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STUDY ON TUMORS DIAGNOSIS BY MRI

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Introduction

Magnetic resonance imaging: -

Magnetic resonance imaging (MRI) is a medical imaging technique used in radiology to form pictures of the anatomy and the physiological processes of the body. MRI scanners use strong magnetic fields, magnetic field gradients, and radio waves to generate images of the organs in the body. MRI does not involve X-rays or the use of ionizing radiation, which distinguishes it from CT and PET scans. MRI is a medical application of nuclear magnetic resonance (NMR) which can also be used for imaging in other NMR applications, such as NMR spectroscopy.

MRI is widely used in hospitals and clinics for medical diagnosis, staging and followup of disease. Compared to CT, MRI provides better contrast in images of soft-tissues, e.g. in the brain or abdomen. However, it may be perceived as less comfortable by patients, due to the usually longer and louder measurements with the subject in a long, confining tube, though "Open" MRI designs mostly relieve this. Additionally, implants and other non-removable metal in the body can pose a risk and may exclude some patients from undergoing an MRI examination safely.

MRI was originally called NMRI (nuclear magnetic resonance imaging), but "nuclear" was dropped to avoid negative associations. Certain atomic nuclei are able to absorb radio frequency energy when placed in an external magnetic field; the resultant evolving spin polarization can induce a RF signal in a radio frequency coil and thereby be detected. In clinical and research MRI, hydrogen atoms are most often used to generate a macroscopic polarization that is detected by antennas close to the subject being examined. Hydrogen atoms are naturally abundant in humans and other biological organisms, particularly in water and fat. For this reason, most MRI scans essentially map the location of water and fat in the body. Pulses of radio waves excite the nuclear spin energy transition, and magnetic field gradients localize the polarization in space. By varying the parameters of the pulse sequence, different contrasts may be generated between tissues based on the relaxation properties of the hydrogen atoms therein.

This technology is employed in the MRI scanner. This is the structure made of a large, strong magnet where the patient lies within. Radiofrequency magnetic fields are used in the alteration of magnetization. Consequently, the magnetic field of the nucleus is caused to rotate. The scanner can detect the magnetic fields from the nuclei, record, and produce images of the particular area. The device also produces different magnetic field gradients. This causes the nucleus to move at different speeds depending on its location. Therefore, this provides spatial information that is necessary to provide 2D and 3D imaging.

Magnetic Resonance Imaging can differentiate between the soft tissues of body organs. This makes it possible to imagine the heart, muscle, and brain. It is also possible to detect cancers using this technology (Damadian, Goldsmith, & Minkoff, 1977). Other technologies that can be used for the same purpose include X-rays and computed tomography (CT) scans. However, the difference is that these two use ionizing radiation.

Since its development in the 1970s and 1980s, MRI has proven to be a versatile imaging technique. While MRI is most prominently used in diagnostic medicine and biomedical research, it also may be used to form images of non-living objects, such as mummies. Diffusion MRI and functional MRI extend the utility of MRI to capture neuronal tracts and blood flow respectively in the nervous system, in addition to detailed spatial images. The sustained increase in demand for MRI within health systems has led to concerns about cost effectiveness and overdiagnosis.

The mechanism behind MRI machines: -

These machines take advantage of the fact that the human body and the tissues contain huge volumes of water. Therefore, the protons can be easily aligned. A radio frequency is then introduced to produce different electromagnetic fields. The frequency of this field is referred to as the resonance frequency. The radiofrequency is then switched off to allow the protons to return to equilibrium. This process defines their relaxation rate. They become aligned with the static magnetic field. During this process, radio frequency signals are generated. They can then be measured by the receivers.

If information about their positions in 3D space is required, more magnetic fields are introduced. Physicians can use 3D images to detect small changes in structures within the human body. These rates vary depending on the type of tissue. Therefore, it is possible to differentiate between the tissues. To make the internal organs and tissues more visible, contrast agents are added. They are injected into the area of investigation to make images easily distinguishable.

For instance, they may be used for producing images of the joints. MRI is usually considered safe as compared to CT scans and x-rays. This is mainly since it does not use ionizing radiation. However, this procedure may not be very safe for individuals with metal implants. These implants may be in the form of cardiac pacemakers. In the case of individuals with cardiac pacemakers, MRI scans are strongly discouraged since they can lead to death. The strong magnetic field generated by the device affects the functioning of such equipment.

