TUMOR IMMUNOLOGY

Malignant Cells: that give rise to clones of cells that can expand in an uncontrolled manner will produce a tumor or neoplasm.

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

Malignant tumor: A tumor that continues to grow and becomes progressively more invasive; the term cancer refers specifically to a malignant tumor. malignant tumors exhibit metastasis, whereby small clusters of cancerous cells dislodge from the original tumor, invade the blood or lymphatic vessels, and are carried to other distant tissues, where they take up residence and 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:

Carcinomas, tumors that arise from epithelial origins such as skin, gut, or the epithelial lining of internal organs and glands.

leukemias, lymphomas, and myelomas are malignant tumors of hematopoietic cells derived from the bone marrow.

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

Transformation

- Transformation can be induced by various chemical substances (such as formaldehyde, DDT, and some pesticides), physical agents (e.g., asbestos), and ionizing radiation; all are linked to DNA mutations.
- Infection with certain viruses, most of which share the property of integrating into the host cell genome and disrupting chromosomal DNA, can also lead to transformation. Examples: HHV-8, HPV, HBV, EBV.

Normal cellular genes that are associated with the formation of cancer fall into three major categories based on their activities:

- **Oncogenes**: growth factors, Signal transducer, Transcription factors.
- **tumor-suppressor genes: Rb, Tp53…and etc.**

- **genes involved in programmed cell death, or apoptosis** as bcl-2,Bcl-Xl…etc.

  Tumor suppressor genes play the opposite role in homeostasis, dampening cellular growth and proliferation. Unlike oncogenes, which become the villain when their activity is enhanced, tumor-suppressor genes, also known as antioncogenes, become involved in cancer induction when they fail.

  Unlike oncogenes where a single allele alteration can lead to unregulated growth, tumor-suppressor genes require a "two-hit" disabling sequence, as the one functional allele is enough to suppress the development of cancer. Probably the single most frequent genetic abnormality in human cancer, found in 60% of all tumors, is a mutation in the TP53 gene. This tumor-suppressor gene encodes p53, a nuclear phosphoprotein with multiple cellular roles, including involvement in growth arrest, DNA repair, and apoptosis.

  Many of the genes involved in apoptosis have also been associated with cancer, as these genes either enforce or inhibit cell death signals.

  Pro-apoptotic genes act like tumor suppressors, normally inhibiting cell survival, whereas anti-apoptotic genes behave more like oncogenes, promoting cell survival. Thus, a failure of the former or overactivity of the latter can encourage neoplastic transformation of cells.

proto-oncogenes: a normal growth-promoting gene . mutations or genetic rearrangements of in situ proto-oncogenes by carcinogens or viruses might alter the normally regulated function of these genes, converting them into cancer inducers, called **cellular oncogenes.**

Tumor Antigens

Most tumor antigens give rise to peptides that are recognized by the immune system following presentation by self major histocompatibility complex (MHC) molecules. In fact, many of these antigens have been identified by their ability to induce the proliferation of antigen-specific cytotoxic T lymphocytes (CTLs) or helper T cells.

tumor antigens recognized by human T cells fall into one of four groups based on their source:

• Antigens encoded by genes exclusively expressed by tumors (e.g., viral genes)

• Antigens encoded by variant forms of normal genes that are altered by mutation

• Antigens normally expressed only at certain stages of development

• Antigens that are overexpressed in particular tumors

There are two main types of tumor antigens, categorized by their uniqueness: tumor-specific antigens (**TSAs**) and tumor-associated antigens (**TAAs**).

TSAs as HPV (cervical carcinoma), HBV (hepatocellular carcinoma)

TAAs as CEA (colon cancer), Alphafeto protein AFP (hepatocellular carcinoma), PSA (prostate).

TSAs are unique proteins that may result from mutations in tumor cells that generate altered proteins and, therefore, new antigens. Cytosolic processing of these proteins then gives rise to novel peptides that are 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.

The immune response to such tumors typically eliminates all of the tumor cells bearing sufficient numbers of these unique antigens, and thus selects for cells bearing few or none.

TAAs are not unique to the cancer. Instead, these represent normal cellular proteins typically expressed only during specific developmental stages, such as in the fetus, or at extremely low levels in normal conditions, but which are upregulated in tumor cells (see Figure 19-6). 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.

Immune response to cancer

There are three proposed mechanisms by which the immune system is thought to control cancer:

• By destroying viruses that are known to transform cells

• By eliminating pathogens and reducing pro-tumor inflammation

• By actively identifying and eliminating cancerous cells. This final mechanism, involving tumor cell identification and eradication, is termed **immunosurveillance.**

immunoediting; it incorporates observations of both tumor-inhibiting and tumor-enhancing processes mediated by the immune system.

Innate immunity

Natural Killer cell: natural killer (NK) cells were among the first cell type to be recognized for their inherent ability to destroy tumor cells, from which their name derives. NK cell recognition mechanisms use a series of surface receptors that respond to a balance of activating and inhibiting signals delivered by self cells. Once engaged, these cells use cytolytic granules that include such compounds as perforin to target their killing machinery at cells expressing these activating ligands. In fact, deficiency in perforin, a cytolytic compound used by both NK cells and CTLs to kill target cells, is linked to increased cancer susceptibility. Indirectly, NK cells may also participate in cancer eradication by secreting IFN-γ, a potent anticancer cytokine that encourages DCs to stimulate strong CTL responses in vitro.

