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The Tumor/Immune Interface: Clinical Evidence of Cancer Immunosurveillance, Immunoediting and Immunosubversion

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Abstract: Problem statement: The interactions of a malignant tumor with the patient's immune system are dynamic, multiple and bi-directional. **Approach:** This article reviews the clinical evidence of the interaction of cancer with immunity with emphasis on recent developments highlighting some of the mechanisms of tumor-mediated regulation of immunity. **Results:** Most of the time, the immune response to a malignancy acts to prevent/contain tumor growth. Immune responses to tumor-associated antigens are frequently detected in the setting of tumor development. Furthermore, individuals with various forms of immune deficiency are at increased risk for the development of malignancies compared with the general population. However, immune responses to tumors rarely lead to eradication of clinically detectable established cancer, and many cancers are thought to become more aggressive in the setting of tumor-targeted inflammation. Individuals with cancer typically exhibit aberrancies in immune function, both within the tumor microenvironment as well as throughout the body. **Conclusion:** Tumors have been demonstrated to produce cell surface molecules, cytokines and growth factors that disrupt normal immunity, supporting the hypothesis that tumors dysregulate the immune system in favor of their progression.

Key words: Immunosuppression, neoplasm antigens, cytokines, apoptosis, regulatory T lymphocytes

INTRODUCTION

The principle that the immune system can recognize and respond to neoplastic cells was first proposed in the 19th century, when William Coley administered killed bacteria (a combination of *Streptococcus pyogenes* and *Serratia marcescens*) to sarcoma patients and observed rare, but dramatic, clinical responses[1]. In 1909, the concept of immunosurveillance was hypothesized when Paul Ehrlich proposed that the immune system prevented the outgrowth of carcinomas that would otherwise occur with high frequency[2]. As the understanding of immunobiology expanded, F. Macfarlane Burnett proposed that tumor-specific neo-antigens were capable of eliciting a protective immune response[3] and Lewis Thomas theorized that organisms sufficiently complex and long-lived to be threatened by cancer must possess mechanisms capable of protecting against tumors[4]. Subsequently, physicians have recognized rare spontaneous regressions and remissions in cancer patients[5,6]. In many instances of partial tumor regression, histologic evaluation reveals leukocytes infiltrating tumors, suggestive of an immune mechanism of tumor regression. Furthermore, reports of increased incidence and aggressiveness of a variety of cancers in patients receiving immunosuppressive therapy (e.g., solid organ transplant recipients) or suffering from AIDS have further supported the hypothesis that the immune system plays a critical role in controlling the generation of malignant tumors. In recent years, investigators have recognized the ability of a variety of cells of the immune system to recognize and destroy tumor cells, suggesting a set of cellular mechanisms for tumor immunosurveillance. Enthusiasm over the purported role of the immune system in combating cancer has led to the development of numerous therapeutic agents designed to modulate endogenous immune responses in order to treat tumors; these range from instillation of the mycobacterium Bacillus Calmette-Guerin (BCG) to treat bladder cancer[7] to the use of antibodies targeting negative regulators of immunity such as blocking antibodies to cytotoxic T lymphocyte antigen 4 (CTLA-4)[8]. Many such agents are currently in development in a wide array of clinical trials for the treatment of different malignancies.

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However, the concept of tumor immunosurveillance in humans is not universally accepted. Skeptics are quick to point out that the vast majority of cancers arise in patients with no known immune deficit. Moreover, many cancers are known to arise in the setting of immune/inflammatory responses[9]. Similar to the concept of immune targeting of tumors, the idea that inflammation promotes cancer formation dates back to the 19th century, when Rudolf Virchow observed an increased incidence of cancers in areas of chronic irritation or inflammation[10]. Immunostimulation, the hypothesis that the immune system promotes rather than retards tumor growth, is supported by the observation that infiltration of tumors by mast cells, macrophages and other immune cells is associated with a poor prognosis[11-13]. Furthermore, increased levels of inflammatory cytokines are seen in patients with a variety of cancers. Excess levels of interleukin (IL)-1, IL-6, IL-17, IL-18, IL-23, Transforming Growth Factor beta (TGFβ) and Tumor Necrosis Factor alpha (TNFα) have all been demonstrated in patients with cancers and are associated with poor survival in[14]. Thus, while the immune system may play a role in tumor surveillance, some immune responses appear to allow and even drive tumor growth.

The concepts of immunosurveillance and immunostimulation, while in opposition to each other, both are scientifically substantiated and illustrate the complexity of the tumor/immune system interactions. Because of this apparent paradox, many investigator now support the idea that the immune system exerts a selective pressure on tumor cells and that those tumor cells that grow in the face of immune pressure become resistant to immune attack by a variety of mechanisms, including immunoediting, the selection of non-immunogenic tumor cell variants and immunosubversion, the active suppression of immune responses by tumor cells. While ample evidence in experimental model systems support the both concepts (immunosurveillance and immunosubversion), this review will focus the clinical evidence for immunosurveillance/immune escape and the cellular mechanisms therein.

