REVIEW

Cancer Immunoediting: Integrating Immunity's Roles in Cancer Suppression and Promotion

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Understanding how the immune system affects cancer development and progression has been one of the most challenging questions in immunology. Research over the past two decades has helped explain why the answer to this question has evaded us for so long. We now appreciate that the immune system plays a dual role in cancer: It can not only suppress tumor growth by destroying cancer cells or inhibiting their outgrowth but also promote tumor progression either by selecting for tumor cells that are more fit to survive in an immunocompetent host or by establishing conditions within the tumor microenvironment that facilitate tumor outgrowth. Here, we discuss a unifying conceptual framework called "cancer immunoediting," which integrates the immune system's dual host-protective and tumor-promoting roles.

The idea that the immune system can control cancer has been the subject of debate for over a century. In the early 1900s, Paul Ehrlich was perhaps the first to reason that cancer would be quite common in long-lived organisms if not for the protective effects of immunity (*1*). However, so little was known about the composition and function of the immune system at the time that it was simply not possible to assess the validity of this prediction. It would take nearly 50 years before the idea of immune control of cancer resurfaced, stimulated in large part by an enhanced understanding of the immune system combined with the demonstration of the existence of tumor antigens (*2*). These advances provided the foundation upon which Burnet and Thomas built their cancer immunosurveillance hypothesis, a concept that formally envisaged that adaptive immunity was responsible for preventing cancer development in immunocompetent hosts (*3*, *4*). However, subsequent studies by Stutman provided little support for this hypothesis. Of particular note were experiments showing that the cancer susceptibility of immunocompetent mice (to both spontaneous and carcinogen-induced tumors) was similar to that of nude mice that had major but not total immunodeficiency (*5*, *6*). On the basis of these findings, the cancer immunosurveillance hypothesis was largely abandoned, and soon additional arguments began to surface as to why cancer immunosurveillance could not possibly occur. Some investigators argued that tumor cells did not possess the appropriate "danger signals" needed to alert the immune system to the presence of a foreign cell (*7*), whereas others suggested that the immune system would ignore or be tolerant to a developing tumor because tumor cells were too similar to the normal cells from which they were derived (*8*). Still others showed that persistent activation of the innate, pro-inflammatory arm of immunity could facilitate cellular transformation and promote cancer outgrowth and argued that this effect of immunity precluded its capacity to fulfill a protective function (*9*, *10*).

By the 1990s, improved mouse models of immunodeficiency on pure genetic backgrounds became commonplace, permitting a few groups to reassess the role of immunity in cancer control. Interest in cancer immunosurveillance was rekindled by the discovery of the importance of interferon-γ (IFN-γ) in promoting immunologically induced rejection of transplanted tumor cells (*11*) and by the demonstration that mice lacking either IFN-γ responsiveness (gene-targeted mice lacking either the IFN-γ receptor or the STAT1 transcription factor required for IFN receptor signaling) or adaptive immunity [$RAG2^{-/-}$ mice lacking T cells, B cells, and natural killer T (NKT) cells] were more susceptible to carcinogen-induced and spontaneous primary tumor formation (Fig. 1) (*12*, *13*). Other laboratories soon began to report similar results, and collectively these findings documented that the immune system can function as an extrinsic tumor suppressor [(*11*–*17*), reviewed in (*18*)].

We now recognize that the immune system plays at least three distinct roles in preventing cancer: (i) It protects the host against viral infection and hence suppresses virus-induced tumors; (ii) it prevents the establishment of an