Applications of MRI: -

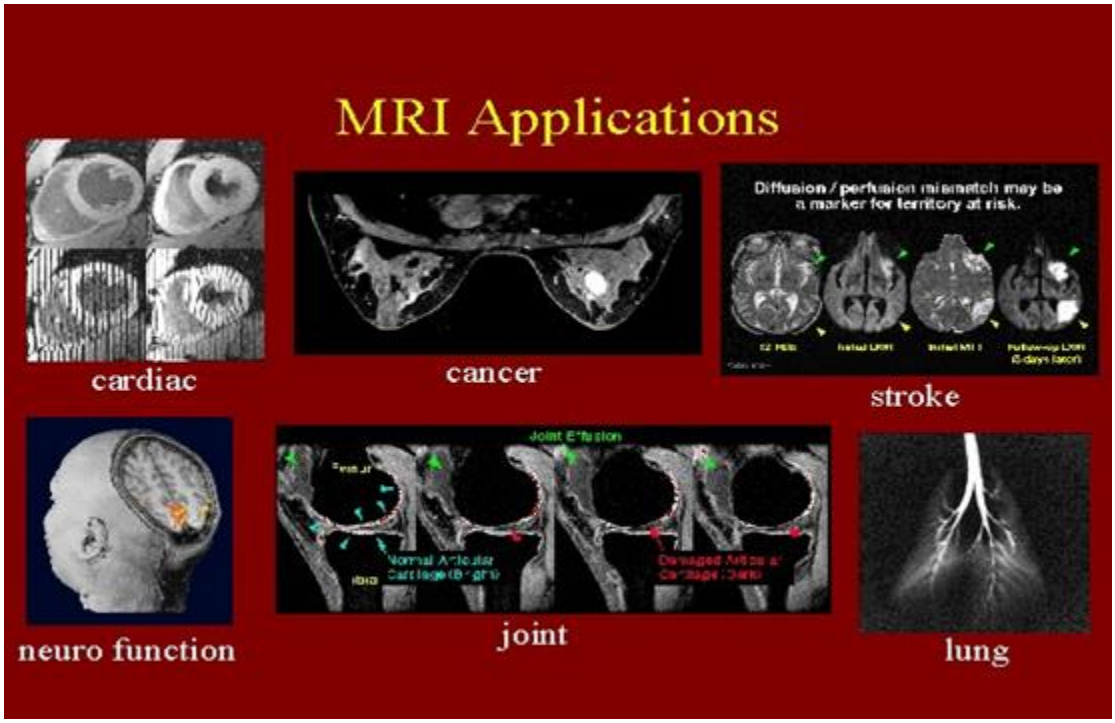
Since MRI can differentiate between normal tissues and pathologic tissues, it may be applicable for detecting brain tumours. Coupled with the safety associated with this process, MRI is widely used in medicine. It also produces better contrast resolution when compared to the CT scans and the traditional X-rays. This technique may also be used to detect multiple sclerosis. Although MRI is used to provide imaging of the soft tissue, it may also be used to produce images of teeth and bones.

MRI may generally be administered to individuals suffering from the following ailments:

1. Inflammations and infections in organs
2. Stroke
3. Degenerative diseases
4. Tumors
5. Musculoskeletal disorders
6. Measuring volumes of brain structures
7. Detection of cancers of the breast, colorectal, liver, and prostate
8. Various other irregularities within tissues or organs

Problems within the nervous system are best investigated using MRI imaging. This is especially because the spinal cord and brain might need to be examined and other methods such as x-rays may not be safe. Functional MRI may be done to determine the functions of different parts of the brain. Certain parts control different functions of the human body. This technology is used to measure changes in brain activity.

The technology behind MRI may be used to burn out disease tissues. This procedure is referred to as magnetic resonance-guided focused ultrasound (MRgFUS) therapy. It is whereby ultrasound beams are focused on the target. The beam is guided to the target tissue by the use of MR thermal imaging. Using 3D imaging, the beam may be directed with precision. When the beams have been focused, the temperatures within the area rise to high temperatures and eventually destroy the tissue.



Risk factors associated with MRIs: -

Despite the many advantages of the use of MRI in medicine, there are several risks associated with its use and they are brought about by the following:

1. The strong magnetic fields
2. Loud noise produced by the magnetic forces
3. Cryogenic liquids
4. Radio waves
5. Cryogenic liquids
6. MRI contrasting agents

- Strong magnetic field – it has been determined that patients with certain medical implants should not undergo MRI examinations (Jost & Kumar, 1998). If such patients must undergo the examinations, the procedure must be done under certain strict conditions. This explains why patients are required to provide complete information about any implants within their bodies before they can enter the examination room. It has been reported that several patients with pacemakers have died while undergoing MRI scanning (Jost & Kumar, 1998). Research indicates that the appropriate precautions were not taken during those scans. However, scientific advancements have enabled the development of implants that can be scanned safely.
- Radio waves – the waves produced in the scanners usually cause a heating effect. A temperature rise occurs when the energy is absorbed by the body. When temperatures increase beyond certain limits, it may be fatal. Therefore, the rate of absorption must be limited.
- Acoustic noise – the noise caused by the MRI scanners is due to the switching of the field gradients. It usually causes changes in Lorentz force. The sound caused by these machines can reach 120 decibels (Price, & Wilde, Papadaki, Curran, & Kitney, 2001). This is equivalent to sound caused by a jet engine during take-off.

