Immunity to Tumors

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Main Topics

- Overview of tumor immunity
- Tumor antigens
- Immune responses to tumors
- Evasion of immune responses by tumors
- Immunotherapy for tumors
- The role of innate and adaptive immunity in promoting tumor growth
- Summary

Introduction

- Cancer is a major health problem worldwide and one of the most important causes of morbidity and mortality in children and adults.
- The concept **of immune surveillance of** cancer, which was proposed by Macfarlane Burnet in the 1950s, states that a physiologic function of the immune system is to recognize and destroy clones of transformed cells before they grow into tumors and to kill tumors after they are formed.

Overview of tumor immunity

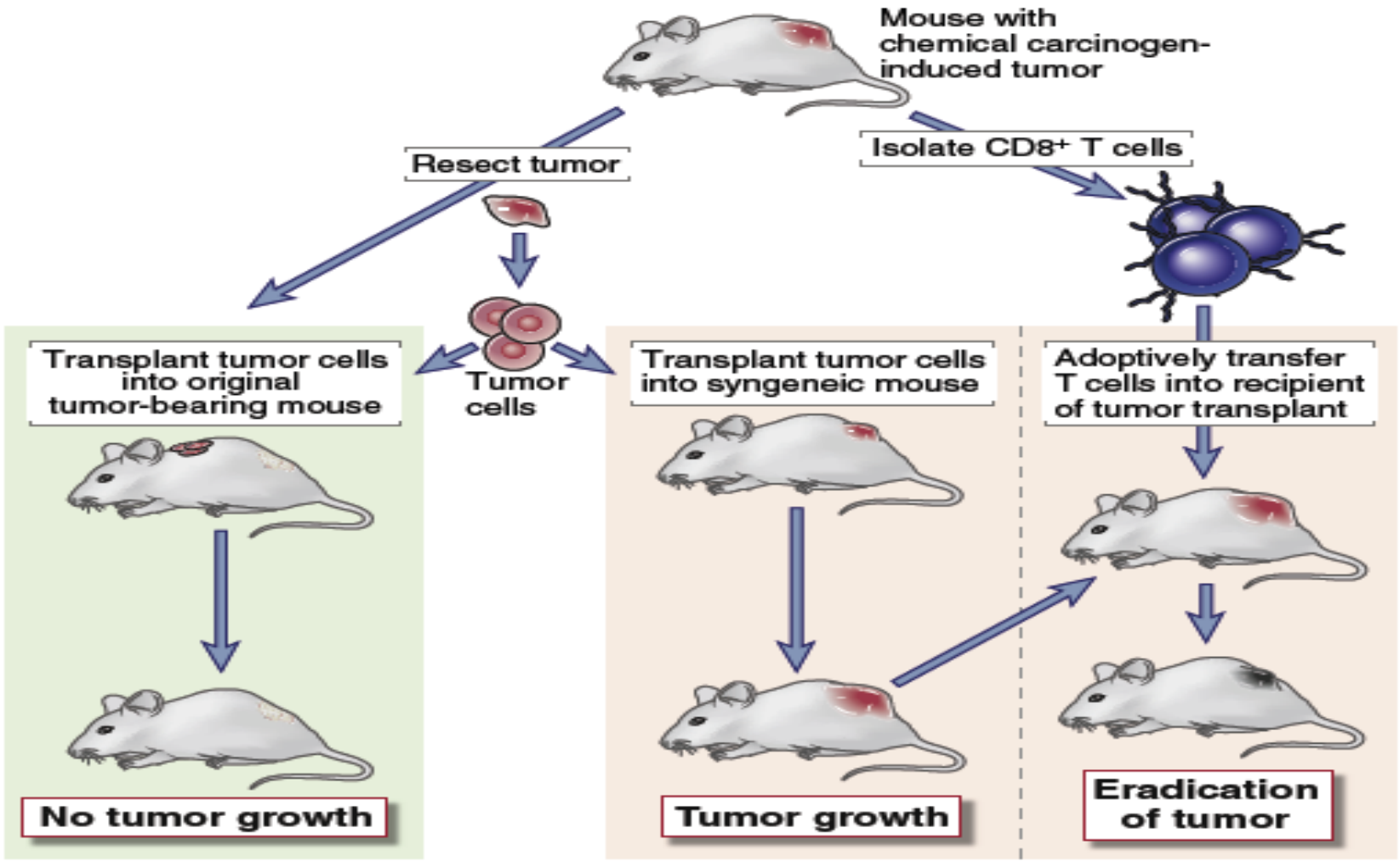
- Several characteristics of tumor antigens and immune responses to tumors are fundamental to an understanding of tumor immunity and for the development of strategies for cancer immunotherapy.

