Cancer: Origin and Terminology

In most organs and tissues of a mature animal, a balance is usually maintained between **cell renewal** and **cell death**.
Under normal circumstances, the production of new cells is regulated so that the number of any particular type of cell remains constant. Occasionally, though, 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.**

Transformation of Cells

Various chemical agents (e.g., DNA-alkylating reagents) and physical agents (e.g., ultraviolet light and ionizing radiation) and certain viruses that cause mutations have been shown to induce transformation.
Induction of malignant transformation with chemical or physical carcinogens appears to involve multiple steps and at least two distinct phases:- initiation and promotion.
Initiation involves changes in the genome but does not, in itself, lead to malignant transformation.
After initiation**, promoters** stimulate cell division and lead to malignant transformation.

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

A tumor that continues to grow and becomes progressively invasive is **malignant;** the term *cancer* refers specifically to a malignant tumor.
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. In this way a primary tumor at one site can give rise to a secondary tumor at another site.
Malignant tumors or cancers are classified according to the embryonic origin of the tissue from which the tumor is derived. Most (>80%) are **carcinomas:** tumors that arise 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, prostate, and lung are carcinomas.

The **leukemias** and **lymphomas** are malignant tumors of hematopoietic cells of the bone marrow

Leukemias proliferate as single cells, whereas lymphomas tend to grow as tumor masses.

Sarcomas, which arise less frequently are derived from mesodermal connective tissues such as bone, fat, and cartilage.

Cancer-Associated Genes Have Many Functions

An **oncogene** is a gene that has the potential to cause cancer, specific genes are capable of inducing cell transformation. Oncogenes and tumor suppressor genes have been shown to play an important role in this process, by regulating either cellular proliferation or cell death. Cancer-associated genes can be divided into three categories that reflect these different activities,

1- INDUCTION OF CELLULAR PROLIFERATION

One category of proto-oncogenes and their oncogenic counterparts encodes proteins that induce cellular proliferation. Some of these proteins function as growth factors or growth factor receptors. Included among these are *sis,* which encodes a form of platelet-derived growth factor, and *fms*, *erbB,* and *neu,* which encode growth-factor receptors.

2- INHIBITION OF CELLULAR PROLIFERATION

A second category of cancer-associated genes—called **tumor suppressor genes,** or anti-oncogenes—encodes proteins that inhibit excessive cell proliferation. Inactivation of these results in unregulated proliferation.

3- REGULATION OF PROGRAMMED CELL DEATH

A third category of cancer-associated genes regulates programmed cell death. These genes encode proteins that either block or induce apoptosis. Included in this category of oncogenes is *bcl-2,* an anti-apoptosis gene.

Tumors of the Immune System

Tumors of the immune system are classified as lymphomas or leukemias. Lymphomas proliferate as solid tumors within a lymphoid tissue such as the bone marrow, lymph nodes, or

thymus; they include Hodgkin's and non-Hodgkin's lymphomas.
Leukemias tend to proliferate as single cells and are detected by increased cell numbers in the blood or lymph.
Leukemia can develop in lymphoid or myeloid lineages.

Tumor Antigens

The sub-discipline of tumor immunology involves the study of antigens on tumor cells and the immune response to these antigens. Two types of tumor antigens have been identified on tumor cells:
1-**Tumor-specific transplantation antigens (TSTAs)** Tumor-specific antigens are unique to tumor cells and do not occur on normal cells in the body. They may result from mutations in tumor cells that generate altered cellular proteins; cytosolic processing of these proteins would give rise to novel peptides that are presented with class I MHC molecules, inducing a cell-mediated response by tumor-specific CTLs
2-Tumor-associated transplantation antigens (TATAs).
Tumor-associated antigens, which are not unique to tumor cells, may be proteins that are expressed on normal cells during fetal development when the immune system is immature and unable to respond but that normally are not expressed in the adult. Reactivation of the embryonic genes that encode these proteins in tumor cells results in their expression on the fully differentiated tumor cells. Tumor-associated antigens may also be proteins that are normally expressed at extremely low levels on normal cells but are expressed at much higher levels on tumor cells. It is now clear that the tumor antigens recognized by human T cells fall into one of four major categories:

