BASICS OF IMMUNOLOGY OF CANCER

By

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SUMMARY

Mutant cell frequently occur during cell division for normal growth and development, which, if not cleared by the immune mechanism of the body (for example, when it is weak or deficient) ultimately grows into malignant tumours. The job of immuno-surveillance for cancer is done by circulating T-lymphocytes with the help of macrophages. At the present time only onco-fetal antigens are available for immuno diagnosis. Both specific i.e. tumour cell vaccine and non-specific i.e. use of general immunostimulents are under trial as immunotherapy. The two great herdles in the immunological dealing of cancer have been—to isolate tumour specific antigen in pure form and to artificially enhance the immunogenicity of cancer cell.

Introduction

In the recent years with the availability and application of array of highly sophisticated methods of investigations, immunology seem to be coming in the fore front in the etiology and hence in the management of cancers. In the present article an attempt has been made to summarise our present state of knowledge in this direction so as to stimulate applied research on this new weapon against cancer also for gynaecological malignancies which is already under way in many centres.

Immunological Basis of Carcinogenesis

It has been postulated that during cell division for normal growth and development mutant cell frequently occur, which, if not cleared by immune mechanism of the body (for example, when the mechanism is weak or deficient), ultimately grows into malignant tumours. This is based on the observation that these mutant or malignant cell often acquire a new antigenic moiety on their surface which leads the body to regard it as 'non-self' and to mount immunological response towards it. These new antigens are called tumour associated antigens (TAA) and it has been found to be one of the weak transplantation on histocompatibility antigens known as HL-A antigen (Disaia and Creasaman, 1981).

Scientific Evidences of Immunological Basis of Malignancy

Here is the summary of it (Disaia and Creasaman, 1981):

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1. Both congenital and acquired immune deficiency syndromes are associated with high incidence of malignancy.
2. Patients on immuno-suppressive drugs for prolonged period e.g. as following renal transplantation have been found to have markedly higher incidence (100 times greater than controls) of malignancy including gynaecological malignancy.
3. Cancer is more common in older age group—the period of life when, as is proven, immunological responses are normally decreased.
4. Even younger patients with malignant diseases have been found have reduced immune responses.
5. Patients with wide spread malignant diseases are often found more immunosuppressed than patients with early diseases.
6. Mice deprived of T-lymphocytes grow injected cancer cell faster.
7. Experimentally: Mice immunised to certain cancer cell by subcuteneous injection—reject the same cancer cells on repeat injection but accept normal tissue from the donor, conversely, immunisation against normal cells is found not to give immunity to cancer cell acceptence. This experiment supports the theory that malignant cells acquire new moiety.

Tumour Immunoserveillance

If during normal growth and development mutant or malignant cells frequently arise—there has to be some mechanism in the body of thorough and strict tumour immuno-surveillance to detect and clear these instantly—otherwise survival would be impossible.

Population of circulating T-lymphocytes (i.e. Thymus dependant lymphocyte) farm this immunosurveilance mechanism. Like the patrolling policemen these lymphocytes, along the blood stream, enter every corner and every tissue of the body and spot any antigenically response towards it in order to clear it (Walter and Israel, 1974 and Disaia and Creasaman, 1981)..

However, recent research shows that in addition to the usual elaborate immune response which require prior sensitisation of immune mechanism by antigenic stimulus, there appears to be another faster mechanism to clear developing malignant cells instantly without prior sensitisation. Ths is done by the newest type of lymphocyte discovered called Natural Killer (NK) lymphocytes which has been found to destroy malignant cell preferentially, in vitro, in several species, without prior sensitisation (Takasugi *et al*, 1973; Disaia and Creasaman, 1981).

Lymphocyte and Immuno-serveillance

T-lymphocytes constitute the so called army of "cell mediated" immunity. Activated T-lymphocytes bring about its effects by producing, on contact with antigen, a variety of soluble effector substances called lymphokines and so far over 25 of them have been discovered. Here are some of the well-known ones in relation of cancer-immunology:

1. Cytotoxic factor—effective against immunologically different cells.
2. Cell growth inhibitor factor—effective as above.
3. Tumour necrosis factor—effective against human neoplastic cell.
4. Lymphocyte activator—general stimulator or lymphocyte activity.
5. Transfer factor—This factor obtained from sensitised lymphocytes is capable of conferring or transfering specific antigenic reactivity to the

non-sensitised or innocent lymphocytes.

6. Interferon—Inhibits replication of viruses and also effective against malignant cells (Walter and Israel, 1974; Disaia and Creasaman, 1981).

Macrophage and Immuno-serveillance

Macrophages seem to perform three distinct functions as regards immuno-surveillance for cancer—

(a) Macrophages, after ingestion of foreign antigen, processes it within itself and then expresses it on its cell surface. It has been found that antigens which escape macrophage processing are poorly immunogenic.

(b) Clearing the antigen (foreign substance) itself is an important function of macrophage.

(c) Most interestingly, macrophages activated by lymphocytes have been found to exert killing effect on cancer cell (Walter and Israel, 1974; Disaia and Creasaman, 1981).