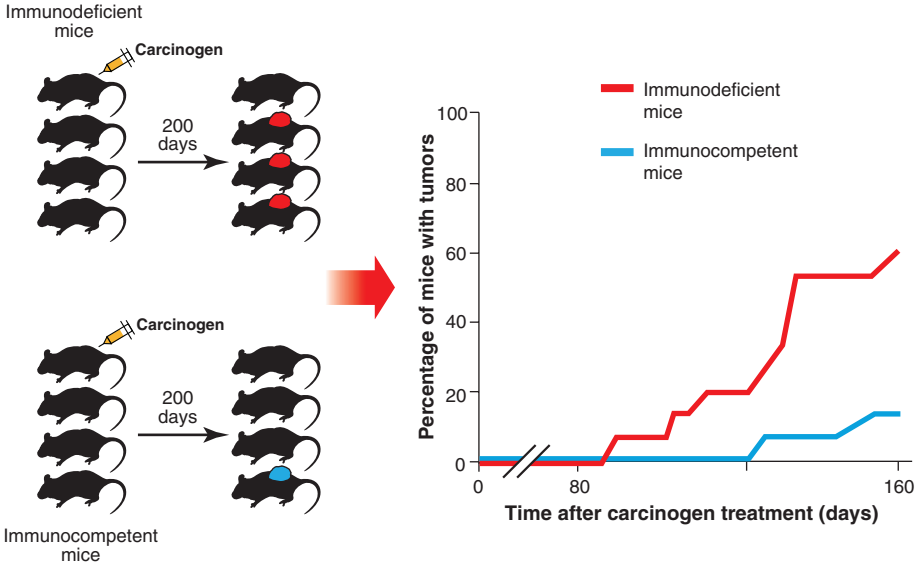

Fig. 1. The immune status of mice is a critical determinant of their susceptibility to tumors induced by chemical carcinogens. Over the past two decades, numerous studies have established that immunodeficient mice are more tumor prone than are immunocompetent mice after treatment with carcinogens such as MCA. The immunodeficient mice tested in such experiments include gene-targeted mice on pure genetic backgrounds with deficits of innate or adaptive immunity as well as wild-type mice rendered immunodeficient by chronic administration of monoclonal antibodies that, for example, deplete $CD4^+$ and $CD8^+$ T cells or interferon-γ. Immunodeficiency has also been found to increase the susceptibility of untreated mice to spontaneously arising tumors and to increase the incidence of tumor formation in mouse genetic models of cancer. Schematic is based on experiments described in (*13*).

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inflammatory environment that facilitates tumorigenesis by eliminating pathogens and by prompt resolution of inflammation; and (iii) it eliminates tumor cells in certain tissues because nascent transformed cells often co-express ligands for activating receptors on innate immune cells and tumor antigens (see below) that are recognized by immune receptors on lymphocytes of the adaptive immune system. This third role is most pertinent to our discussion.

Tumor Antigens and Cancer Immunosurveillance

A fundamental tenet of tumor immunology in general and of cancer immunosurveillance in particular is that cancer cells express antigens that differentiate them from their nontransformed counterparts. The existence of tumor antigens was first demonstrated by the finding that mice immunized with chemically induced tumors were protected against subsequent rechallenge with the same tumor [reviewed in (*2*)]. These types of tumor antigens became known as "transplantation rejection antigens," and similar antigens have since been demonstrated in a wide variety of experimentally induced tumors [such as those induced by different carcinogens, viruses, or ultraviolet (UV) irradiation] and even in spontaneous tumors. Subsequent molecular studies revealed that these antigens were often products of mutated cellular genes, aberrantly expressed normal genes, or genes encoding viral proteins. In the case of human cancer, identification of tumor antigens required the development of novel in vitro detection and cloning methods that used as probes antibodies and cytolytic T lymphocytes ($CD8^+$ T cells) derived from cancer patients that were specific for the autologous tumor (*19*–*22*). The human tumor antigens discovered in these and other ways include differentiation antigens (such as melanocyte differentiation antigens), mutational antigens (such as p53), overexpressed cellular antigens (such as HER-2), viral antigens (such as human papillomavirus proteins), and cancer/testis (CT) antigens that are expressed in germ cells of testis and ovary but silent in normal somatic cells (such as MAGE and NY-ESO-1) (*23*). Thus, the identification of this large array of immunogenic mouse and human tumor antigens puts to rest the long-held view that tumor antigens are overexpressed normal proteins and therefore were subject to immunological tolerance.

The Cancer Immunoediting Hypothesis

The discovery in 2001 that the immune system controls not only tumor quantity but also tumor quality (immunogenicity) (*13*, *24*) prompted a major revision of the cancer immunosurveillance hypothesis. This study revealed that tumors formed in mice that lacked an intact immune system were, as a group, more immunogenic (and hence were classified as "unedited") than similar tumors derived from immunocompetent mice (and hence were termed "edited") (Fig. 2). The notion that the immune system not only protects the host against tumor formation but also shapes tumor immunogenicity is the basis of the cancer immunoediting hypothesis, which stresses the dual host-protective and tumor-promoting actions of immunity on developing tumors.

