**Cancer** is altered self cells that have escaped normal growth regulating mechanisms. Occasionally, cells arise that no longer respond to normal growth-control mechanisms. These cells give rise to clones of cells that can expand to a considerable size, producing a tumor, or **neoplasm.**

 A tumor that is not capable of indefinite growth and does not invade the healthy surrounding tissue extensively is **benign.**

A tumor that continues to grow and becomes progressively invasive is **malignant;** the term **cancer**refers specifically to a malignant tumor. In addition to uncontrolled growth, malignant tumors exhibit **metastasis;** in this process, 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.

**Malignant transformation of cells:**

**Transformation**: is alteration of cell morphology & growth properties.

* Mutation of cells caused by various physical agents (UV light & ionizing irradiation) and Chemical agents ( alkylating agents)These chemical & physical Ag that induce tu are called **carcinogen**, of which, if it induces 2 separate tu at different sites in the same patient → the tu Ag are distinct, so, the immune response to one tu does not protect against other tu. i.e. they were highly specific.
* In contrast, in virally induced tu , the tu express tu Ag that, were shared by all tu induced by the same virus, even if in different site, i.e. there is cross-reaction, while, tu cell induced by different viruses do not cross-react. A number of DNA and RNA viruses have been shown to induce malignant transformation.

**TUMOR ANTIGENS**

* **Tu specific transformation Ag (TSTA),** which, is unique to tu cell & not found in normal cell. Result from mutations in tumor cells that generate altered proteins and, therefore, new antigens gives rise to be presented with class I MHC molecules, inducing a cell-mediated response by tumor-specific CTLs. TSAs have been identified on tumors induced with chemical or physical carcinogens, as well as on some virally induced tumors.
* **Tu associated transplantation Ag (TATA),** which is not unique to tu but, may be protein that expressed on normal cell also which are:
1. **Oncofetal Ag** a Those derived from mutation-induced reactivation of certain fetal or embryonic genes, called oncofetal tumor antigens, normally only appear early in embryonic development, before the immune system acquires immunocompetence. When transformation of cells causes them to appear at later stages of development on neoplastic cells of the adult, they are recognized as nonself and induce an immunologic response.

 **\*** Alpha-fetoprotein (AFP), that is normally present only during fetal life so, if it ↑ in adult life, it indicate liver cancer.

 **\*** Carcinoembryonic Ag (CEA) which, if ↑ in adult so, indicate colorectal carcinoma.

B.Over expression of normal Ag, **as growth factor & growth factor receptor** .These proteins, although transcribed in the adult, are normally tightly regulated and expressed only at low levels. For instance, a variety of tumor cells express:

1. the epidermal growth factor (EGF) receptor at levels 100 times greater than in normal cells.
2. Another, melanotransferrin, designated p97, has fibroblast growth factor-like activities. Whereas normal cells express fewer than, melanoma cells express.

Many clinical research studies aim to utilize these antigens as diagnostic or prognostic indicators, as well as therapeutic targets for tumor elimination.

**IMMUNE RESPONSES TO TUMORS**

Adaptive immune responses, mainly mediated by T cells, have been shown to control the development and progression of malignant tumors.HOW??

1. **T Lymphocytes**

The principal mechanism of adaptive immune protection against tumors is killing of tumor cells by CD8+ CTLs.

🡪**CD8+ T cell** responses specific for tumor antigens may require cross-presentation of the tumor antigens by dendritic cells.

 🡪CD4+ cells may play a role in anti-tumor immune responses by providing cytokines for differentiation of naive CD8+ T cells into effector and memory CTLs.

🡪 helper T cells specific for tumor antigens secrete cytokines, such as TNF and IFN-γ, that can increase tumor cell class I MHC expression and sensitivity to lysis by CTLs.

🡪IFN-γ may also activate macrophages to kill tumor cells.

1. **Antibodies**

🡪Antibodies may kill tumor cells by activating complement or by antibody-dependent cell-mediated cytotoxicity, in which Fc receptor–bearing macrophages or NK cells mediate the killing.

🡪Others called blocking Ab, enhance tu growth by blocking recognition of tu Ag by the host.

🡪Antibodies specific for tumor cell antigens are used for diagnosis, and the antigens are potential targets for antibody therapy.

1. **Natural Killer (NK) Cells**

NK cells kill many types of tumor cells,

🡪especially cells that have reduced class I MHC expression giving NK cells stimulatory signals (some tumors lose expression of class I MHC molecules, makes the tumors good targets for NK cells.)

🡪express ligands for NK cell–activating receptors.

🡪NK cells can be targeted to IgG antibody–coated tumor cells by Fc receptors.

🡪The tumoricidal capacity of NK cells is increased by cytokines, including interferon-γ (IFN-γ), IL-15, and IL-12, and the anti-tumor effects of these cytokines are partly attributable to stimulation of NK cell activity.

🡪IL-2–activated NK cells, called lymphokine-activated killer (LAK) cells, are derived by culture of peripheral blood cells or tumor-infiltrating lymphocytes from tumor patients with high doses of IL-2.

1. **Macrophages**

Macrophages are capable of both inhibiting and promoting the growth and spread of cancers, depending on their activation state.possible mechanism formacrophages activation include recognition of damage-associated molecular patterns from dying tumor cells by macrophage TLRs and other innate immune receptors, and activation of macrophages by IFN-γ produced by tumor-specific T cells.

1. **The Role of Cytokines**

**🡪IFN-γ**. This cytokine can exert direct anti-tumor effects on transformed cells, including enhanced class I MHC expression, making neoplastic cells better targets for CD8+ T cell recognition and destruction.

🡪The **cytokine IL-12** has ability to enhance anti-tumor immunity by driving the development to T-cell pathways: this cytokine encourages DCs to activate strong TH1 and CTL responses.