Tumors stimulate specific adaptive immune responses.

- Clinical observations and animal experiments have established that although tumor cells are derived from host cells, the tumors elicit immune responses.
- Histopathologic studies show that many tumors are surrounded by mononuclear cell infiltrates composed of T lymphocytes, natural killer (NK) cells, and macrophages, and that activated lymphocytes and macrophages are present in lymph nodes draining the sites of tumor growth.

A sarcoma may be induced in an inbred mouse by painting its skin with the chemical carcinogen methylcholanthrene (MCA). If the MCA induced tumor is excised and transplanted into other syngeneic mice, the tumor grows. In contrast, if cells from the original tumor are transplanted back into the original host, the mouse rejects this transplant and no tumor grows. The same mouse that had become Immune to its tumor is incapable of rejecting MCA induced tumors produced in other mice. Furthermore,

T cells from the tumor-bearing animal can transfer protective immunity against the tumor to a tumor-free animal. Thus, immune responses to tumors exhibit the defining characteristics of adaptive immunity, namely, specificity, memory, and the key role of lymphocytes. As predicted from these transplantation experiments, the most effective response against naturally arising tumors appears to be mediated mainly by T lymphocytes.



Experimental demonstration of tumor immunity. Mice that have been surgically cured of a chemical carcinogen (MCA)–induced tumor reject subsequent transplants of the same tumor, whereas the transplanted tumor grows in normal syngeneic mice. The tumor is also rejected in normal mice that are given adoptive transfer of T lymphocytes from the original tumor-bearing animal.

- Thus, immune responses to tumors exhibit the defining characteristics of adaptive immunity, namely, specificity, memory, and the key role of lymphocytes. As predicted from these transplantation experiments, the most effective response against naturally arising tumors appears to be mediated mainly by T lymphocytes.

Immune responses frequently fail to prevent the growth of tumors

- *First*, many tumors have specialized mechanisms for evading host immune responses.
- *Second*, tumor cells are derived from host cells and resemble normal cells in many respects. Therefore, many tumors tend to be weakly immunogenic.
- *Third*, the rapid growth and spread of a tumor may overwhelm the capacity of the immune system to effectively control the tumor, which requires that all the malignant cells be eliminated.

The immune system can be activated to effectively kill tumor cells and eradicate tumors

- The existence of specific anti-tumor immunity implies that tumors must express antigens that are recognized as foreign by the host.

TUMOR ANTIGENS

- The earliest classification of tumor antigens was based on their patterns of expression. Antigens that are expressed on tumor cells but not on normal cells are called **tumor-specific antigens.**
- Tumor antigens that are also expressed on normal cells are called **tumor-associated Antigens.**

- The modern classification of tumor antigens is based on the molecular structure and source of antigens expressed by tumor cells that stimulate **T cell** or **antibody responses** in their hosts.

How to identify antigen?

- For tumor antigens recognized by **CD8+ cytotoxic T lymphocytes (CTLs)**, investigators have established cloned lines of tumor-reactive CTLs from cancer patients and used these as probes to specifically identify the relevant peptide antigens or the genes encoding the peptides.
- These tumor antigen–specific CTL clones can detect responses to tumor-derived peptides or responses to proteins made by **complementary DNA (cDNA)** libraries of the tumor. Such approaches were first employed to identify human melanoma antigens that stimulated CTL responses in patients with the tumor.

TABLE 18-1 Tumor Antigens

Type of Antigen	Examples of Human Tumor Antigens
Products of mutated oncogenes, tumor suppressor genes	Oncogene products: Ras mutations (~10% of human carcinomas), p210 product of Bcr/Abl rearrangements (CML) Tumor suppressor gene products: mutated p53 (present in ~50% of human tumors)
Unmutated but overexpressed products of oncogenes	HER2/Neu (breast and other carcinomas)
Mutated forms of cellular genes not involved in tumorigenesis	Various mutated proteins in melanomas recognized by CTLs
Products of genes that are silent in most normal tissues	Cancer/testis antigens expressed in melanomas and many carcinomas; normally expressed mainly in the testis and placenta
Normal nononcogenic proteins overexpressed in tumor cells	Tyrosinase, gp100, MART in melanomas (normally expressed in melanocytes)
Products of oncogenic viruses	Papillomavirus E6 and E7 proteins (cervical carcinomas) EBNA-1 protein of EBV (EBV-associated lymphomas, nasopharyngeal carcinoma)
Oncofetal antigens	Carcinoembryonic antigen on many tumors, also expressed in liver and other tissues during inflammation α-Fetoprotein
Glycolipids and glycoproteins	GM_2, GD_2 on melanomas
Differentiation antigens normally present in tissue of origin	Prostate-specific antigen in prostate carcinomas CD20 on B cell lymphomas

CML, chronic myelogenous leukemia; *CTL*, cytotoxic T lymphocyte; *EBNA*, Epstein-Barr nuclear antigen; *EBV*, Epstein-Barr virus; *MART*, melanoma antigen recognized by T cells.