Therefore, everyone in the room requires ear protection.

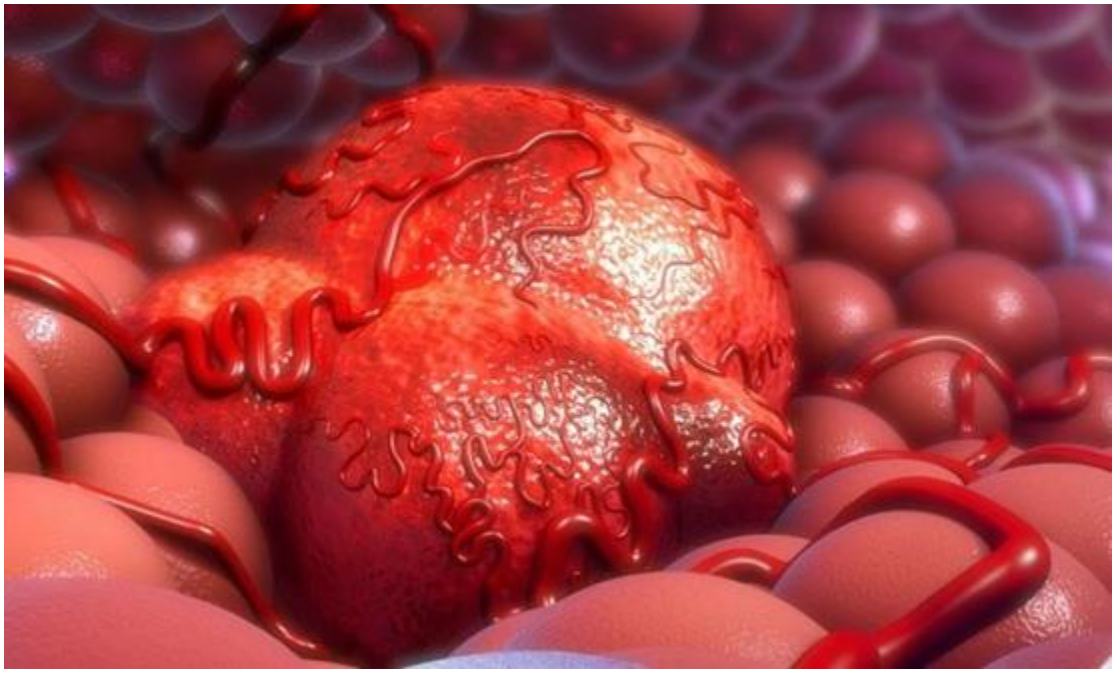
- Cryogenic liquids – the properties of the liquids used for enhancing superconductivity of the coils may be hazardous. The release of helium during 'quenching' may cause displacement of oxygen in the room. This may cause asphyxiation.
- Discomfort – some individuals find lying inside a scanner uncomfortable.

Claustrophobic individuals also find it hard to tolerate the long and narrow tunnel in the scanner. Therefore, modern scanners have been designed in such a way as to accommodate such individuals.

Tumors:

A tumor (L. tumere = to swell) is a growth or lump of tissue resulting from neoplasia or abnormal new cell growth and reproduction due to the loss of normal growth-control mechanisms. There are two major types of tumors, benign and malignant, with respect to overall form or growth pattern.

A tumor that is not capable of indefinite growth and does not invade the healthy surrounding tissue extensively is called benign, whereas a tumour that continues to grow and becomes progressively invasive is referred to as malignant; the term cancer refers specifically to a malignant tumour.



Malignant or cancerous tumor cells can actively spread throughout the body in a process known as metastasis. Metastasis is a process in which small clusters of cancerous cells dislodge from a tumor, invade the blood or lymphatic vessels, and are carried to other tissues where they continue to proliferate establishing secondary tumors. Malignant tumors or cancers are classified according to the embryonic origin of the tissue from which the tumor is derived.