INCREASED INCIDENCE OF CANCERS IN PATIENTS WITH IMMUNODEFICIENCIES

The primary clinical data that support the importance of immunosurveillance as a mechanism of tumor prevention have been generated by epidemiologic studies of immunodeficient patient populations. While an increased risk of developing malignancies has been demonstrated in patients with several primary immunodeficiencies including Common Variable Immunodeficiency (CVID), Severe Combined Immunodeficiency (SCID) and Wiskott Aldrich syndrome[15], the largest studies of cancer incidence in immunodeficient populations have been in patients on immunosuppressive medications following organ transplantation and in patients with Human Immunodeficiency Virus (HIV) infection and Acquired Immune Deficiency Syndrome (AIDS).

It is perhaps not surprising that immunodeficient patients are more prone to develop virus-associated cancers such as cervical cancer, Kaposi sarcoma and Epstein-Barr Virus (EBV)-mediated non-Hodgkin lymphoma at an increased rate compared to the general population. However, accumulating evidence has shown that transplant and AIDS patients are at elevated risk for developing multiple other tumor types that are not associated with any known infection, including lung cancer, colorectal cancer, testicular cancer, melanoma and multiple myeloma[16,17]. The predominating hypothesis explaining this increased tumor risk is that immunodeficient patients lack appropriate immunosurveillance and cannot prevent tumor outgrowth as effectively as immunocompetent patients. However, competing explanations include oncogenic effects of some types of immunosuppressive agents and antiretroviral agents[18,19].

Patients undergoing long-term immunosuppressive therapy: Patients who have undergone allogenic organ transplantation require long-term immunosuppression to prevent graft threatening immune rejection. While the risk for allograft rejection is highest within the first few years after transplantation, transplant patients generally require lifelong immunosuppression. As rates of organ loss due to acute rejection and death due to infection have decreased, malignancy has emerged as a significant cause of morbidity and mortality in this population[20]. Currently, the incidence of malignancy in transplant recipients is estimated at 20% after ten or more years of chronic immunosuppression[21,22]. As the use of steroid-sparing and steroid limiting immunosuppressive regimens becomes more common, cancer may surpass cardiovascular disease as the leading cause of mortality in transplant recipients[16].

Transplant patients have long been known to be at increased risk for multiple types of non-Hodgkin lymphomas[20]; these cancers are now collectively termed Posttransplant Lymphoproliferative Disorder (PTLD). Most cases of PTLD appear to be associated with EBV infection[23]. Of those cases of PTLD not

associated with EBV infection, other viruses including cytomegalovirus and polyomavirus[24] have been implicated in some, but other cases of PTLD do not appear to be virally associated. The risk for PTLD appears to be linked to immunosuppression dose[16].

In addition to PTLD, transplant recipients have a markedly higher incidence of non-melanoma skin cancers than age-matched controls in[25]. Incidence of skin cancer has been shown to increase with length of follow-up, suggesting a dose response to immunosuppression[26]. While skin cancers in general have a low incidence of morbidity and mortality relative to other cancers in general, transplant recipients frequently suffer from aggressive cancers that present as multifocal disease (42%) or that recur or metastasize (15%)[16].

More recently, a large registry of transplant patients from Australia and New Zealand has determined Standardized Incidence Ratios (SIR) for cancer risk in kidney transplant recipients[27]. For all registered cancers (non-melanoma skin cancers were excluded), the SIR for transplant recipients was 3.12 (95% confidence interval 2.97-3.28). Besides tumors with known viral etiology, a greater than twofold risk was seen in solid organ cancers involving the head and neck (SIR 2.77), esophagus (SIR 4.73), liver (SIR 4.78), gallbladder (SIR 2.49), lung (SIR 2.01), skin (melanoma, SIR 3.18), soft tissue (SIR 3.16), kidney (SIR 8.49), bladder (SIR 5.14) and thyroid (SIR 4.53). As has been the case with non-melanoma skin cancer, transplant recipients with solid organ tumors tend to have a much more aggressive clinical course when compared to non-immunocompromised patients[28].

Patients with HIV infection and AIDS: The association between advanced infection with HIV and the incidence of certain cancers is so well-established that development of the viral-associated cancers Kaposi's sarcoma (mediated by human herpesvirus 8), non-Hodgkin lymphoma (often mediated by EBV) and invasive cervical cancer (mediated by human papillomavirus) are included in the United States Center for Disease Control's definition of AIDS in[29]. However, accumulating evidence has shown that AIDS patients are at increased risk for development of multiple other cancers as well. Large cohort studies from the United States[30,31], Australia[29] and Italy[32] have shown significantly increased risk for non-AIDS-defining malignancies in AIDS patients. Based on these cohort studies, AIDS patients are at elevated risk (reported as relative risk or SIR) for Hodgkin disease (8.0-11.5), anal cancer (3.3-33.8), lung cancer (1.44-4.5), testicular cancer (1.46-2.0), cancer of the lip (2.26-3.1), melanoma (1.3-2.5), hepatoma (1.8-7.7), multiple myeloma (2.6-4.15), CNS tumors (1.1-3.5), leukemia (1.4-3.38) and sarcomas (3.3-9.71) in[17]. As with transplant-associated malignancies, cancers in AIDS patients frequently are of higher grade and more aggressive clinical course than cancers in immunocompetent patients[33]. Additionally, systemic treatment of AIDS-associated malignancies is greatly complicated by concurrent highly active anti-retroviral therapy (HAART) treatment, as many common chemotherapeutics, including alkylating agents, anthracyclines, campothecins, etoposide, taxanes and vincristine dramatically affect levels of multiple anti-retroviral agents[34-36]. However, the clinical outcomes of patients with AIDS-related non-Hodgkin's lymphoma whose HIV infection is contained by HAART are similar to those of non-AIDS patients with the same lymphomas treated with the same agents[37]. The latter suggests that "repair" of immune competence with HAART improves the clinical behavior/outcomes of malignant lymphomas, suggesting the clinical relevance of cancer immunosurveillance.