Products of mutated genes

- **Oncogenes** and **mutated tumor suppressor genes** produce proteins that differ from normal cellular proteins and, therefore, can induce immune responses.

- The products of many of these mutant oncogenes and tumor suppressor genes are cytosolic or nuclear proteins that are degraded in proteasomes and can be presented on **class I MHC** molecules in tumor cells.
- These proteins may enter the MHC class I and class II antigen presentation pathways in dendritic cells that have phagocytosed dead tumor cells or apoptotic bodies derived from tumor cells. Because the mutated genes are not present in normal cells, peptides encoded by them do not induce self-tolerance and may stimulate T cell responses in the host.

Tumor antigens may be produced by randomly mutated genes whose products are not related to the malignant phenotype.

- Tumor antigens that were defined by the transplantation of carcinogen-induced tumors in animals, called tumor-specific transplantation antigens, are mutants of various host cellular proteins.

Abnormally Expressed but Unmutated Cellular proteins

- ***Tumor antigens that elicit immune responses may be normal cellular proteins that are abnormally expressed in tumor cells*.**
- Many such antigens have been identified in human tumors, such as melanomas
- Some tumor antigens are unmutated proteins that are produced at low levels in normal cells and overexpressed in tumor cells. One such antigen is tyrosinase.

Cancer/testis antigens are proteins expressed in gametes and trophoblasts and in many types of cancers but not in normal somatic tissues

- The first cancer/testis antigens were identified by cloning genes from human melanomas that encoded cellular protein antigens recognized by melanoma-specific CTL clones derived from the melanoma-bearing patients. These were called MAGE proteins.

- Like the MAGE proteins, these other melanoma antigens are silent in most normal tissues, except the testes or trophoblasts in the placenta, but they are expressed in a variety of malignant tumors.

Antigens of Oncogenic Viruses

- ***The products of oncogenic viruses function as tumor antigens and elicit specific T cell responses that may serve to eradicate the tumors*.**
- DNA viruses are implicated in the development of a variety of tumors in humans and experimental animals.

- Examples in humans include :the Epstein-Barr virus (EBV), which is associated with B cell lymphomas and nasopharyngeal carcinoma
- human papillomavirus (HPV), which is associated with carcinomas of the uterine cervix, oropharynx, and other sites; and
- Kaposi sarcoma–associated herpes virus (KSHV/HHV-8), which is associated with vascular tumors. Papova viruses, including polyomavirus and simian virus 40 (SV40), and adenoviruses induce malignant tumors in neonatal or immunodeficient adult rodents.

- The realization that immune responses against viruses protect individuals from virus-induced cancers has led to the development of vaccines against oncogenic viruses. For example, a vaccine against HPV, which is now in use for women and men.

Oncofetal Antigens

- ***Oncofetal antigens are proteins that are expressed at high levels in cancer cells and in normal developing fetal but not adult tissues.***
- There is no evidence that oncofetal antigens are important inducers or targets of antitumor immunity.
- The two most thoroughly characterized oncofetal antigens are carcinoembryonic antigen (CEA) and α-fetoprotein (AFP).

- CEA (CD66) is a highly glycosylated membrane protein that is a member of the immunoglobulin (Ig) super family and functions as an intercellular adhesion molecule. Expressed in liver and other tissue during inflammation.
- AFP is a circulating glycoprotein normally synthesized and secreted in fetal life by the yolk sac and liver.

Altered Glycolipid and Glycoprotein Antigens

- ***Most human and experimental tumors express higher than normal levels or abnormal forms of surface glycoproteins and glycolipids, which may be diagnostic markers and targets for therapy.***
- These altered molecules include gangliosides, blood group antigens, and mucins.

- Gangliosides, including GM2, GD2, and GD3, are glycolipids expressed at high levels in neuroblastomas, melanomas, and many sarcomas.
- Mucins are high–molecular weight glycoproteins containing numerous O-linked carbohydrate side chains on a core polypeptide.
- Several mucins have been the focus of diagnostic and therapeutic studies, including CA-125 and CA-19-9, expressed on ovarian carcinomas, and MUC-1, expressed on breast and colon carcinomas.