Mechanisms of Escape from Immune Serveillance

If there are such good detection and clearing mechanisms—how does the cancer occur then? So, there must be mechanisms of escape from immune surveillance. The following are the suggested mechanisms:

1. Low tumour antigenicity—Cells of sponteneously occurring malignant tumours are generally poorly antigenic and hence may not stimulate enough immune response.

2. Immunosuppressed individuals — Most cancer patients are found to have some degree of spontaneous immunosuppression already—allowing easy proliferation of mutant malignant cells. The findings of immunosuppressive factors in the serum of cancer patients go to support the above finding (Disaia and Creasaman, 1981).

3. Dodging effect of initial invaginating blood vessels—Neoplastic cells proliferate with their antigen tucked away behind the normal endothelial cells of ingrowing blood vessels and hence remain unspotted and unattacked by lymphocytes—the policeman (Disaia and Creasaman, 1981).

4. Development of Immune resistance and immune blocking factors by the malignant cells—by one of the following occurrences—

(a) Decrease of cell surface antigen thereby making them less antigenic.

(b) Decrease of antibody binding sites so that they remain unattacked by the antibodies directed against them.

(c) Shedding of excess of antigen in the surrounding extra cellular fluid which engage and paralyse lymphocytes—the policemen.

(d) Presence of excess of *blocking* antibodies in the surrounding extracellular fluid which saturate the antigenic sites on the surface of malignant cells leaving no site for lymphocytes to stick on and destroy the malignant cell (Disaia and Creasaman, 1981).

Immuno-diagnosis of Cancer

If immune mechanism is the basis of carcinogenesis—there should be methods of immuno-diagnosis. The endeavours in this line have been to find either specific tumour associated antigen or tumour specific antibody in patients blood. However, at the present time, due to extreme difficulty in isolation in pure form of tumour associated antigens, immune diag-

nosis, for most cancers, are not possible yet.

However, onco-fetal antigens e.g. Carcino-embryoinic antigen and alfa feto protein are examples of non-specific tumour associated antigen and are used in the immunodiagnosis of cancer including cancer vulva and other gynaecological cancer. Onco-fetal antigens are antigens found both in the fetus and also in malignant tissue, but not normally after birth. These antigens, which are normal in a fetus, are repressed as the process of intra-uterine development proceeds towards birth but are depressed during malignant transformotion process (Disaia and Creasaman, 1981).

It is interesting that extract of some malignant ovarian tumour has recently been found to show specific antigenicity and is being tried at test (Levi, 1971; Disaia and Creasaman, 1981).

Immunotherapy

Immunotherapy are of two types—non-specific and specific.

Non-specific immunotherapy: It consists of administration of some non-specific immunostimulents so that there occurs generalised enhancement of body's immune response menhanism towards any immunological challenge and cancer arrest occurs as a by-product. Non-specific immunotherapy aims to do the following—increase macrophage activity, increase maturation T-lymphocytes and also increase production of humoral antibodies. Agents used for this purpose are (Disaia and Creasaman, 1981)—

Those of bacterial origin—BCG vaccine, methanol extract of BCG and Corynebacteriam parvum.

Chemicals—Levamisole (the common anthalmentic), Interferons, and Thymocin (extract of Thymus).

Specific immunotherapy: This can be of three types—active, passive and adoptive.

Active immunotherapy consists of injection of patients own or syngenic or allogenic irradiated cancer cells to the patients so as to stimulate specific immune response in her, against those particular cells. To enhance antigenicity various pre-treatment of cancer cells is often done before injecting these to the patients like—enzyme treatment, viral incorporation, physical treatment, chemical modification etc. (Hudson *et al*, 1978).

Passive immunotherapy is similar to giving anti-tetanus serum (ATS) to a tetanus victim. Here antisera against patient's cancer cell, prepared by injecting patient's cancer cell into some animal, is given to the patient. However, besides the problem of foreign protein reaction, the main drawback of this technique is—it is supplying humoral antibodies (as opposed to cellular i.e. lymphocytes) which is not very effective against checking cancer growth.

Adoptive immunotherapy aims to supply cellular antibody i.e. lymphocyte. Syngenic or allogenic lymphocytes obtained from a donor immunised against patients cancer cell are transfused to the patient. But there are two major problems about this therapy—firstly, getting an allogenic donor agreeable to take the injection of cancer cell (even though rendered harmless by irradiation) and secondly, the problem of graft versus host reaction and rejection of the transfused cell.

To oviate the above difficulty, instead of transfusing the whole lymphocyte, administration of a lymphocyte product called 'transfer factor' is being tried. This 'transfer factor', obtained from the lymphocytes of a donor sensitised against patients cancer cell, when given to the

patient, is expected to convert non-sensitised lymphocytes of the patient to a responsive state against specific antigens in patient's cancer cells (Disaia and Creasaman, 1981).

Conclusion

From the available evidence it would appear that in near future—immunodiagnosis, immunotherapy and even immunoprophylaxis of cancer will form a part of routine management of cancer.

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