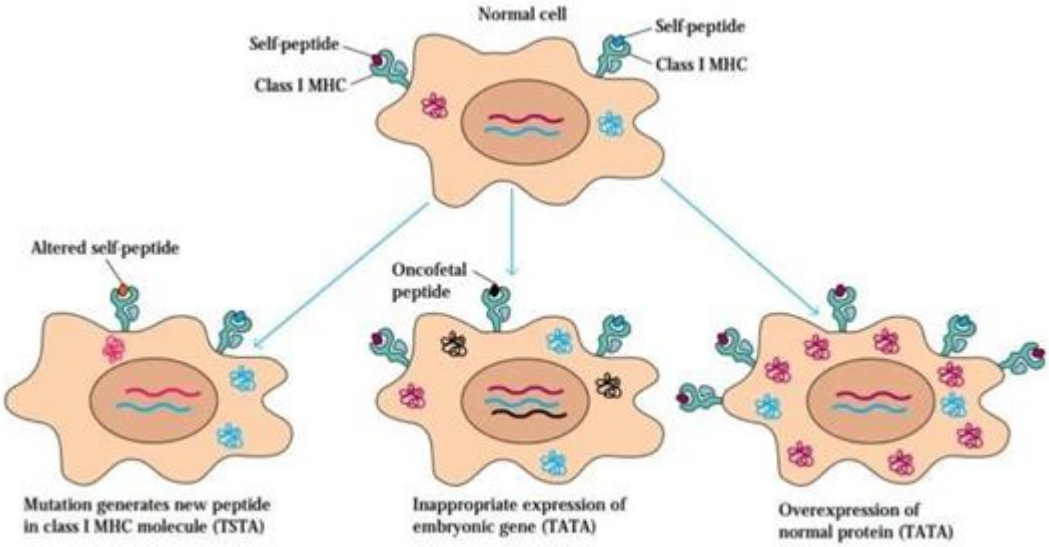
Most malignant tumors or cancers are carcinomas, the tumors which develop from endodermal or ectodermal tissues such as skin or the epithelial lining of internal organs and glands. The majority of cancers of the colon, breast, prostrate, and lung are carcinomas. Other malignant tumors or cancers are leukemias, lymphomas, and sarcomas.

The leukomas and lymphomas are the malignant tumors or cancers of hematopoietic cells of the bone marrow; these tumors are not solid like carcinomas, but cell suspensions. Leukemias proliferate as single cells, whereas lymphomas tend to grow cell masses. Sarcomas are derived from mesodermal connective tissues (e.g. bone, fat, cartilage) and arise less frequently.

Tumor Antigens:

Two types of antigens express on tumour cells:

1) Tumor-specific antigens (TSAs) and
2) Tumor-associated transplantation antigens (TATAs).



1. Tumor-specific antigens (TSAs):

Tumor-specific antigens (TSAs) are unique to tumor cells and do not occur on normal cells in the body. These antigens may result from mutations in tumor cells that generate altered cellular proteins. Cytosolic processing of these proteins gives rise to novel peptides that are presented with class I MHC molecules.

Virus induced tumor cells may express virus specific antigens with a cross- reactivity specificity in all tumors induced by the same virus. For convenience, the common oncogenic RNA virus causes T-cell leukemia in man where viral antigen activates cellular oncogenes to transform cell into a malignant one.

There are some tumors which are induced by chemical carcinogens (e.g., methylcholanthrene, azodyes). These chemically induced tumors have distinct tumour-specific antigens characteristic of that chemical, and do not show any cross-reactive pattern as in case of virally induced tumors.

2. Tumor-associated transplantation antigens (TATAs):

Tumor-associated transplantation antigens (TATAs). are proteins and are not unique to tumour cells. They are expressed both on normal and tumour cells but to a much greater extent on tumour cells. The best studied tumour-associated transplantation antigens are the oncofetal antigens which are normally associated with embryogenesis.

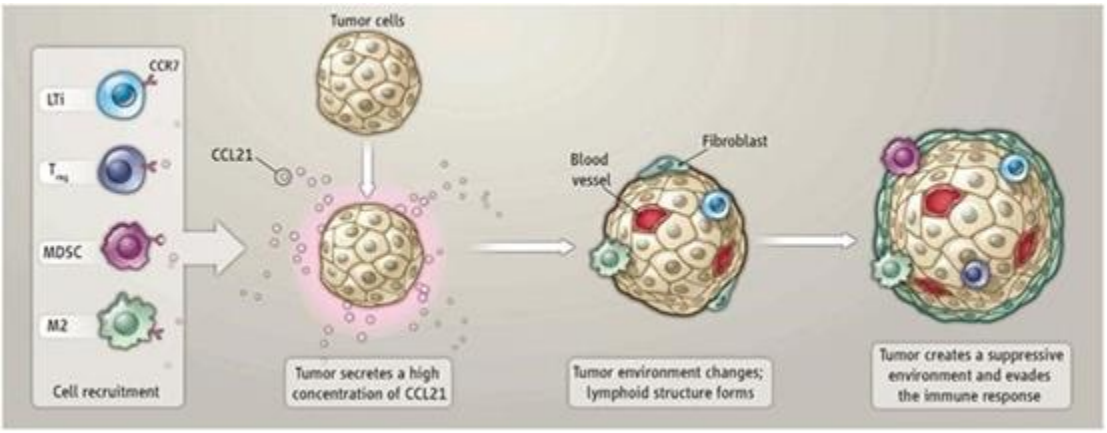
These antigens are expressed on normal cells during embryonic development when the immune system is immature and unable to respond but that normally are not expressed in adults. Reactivation of embryonic genes that encode these proteins in tumour cells results in their expression on the fully differentiated tumour cells.