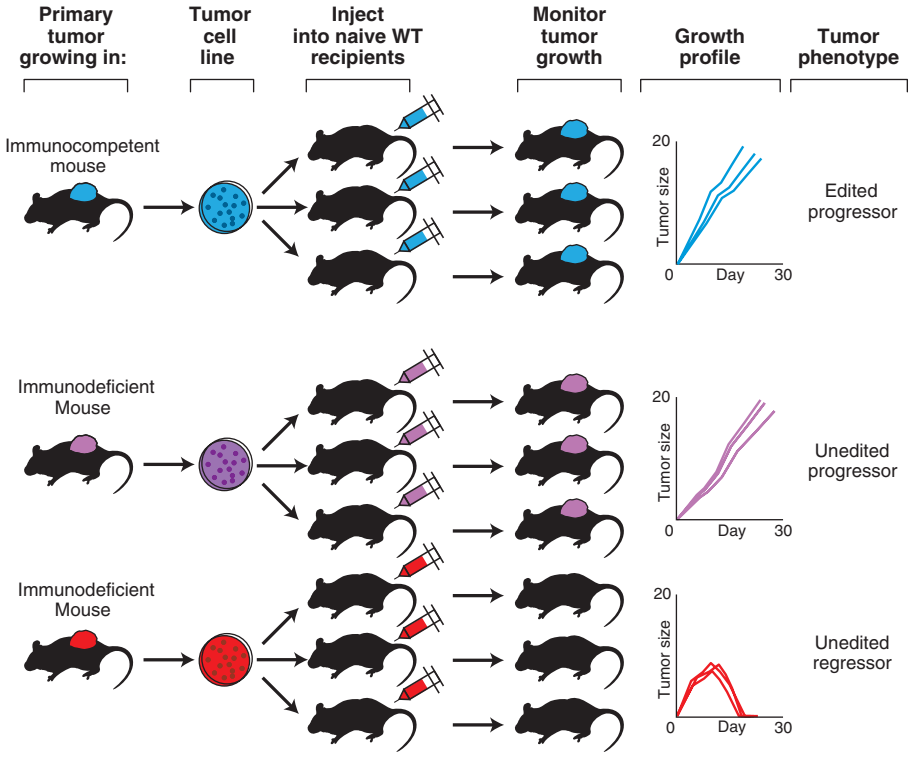

Fig. 2. Tumors in immunocompetent mice are qualitatively different from tumors in immunodeficient mice. This observation, which led to the formulation of the cancer immunoediting hypothesis, is based on comparative analyses of carcinogen-induced tumors harvested from immunocompetent and immunodeficient mice. In these experiments, tumor cell lines were established from tumors arising in each group of mice, and these cells were then injected into immunodeficient recipient mice or immunocompetent wild-type (WT) recipient mice. Tumor cells from carcinogen-treated WT mice formed progressively growing tumors in both immunodeficient mice (not shown) and naïve syngeneic immunocompetent mice (blue) 100% of the time. In contrast, although tumor cells from carcinogen-treated immunodeficient mice grew progressively when transplanted into immunodeficient mice (not shown), only half of the tumor cell lines were capable of forming progressively growing tumors in naïve syngeneic immunocompetent recipients (purple), whereas the other half of the cell lines were rejected by the recipients (red). Thus, tumors from immunodeficient mice are termed "unedited" and further designated as "progressor" or "regressor" to denote their growth phenotypes after injection into naïve WT recipients. Carcinogen-induced tumors from immunocompetent mice are termed "edited" because they are less immunogenic and show only a progressor growth phenotype. Schematic is based on experiments described in (*13*).

We postulate that the cancer immunoediting process, in its most complex embodiment, proceeds sequentially through three distinct phases that we have termed "elimination," "equilibrium," and "escape" (Fig. 3) (*18*, *24*–*29*). However, in some cases tumor cells may directly enter into either the equilibrium or escape phases without passing through an earlier phase. In addition, external factors may influence the directionality of the flow. The latter consideration may help explain the influences of environmental stress, immune system deterioration accompanying aging, and even immunotherapeutic intervention on tumor cell outgrowth in human cancer patients.

Elimination. The elimination phase is best described as an updated version of cancer immunosurveillance, in which the innate and adaptive immune systems work together to detect the presence of a developing tumor and destroy it before it becomes clinically apparent. The mechanisms by which the immune system is alerted to the presence of a developing tumor are not fully understood. Among the possibilities are the classical "danger signals" such as Type I IFNs as originally described by Matzinger (*7*), which we now know are induced early during tumor development. These cytokines activate dendritic cells and promote induction of adaptive anti-tumor immune responses. However, roles for different damage-associated molecular pattern molecules (DAMPs) need also to be considered because they are released either directly from dying tumor cells [such as high mobility group box 1 (HMGB1)]

or from damaged tissues (such as hyaluronan fragments) as solid tumors begin to grow invasively (*30*). A third potential mechanism may involve stress ligands such as RAE-1 and H60 (mouse) or MICA/B (human) that are frequently expressed on the surface of tumor cells. Such ligands bind to activating receptors on innate immune cells, leading to release of pro-inflammatory and immunomodulatory cytokines, which in turn establish a microenvironment that facilitates the development of a tumor-specific adaptive immune response (*31*). Although in some experimental systems, activation of innate immunity can protect against tumor development, in most systems effective cancer immunosurveillance responses require the additional expression of tumor antigens capable of propagating the expansion of effector $CD4^+$ and $CD8^+$ T cells. Thus, coordinated and balanced activation of both innate and adaptive immunity is needed to protect the host against a developing tumor. If tumor cell destruction goes to completion, the elimination phase represents an endpoint of the cancer immunoediting process.