Does increased incidence of cancer in immunosuppressed patients prove that immunosurveillance is relevant in preventing cancer?

Interestingly, while there is clearly overlap in the type of cancers for which transplant recipients and AIDS patients are at increased risk, other cancers pose an increased threat only to transplant recipients and others only to AIDS patients. According to a meta-analysis of seven studies of people with HIV/AIDS and five studies of transplant recipients[38], transplant recipients carry an increased SIR for bladder cancer and thyroid cancers, whereas HIV/AIDS patients have no increased risk. Conversely, HIV/AIDS patients are at increased risk for CNS and testicular cancers, while transplant patients are not. The disparity between increased risk for cancer in AIDS and transplant patients suggests that additional factors beyond simply degree of immunosuppression convey increased cancer risk in these immunocompromised populations.

The disparity in cancer risk between different populations of immunocompromised patients has suggested to some investigators that other mechanisms besides impaired immunosurveillance may be primarily responsible for increased cancer incidence in these populations. In transplant patients, the type of immunosuppressant used has been strongly linked to risk for cancer development as well as the degree of immunosuppression maintained. Calcineurin inhibitors such as cyclosporine and tacrolimus and antimetabolites such as azathioprine are associated with an increased risk for malignancy beyond that expected for the degree

of immunosuppression they impart[18]; this is thought to be at least in part due to pro-oncogenic effects including inhibition of DNA damage repair mechanisms[39,40]. In contrast, use of sirolimus does not appear to confer an increased risk for cancer development[41]. In fact, the mammalian Target Of Rapamycin (mTOR) pathway, which is inhibited by sirolimus, has been targeted by several newer chemotherapeutic agents. Nonetheless, the observation that only some immunosuppressants are associated with increased cancer risk has been interpreted to suggest that it is the presence of pro-oncogenic drugs rather than the absence of immunosurveillance that is responsible for increased cancer risk in transplant recipients.

In AIDS-associated cancer development, oncogenic drug effects are more difficult to implicate as causes for increased cancer risk, as cohort studies demonstrate increased cancer risk in pre-as well as post-HAART era patients[17,19]. However, HIV/AIDS patients have been shown to have a higher rate of participation in other behavior patterns known to increase cancer risk, including smoking and alcohol use[42]. Studies comparing cancer risk between HIV-infected and non-infected individuals while adjusting for smoking and other risk factors have concluded that HIV infection confers a higher risk for malignancy independent of behavioral and other factors[43,44].

The increase in cancer incidence in patients with multiple forms of immunosuppression, including HIV infection, immunosuppressive drug use and primary immunodeficiency strongly suggests that immunodeficiency itself is important in cancer susceptibility, independent of other risks associated with various modes of immunocompromise. This hypothesis is also supported by numerous genetic studies in animal models in[45,46]. Based on these data, most investigators currently affirm that the immune system plays an important role in preventing cancer development.

TYPES OF LEUKOCYTES THAT PARTICIPATE IN ANTI-TUMOR IMMUNE RESPONSES

Much of what is known regarding the cellular and molecular mechanisms responsible for human anti-tumor immune responses has come indirectly from pathologic examination of tumors and *in vitro* co-cultures of tumor cells and leukocytes. As such, it is difficult to ascertain the relative importance of various cell types and molecular pathways in the prevention and control of human cancer. However, associational studies highlight the importance of both myeloid and lymphoid leukocytes in generating anti-tumor immune responses. The predominant cellular mediators of immunosurveillance are discussed below:

Macrophages and dendritic cells: Macrophages and Dendritic Cells (DC) are myeloid-derived cells of the innate immune system. DC reside throughout the body and are concentrated in the lymph nodes, where their primary function is to interact with antigen-naïve T cells to initiate immune responses. Dendritic cells are capable of phagocytosing tumor cells and degrading tumor-derived proteins within lysosomes. As proteins are degraded into short peptides, these peptides are presented on the DC surface in the context of MHC class I and class II molecules in[47]. These MHC-peptide complexes can then be recognized by T cells. DC subsets are derived from both lymphoid and myeloid precursors in the bone marrow and develop into immature DC (iDC), at which point they may traffic either to tumor tissues or to lymph nodes. In order for DC to elicit potent immune responses from naïve T cells, they must become activated or "mature". This typically occurs through ligation of pattern recognition receptors on the DC surface, including Toll-Like Receptors (TLR) and receptors of the Tumor Necrosis Factor (TNF) superfamily[48,49]. While tumors do not contain the extent of molecular pattern motifs found on bacterial and viral pathogens, malignant cells frequently also induce proinflammatory signals recognized by DC, including uric acid[50], heat shock proteins[51,52] and extracellular matrix derivatives[53,54]. Upon recognizing proinflammatory proteins elaborated by tumors, DC upregulate MHC class I and class II molecules; they also upregulate costimulatory molecules such as CD80 (B7-1), CD86 (B7-2) and CD137 (4-1BB)[48,49].