Tissue-Specific Differentiation Antigens

- ***Tumors may express molecules that are normally expressed only on the cells of origin of the tumors and not on cells from other tissues.***
- These antigens are called differentiation antigens because they are specific for particular lineages or differentiation stages of various cell types.

IMMUNE RESPONSES TO TUMORS

- ***Adaptive immune responses, mainly mediated by T cells, have been shown to control the development and progression of malignant tumors.***
- Both innate and adaptive immune responses can be detected in patients and experimental animals, and various immune mechanisms can kill tumor cells in vitro.
- **Innate immunity : NK cells , macrophages**
- **Adaptive immunity : T lymphocytes, antibodies**

T Lymphocytes

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

- How ????????

Antibodies

- Tumor-bearing hosts may produce antibodies against various tumor antigens the ability of antibodies to eliminate tumor cells has been demonstrated largely in vitro, and there is little evidence for effective humoral immune responses against tumors.

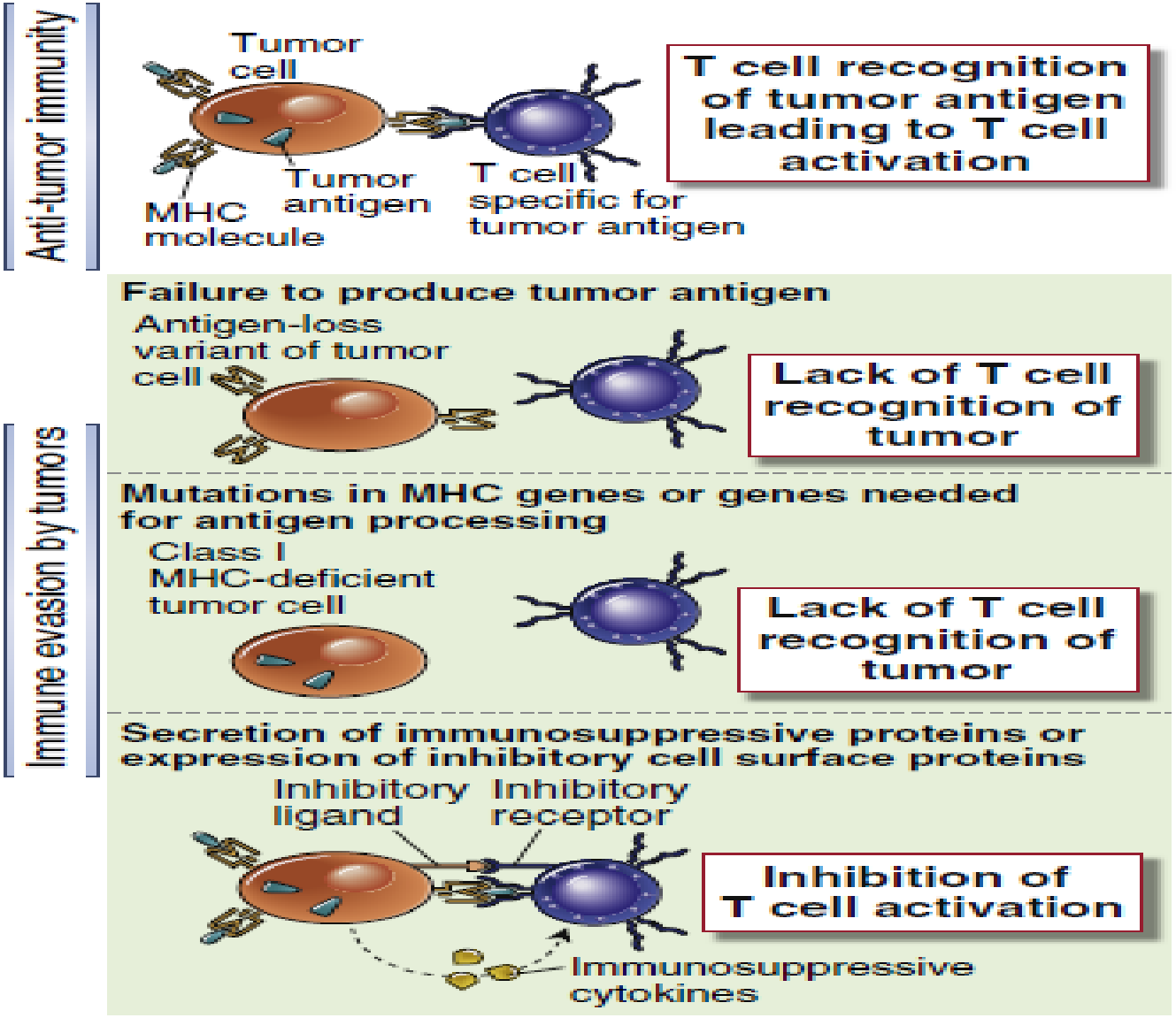
Natural Killer (NK) Cells

- ***NK cells kill many types of tumor cells, especially cells that have reduced class I MHC expression and express ligands for NK cell–activating receptors.***
- In vitro, NK cells can kill virally infected cells and certain tumor cell lines, especially hematopoietic tumors. But in vivo importance unclear.

Macrophages

- ***Macrophages are capable of both inhibiting and promoting the growth and spread of cancers, depending on their activation state.***
- ***M1 :*** can kill tumor cell
- ***M2:*** can promote tumor growth

EVASION OF IMMUNE RESPONSES BY TUMORS



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*.**
- Tumor editing – tumors become less immunogenic over time.