Most commonly studied oncofetal antigen is carcino embryonic antigen (CEA) which is a faulty glycosylated protein appearing on the fetal gut and cancer cells found on the human colon. However, tumor-associated transplantation antigens (TATAs) are capable of inducing graft-rejection reactions in syngeneic hosts.

Tumor Evasion of the Immune System:

Although the immune system of the body clearly can respond to malignant tumour cells (cancerous cells) and destroy them, the fact that a large number of individuals become the victims of cancer every year and finally die suggests that the immune response to tumour cells is often ineffective.

The tumor cells, with the help of certain mechanisms, appear to evade the immune system of the body and cause death of the individual.



Some important mechanisms of tumor evasion of immune system are the following:

1. Serum blocking factors:

Experimental search was conducted about three decades ago to test the ability of serum (taken from tumor bearing individuals) to block tumor cell killing by lymphocytes of the immune system.

The result demonstrated was that the serum from tumor bearing individuals (animals as well as humans) do contains certain 'blocking factors' that can abrogate killing of the target tumour cells by lymphocytes immune to their specific antigens. These blocking factors are, most probably, the complexes formed between the antigens released from the tumors and antibodies formed by the host.

2. Antitumor antibody as a blocking factor:

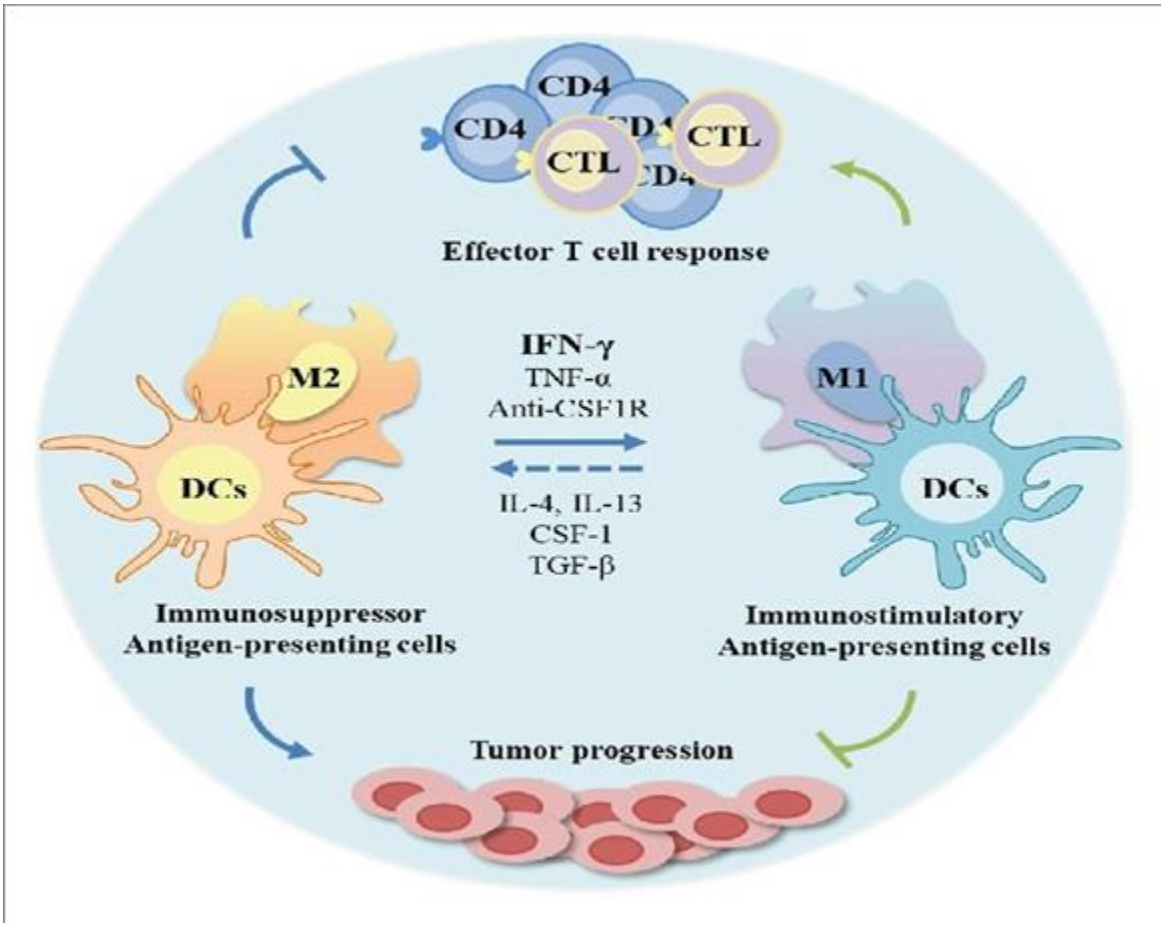
Antitumor antibodies itself function as a blocking factor in certain cases. It is considered that the antitumor antibody binds to tumour specific antigens and masks the antigens from cytotoxic T-cells.