Like DC, macrophages are efficient phagocytic cells and serve to present antigens to T cells. However, while DC generally interact with naïve T cells in lymph nodes, macrophages more commonly interact with activated T cells in areas of tissue inflammation, including tumors. Depending on surrounding signals from the local tissue environment, macrophages are capable of elaborating numerous cytokines that either promote or suppress active inflammation[55]. As macrophages commonly reside within tumors, they are particularly influenced by pro- and anti-inflammatory factors that are produced by tumors. Thus, macrophages are highly plastic in nature and can have either augment immunosurveillance or promote tumor growth. When working toward immunosurveillance, macrophages operate to both directly destroy tumors and to augment the functions of natural killer cells and T cells. Direct

anti-tumor functions of macrophages include killing of neoplastic cells by phagocytosis. In addition, cytokines produced by activated macrophages include type I interferons[56], TNFα, IL-1, IL-6 and IL-8[57,58]. These cytokines can mediate direct anti-tumoral (and pro-tumoral) effects; they also serve to modulate natural killer cell and T cell anti-tumor responses.

The importance of macrophages in tumor immunosurveillance and immunoediting has been suggested by studies in patients with surgically resected tumors. Here, clinical outcomes were compared with the degree of infiltration of tumors by macrophages and other innate immune cells. In one study of patients with resected colorectal cancer, patients whose tumor samples were highly infiltrated by macrophages and mast cells had a lower level of invasion and higher overall survival than patients with sparsely infiltrated tumors[59]. Similar outcomes have been seen in patients with follicular lymphoma[60], hepatocellular carcinoma[61] and nasopharyngeal carcinoma[62]. However, other correlative pathologic studies done in bladder cancer[63], leiomyosarcoma[64], lung cancer[65] and breast cancer[12] have shown a detrimental effect of tumor-associated macrophages. Thus, while it appears that both macrophages and DC participate in tumor immunosurveillance, macrophages may be involved in tumor promotion and immunosubversion as well.

Natural killer cells: Natural Killer (NK) cells are lymphocytes of the innate immune system. The "natural killer" designation reflects investigators' early recognition of the ability of these cells to kill tumor cells without immune priming[66]. For several years, the triggers for NK cytotoxicity were unknown. However, investigators discovered that NK cells selectively lyse cells deficient in class I molecules; this led to the hypothesis that NK cells recognize the absence of MHC class I, or "missing self"[67]. However, the missing self hypothesis does not explain why NK cells to not lyse red blood cells or other MHC class I-negative cell types, or why they do lyse certain class I-positive tumor cells. As the molecular basis for NK cell recognition of tumor cells and virally infected cells has been elucidated, it is now understood that targeting of NK cells is highly complex, with both positive and negative signals. Negative signals are generated by Killer-Inhibitory Receptors (KIR) binding to MHC class I molecules and inhibiting NK cell activity[68]. One of the most prominent positive triggers for NK cytotoxicity is the receptor NKG2D[69]. This receptor is expressed by both NK cells and certain subsets of T cells. NKG2D recognizes a host of MHC class I-like protein ligands, including MHC class I-chain-related protein (MIC) A and MIC B[70] and the Retinoic Acid Early inducible-1 (RAE-1) family of proteins[71]. Binding of these proteins to NKG2D enhances their ability to lyse tumor cells as well as the ability to secrete interferon gamma (IFNγ). IFNγ secretion leads to a host of anti-tumor effects, including upregulation of MHC class I and class II expression, inhibition of angiogenesis, upregulation of pro-apoptotic genes, activation of macrophages and augmentation of cytotoxic T cell responses in[72].

Unlike macrophages, robust infiltration of solid tumors by NK cells is nearly always associated with a favorable prognosis[73-75]. However, perhaps the strongest evidence for the role of NK cells in tumor surveillance is patients who receive autologous stem cell transplants for non-Hodgkin lymphoma and other hematologic malignancies. Patients who recover their Absolute Lymphocyte Count (ALC) to normal levels by day 15 post-transplantation have a significantly better prognosis than patients whose ALC remains abnormal for a prolonged period. Analysis of the ALC cellular components has shown that of the lymphocyte subsets, NK cells are most critical for improved survival[76]. These data strongly suggest that NK cells play a vital role in immunosurveillance of multiple types of solid and liquid tumors.

