

مقدمة في علم المناعة الطبّي



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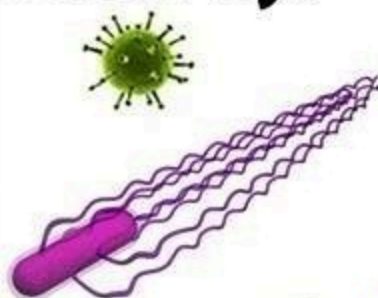
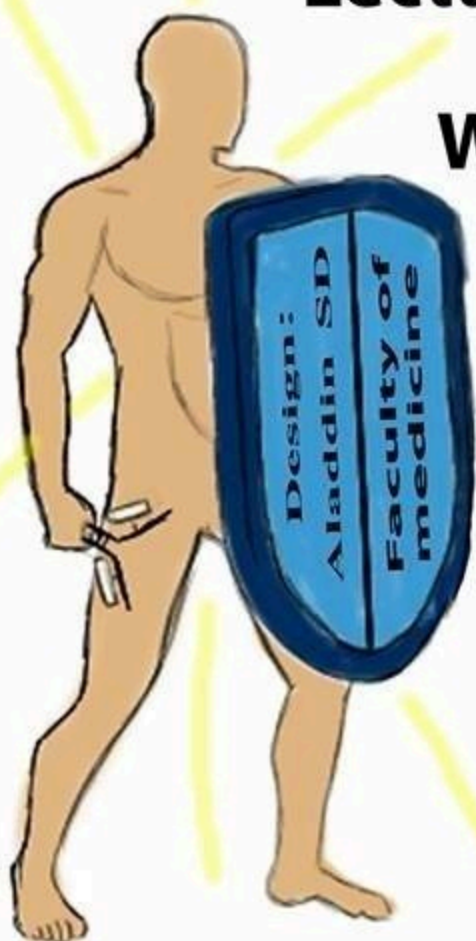
IMMUNOLOGY

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Subject: Tumors

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Tumour Immunology.

Immune surveillance : not well proven, but suspected to occur.

Tumours can be immunogenic : mononuclear cell infiltrate of T-cells, NK cells and macrophages are found around tumours.

Hyperplasia of draining lymph nodes.

Tumours with infiltrate may have better prognosis.

Immunodeficient patients have a higher incidence of some tumours.

Tumours are common in young and elderly (immune system not very efficient).

Thus it is reasonable to assume that tumour cells exhibit novel antigens.

Immune surveillance(if present) must often fail for tumours to occur.

Tumours occur as a result of mutation, physical or chemical agents, and viral infection. Oncogenic genes are activated and become out of control.

Tumour cells have antigens :

Antigens recognised by T-cells :

Transplantation antigens on carcinogen-or-radiation induced tumours. These are called tumour specific transplantation antigens (TSTA), they are very diverse and their nature is unknown.

Most human tumours are attributed to this type of tumour, they are not amenable to diagnosis, prophylaxis and treatment.

Experimental transplantation of tumours :

Chemical carcinogen induced sarcoma, transplant to another syngeneic inbred mouse, tumour grows. Transplant to original mouse, tumour is rejected because of immunity developing. Transplant to another syngeneic inbred mouse after adoptive transfer of CD8 cells from original mouse, tumour is rejected (protection through transferred CD8 cells).

Tumour in strain A to another strain A mouse : tumour either grows or regresses (rejected).
Tumour in strain A to strain B regresses.

(Immunize mouse with irradiated tumour cells, then plant live tumour cells, these are rejected. This does not occur in T cell deficient mice.)

These TSTA (tumour specific transplantation antigens) are tumour peptides presented by MHC.

Antigens that are abnormally expressed on tumour cells and may be normally expressed on normal cells at some stage or another of differentiation, are called tumour associated antigens and can be detected by the use of serology (specific antibodies).

What are these antigens :

1- Gene mutation products (new proteins or surface molecules).

2- Reactivation of silent gene products.

3- Differentiation antigens : e.g. immunoglobulins on B cell tumours. CD10 on B cells.

4- Embryonic and foetal antigens.

5- Antigens encoded by oncogenes : p53 (suppressor gene).

6- Antigens associated with oncogenic viruses :

Epstein-Barr virus is associated with B cell lymphoma, Hodgkin's lymphoma and nasopharyngeal carcinoma.

Human papilloma virus is associated with cervical carcinoma.

In animals but not in humans, these antigens are cross-reactive for different cases of the same virus induced tumour (contrast TSTA)

Some viruses carry well-defined oncogenes e.g. acute transforming retrovirus, producing tumours in animals. The only well recognised example in Humans is the HTLV-1 (human T cell lymphotropic virus-1) which causes adult T cell leukaemia which is an aggressive tumour of CD4 cells.

Hepatitis B and liver cell carcinoma.

Some of these antigens are encoded by the virus but are distinct from the virion antigens e.g. E1A found on human-adenovirus induced tumour in animals.