🡪The **cytokine TNF-α** was named for its anticancer activity. When it was injected into tumor-bearing animals, it induced hemorrhage and necrosis of the tumor.

**Immunoediting**

Role of the immune system in responding to cancer, it includes three phases (elimination, equilibrium, and escape) and incorporates both positive (anti-tumor) and negative (pro-tumor) processes mediated by the immune system in responding to malignancy.

* **The first phase, elimination**, is the traditional view of the immune system as a major player in the identification and destruction of newly formed cancer cells.
* **Equilibrium is the proposed second phase,** characterized by a state of balance between destruction and survival of a small number of neoplastic cells. Ample clinical evidence now suggests that phase 2 can continue for up to decades after the emergence of a tumor. However, identifying residual transformed cells and targeting them during this window is challenging.
* **Escape is the final phase** of cancer progression, when the most aggressive and least immunogenic of the residual tumor cells begin to thrive and spread.

**Tumor evasion of the immune system:**

1. **Escaping Immune Recognition by Loss of Antigen Expression:**

Immune responses to tumor cells impart selective pressures that result in the survival and outgrowth of variant tumor cells with reduced immunogenicity, a process that has been **called tumor immunoediting**. -loss of tumor-specific antigens- class I MHC expression may be downregulated on tumor cells so that they cannot be recognized by CTLs.

1. **Active Inhibition of Immune Responses:**
2. **Tumors may engage inhibitory mechanisms that suppress immune responses.** T- cell responses to some tumors are inhibited by the involvement of CTLA-4 one of the inhibitory pathways in T cells . A possible reason for this role of CTLA-4 is that tumor antigens are presented by APCs in the absence of strong innate immunity and thus with low levels of B7 costimulators. These low levels may be enough to engage the high-affinity receptor CTLA-4.
3. **Secreted products of tumor cells may suppress anti-tumor immune responses.** An example of an immunosuppressive tumor product is TGF-β, which is secreted in large quantities by many tumors and inhibits the proliferation and effector functions of lymphocytes and macrophages
4. **Regulatory T cells may suppress T cell responses to tumors. A** numbers of regulatory T cells are increased in tumor-bearing individuals, and these cells can be found in the cellular infiltrates in certain tumors.
5. **Tumor-associated macrophages may promote tumor growth and invasiveness by altering the tissue microenvironment and by suppressing T cell responses.** These macrophages have an phenotypesecrete mediators, such as IL-10 and prostaglandin E2, that impair T cell activation and effector functions. Conversely, tumor-associated macrophages also secrete factors that promote angiogenesis, such as TGF-β, which may enhance tumor growth.
6. **Ab can modulate tu Ag of which**, certain tu specific Ag have been observed to disappear from the surface of tu cell in the presence of serum Ab & then re-appear after the Ab is no longer present. This is called **Agic modulation.**

**Cancer immunotherapy:**

Approach of treatment is to augment natural defense mechanisms by:

|  |  |
| --- | --- |
| ◙ Manipulation of co-stimulatory signal through providing signal necessary for activation of CTL precursor. For e.g. if melanoma cell transfected with B7 ligand gene, then CTL-P will differentiate into effector CTL resulting in tu destruction. |   |

◙ Enhancement of APC activity as for e.g. culture of dendritic cell (from peripheral blood progenitor cell) in the presence of GM-CSF, TNF-α, & IL-4. All these 3 cytokines induce the generation of large number of dendritic cell.

◙ Cytokines therapy as,

**A.** IFN will ↑ class I MHC.

1. TNF- α & β which, have direct anti tu activity by killing some tu cell & ↓ the rate of proliferation of other, while sparing normal cell. TNF-α inhibit tu induced vascularization (angiogenesis) by damaging the vascular endothelial cell of a tu.
2. IL-2: (in high concentration) will activate one type of NK cell called **LAK cell** (lymphocyte activated killer cell), which are activated NK cell with TCR that kill tu cell & not normal cell.

**So, Lymphocyte + IL-2 → LAK → tu cell destruction.**

Also the tu contain specific lymphocyte that infiltrated the tu & have antitu response. These are called **TILs** (tu-infiltrating lymphocyte), these are indistinguishable from LAK cell, but have specific cytolytic activity against autologous tu & it need 100-fold lower level of IL-2 for their activation.As well, IL-1, 2, 4, 5, 12. GM-CSF. All augment immune response against tu. But the difficulty is that all have side effect as:

1. Some cytokine act antagonistically.
2. Difficulty in administration locally & if given systemically, it have serious effect & life threatening consequences.

◙ Monoclonal Ab as:

1. Anti growth factor receptor e.g, anti HER-2 for breast cancer.
2. Anti to tu specific Ag, that is coupled with radio-isotopes, which is called **guided missile therapy**.
3. Also the use of what is called **immunotoxin** of which, monoclonal Ab that contain or attached to diphtheria toxin will bind tu cell & the toxin part will destroy the cell.
4. BCG vaccine used to boost tu immunity by activating macrophage & ↑ the expression of various cytokine.

**Tu vaccine:** aim is to focus the cellular arm of immune system against the tu – associated Ag that exist in the body. So if immune system recognizes this Ag, it will act against it. An e.g. of this is the use of the tu that were biopsied or surgically removed, then placed in culture, to be used afterward as an immunogen. Of which sample from different tu can be prepared & frozened in order to be used as needed.

**So tu Ag + cell contain MHC I (dendritic cell) → Hybrid → immunogen**. The advantage of this is that, the hybrid cell has the Ag presenting capability of a dendritic cell but, also contains the Ag from the patient’s tu cell, then dendritic cell process tu Ag & present it to immune system of the patient.