by macrophages. Cancer cells can evade immune system by several mechanisms. There is formation of antibodies which act as blocking factors and mask the tumor antigens from cytotoxic T cells. The antigens specific to tumor disappear in the presence of such antibodies as antibody binding induces their endocytosis or the antigen antibody complex gets shed from the cell surface. There is also decreased expression of Class I MHC molecules on transformed cells resulting in decreased CD8 cytotoxic T- cell recognition. Other mechanisms include deletion of immune effector cells by death signalling, suppression of tumor-reactive T cells by regulatory T cells and spatial separation of Tcells and tumor cells. Several tumor-derived factors block dendritic cell ability to uptake, process, and present tumor antigens to T cells.[1]

Cancer immunotherapy works by stimulating the immunity against cancer cells by recognising certain antigens on them. The ideal tumor antigen is expressed in a significant proportion of patients with a particular cancer type, not expressed (or expressed at low levels) in normal tissues and is vital to the cancer's growth and/or survival.

Immunotherapy can be active or passive.

Active immunotherapy stimulates the immune system so that an anti tumor activity is initiated in the body while passive therapy makes use of immune system components prepared outside the body which may be cytokines, antibodies, immune cells or specific DNA.



Active immunotherapy

Active specific immunotherapy is based on capacity of T cells to recognize target antigens in the form of peptides complexed to surface MHC molecules. Specific cancer vaccines are cancer cells, parts of cells or pure antigens to stimulate the immune response against cancer cells. Thus, it causes the immune system to make antibodies to one or several specific antigens and/or vaccine presents tumor antigens to immune cells and activate CD4 (helper T-cells) and CD8 T-cells (cytotoxic/killer T-cells). Dendritic cell vaccine Sipuleucel T was the first cancer vaccine to be successfully tried for treatin hormone resistant prostate cancer. These vaccines lead to expansion of dendritic cells and optimal T cell activation by increasing the antigen presentation. The vaccines consist of an antigen which can be a protein, peptide, recombinant bacterium or a virus or tumor cells or parts of cells. For optimal activation of dendritic cells, the antigens are generally linked to dendritic cell growth and differentiation factor and a pattern recognition receptor or a bacterial or viral vector which can infect dendritic cells

and activate them. Vaccines carried by afferent lymphatics reach lymph nodes where antigen is presented to T cells. The activated T cells reach blood stream via efferent lymphatics and from there to peripheral tissues to initiate their anti tumor action. Other compounds are being tried using this principle including GRNVAC1 for acute myeloid leukemia, IDM-2 for superficial bladder cancer, IDD-3 for melanoma, INGN 225 for small-cell lung cancer, Prostvac-VF for prostate cancer and lapuleucel-T for breast, ovarian, and colon cancers.[3-8] Patient specific vaccine is produced by incubating patient's own peripheral blood mononuclear cells with a protein consisting of the target antigen linked to growth factor.

Adoptive T-cell therapy involves the ex vivo cultivation of T cells with activity against a specific target cancer antigen to increase the frequency of these T cells to achieve therapeutic levels and then infuse them back into the patient.[9,10] This approach is highly specific and has been investigated for the treatment of melanoma as the lymphocytes in this tumor are a rich source of tumor-specific CD4 + and CD8 +Tcells as compared to other malignancies.

Oncolytic viruses

Administering viruses that selectively infect, replicate in, and kill tumor cells with no or limited impact on normal tissues which means that tumor cells have surface receptors to bind the virus. First oncolytic virus (OV) was approved in China in 2005 for treating nasopharyngeal cancer and several others are undergoing phase III clinical trials in the US.[11,12] E.g. Human (eg, herpes simplex virus [HSV], adenovirus [Ad], measles virus [MV]) or veterinary (eg, vesicular stomatitis virus[VSV], Newcastle disease virus [NDV], myxomavirus [MYXV]).[13]

Tumor cell infection leads to cell death and release of progeny virions that are able to infect adjacent tumor cells. OV infection produces immuno stimulatory molecules to reactivate antitumor immunity. Viral antigens are presented on the surface of infected tumor cells or released in the tumor microenvironment. The stress induced by OV infection also releases cytokines and chemokines, damage-associated molecular patterns (DAMPs) eg, uric acid and heat-shock proteins.[14,15,16] All these inflammatory molecules contribute to dendritic cell (DC) maturation leading to improved antigen presentation, increased production of T cell costimulatory molecules like CD80, CD83, CD86 AND CD40.[17] After taking up released antigens, mature DCs can present them to T cells, including cytotoxic T lymphocytes(CTLs), which undergo proliferation. The specific CTLs can then migrate to the tumor site and kill tumor cells that have not been infected by OVs. DC activation stimulates natural killer cell-mediated antitumor activity.