Cell surface antigens of Burkitt's lymphoma, colon carcinoma and melanoma may exhibit cross-reactivity between different patients.

Antigens defined by xenogenic antibodies : these are called tumour associated antigens :

1- Oncofoetal antigens : alpha-fetoprotein and carcinoembryonic antigen. These are useful diagnostic markers for hepatic and colonic carcinoma respectively. NB they may be elevated in inflammatory conditions.

2- Altered glycoprotein and glycolipids : e.g. aberrant expression of high level of blood group antigens on some carcinomas.

3- Tissue-specific (differentiation) antigens on tumour cells : these are useful for diagnosis when the histological appearance does not permit the diagnosis of the normal tissue of origin of the tumour, these are surface markers present on both normal and tumour cells e.g. surface immunoglobulins on mature B cells and tumours arising from these cells, CD4 and CD8 molecules on T-cell tumours.

Anti-tumour immunity :

Both humoral and cell-mediated responses have been demonstrated in vivo.

1)- T-lymphocytes : Tc cells is the most established CD8, Tc cells may have a surveillance role. Tc cells can be isolated from cancer patients that are cytolytic to tumour cells.

CD4 cells may produce cytokines that provide help to Tc cells, these are stimulated by macrophages (APC).

2)- NK cells : ADCC through Fc receptors. Their function may be enhanced by cytokines i.e. LAK cells. NK cells may play a role in immune surveillance. Lack of MHCI molecules.

3)- Macrophages : ADCC Fc receptor mediated. ? hypersensitivity reaction mediated by CD4 cells producing cytokines. Activated macrophages secrete TNF which binds to high affinity receptors on the surface of tumour cells, this is directly toxic to the cell. TNF also causes thrombosis of blood vessels of tumours causing their necrosis (hence the name).

4)- Antibodies : These are not specific for antigens present on tumours, as the antigens are present on normal cells as well. These antibodies may be against virus antigens in virally induced tumours. In general, these antibodies are of little protective value. In vitro they appear to act through complement activation and ADCC. Probably action through ADCC mainly in vivo (CD59).

Evasion of the immune system by tumours :

This may be due to several factors :

1)- Downregulation of class I expression, thus CTL would not function effectively.

2)- Lack of class II molecules : most cells do not possess class II molecules and cannot act as APC, normal APC's would have to thoroughly penetrate a tumour in large enough numbers to stimulate an immune response.

3)- The lack of co-stimulatory signals on tumour cells.

4)- Tumours may produce suppressing agents, TGF- β is secreted in large amounts by many tumours, this is an inhibitor of a wide range of lymphocyte and macrophage activities.

5)- The tumour antigens may be presented in a way that induces tolerance rather than immunity.

6)- Antigenic modulation : this is due to endocytosis or shedding of antigen-antibody complexes.

7)- Masking of tumour antigens by glycocalyx molecules which are more abundant on tumour cells, or by the activity of the coagulation system that results in their covering with fibrin.

8)- Presence of suppresser cells.

9)- Tumour mass : " sneaking through " transplantation of small numbers of tumour cells leads to lethal tumours, while transplantation of large tumours leads to rejection.

Immunotherapy of tumours :

1)- Non-specific stimulation of the immune system : local (i.e. at the site of tumour) BCG administration.

Experimental : low doses of anti-CD3 to stimulate T-lymphocytes.

2)- Active immunisation against tumours : inject killed or irradiated cells with adjuvant. This is largely unsuccessful.

Tumour cells are poor APC's because of the lack of costimulatory signals. Transferring into these cells genes that produce cytokines, B7 may increase the T-lymphocyte response.

Direct immunisation with purified tumour antigen.

Vaccination against viruses may be prophylactic against viral associated tumours.

3)- Adoptive cellular therapy : LAK cells produced in vitro under high IL-2 [] then re-injected into host. Also Tc cells removed from around the tumour which are presumed to be specific against the tumour.

4)-Passive therapy with anti-tumour antibodies : Magic bullets.

Radioactive or cytotoxic drug may be coupled to specific antibody against the tumour. The antibody has to be very specific which is problematic. Anti-idiotypic antibodies used in B cell tumours. Antibody against IL-2 receptor in adult T-cell leukaemia.

5)- Cytokines : enhance immune function. IL-2 increases blood lymphocytes and NK cells, it is toxic and its use is restricted to a few terminal cases.

IL-1 and INF gamma may be useful in melanoma and renal cell carcinoma. INF gamma activates macrophages and NK cells and upregulates expression of MHC molecules.

TNF is toxic at therapeutic levels. INF alpha potentially useful.

Prostatic specific antigen : prostate cancer.

P acid phosphatase : prostate cancer.

CA-125 : ovarian cancer.

CA 15-3 : breast cancer.

CA 19-9 : pancreatic cancer.

HCG : germ cell cancers, testicular & ovarian.

CEA : colon cancer.

Alpha fetoprotein : hepatocellular carcinoma.