IMMUNOTHERAPY FOR TUMORS

- Current therapies rely on drugs that kill dividing cells or block cell division, and these treatments have harmful effects on normal proliferating cells.
- Immune responses to tumors may be specific for tumor antigens and will not injure most normal cells. Therefore, immunotherapy has the potential of being the most tumor-specific treatment that can be devised.
- Immunotherapy for tumors aims to augment the weak host immune response to the tumors (active immunity) or to administer tumor-specific antibodies or T cells, a form of passive immunity.

Stimulation of Active Host Immune Responses to Tumors

- ***Vaccination with Tumor Antigens***
- ***Immunization of tumor-bearing individuals with tumor antigens may result in enhanced immune responses against the tumor.***
- An approach that has shown some success is the use of immunogenic long peptides that contain single amino acid changes corresponding to tumor mutations, along with selected adjuvants.

TABLE 18-2 Tumor Vaccines

Antigen Type	Examples	Features
Products of mutated genes	FNDC3B (for CLL), NeoVax	Epitopes generated from somatic tumor mutations; not present in normal cells
Overexpressed but unmutated cellular proteins	Gp100, Tyrosinase (melanoma)	Native proteins; preferentially over-expressed in tumors
Cancer/testis antigens	NY-ESO1	Aberrant expression in tumor cells; not present in normal differentiated tissue
Whole inactivated tumor cells/tumor cell lysates	GVAX, Canavaxin	Complex mixtures of antigens generated from autologous whole tumor cells or human cancer cell lines
HSP-associated antigens	HSPPC-96	Misfolded proteins bound to HSPs destined for degradation by the proteasome
In situ tumor	OncoVAX	Infection of tumor cells in situ with an oncolytic virus that can intiate an immune reaction that extends systemically