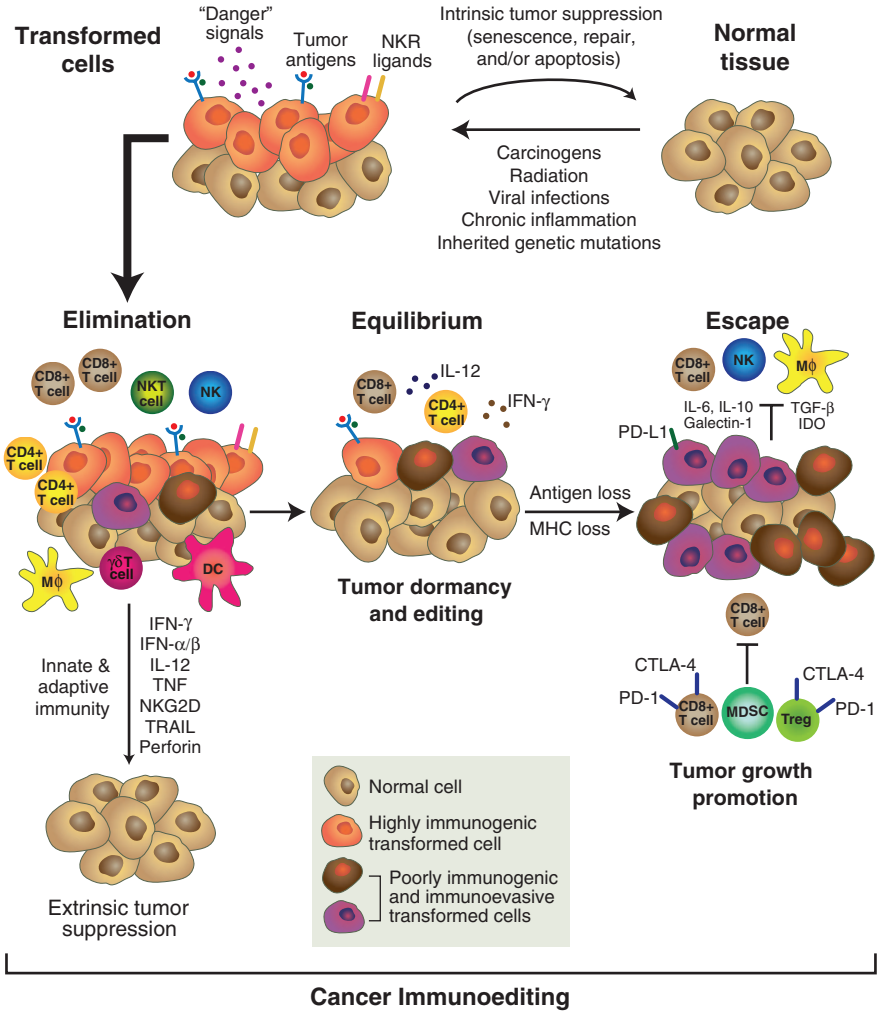

Fig. 3. The cancer immunoediting concept. Cancer immunoediting is an extrinsic tumor suppressor mechanism that engages only after cellular transformation has occurred and intrinsic tumor suppressor mechanisms have failed. In its most complex form, cancer immunoediting consists of three sequential phases: elimination, equilibrium, and escape. In the elimination phase, innate and adaptive immunity work together to destroy developing tumors long before they become clinically apparent. Many of the immune molecules and cells that participate in the elimination phase have been identified, but more work is needed to determine their exact sequence of action. If this phase goes to completion, then the host remains free of cancer, and elimination thus represents the full extent of the process. If, however, a rare cancer cell variant is not destroyed in the elimination phase, it may then enter the equilibrium phase, in which its outgrowth is prevented by immunologic mechanisms. T cells, IL-12, and IFN-γ are required to maintain tumor cells in a state of functional dormancy, whereas NK cells and molecules that participate in the recognition or effector function of cells of innate immunity are not required; this indicates that equilibrium is a function of adaptive immunity only. Editing of tumor immunogenicity occurs in the equilibrium phase. Equilibrium may also represent an end stage of the cancer immunoediting process and may restrain outgrowth of occult cancers for the lifetime of the host. However, as a consequence of constant immune selection pressure placed on genetically unstable tumor cells held in equilibrium, tumor cell variants may emerge that (i) are no longer recognized by adaptive immunity (antigen loss variants or tumors cells that develop defects in antigen processing or presentation), (ii) become insensitive to immune effector mechanisms, or (iii) induce an immunosuppressive state within the tumor microenvironment. These tumor cells may then enter the escape phase, in which their outgrowth is no longer blocked by immunity. These tumor cells emerge to cause clinically apparent disease. [Figure adapted from (*18*)]

Equilibrium. Rare tumor cell variants may survive the elimination phase and enter the equilibrium phase, in which the adaptive immune system prevents tumor cell outgrowth and also sculpts the immunogenicity of the tumor cells. We envisage equilibrium to be the longest phase of the cancer immunoediting process—perhaps extending throughout the life of the host. As such, it may represent a second stable endpoint of cancer immunoediting. In equilibrium, the immune system maintains residual tumor cells in a functional state of dormancy, a term used to describe latent tumor cells that may reside in patients for decades before eventually resuming growth as either recurrent primary tumors or distant metastases (*32*). Equilibrium thus represents a type of tumor dormancy in which outgrowth of occult tumors is specifically controlled by immunity.