B lymphocytes: B cells are found primarily in the bone marrow and in lymphoid organs. They recognize antigens via somatically rearranged B Cell Receptors (BCR). Once B cells are engaged via the BCR, they generally require additional input from CD4 T lymphocytes to become activated. Once activated, they proliferate and differentiate into antibody-producing plasma cells. Antibodies in turn serve to coordinate immune responses by neutralizing very small antigens, fixing complement and enhancing phagocytosis and Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC). These latter effects are mediated through specialized antibody receptors known as Fc receptors[77]. Fc receptors on DC and macrophages enhance their ability to engulf antibody-labeled target cells, whereas Fc receptors on NK cells serve to activate killing via perforin and granzyme secretion[68].

Antibody responses in the setting of cancer were initially discovered as being responsible for a host of unfavorable clinical effects including neurologic and neuromuscular toxicities. These maladies, known as paraneoplastic antibody syndromes, occur in a wide variety of cancers and are thought to be due to crossreactivity between tumor and normal host tissues[78]. Interestingly, patients with paraneoplastic antibody syndromes often have more indolent tumor

growth than patients with the same tumor type who do not have evidence of a paraneoplastic syndrome[79]. This suggests that endogenous antibody responses to tumors may be an effective means to control tumor growth.

T lymphocytes: T cells are present both in primary lymphoid tissue and in sites of inflammation. Like B cells, they recognize antigens via clonotypic receptors (T Cell Receptors-TCR) that have undergone somatic rearrangement. However, T cells do not recognize native antigens, but rather fragments of antigens presented by MHC molecules. Thus, T cells must interact with antigen presenting cells in order to recognize antigen. Naïve T cells reside primarily in the lymphatic tissues, where they may become activated through interactions with DC. T lymphocytes may be broken down into subsets based on cell surface molecule expression and function. T cells bearing the CD8 antigen co-receptor recognize peptide antigens in the context of MHC class I molecules; once activated, they function primarily to lyse antigen-bearing target cells and to secrete proinflammatory cytokines such as IFNγ. As such, they are frequently termed Cytotoxic T Lymphocytes (CTL). By contrast T cells with the CD4 co-receptor recognize antigens bound by MHC class II molecules. Upon activation, CD4 T cells generally do not directly kill antigen-bearing cells, but rather serve to augment immune responses by macrophages, B cells, NK cells and CTL; thus, they are often referred to as T helper cells. T helper cells have divergent functions, depending primarily on paracrine cytokine production by DC and other antigen presenting cells. The most prevalent types of T helper cells are termed T helper 1 (Th1) and T helper 2 (Th2). Th1 cells are formed primarily when DC produce IL-12 during antigen presentation[80]. Th1 cells produce IFNγ; in doing so, they enhance the cytotoxicity of macrophages, NK cells and CTL. Th2 cells, by contrast, produce a host of cytokines, including IL-4, IL-5 and IL-13. These promote a chronic inflammatory environment but downregulate cytotoxic functions in immune effector cells. While Th1-driven immune responses have been shown to eradicate tumor cells, Th2 responses are typically associated with ineffective immune responses and tumor persistence[81]. A third T helper subset, regulatory T cell (Treg), serves to downmodulate immune responses. This subset is important in maintaining self-tolerance but is detrimental to tumor immunosurveillance. Regulatory T cells will be discussed in more detail later in this article.

In addition to the T lymphocyte subsets mentioned above, investigators have described several additional groups of T cells with a more limited spectrum of T cell receptor structure and reactivity. These include NKT cells and gamma-delta T cells. NKT cells bear both TCR and NKG2D. The reactivity of NKT cell TCR appears to be toward lipid antigens presented by the non-classical MHC molecule CD1d[82]. NKT cells have been demonstrated to recognize human tumor cells[83]. However, different NKT cell subsets appear to play divergent roles in response to tumors in that while some NKT cells secrete IFNγ and promote CTL activity, other NKT cell subsets inhibit anti-tumor immune responses[84]. Gamma-delta T cells are a small subset of T cells that utilize a TCR made up of chains encode by the gamma and delta regions of the TCR locus rather than the more common alpha and beta chains. Gamma-delta T cells use relatively invariant TCR to recognize non-classical MHC-like molecules including MICA and MICB and CD1d[85]. Recent recognition that these cells can recognize and lyse cancer cells has led to consideration of how they can be manipulated for the therapy of cancer patients[86].

The importance of T cells in tumor immunity has long been established in model systems and *in vitro* tissue culture experiments. However, in recent years, spontaneous T cell immunity to a variety of tumors has been identified and is linked to clinical outcomes. Tumor-Infiltrating Lymphocytes (TIL) in histologic tumor specimens have been correlated with favorable clinical outcomes in multiple types of tumors, including cancers of the breast[87], colonp[88], lung[89], ovary[90] and kidney[91], as well as in melanoma[92]. Furthermore, TIL have been demonstrated to recognize tumor antigens and provide clinical benefit in patients with melanoma[93,94]. Together, these data highlight the importance of T lymphocytes in mediating tumor immunosurveillance and immunoediting.