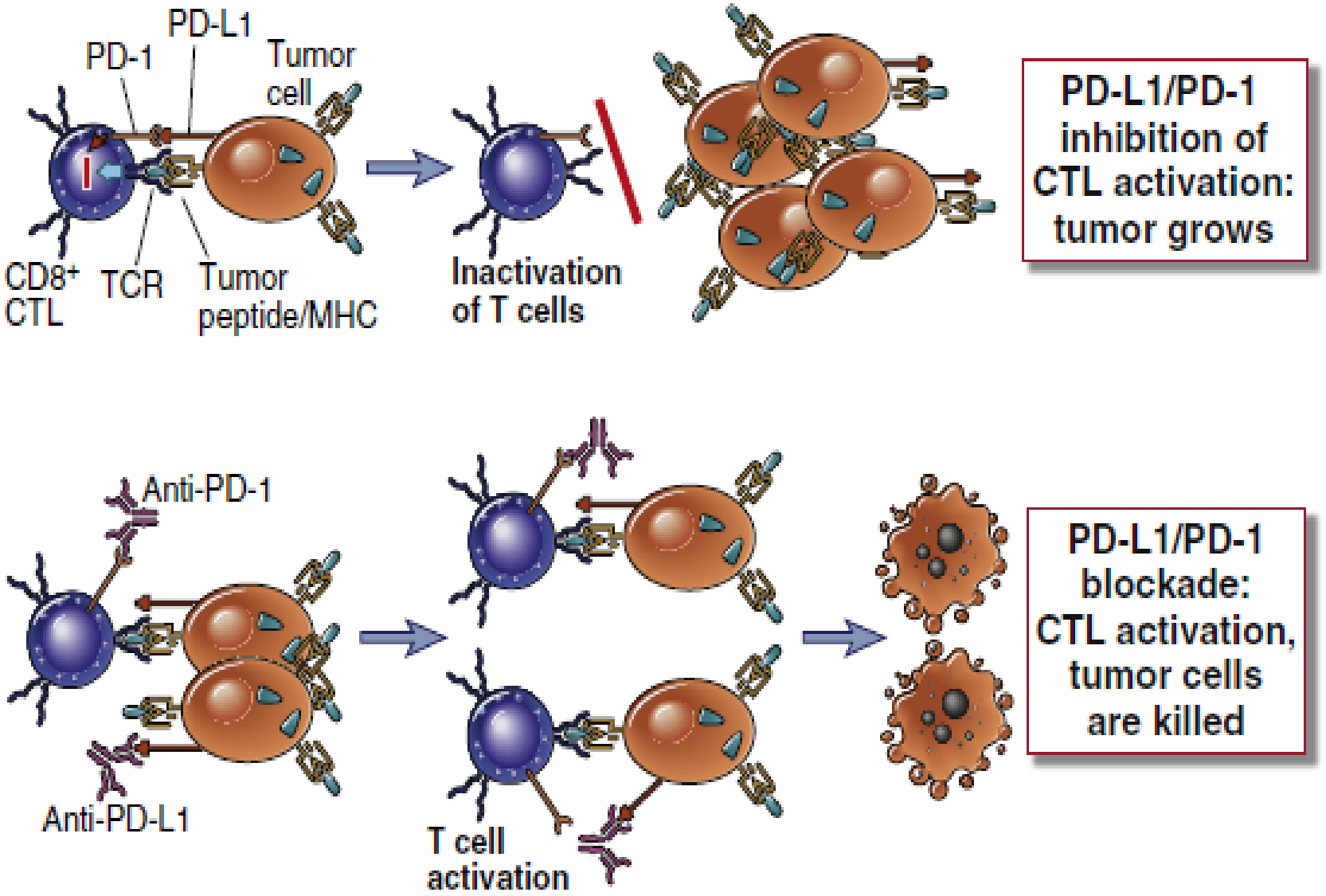
CLL, chronic lymphocytic leukemia; *HSP*, heat shock protein.
This table was compiled with the assistance of Dr. Catherine Wu, Dana-Farber Cancer Institute and Harvard Medical School, Boston, Massachusetts.

- ***Tumor vaccination strategies employ a variety of adjuvants and delivery methods.***
- Proinflammatory molecules are used to enhance the numbers of activated dendritic cells at the vaccination site.
- The tumor antigens are delivered in the form of dendritic cell vaccines. In this approach, dendritic cells are purified from patients, incubated with tumor antigens, and then injected back into the patients

- Another approach is the use of DNA vaccines and viral vectors encoding tumor antigens; some of these are in active or planned clinical trials.
- Most tumor vaccines are therapeutic vaccines; they have to be given after the host has encountered the tumor (unlike preventive vaccines for infections), and in order to be effective, they have to overcome the immune regulation that cancers establish.

Blocking Inhibitory Pathways to Promote Tumor Immunity

- ***Blockade of T cell inhibitory molecules has emerged as one of the most promising methods for effectively enhancing patients' immune responses to their tumors.***
- This approach is based on the idea that tumor cells exploit various normal pathways of immune regulation or tolerance to evade the host immune response, as discussed earlier. Because these inhibitors establish checkpoints in immune responses, the approach of stimulating immune responses by removing inhibition is often called **checkpoint blockade.**



Cell inhibitor blockade

Augmentation of Host Immunity to Tumors with Cytokines

- ***Cell-mediated immunity to tumors can theoretically be enhanced by treating tumor-bearing individuals with cytokines that stimulate the proliferation and differentiation of T lymphocytes and NK cells*.**
- One potential approach for boosting host responses to tumors is to artificially provide cytokines that can enhance the activation of dendritic cells and tumor-specific T cells, particularly CD8+ CTLs. Many cytokines also have the potential to induce non-specific inflammatory responses, which by themselves may have anti-tumor activity.

- IL-2 : melanoma , renal and colon cancer
- IFN- α : melanoma, carcinoid tumor
- TNF : sarcoma , melanoma
- GM-CSF : to promote bone marrow recovery.