Non-specific immunotherapies

These do not target a certain cell or antigen. Some non-specific immunotherapies can be given as cancer treatments. Others are used as adjuvants along with a main treatment. Large number of natural and synthetic products like cytokines, various bacterial lipopolysaccharides and glycoproteins have been tried e.g. Bacillus Calmette-Guerin (BCG), *Corynbacterium parvum* , *Propionibacterium acnes*, OK432 (picibanil) from *Streptococcus pyogenes*, biostim glycoprotein extract from *Klebsiella pneumoniae*, and bestatin from *Streptomyces* olivoreticuli.[18]

Bacillus Calmette-Guerin vaccine

It has been studied as a possible cancer therapy in the 1970s and evaluated as a cancer treatment via intralesional injection especially for melanoma. However, randomized trials failed to show a benefit for adding BCG in the adjuvant treatment of breast cancer or melanoma.[19-25] It

has been tried in bladder carcinoma and shown that after instillation of BCG, the bacterial organisms are internalized by the bladder epithelium. The resulting mycobacteria glycoprotein complexes induce an inflammatory response involving cellular infiltration and the local release of toxic cytokines.[18]

Cytokines – Interleukins

The cytokines that have been evaluated in cancer immunotherapy are IFN-α, β, ɣ and ; IL-1, IL-2, IL-4, IL-5, and IL-12; GM-CSF; and TNF. Their anticancer effects are due to their effects on immune cells.

Interferon – α

This cytokine has been extensively studied in virtually every malignancy. Daily injections have been shown to induce partial or complete tumor regression in some patients with hematologic malignancies such as leukemias, lymphomas, and myelomas and with solid tumors such as melanoma, Kaposi's sarcoma, renal cancer, and breast cancer.this cytokine increases class I MHC expression on tumor cells thereby increasing CTL activity against tumors. They inhibit cell division of both normal and malignantly transformed cells in vitro. Finally, IFN- directly or indirectly increases the activity of T cells, macrophages, and NK cells enhancing the anti tumor immunity. It was approved in 1986 for use in treatment of hairy cell leukemia. It has been also found active in hairy cell leukemia and as an adjuvant in treatment of melanoma after its resection.[26-32]

Granulocyte-macrophage colony-stimulating factor (GMCSF)

Another cytokine which has been tried in immunotherapy is Granulocyte-macrophage colony-stimulating factor (GMCSF). It has effects on myeloid cells, has been approved in 1992 to improve recovery of these cells after cytotoxic therapy.[33-35]

Interleukin -2

It has been shown to improve survival in advanced renal cell cancer in high doses.[36-38]

Tumor Necrosis Factors

TNF-α and TNF-β - exhibit direct antitumor activity, killing some tumor cells and reducing the rate of proliferation of others while sparing normal cells. TNF- α inhibits tumor-induced vascularization (angiogenesis). It damages the vascular endothelial cells in the vicinity of a tumor, decreasing the blood and oxygen supply that is necessary for tumor growth[39, 40].

Although many of cytokines are useful immunotherapeutic agents but there are many complexities making their use difficult. Most notable obstacle is to know how intervention with a given recombinant cytokine will affect the production of other cytokines. Some cytokines act antagonistically, so it is possible that intervention with a recombinant cytokine may lead to suppression of the effect. It is difficult to administer the cytokines locally. Sometimes, even life-threatening consequences may result.[41]

In vitro Lymphokine activated killer (LAK) cells and Tumor infiltrating lymphocytes (TIL) cells

Lymphocytes can be activated against tumor antigens in vitro by culturing them with irradiated tumor cells in the presence of IL-2 and added tumor antigens. Activated lymphocytes are capable of more effective tumor destruction than untreated lymphocytes when they are reinjected. These cells are It was observed that activated lymphoid cells could kill fresh tumor cells but not normal cells. But it is difficult to activate enough lymphocytes in vitro to be useful in cancer therapy.[42-44] Tumors contain lymphocytes that have infiltrated and take part in an antitumor response. These are tumor infiltrating lymphocytes (TILs). Many TILs have wide range of antitumor activity and indistinguishable

from LAK cells. Some TILs cells have specific cytolytic activity against their autologous tumor. They have increased antitumor activity and require 100 times lower amount of IL-2 for their activity than LAK cells do.[45]