An early suggestion that the immune system could maintain tumor cells in a dormant/equilibrium state came from tumor transplantation experiments in which mice were primed with a transplantable tumor and then rechallenged with the same tumor in order to induce tumor latency (*33*). However, stronger evidence for the existence of an immunologically mediated equilibrium phase came from primary tumorigenesis experiments showing that immunocompetent mice treated with low-dose carcinogen [3′-methylcholanthrene (MCA)] harbored occult cancer cells for an extended time period even when the mice did not develop any apparent tumors (*34*). When the immune system of these mice was ablated [by administering monoclonal antibodies (mAbs) that

deplete T cells and IFN-γ], tumors rapidly appeared at the original MCA injection site in half of the mice. Tumor cells isolated from these lesions were highly immunogenic and thus resembled unedited sarcoma cells derived from MCA-treated immunodeficient RAG2$^{-/-}$ mice. Further analyses revealed that adaptive immunity—specifically, interleukin-12 (IL-12), IFN-γ, CD4$^+$, and CD8$^+$ T cells—but not innate immunity was responsible for maintaining the occult tumor cells in equilibrium. This observation mechanistically distinguishes equilibrium from elimination because the latter displays an obligate requirement for both innate and adaptive immunity. Additional studies with different mouse tumor models have confirmed the capacity of the immune system to control the outgrowth of occult primary carcinomas and metastases for extended periods of time (*35*, *36*). In the low-dose MCA system, equilibrium appears to be the result of both the growth inhibitory and cytocidal actions of immunity on the residual tumor cells (*34*). Conceivably, the same immune functions also provide the selective pressure that promote outgrowth of tumor cells that have acquired the most immunoevasive mutations.

Escape. In the escape phase, tumor cells that have acquired the ability to circumvent immune recognition and/or destruction emerge as progressively growing, visible tumors. Progression from equilibrium to the escape phase can occur because the tumor cell population changes in response to the immune system's editing functions and/or because the host immune system changes in response to increased cancer-induced immunosuppression or immune system deterioration.

Tumor cell escape can occur through many different mechanisms [reviewed in (*18*, *24*–*26*, *28*, *37*, *38*)]. At the tumor cell level, alterations leading to reduced immune recognition (such as a loss of antigens) or increased resistance to the cytotoxic effects of immunity (for example, through induction of anti-apoptotic mechanisms involving persistent activation of pro-oncogenic transcription factors such as STAT3 or expression of anti-apoptotic effector molecules such as BCL-2) promote tumor outgrowth. Loss of tumor antigen expression is one of the best-studied escape mechanisms, and it can occur in at least three ways: (i) through emergence of tumor cells that lack expression of strong rejection antigens, (ii) through loss of major histocompatibility complex (MHC) class I proteins that present these antigens to tumor-specific T cells, or (iii) through loss of antigen processing function within the tumor cell that is needed to produce the antigenic peptide epitope and load it onto the MHC class I molecule. All of these alterations are probably driven by a combination of genetic instability inherent in all tumor cells and the process of immunoselection (*24*, *38*). The end result is the generation via a Darwinian selection process of poorly immunogenic tumor cell variants that become "invisible" to the immune system and thus acquire the capacity to grow progressively.

Alternatively, escape may result from the establishment of an immunosuppressive state within the tumor microenvironment (*39*). Tumor cells can promote the development of such a state by producing immunosuppressive cytokines such as vascular endothelial growth factor (VEGF), transforming growth factor–β (TGF-β), galectin, or indoleamine 2,3-dioxygenase (IDO) and/or by recruiting regulatory immune cells that function as the effectors of immunosuppression [reviewed in (*18*)]. Regulatory T cells (T_{reg} cells) and myeloid-derived suppressor cells (MDSCs) are two major types of immunosuppressive leukocyte populations that play key roles in inhibiting host-protective antitumor responses. T_{reg} cells are CD4$^+$ T cells that constitutively express CD25 and the transcription factor Foxp3. When stimulated, they inhibit the function of tumor-specific T lymphocytes by producing the immunosuppressive cytokines IL-10 and TGF-β; by expressing the negative co-stimulatory molecules CTLA-4, PD-1, and PD-L1; and by consuming IL-2, a cytokine that is critical for maintaining CTL function. MDSCs are a heterogeneous group of myeloid progenitor cells and immature myeloid cells that inhibit lymphocyte function by inducing T_{reg} cells; producing TGF-β; depleting or sequestering the amino acids arginine, tryptophan, or cysteine required for T cell function; or nitrating T cell receptors or chemokine receptors on tumor-specific T cells.