- Antigens encoded by genes exclusively expressed by tumors
- Antigens encoded by variant forms of normal genes that have been altered by mutation
- Antigens normally expressed only at certain stages of differentiation or only by certain differentiation lineages
- Antigens that are over expressed in particular tumors

Many tumor antigens are cellular proteins that give rise to

peptides presented with MHC molecules; typically, these antigens have been identified by their ability to induce the proliferation of antigen-specific CTLs or helper T cells.

Tumors Can Induce Potent Immune Responses

tumor antigens can be shown to induce both humoral and cell-mediated immune responses that result in the destruction of the tumor cells. In general, the cell-mediated response appears to play the major role. A number of tumors have been shown to induce tumor-specific CTLs that recognize tumor antigens presented by class I MHC on the tumor cells.

NK Cells and Macrophages Are Important in Tumor Recognition

The recognition of tumor cells by NK cells is not MHC restricted. Thus, the activity of these cells is not compromised by the decreased MHC expression exhibited by some tumor cells. In some cases, Fc receptors on NK cells can bind to antibody-coated tumor cells, leading to ADCC.

macrophages are often observed to cluster around tumors, and their presence is often correlated with tumor regression. Like NK cells, macrophages are not MHC restricted and express Fc receptors, enabling them to bind to antibody on tumor cells and mediate ADCC. The antitumor activity of activated macrophages is probably mediated by lytic enzymes and reactive oxygen and nitrogen intermediates. In addition, activated macrophages secrete a cytokine called tumor necrosis factor (TNF-_) that has potent antitumor activity. When TNF-_ is injected into tumor bearing animals, it has been found to induce hemorrhage and necrosis of the tumor.

IMMUNE SURVEILLANCE THEORY

The immune surveillance theory was first conceptualized in the early 1900s by Paul Ehrlich. He suggested **that cancer cells frequently arise in the body but are recognized as foreign and eliminated by the immune system.** Lewis Thomas suggested that the cell-mediated branch of the immune system had evolved to patrol the body and eliminate cancer cells.

According to these concepts, tumors arise only if cancer cells are able to escape immune surveillance, either by reducing their expression of tumor antigens or by an impairment in the immune response to these cells.

The immune system continually surveyed the body for the presence of abnormal cells, which were destroyed when recognized. The immune system also played an important role in delaying the growth, or causing regression of established tumors, these ideas supported by a variety of evidence like:

1- Many tumors contain lymphoid infiltrates.
2- Spontaneous regression of tumors occurs.
3- Tumors occur more frequently in the neonatal and in old age, when the immune system function less effectively.
4- Tumors arise frequently in immunosuppressed individuals

Tumor Evasion of the Immune System

— Although the immune system clearly can respond to tumor cells, the fact that so many individuals die each year from cancer suggests that the immune response to tumor cells is often ineffective. This section describes several mechanisms by which tumor cells appear to evade the immune system:-

— 1-Many tumors have the capacity to ***modulate their surface Ags,*** expressing different Ags if the original Ags have been recognized

— 2-Tumors can also produce substances, such as sialomucin, that can bind to the surface of tumor cells and '***Mask***" any Ags that may be present