LOCAL IMMUNE DYSREGULATION BY CANCERS

The cellular and molecular mechanisms mentioned above are reasonably well-established as relevant means through which the immune system attacks neoplastic cells and prevents or limits tumor growth. However, the reality that the majority of clinically apparent cancers grow relentlessly despite the response of an apparently intact immune system suggests that somehow the immune response to tumors is or becomes ineffective. Cancers have been found to utilize diverse mechanisms to avoid, suppress and alter both innate and adaptive anti-tumor immune responses. Much of this downregulation is the result of tumor-directed alterations in both the neoplastic cells themselves as

well as the surrounding stromal tissues. As such, the majority of the clinical evidence for immunosubversion by tumors has been demonstrated within the tumor microenvironment.

Decreasing tumor antigenicity: The majority of the leukocytes responsible for immunosurveillance and immunoediting utilize the recognition of antigens in order to target abnormal tissues and prevent damage to healthy tissues. As such, tumors that reduce antigen expression are able to avoid immune recognition and targeting. CTL, NKT cells and gamma-delta T cells use complexes of small molecules (peptides and lipids) bound to MHC class I or class I-like molecules for targeting of effectors functions and NK cells are targeted by class I-like molecules independent of small molecule binding. Tumors may therefore reduce their antigenicity either by decreasing expression of peptides or by decreasing expression of class I and/or class I-like molecules[95]. Under the selective pressure of an anti-tumor immune response, cancer cells that are able to survive and proliferate despite loss of expression of the protein containing a given peptide antigen can replace antigen-bearing cells; this form of antigen loss leads to a tumor-wide change in gene expression[96,97]. However, cancers have also been shown to avoid immune recognition via loss of the MHC class I-binding protein beta-2-microglobulin (β2m)[98], loss of antigen processing machinery[99], loss of the MHC class I loci themselves through chromosomal loss, hypermethylation, or loss of transcriptional factors[100-102] and mutations in class I molecules[103,104]. Furthermore, the typical upregulation in MHC class I and antigen processing machinery that occur in the presence of IFNγ may be abrogated by cancer cell loss of interferon response element genes[105]. While loss of MHC class I expression may remove an important inhibitory signal from NK cells (KIR signaling), NK activity is also subject to immunoselection, as tumor cells have been shown to downregulate the MHC-like molecules MIC A and MIC B via shedding them; these soluble forms of MIC A and MIC B then further inhibit NK function by inhibiting NKG2D expression and function[106,107].

Modulation of leukocyte trafficking to tumors and killing of tumor-infiltrating leukocytes: In addition to the prevention of immune recognition through various forms of antigen loss, cancers avoid immune destruction by regulating which immune cells traffic into tumors and by killing pro-inflammatory leukocytes that do enter the tumor microenvironment. Homing of leukocytes to tumors is an extremely complex process mediated by tumor cells and by tumor-associated endothelial cells, as well as by leukocytes themselves. To create a cancer-promoting environment, tumors must attract certain leukocytes such as anti-inflammatory macrophages, while at the same time excluding cells cytotoxic to the tumor such as CTL and NK cells. To accomplish this, tumors express different chemoattractant cytokines (chemokines) that promote trafficking of anti-inflammatory cells into the tumor[108]. For example, the chemokine CCL9 (macrophage inhibitory protein 1 gamma-MIP-1γ) recruits immunosuppressive immature myeloid cells, while the chemokines CCL2 (monocyte chemoattractant protein 1-MCP-1), CCL3 (MIP-1a) and CCL5 (regulation on activation, normal T cell expressed and secreted-RANTES) recruit macrophages[109]. Dependent on other cytokines present in the tumor microenvironment, recruitment of these cell types may lead to reduced immune control on the tumor and more rapid tumor progression[110-112]. On the other hand, the chemokines CXCL16 and CX3CL1 serve to recruit T cells into tumors; tumors expressing these chemokines generally have a more indolent clinical course with improved patient survival[113]. Vascular growth factor-receptor networks also play an important role in governing leukocyte adhesion to tumor vasculature and subsequent intratumoral trafficking. Endothelin B receptor (ET_BR), which binds to endothelin-1, prevents T cell migration into tumors; expression of ET_BR correlates with both the absence of TIL and shortened survival[114].

Lymphocytes that successfully migrate into tumors may subsequently be killed by cell-cell interactions with tumor cells. This contact-dependent killing is mediated by aberrant tumor cell expression of CD95L (Apoptosis Stimulating Fragment ligand-FasL), TNF-Related Apoptosis-Inducing Ligand (TRAIL) and the receptor-binding cancer antigen expressed on SiSo cells (RCAS1). Upon activation, T cells express CD95 (Fas) and other receptors that can induce apoptosis; binding of these receptors mediates T cell death, thus serving as a homeostatic means to downregulate T cell immune responses[115,116]. Expression of death receptor ligands by tumor cells leads to increased killing of intratumoral T cells via apoptosis. Furthermore, a soluble form of FasL can be produced by melanoma and other forms of tumor and has been associated with poor outcomes[117].

Resistance to immune-mediated tumor killing: Cells of the immune system, when properly activated and targeted, can kill neoplastic cells via a variety of mechanisms, including the above-mentioned Fas/FasL system and other cell surface death receptor pathways, as well as through the use of perforin and granzymes.