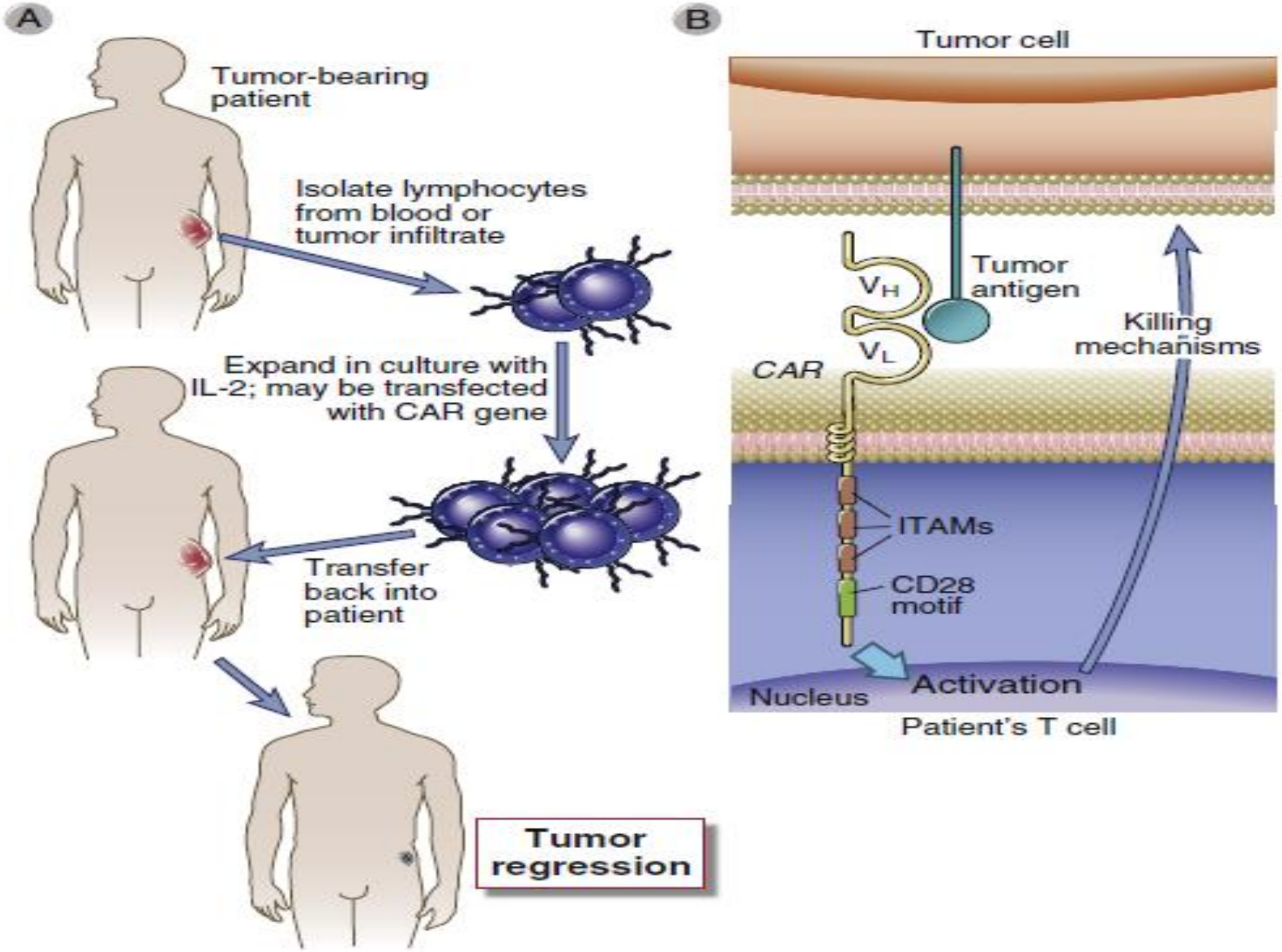
Non-Specific Stimulation of the Immune System

- *Immune responses to tumors may be stimulated by the local administration of inflammatory substances or by systemic treatment with agents that function as polyclonal activators of lymphocytes*.

Passive Immunotherapy for Tumors with T Cells and Antibodies

- Passive immunotherapy involves the transfer of immune effectors, including tumor-specific T cells and antibodies, into patients. Passive immunization against tumors is rapid but does not lead to long-lived immunity.