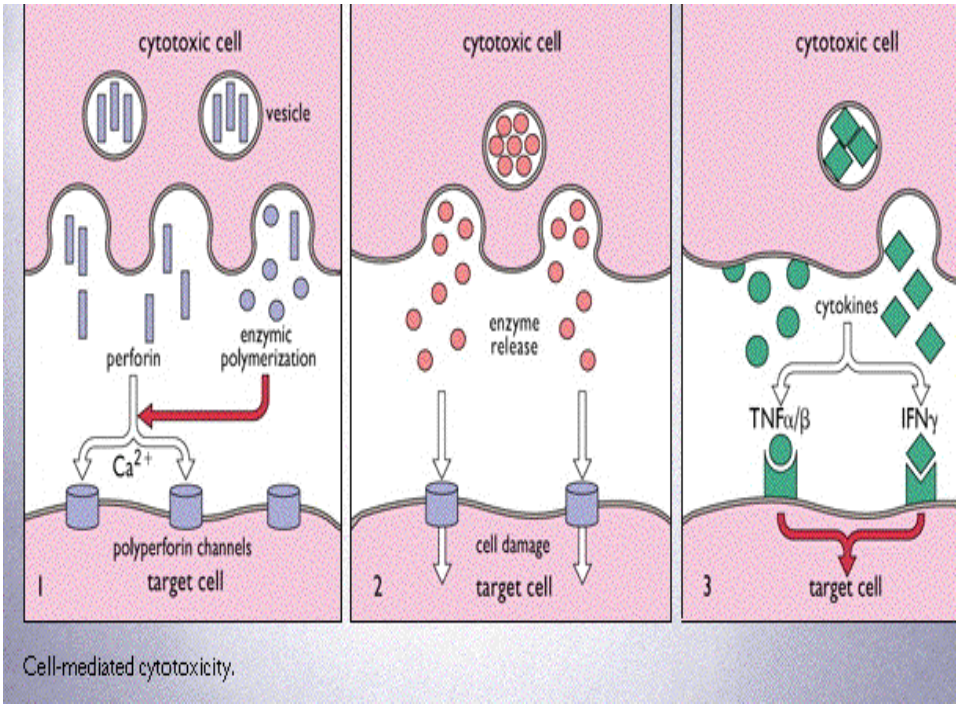
— 3-Tumor Cells Frequently Express Low Levels of Class I MHC Molecules

— 4-Tumor Cells May Provide Poor Co-Stimulatory

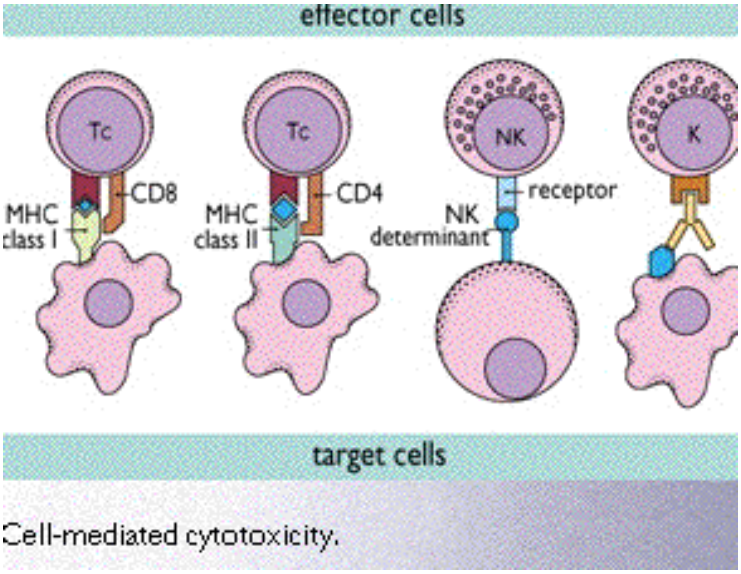
— ***5- Ag shed*** from the tumor have been detected in human serum, these soluble Ags may saturate the receptors on T- or B- cells.

— 6-Tumor cells may also lack other molecules required for adhesion of lymphocytes such as LFA-1, LFA-3 or ICAM-1,

— 7-Tumor may also secrete immunosuppressive cytokines such as TGFB and vascular endothelial growth factor (VEGF), and prostaglandin E2 that inhibit development and proliferation of T-cells.



Cell-mediated cytotoxicity.



Cell-mediated cytotoxicity.