Cancer Immunoediting Versus Inflammation

Inflammation is a complex physiological process that normally functions to maintain tissue homeostasis in response to tissue stressors such as infection or tissue damage (*40*). Acute inflammation (innate immunity) frequently precedes the development of protective adaptive immune responses to pathogens and cancer. Chronic inflammation, on the other hand, has been shown to contribute to tumorigenesis at all stages. It contributes to cancer initiation by generating genotoxic stress, to cancer promotion by inducing cellular proliferation, and to cancer progression by enhancing angiogenesis and tissue invasion (*41*). On the basis of these observations, it has been proposed that inflammation and tumor immunity are mutually exclusive processes (*9*, *10*).

In our view, a more likely interpretation is that tumor-promoting inflammation and protective tumor immunity are dynamically interconnected processes that vie for dominance as tumor cells develop and transit through cancer immunoediting (*42*). This scenario is supported by data from several different experimental systems. First, although tumor induction in MCA-treated mice requires the participation of pro-inflammatory cytokines/signaling (such as IL-1β, IL-23, or MyD88) the tumors, once formed, became susceptible to control by other components of immunity (such as IFN-γ, IFN-α/β, IL-12, or T cells) (*43*). Thus, tumor-promoting inflammation and cancer immunosurveillance/immunoediting can coexist within the same tumor model. Second, immune components with pro-oncogenic activity can also promote induction of tumor immunity, depending on when they are recruited into the cancer development process. For example, whereas MyD88 and IL-1β clearly promote carcinogen-induced tumorigenesis in mouse models (*44*–*47*), the same proteins have the opposite effect at later stages of tumorigenesis—that is, they promote development of protective immune responses against established tumors by facilitating recognition of tumor cells undergoing "immunogenic death" (*48*–*50*). This paradoxical role of inflammatory cytokines and the immune response in cancer is also illustrated by the observation that tumor necrosis factor–α (TNF-α) has both tumor-promoting and antitumor activities in mouse and *Drosophila* tumor models (*51*) and by more recent work showing that in a mouse melanoma model, IFN-γ is required both for UVB-induced tumor formation and for immune rejection of these tumors (*52*). Lastly, inflammation can play an important role during tumor escape, when inflammatory cells are recruited to the site of a progressively growing tumor, undergo activation by cancer-derived products (such as VEGF), and suppress protective tumor immunity (*41*).

Cancer Immunoediting in Humans

Although studies of tumor development in mice served as the main driver for the formulation of the cancer immunoediting hypothesis, evidence has since been obtained indicating that immunoediting also occurs in humans and can alter the course of tumor development in cancer patients. We discuss three key types of evidence supporting this conclusion; more comprehensive summaries can be found in (*18*, *24*).

Intratumoral immune responses predict patient prognosis. The strongest evidence of cancer immunoediting in humans comes from reports that correlate the quantity, quality, and spatial distribution of tumor-infiltrating lymphocytes (TILs) with patient survival. Tumor infiltration by IFN-γ producing Th1 CD4$^+$ T cells and CD8$^+$ T cells, and the presence of cytokines such as IFN-γ and TNF-α that promote tumor control, has been associated with an improved prognosis for patients with many different cancers. A study of melanoma patients provided an early indication that TILs are associated with a favorable patient prognosis (*53*, *54*). A subsequent landmark study by Naito *et al.* demonstrated that the presence and location of one particular type of TIL, CD8$^+$ T cells, in colon cancers had a particularly important influence on clinical outcome; specifically, accumulation of CD8$^+$ T cells within the tumor predicted improved patient survival, whereas accumulation of the same cells at the tumor margin had no effect

on survival (*55*). Subsequent studies in ovarian cancer, melanoma, and colon cancer confirmed this observation and further showed that the ratio and distribution patterns of intratumoral $CD8^+$ T cells and T_{reg} cells were critical determinants of prognosis (*56*–*59*). Recent exciting studies of human colon and lung cancers have not only confirmed these observations but have provided quantitative insights into the key variables involved (*58*, *59*). Remarkably, the type and density of lymphocytes infiltrating these cancers was found to be a more powerful prognostic indicator than previous pathological criteria for tumor staging and was even more predictive than correlating disease progression with oncogene expression.