In other cases, the antitumor antibodies do not act alone as blocking factor but rather they bind to tumour antigens forming antigen-antibody complexes that act as blocking factors and block the cytotoxic T-lymphocyte response. These complexes also may inhibit antibody-dependent cell- mediated cytotoxicity (ADCC) by binding to F_c receptors or natural killer cells (NK cells) or macrophages and blocking their activity.

3. Antigenic modulation:

It has been observed that certain tumour specific antigens (TSAs) disappear from the surface of tumour cells in presence of serum antibody and reappear after the serum antibody is no longer present. This phenomenon

is called antigenic modulation. The antigenic modulation is readily demonstrated when leukemic T-cells are injected into mice previously immunized with a leukemic T-cell antigen (TL antigen).



The injected mice develop high titers of anti-TL antibody which binds to the TL antigen on the leukemic cells and induces capping, endocytosis, and/or shedding of the antigen-antibody complex. As long as the antibody is present, these leukemic T-cells do not display the TL antigen and thus cannot be eliminated. It is concluded therefore that as long as the antibody is present it tends to acquire blocking action and protects the target against cell-mediated host defense.

4. Immunosuppressive secretions:

Some tumor cells may secrete immunosuppressive compounds, which inhibit the activity of nearby immune cells. This immunosuppressive activity is exhibited by alpha fetoprotein secreted by tumor cells and prostaglandins released by macrophages of tumor-bearing hosts.

5. Low level expression of class I MHC molecules:

A number of tumors have been demonstrated to express every low level of class I

MHC molecules on the surface of their cells. This low-level expression of class I

MHC molecules can be accompanied by progressive tumor growth because $CD8^+$ cytotoxic T-lymphocytes ($CD8^+$ CTLs) recognize only class I MHC molecule as antigens and any alteration in the expression of these antigens on tumour cells exerts a profound effect on the cytotoxic T-lymphocyte (CTL) mediated immune response.

6. Poor co-stimulatory signals:

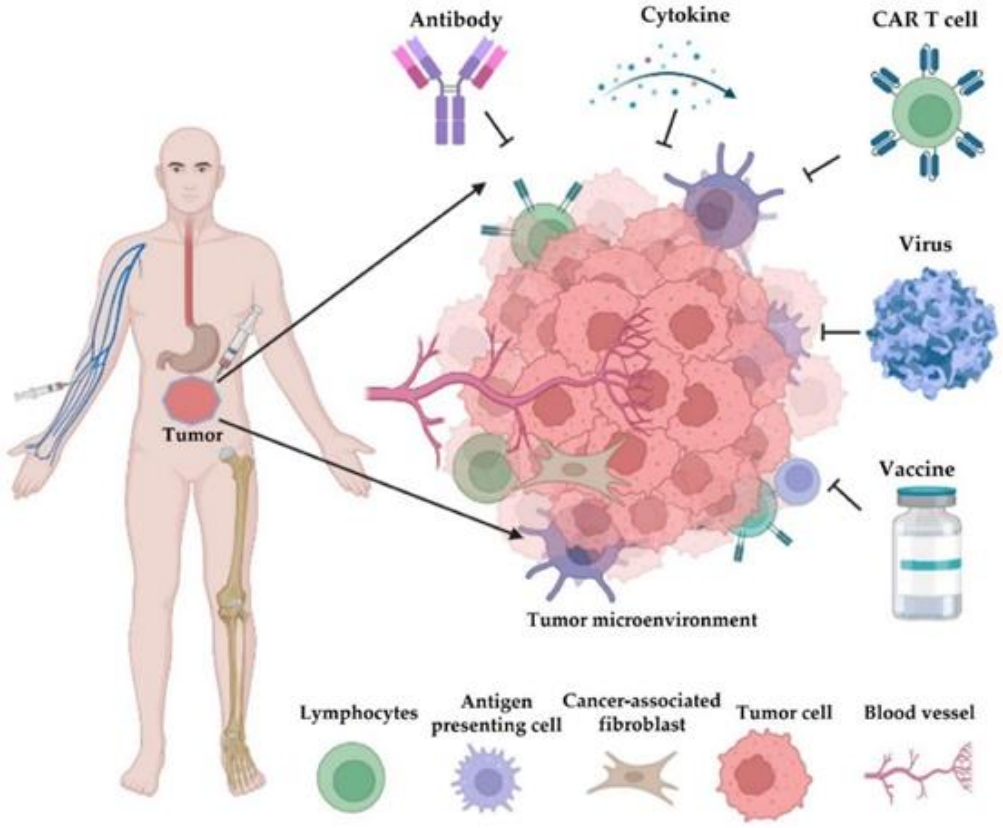
For immune response, T-cells require to be activated involving an activating signal and a co-stimulatory signal. Both signals are needed to induce interleukin-2 (IL-2) production and T-cell proliferation.