Adjuvants

Traditional adjuvants act as immune stimulators or antigen delivery systems, or both. These include killed bacteria, bacterial components, aluminum salts, oil emulsions, polysaccharide particles and biopolymers, which when co administered with a protein antigen, enhance its immunogenicity.[46]

Monoclonal antibodies (mAbs)

They are a form of passive immunotherapy, do not generate immunologic memory and, therefore, require chronic infusion-based treatment. These are the immunoglobulins derived from a single clone of B cells, initially thought to work by inducing complement mediated cytoxicity but now it has become clear that they act by targeting an antigen which acts a ligand of receptor involved in signal transduction within the cell.[47-49] Earlier only murine antibodies were being used but now totally humanised antibodies are available. There are two types of monoclonal antibodies, naked or unconjugated and conjugated.[50]

Naked or unconugated mAbs

Antibodies that work by themselves are the most commonly used mAbs with no drug or radioactive material attached to them. Some of the examples are **Alemtuzumab** which binds to CD52 antigen found on B cells and T cells. Once attached, the antibody triggers the destruction of the cell by the immune system. It has been used to treat chronic lymphocytic leukemia.[51,52] Another example is **Trastuzumab** which is an antibody against the HER2/neu protein. When HER2/neu is activated, cells grow. Trastuzumab stops these proteins from becoming active.[53,54]

Conjugated antibodies

They may carry radioactive molecule, drug or a toxin to enhance the cytotoxicity. mAbs with radioactive particles attached are referred to as *radiolabeled, &* treatment with these type of antibodies is known as *radioimmunotherapy (RIT)* while those bound to chemotherapy drugs are referred to as *chemolabeled* and those attached to cell toxins are called *immunotoxins.* E.g. **Ibritumomab tiuxetan** and **tositumomab**, both of which are antibodies against the CD20 antigen, but with different radioactive particle attached. They deliver radioactivity to B cells and are used to treat some types of non-Hodgkin lymphoma.[55-59]

Examples of chemolabelled antibodies are Brentuximab vedotin, made up of an antibody that targets the CD30 antigen (found on B cells and T cells), attached to a chemo drug called *MMAE* and **Ado-trastuzumab emtansine** which is made of an antibody that targets the HER2 protein attached to a chemo drug called DM1.[60]

There are certain limitations of the passive antibody therapy, most notable being poor penetration into large tumor masses. This might be overcome by smaller molecules that retain specific antigen binding capacity. There are normal cells expressing a target antigen as well as cells bearing receptors for immunoglobulin carbohydrates which bind to antibodies thereby creating problems of specificity. Chemically modifying or genetically altering antibodies may overcome these difficulties to an extent. Moreover, antibodies are immunogenic and maybe attacked by immune system. Humanized antibody can be used to avoid this problem.

Immunotoxins/Magic Bullets

These are composed of tumor-specific monoclonal antibodies coupled to lethal toxins and are potentially valuable therapeutic reagents. Examples include Ricin, Shigella toxin, and

diphtheria toxin, which inhibit protein synthesis. They consist of two types of polypeptide components, an inhibitory (toxin) chain and one or more binding chains, which interact with receptors on cell surfaces. The toxin cannot get into cells without the binding polypeptide(s) and therefore is harmless. An immunotoxin is prepared by replacing the binding polypeptide(s) with a monoclonal antibody that is specific for a particular tumor cell and have been used in leukemia, lymphoma. The toxin binds to a receptor and the immunotoxin binds to a tumor-associated antigen. In either case, the toxin is internalized in an endosome. The toxin chain is released into cytoplasm, inhibits protein synthesis by inactivation of elongation factor 2 (EF-2).[61,62]

Conclusion

We have many options but assessment of these anticancer agents can be done by evaluating patient outcome in the terms of quality of life, cost benefit ratio and toxicity profile of these agents. Dendritic cell vaccines induce good antitumor activity and are safe while monoclonal antibodies are being increasingly included in the chemotherapy regimens. There is a hope that we can combat cancer by using multi modality regimens and increase the patient survival and quality of life in non curative settings.

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