Spontaneous immune responses in cancer patients. A major advance to the field of tumor immunology came from the demonstration that cancer patients can develop high levels of antibody and T cell responses to antigens expressed in their tumors [reviewed in (*60*)]. These immune responses are generally observed in patients with progressively growing tumors, indicating that immune recognition of cancer does not always result in immune protection. However, there is presently no way to know whether such immune responses influence the rate or pattern of tumor growth in these patients and whether these responses represent the footprint of incomplete or ongoing elimination or equilibrium phases of cancer immunoediting. An example of the latter comes from the analysis of individuals with paraneoplastic neurologic disorders (PNDs). PNDs arise as a consequence of antibody and T cell responses against certain autologous tumors that ectopically express proteins normally expressed only in cells of the nervous system (*61*, *62*). This antitumor response develops into an autoimmune response as it attacks normal neurons that express the tumor-associated antigens. The neurologic dysfunctions observed in PND usually become evident before the tumor is discovered.

Immunodeficiency is associated with a higher risk of cancer. Immunodeficiency has been linked to increased cancer risk in patients with AIDS and in transplant recipients maintained on immunosuppressants [reviewed in (*18*, *24*)]. Although the cancers arising in these patients are typically those with a viral etiology such as lymphomas (Epstein-Barr virus), Kaposi's sarcoma (herpesviruses), and cervical cancer (human papilloma viruses), there is at least some evidence that these patients are at greater risk for malignancies of the colon, lung, pancreas, kidney, head and neck, and endocrine system as well as nonmelanoma skin cancers. Melanoma incidence rates are also 2 to 10 times higher than average in renal transplant patients. Interestingly, increased incidences of other cancers—including breast, prostate, ovarian, brain, and testes—have not been observed in immunosuppressed transplant patients.

Insights into the role of the immune system in human cancer have also come from anecdotal reports of cancer being transferred from an organ donor to the immunosuppressed recipient (*63*, *64*). In one study, two individuals received kidney transplants from the same cadaver donor, and both recipients later succumbed to malignant melanoma that was shown by tissue typing to be of donor origin. Medical records revealed that 16 years before her death, the donor had been diagnosed with malignant melanoma and successfully treated. One interpretation of these findings is that the donor's kidneys contained dormant melanoma cells held in equilibrium by the donor's immune system. The transfer of the kidney to naïve and immunosuppressed recipients may have removed the immune pressure holding the tumor cells in equilibrium and thus allowed the occult melanoma cells to grow out into clinically apparent cancer. Together, these clinical observations are consistent with the hypothesis that de novo malignancies arise only in certain permissive microenvironments created by immunosuppressive regimens that suspend or severely compromise the elimination and/or equilibrium phases of cancer immunoediting.

Cancer Immunoediting in Immunotherapy

With our newfound knowledge of the immune system's capacity to not only recognize and destroy cancer but also to shape cancer immunogenicity, more informed attempts to control cancer via immunological means can now be pursued. It is now well accepted that progressively growing, clinically apparent tumors in cancer patients have developed successful strategies to circumvent the natural, extrinsic tumor-suppressor mechanisms of immunity. Thus to be effective, immunotherapies will have to increase the quality or quantity of immune effector cells, reveal additional protective tumor antigens, and/or eliminate cancer-induced immunosuppressive mechanisms. Multiple forms of immunotherapy are being explored to achieve these objectives. These include (i) vaccine approaches to elicit strong specific immune responses to tumor antigens such as MAGE-3 and NY-ESO-1; (ii) approaches involving adoptive transfer of in vitro expanded, naturally arising, or genetically engineered tumor-specific lymphocytes; (iii) therapeutic administration of monoclonal antibodies such as Rituximab (directed against CD20 on leukemia and lymphoma cells) and Herceptin (directed against HER2 on breast cancer cells) to target and eliminate tumor cells; and (iv) approaches that inhibit or destroy the molecular or cellular mediators of cancer-induced immunosuppression such as CTLA-4, PD-1, or T_{reg} cells.

Quantitative analyses performed on patients undergoing various forms of cancer immunotherapy have revealed that the cancer immunoediting process reoccurs either in part or in its entirety during therapy. Specifically, whereas some treated patients display responses that recapitulate the elimination phase of cancer immunoediting (for example, they develop increased numbers of tumor-specific T cells with intact effector function, or they show destruction of some or all tumor cells) others show evidence for establishment of a therapeutically induced equilibrium phase, and still others display evidence for development of additional escape mechanisms, such as outgrowth of antigen-loss variants. Recently, the occurrence of all three phases of cancer immunoediting has been documented in a melanoma patient with preexisting NY-ESO-1 immunity undergoing CTLA-4 blockade monotherapy (*65*). When observed over a 28-month period after initiation of immunotherapy, melanoma lesions could be identified that disappeared (elimination), were held in a protracted state of growth dormancy (equilibrium), or continued to grow (escape). Thus, cancer immunoediting can occur not only when the unmanipulated immune system encounters a developing tumor but also when an established tumor is subjected to immunotherapy.