These pathways converge to target intracellular apoptotic pathways, including members of the B Cell Lymphoma 2 (BCL-2) family of proteins, caspases and endonucleases, ultimately resulting in tumor cell death. To combat this, tumors decrease expression of cell surface ligands such as Fas and numerous pro-apoptotic pathway proteins including BCL-2 interacting mediator of cell death (BID), BH3-interacting domain death agonist (BID), p53-upregulated modulator of apoptosis (PUMA) and several members of the caspase family[118]. Tumors also increase levels of anti-apoptotic proteins such as BCL-2, BCL-X_L and members of the cellular inhibitor of Apoptosis Protein 1 (cIAP1) family[118]. These changes result in resistance to both immune and non-immune-mediated tumor cell death. In particular, the absence of Fas in cancers of several tissues is associated with poor outcomes[119,120].

Alterations in T cell signaling: T cell responses to tumors and other antigens are governed not only by antigen-specific signaling through the TCR, but also through numerous regulatory signals. One potent negative regulatory signal for T cells is through CTLA-4. T cell downregulation through CTLA-4 normally occurs toward the end of an acute immune response and serves to restore immune homeostasis. However, in situations in which the antigen is not rapidly cleared, such as cancers, CTLA-4 interrupts ongoing anti-tumor immune responses[121]. The use of blocking antibodies to CTLA-4 as a means to augment endogenous and vaccine-driven anti-tumor immunity has produced clinical responses in some patients with melanoma[122] and clinical trials of anti-CTLA-4 are underway.

An additional checkpoint for T cells involves the molecule programmed death-1 (PD-1), expressed on activated CTL. PD-1 is bound by the ligands B7-H1 (PD-L1) and B7-H2 (PD-L2)[123]; this results in inhibition of T cell activation through recruitment of the inhibitory phosphatase Src homology phosphatase-2 (SHP-2)[124]. B7-H1 is expressed by numerous tumor cells and induces apoptosis of tumor-specific CTL. Furthermore, blockade of B7-H1 was shown to augment immune-mediated tumor rejection[124], suggesting that targeting of PD-1-B7-H1 interactions may be important in potentiating anti-tumor CTL responses.

Several additional negative regulators of T and B cell function have recently been identified. B and T Lymphocyte Attenuator (BTLA) is expressed upon T cell activation and Th1 (but not Th2) differentiation[125]. Additionally, suppressive macrophages from human ovarian tumors have been shown to express B7-H4[126]. B7-H4 blockade restored the ability of macrophages to stimulate T cell effectors functions. Thus, multiple cell surface negative regulatory molecular interactions exist; several of these are used directly by tumors to inhibit the function of TIL.

Alterations in tryptophan metabolism: Cancers cells also co-opt the use of tryptophan pathway enzymes to disrupt effective anti-tumor immunity. Indoleamine 2, 3-dioxygenase IDO catalyzes the rate-limiting first step in tryptophan metabolism[127]. Increased expression of this enzyme leads to accumulation of tryptophan metabolites and uncharged tRNA. These byproducts act by mechanisms not fully understood to inhibit T and NK cell function by inducing T cell energy (unresponsiveness to antigens), cell cycle arrest and apoptosis, as well as by inducing activation of Treg. Additionally, depletion of tryptophan itself may prevent effective lymphocyte activation. IDO is induced by TLR ligands, IFNα and IFNγ and by CD137[128]; thus, it serves as part of a negative feedback loop to downmodulate Th1 immune responses. IDO is expressed both by tumor cells and by immature DC; thus it is active in inducing immune tolerance directly in the tumor microenvironment and in tumor-draining lymph nodes.

The importance of IDO as a mediator of immune tolerance was first described in maternal-fetal interactions[129]. Here, IDO inhibition in animal models led to rejection of allogenic fetuses. IDO is now known to be expressed by multiple human tumors. IDO expression in tumors[130-132] and tumor-draining lymph nodes[133] has been found to be a poor prognostic indicator in many cases; however, at least one study has shown favorable clinical courses in patients with IDO-expressing tumors[134]. Studies of IDO inhibition as a therapeutic for solid organ tumor patients with 1-methyl-D-tryptophan are currently underway.

Proteoglycans: Carbohydrate-modified proteins play a number of roles in various aspects of cancer biology, including metastasis and angiogenesis[135]. As such, they are expressed by numerous tumors and proteoglycan expression is linked to aggressive phenotype[136]. In addition to their other tumor-promoting actions, a number of proteoglycans have been implicated in T cell inhibition. Galectins, including galectin-1, -2, -3 and -9 adversely affect T cell effecter functions by induction of apoptosis[137-139], blockade of TCR signaling[140], augmentation of CD95 (Fas)-mediated T cell killing[141] and inhibition of Th1 responses[142]. As galectins are expressed within tumors (as well as detected in peripheral blood), they are poised to disrupt the effector arm of T cell-mediated tumor immunity.