- ***Adoptive Cellular Therapy***
- Adoptive cellular immunotherapy is the transfer of cultured immune cells that have anti-tumor reactivity into a tumor-bearing host.
- ***Adoptive therapy using T cells expressing chimeric antigen receptors (CARs) has proven successful in some hematologic malignancies, and this approach is in trials for other tumors*.**


A
Tumor-bearing patient
Isolate lymphocytes from blood or tumor infiltrate
Expand in culture with IL-2; may be transfected with CAR gene
Transfer back into patient
Tumor regression
B
Tumor cell
Tumor antigen
V_H
V_L
CAR
Killing mechanisms
ITAMs
CD28 motif
Nucleus
Activation
Patient's T cell

- ***Graft-Versus-Leukemia Effect***
- ***In leukemia patients, administration of T cells and NK cells together with hematopoietic stem cells from an allogeneic donor can contribute to eradication of the tumor.***
- Donor NK cells respond to the tumor cells because tumors may express low levels of class I MHC molecules, which normally inhibit the activation of NK cells .The challenge in use of this treatment to improve clinical outcome is to minimize the dangerous graft-versus-host disease that may be mediated by the same donor T cells.

Therapy with Anti-Tumor Antibodies

- ***Tumor-specific monoclonal antibodies may be useful for specific immunotherapy for tumors.***
- These mechanisms are likely at work in B cell lymphoma patients treated with anti-CD20, one of the most successful anti-tumor antibody treatments to date.

- One of the most difficult problems with the use of anti-tumor antibodies is the outgrowth of antigen loss variants of the tumor cells that no longer express the antigens that the antibodies recognize. One way to avoid this problem may be to use cocktails of antibodies specific for different antigens expressed on the same tumor.

- Many variations on anti-tumor antibodies have been tried in attempts to improve their effectiveness. Tumor specific antibodies may be coupled to toxic molecules, radioisotopes, and anti-tumor drugs to promote the delivery of these cytotoxic agents specifically to the tumor.
- Antibodies that block the epidermal growth factor receptor are approved for the treatment of colorectal tumors. Tumors depend on the formation of new blood vessels that supply the tumor with oxygen and nutrients. This process, called tumor angiogenesis.

The Role Of Innate And Adaptive Immunity In Promoting Tumor Growth

- Cells of the innate immune system are considered the most direct tumor-promoting culprits among immune cells. chronic activation of some innate immune cells is characterized by angiogenesis and tissue remodeling, which favor tumor growth and spread.

- The adaptive immune system can promote chronic activation of innate immune cells in several ways, including T cell–mediated activation of macrophages in the setting of persistent intracellular microbial infections as well as during early malignant disease even when infectious agents are not present.

Summary

- Tumors express antigens that are recognized by the immune system, but most tumors suppress immune responses or are weakly immunogenic, and immune responses often fail to prevent the growth of tumors. The immune system can be stimulated to effectively kill tumors.
- Tumor antigens recognized by CTLs are the principal inducers of and targets for anti-tumor immunity. These antigens include mutants of oncogenes and other cellular proteins, normal proteins whose expression is dysregulated or increased in tumors, and products of oncogenic viruses.

- Antibodies specific for tumor cell antigens are used for diagnosis, and the antigens are potential targets for antibody therapy. These antigens include oncofetal antigens, which are expressed normally during fetal life and whose expression is dysregulated in some tumors; altered surface glycoproteins and glycolipids; and molecules that are normally expressed on the cells from which the tumors arise and are thus differentiation antigens for particular cell types.
- Immune responses that are capable of killing tumor cells are mediated by CTLs, NK cells, and activated macrophages. Among these immune effector mechanisms, the role of CTLs in protecting individuals from tumors is best defined.

- Tumors evade immune responses by several mechanisms, including downregulation of expression of MHC molecules, selective outgrowth of cells that do not express tumor antigens, production of soluble immunosuppressive substances, the engagement of inhibitory receptors on lymphocytes by their ligands expressed on the tumor cells, and the induction of regulatory T cells. Tumor-associated macrophages and myeloid-derived suppressor cells, found in most solid tumors, can suppress anti-tumor immunity

- Immunotherapy for tumors is designed to augment active immune responses against these tumors or to administer tumor-specific immune effectors to patients. Anti-tumor immunity may be enhanced by blocking mechanisms of immune regulation.
- Immune responses may also be actively stimulated by vaccination with tumor cells or antigens, and by systemic administration of cytokines that stimulate immune responses.
- The most recent successful strategy is checkpoint blockade, in which antibodies against inhibitory receptors on T cells or their ligands are administered to remove the brakes on lymphocyte activation and thus promote anti-tumor immunity.

- Approaches for passive immunotherapy include the administration of anti-tumor antibodies, antibodies conjugated with toxic drugs (immunotoxins), and tumor-reactive T cells and NK cells isolated from patients and expanded by culture with growth factors.
- A promising new approach is adoptive transfer of T cells transfected to express chimeric antigen receptors specific for tumor antigens.