Future Directions

We envision that future work on cancer immunoediting will address five major questions:

(i) What immune effector processes mediate cancer elimination, equilibrium, and escape? T cells play a critical role in mediating both natural and therapeutically induced cancer immunoediting responses. However, it remains unclear whether they represent the ultimate effectors of these processes. Although activated T cells and other lymphocytes can certainly kill tumor cells, they also elaborate a variety of cytokines such as IFN-γ and TNF-α that can exert profound cytostatic and cytocidal effects on tumor cells, activate tumor cytotoxicity in other cell types (such as macrophages) present in the tumor microenvironment, and block tumor angiogenesis. Identifying the molecular mechanisms and targets responsible for cancer elimination, equilibrium, and escape will determine whether the three phases of cancer immunoediting are manifest by similar or distinct effector processes.

(ii) How do the antigens of nascent tumors differ from the antigens of established, clinically apparent tumors? Almost all of our knowledge of tumor antigens is based on analyses of advanced cancers in imunocompetent hosts. It is important to identify the antigens expressed in early developing tumors because these are the initial targets of the elimination phase of cancer immunoediting. In addition, it would be interesting to define the antigens of tumors from immunosuppressed individuals because these antigens may not have undergone extensive editing and thus may be similar to the antigens of nascent tumors. Are the major antigens of unedited tumors more likely to be associated with driver or passenger mutations? An answer to this question may provide insights into the capacity of immunity to eliminate developing tumor cells, hold them in an equilibrium state, or facilitate their outgrowth. Can we use

information from high-throughput screening of cancer genomes and proteomes or other cutting-edge techniques to rapidly identify the mutations and epigenetic changes in unedited and edited cancer cells that result in formation of functionally relevant tumor antigens?

(iii) What is the link between the types of antigens expressed in a tumor and the mechanism of cellular transformation? With the exception of viral-mediated oncogenesis, little is known about whether and how the mechanisms leading to cell transformation affect the quality or quantity of tumor antigens. The possibility should be considered that experimental tumors, in which transformation is driven by strong oncogenes, may harbor fewer passenger mutations than do spontaneous tumors (*66*). Because passenger mutations can produce tumor antigens, oncogene-driven cancer models may therefore not always be optimal models for exploring the immunology of naturally developing tumors. However, a recent study revealed a previously unknown capacity of the immune system to sustain tumor regression upon oncogene inactivation (*67*). These considerations emphasize the need for further work on defining the relationships between cellular transformation mechanisms and tumor immunogenicity. In the future, careful consideration should be given to the use of cancer models that most closely recapitulate both the biology and immunology of human cancers.

(iv) Is a durable state of equilibrium a desirable and attainable endpoint for cancer immunotherapy? We currently know very little about the effector mechanisms that operate in the equilibrium phase. To date, mouse studies reveal that T cells and IFN-γ contribute to equilibrium, but the recognition pathways and immune network and mechanisms remain unclear. If these can be identified, it might be possible to develop cancer therapies aimed at recapitulating immunological tumor dormancy. It will also be important to understand what effect conventional interventions, such as surgery, radiotherapy, and chemotherapy have on the equilibrium phase.

(v) How can we most effectively inhibit cancer-induced immunosuppressive mechanisms at the tumor site so as to boost the host-protective antitumor effects of preexisting or therapeutically induced immunity without concomitantly inducing life-threatening autoimmunity? Arguably, this may be the most pressing question in all of tumor immunology. Unlike other therapies that target cancer cells, therapies aimed at inhibiting immunosuppression target the immune system itself. An exciting approach being evaluated in clinical trials involves the use of monoclonal antibodies to blockade immunosuppressive molecules such as CTLA-4 or PD-1 expressed by T cells. In a related approach, the effectiveness of monoclonal antibodies that block the PD-1 ligand, PD-L1, which can be expressed on both tumor cells and normal host cells, is also being explored. These types of therapies have been designated "checkpoint blockade" (*68*). In the case of CTLA-4 blockade, a recent phase III clinical trial reported that therapy with CTLA-4–blocking antibodies imparted a significant survival benefit in approximately one-third of patients with metastatic melanoma, making this drug a promising treatment for cancer (*69*). The success of the current CTLA-4 blockade clinical trials has stimulated interest in blocking other potential effectors of immunosuppression, including the soluble (such as IDO and TGF-β) and cellular (such as T_{reg} cells and MDSCs) mediators of the process. Clearly, there is much to be learned about the benefits and risks of inhibiting the different immunosuppressive mechanisms that may be concurrently operating in the cancer patient.

Conclusion

The cancer immunoediting concept attempts to integrate the diverse effects of the immune system on tumor development and outgrowth. With elucidation of the molecular and cellular mechanisms that underlie the elimination, equilibrium, and escape phases of this process, it should be possible to develop new cancer immunotherapies that are safer and more efficacious in a substantial percentage of cancer patients. Given the well-established effects of immunity on cancer development and outgrowth, escape from immune control can now be viewed as one of the "Hallmarks of Cancer" (*70*).

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