Macrophage: Numerous observations indicate that activated macrophages also play a significant role in the immune response to tumors. macrophages are often observed to cluster around tumors, and the presence of pro-inflammatory macrophages, such as type M1, is 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 to mediate antibody-dependent cell-mediated cytotoxicity (ADCC; discussed further below). The anti-tumor activity of activated macrophages is likely mediated by lytic enzymes, as well as reactive oxygen and nitrogen intermediates. In addition, activated macrophages secrete a cytokine called tumor necrosis factor alpha (TNF-α) that has potent anti-tumor activity.

Eosinophil : animal lack chemoattractants of this cell become more susceptible for carcinogens.

Adaptive Cell Types Involved in Cancer Eradication

tumor antigens induce humoral and cell-mediated immune responses that lead to the destruction of transformed cells expressing these proteins. Animals that lack either αβ or γδ T cells are more susceptible to a number of induced and spontaneous tumors. Several tumors have been shown to induce CTLs that recognize tumor antigens presented by class I MHC on these neoplastic cells.

B cells respond to tumor-specific antigens by generating anti-tumor antibodies that can foster tumor-cell recognition and lysis. Using their Fc receptors, NK cells and macrophages again participate in this response, mediating ADCC.

The Role of Cytokines in Cancer Immunity

cytokine can exert direct anti-tumor eff ects on transformed cells, including enhanced class I MHC expression, making neoplastic cells better targets for CD8T cell recognition and destruction. Both type I (α/β) and type II (γ) interferons have immune cell-enhancing activities that can render these cells more efficient at tumor-cell removal**.**

IL-12: 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. However, this cytokine was later shown to have both tumor-inhibiting and tumor-promoting effects.

Evasion the tumor from immune system

Reduced MHC Expression in Tumor Cells Defects in antigen processing and presentation are common among the escape mutants arising in many tumors. These could include mutations that lead to reduced MHC expression, secretion of TSAs (rather than surface expression), defective transporter associated with antigen processing (TAP) or β2-microglobulin, and IFN-γ insensitivity. Each of these types of mutations results in decreased class I MHC presentation of tumor antigens and profound inhibition of CD8T-cell recognition.

Tumor Cell Subversion of Apoptosis Signals

The up-regulation of anti-apoptotic mediators and the expression of mutated or absent death receptors can lead to tumors that are resistant to programmed cell death signals.

Poor Costimulatory Signals Provided by Tumor Cells

As we know complete T-cell activation requires two signals: an activating signal, triggered by recognition of a peptide-MHC molecule complex by the T-cell receptor, and a costimulatory signal, triggered by the interaction of CD80/86 (B7) on antigen-presenting cells (APCs) with costimulatory molecules such as CD28 on T cells. Both signals are needed to induce IL-2 production and proliferation of T cells.

tumors have fairly poor immunogenicity and tend to lack costimulatory molecules. Without sufficient numbers of APCs in the immediate vicinity of a tumor and with few stimulators to drive the activation of these cells, responding T cells may receive only a partial activating signal. This can lead to clonal anergy and immune tolerance.

Immunotherapy

Monoclonal Antibody

Monoclonal antibodies (mAbs) have long been used as experimental immunotherapeutic agents for treating cancer. These mAbs may be used unmodified or can be conjugated with an agent to increase their efficacy. For instance, toxins, chemical agents, and radioactive particles can be attached to a mAb, which then delivers the conjugated substance to the target cell**.** mAb activated the complement system and lysed the malignant cells without harming other cells.

Some of the mAbs in clinical use can be coupled with radioactive isotopes, chemotherapy drugs, or potent toxins of biological origin. In such “guided missile” therapies, the toxic agents are delivered specifically to tumor cells. This ideally focuses the toxic eff ects on the tumor and spares normal tissues. Reagents known as immunotoxins have been constructed by coupling the inhibitor chain of a toxin (e.g., diphtheria toxin) to an antibody against a tumor-specific or tumor-associated antigen. In vitro studies have demonstrated that these “magic bullets” can kill tumor cells without harming normal cells.

Cytokines

The isolation and cloning of the various cytokine genes has facilitated the large-scale production of cytokines for use in clinical settings. Several of these have been used either singly or in combination to augment the immune response against cancer in clinical trials. Among these are all three interferons (IFN-β, -α, and -γ), the tumor necrosis factors (TNF-α and Lymphotoxin-α [TNF-β]), granulocyte-macrophage colony stimulating factor (GM-CSF) and several interleukins (IL-2, -4, -6, and -12).

Vaccine

Therapeutic vaccines, on the other hand, aim to enhance or redirect an existing immune response. Immunogens that make successful prophylactic vaccines do not always work once infection has been established. For example, the HPV vaccine, which is up to 99% effective at preventing infection by the strains that most commonly cause cervical cancer, is not effective once a women is already infected with one of these strains. Therefore, vaccines for use in patients with existing infections or malignant cells must be designed to redirect an already engaged immune response.

Manipulation of costimulatory molecules

tumors cells frequently lack the costimulatory signals required for full T-cell activation. Several research groups have demonstrated that tumor immunity can be enhanced when these costimulatory signals are modified.