The poor immunogenicity of many tumour cells may be due in large part to lack the co-stimulatory signals provided by antigen-presenting cells (APCs). Since the APCs are very poor in number in the immediate vicinity of a tumour, the T-cells will receive only a partial activating signal, which may lead to clonal anergy.

In addition to the above mentioned, certain other mechanisms, for example, immunosuppression brought about by X-irradiation, immunosuppressive drugs, immunological tolerance, or the natural decline in immune reactivity with old age may be involved in tumour evasion of the immune system.

Tumour Immunotherapy:

Since it was recognized that many tumour cells do evade an immune response and make large number of individuals victims of cancer each year, much effort has been made to make immunotherapy a successful approach to treat cancer. One such immunotherapy approach to treat cancer is to augment or supplement the natural defense mechanisms of the body.



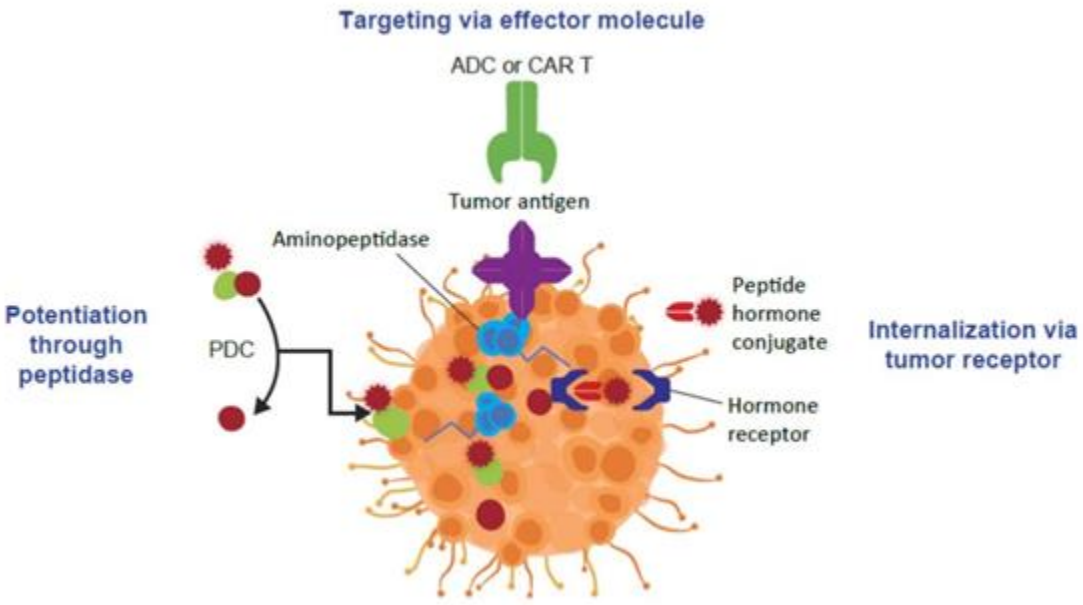
Several types of immunotherapy devices to treat cancer are in current use or under development; some important ones are the following:

1. Monoclonal antibody-polypeptide conjugate treatment:

Monoclonal antibodies specific to a cell-type yield a conjugate molecule called immunotoxin when linked with a toxin polypeptide. The antibody component of immunotoxin ensures its binding specifically and only to the target cells, and the attached toxin kills such cells.

This approach has been used to kill tumour cells in which the monoclonal antibodies specific to tumour cells have been linked to Ricin A, the toxic polypeptide of the natural toxin 'Ricin' found in the endosperms of castor (Ricinus communis), to obtain antibody-Ricin A conjugate (the immunotoxin).

The antibody-Ricin A conjugate has been shown to kill target tumour cells by inhibiting protein synthesis in them. In fact, the antibody used in the conjugate binds specifically to the antigen molecules present on the surface of target tumour cells, and the Ricin A polypeptide enzymatically and irreversibly modifies the larger subunit of ribosomes (actually their EF2 binding site) making them incapable of protein synthesis. It is noteworthy that the antibody-Ricin A conjugate (the immunotoxin) docs not bind to either other tumour cells or the normal cells.



2. Monoclonal antibody treatment:

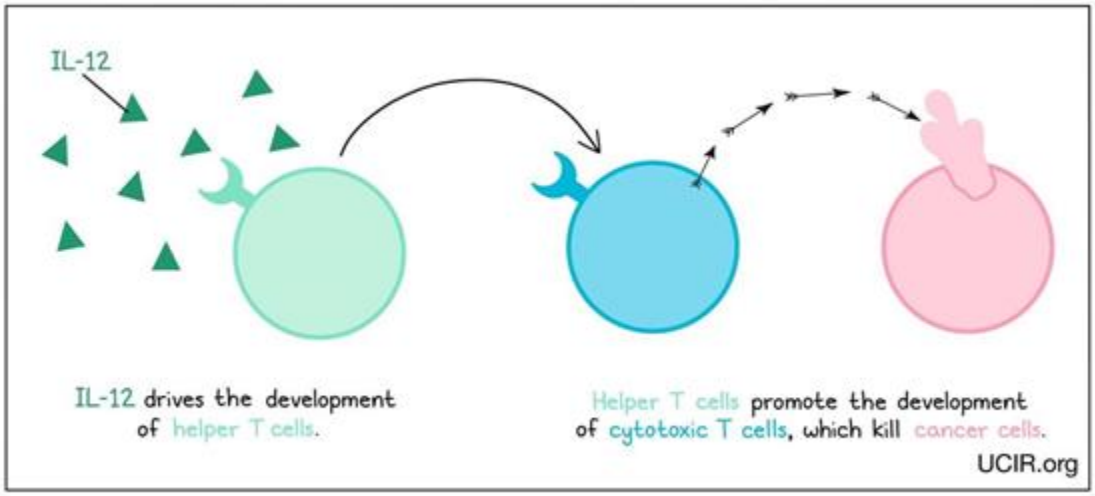
Monoclonal antibodies have been used in various ways as experimental immunotherapeutic agents for cancer.

Some such experimental achievements are the following:

1. Anti-idiotype monoclonal antibodies have been used with some success in treating human B-cell lymphomas and T-cell leukemias. But this approach requires that a custom monoclonal antibody be raised for each lymphoma patient. This is prohibitively expensive and cannot be used as a general therapeutic approach for the thousands of patients diagnosed each year with B-cell lymphoma.
2. A more general approach of monoclonal antibody therapy for B-cell lymphoma is demonstrated recently. Most B-cells, whether normal or cancerous, bear CD20 antigens. When a monoclonal antibody (raised in mice and engineered to contain mostly human sequences) binds to this antigen, the result is the treatment of B-cell lymphoma to a considerable extent. Aside from CD20, a number of tumor associated antigens are being tested in clinical trials for their suitability as targets for monoclonal antibody-mediated anti-tumour therapy.

3. Cytokine therapy:

Various cytokines are produced at large-scale by way of gene cloning. A number of experimental and clinical approaches have been developed to use these recombinant cytokines, cither singly or in combination, to augment the immune response against cancer.



The cytokines that have shown useful in cancer immunotherapy are interferon-α, β and γ; interleukin-1, 2, 4, 5, and 12; and TNF. However, this immunotherapeutic approach to treat cancer is still in its infancy because though the cytokines have produced occasional encouraging results in clinical trials, a number of obstacles still remain to be solved for successful use of cytokines to treat cancer.

4. Vaccination:

Vaccination is another approach to counter cancer. Chickens have been protected from Merek's lymphoma by vaccination. Mice has been vaccinated against malignant melanoma. In this case the normal mice were first vaccinated (immunized) with irritated melanoma cells and then challenged with unaltered malignant melanoma cells.

The 'vaccine' was found to protect a high percentage of the mice. It is hoped from these experimental results that a similar vaccine might prevent metastasis after surgical removal of primary melanoma in human patients.

5. Mutagenic drugs:

Treatment of cancer cells with mutagenic drugs leads to expression of new (and hopefully strong) antigenic determinants on cancer cells which can mount a powerful immunological response against cancer cells.

Conclusion: -

A plan for the diagnosis and treatment of cancer is a key component of any overall cancer control plan. Its main goal is to cure cancer patients or prolong their life considerably, ensuring a good quality of life. In order for a diagnosis and treatment program to be effective, it must never be developed in isolation. It needs to be linked to an early detection program so that cases are detected at an early stage, when treatment is more effective and there is a greater chance of cure. It also needs to be integrated with a palliative care program, so that patients with advanced cancers, who can no longer benefit from treatment, will get adequate relief from their physical, psychosocial and spiritual suffering. Furthermore, programs should include a awareness-raising component, to educate patients, family and community members about the cancer risk factors and the need for taking preventive measures to avoid developing cancer.

Where resources are limited, diagnosis and treatment services should initially target all patients presenting with curable cancers, such as breast, cervical and oral cancers that can be detected early. They could also include childhood acute lymphatic leukemia, which has a high potential for cure although it cannot be detected early. Above all, services need to be provided in an equitable and sustainable manner. As and when

more resources become available, the program can be extended to include other curable cancers as well as cancers for which treatment can prolong survival considerably.

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