SYSTEMIC IMMUNE DYSREGULATION BY CANCERS

Based on successful protection from cancer in preclinical models, numerous investigators have designed therapeutic vaccines for cancer patients. Vaccine strategies have included injection of tumor lysates, tumor-derived proteins, tumor-associated peptides, DNA and patient-derived or allogenic dendritic cells pulsed with tumor antigens. A multitude of vaccine adjuvants have been used and vaccines have been administered to several different tissues, including intra-tumoral injection, injection into lymph nodes and injection into skin, subcutaneous tissue and muscle. Although some vaccines have been given to patients without gross disease, most clinical trials have been in patients with metastatic cancer. Unfortunately, of over 2000 vaccine clinical trials to date, none has provided consistent benefit to patients[143]. As many of the vaccines tried have been administered in sites distant to tumors, immunosuppression at the level of the tumor microenvironment does not adequately explain the ability to generate robust anti-tumor T cell responses.

Several distinct reasons exist that might explain the poor immunogenicity of anti-tumor vaccines in patients. One difficulty with cancer vaccines, as compared with pathogen vaccines, is that in cancer vaccines the target antigen to be destroyed (the tumor) is derived from patient tissue; thus, the vaccine-generated immune response must overcome normal self-tolerance mechanisms. This is almost certainly a prominent barrier to anti-tumor vaccine efficacy. However, cancer patients have additionally been shown to have abnormal immune responses to other antigens, including recall vaccine responses and responses to pathogens. For example, patients with metastatic melanoma had very poor recall Delayed-Type Hypersensitivity (DTH) responses to mumps and *Candida* antigens when compared with the general population[144]. Also, patients with malignant gliomas have been shown to have a variety of immune defects, including impaired DTH responses, energy to bacterial antigens and inability to generate appropriate proliferative responses to *in vitro* mitogen stimulation[145]. Furthermore, many cancer patients have a diminished ability to respond to prophylactic vaccines against influenza and *Streptococcus pneumonia*[146]. In addition to decreased reactivity to microbial vaccines and antigen challenges, cancer patients have a heightened incidence and severity of a variety of infections[147,148]. While it is difficult to dissect the relative roles of tumors versus cytotoxic chemotherapy in contributing to the increased infection risk seen in cancer patients, it appears that even cancer patients not on chemotherapy have an elevated risk for infection and for poor vaccine responses compared to healthy controls[149]. Taken together, these data suggest that tumors may promote a global state of immune dysfunction rather than simply dysregulating the tumor microenvironment.

The difficulty in obtaining robust anti-tumor vaccine responses in patients with metastatic cancer has prompted some investigators to bypass the step of eliciting immune responses *in vivo* and to instead transfer *ex vivo* expanded tumor-specific CTL into patients. One study utilized melanoma-reactive clones from patient PBMC that were expanded *in vitro* and re-infused into the same patient[93]. A subsequent trial utilized adoptive transfer of melanoma-specific CTL cloned from autologous TIL into metastatic melanoma patients who were pre-treated with lymphodepleting chemotherapy[94]. In both trials, CTL that were expanded ex vivo were functionally active upon reinfusion, as clinical responses and autoimmune melanocyte destruction (vitiligo) were seen in some patients. Although they are not practical to perform in large numbers of patients, these trials demonstrate the principle that CTL directed against melanoma-associated peptide antigens can mediate clinical responses in melanoma patients. The disparity between the efficacy of exansion of antigen-specific CTL *in vivo* (via vaccination) and *in vitro* (via adoptive transfer) highlights the global suppression of anti-tumor immune resposnes seen in patients with metastatic cancer. Several integrated immune mechanisms of tumor-mediated regulation have been elucidated that impact not only the effector arm of immune responses within tumors, but also the generation of immune responses systemically.

Self-tolerance and regulatory T cells: The existence of CD4 T cells capable of interrupting anti-tumor immune responses has been known since the 1980s[150]. However, it has been difficult to distinguish these immunity-suppressing cells from immunity-promoting T helper cells until recently. Presently, immunosuppressive T cells, known as regulatory T cells are a well-established population of lymphocytes that mediate suppression of inflammatory responses[151]. Regulatory T cells are implicated as critically important in the prevention of autoimmunity[152]. These immunosuppressive cells have been further divided into subsets. T regulatory cells (Treg) are characterized by cell surface expression of CD25 and expression of the transcription factor FoxP3[153,154]. By contrast, type 1 regulatory T cells (Tr1) are characterized not by cell

surface expression, but by the capacity to secrete large amount of the immunosuppressive cytokine IL-10[155]. These subsets represent distinct cell populations, as clones have been identified that either are CD25-negative and secrete IL-10 or are immunosuppressive and secrete TGFβ, but not IL-10[156]. However, both types of regulatory T cells appear to downregulate activity of Th1 and CTL.

Regulatory (or suppressor) T cells were originally described based on their ability to inhibit anti-tumor immune responses in mice. Their role in human cancer was initially suggested when increased numbers of Treg were found in the blood of patients with lung cancer[157]. Subsequent studies have confirmed the presence of expanded numbers of Treg and/or Tr1 in the peripheral blood of patients with head and neck cancer[158], gastrointestinal cancers[159], breast cancer[160] and melanoma[161]. The presence of increased numbers of Treg and Tr1 in tumor tissue and in peripheral blood has been seen to correlate with high stage and poor prognosis[162,163].

Treg and Tr1 are produced *in vitro* by the culture of T cells with DC that secrete IL-10[156]. As many tumors secrete high levels of IL-10, this represents a potential mechanism for the excess Treg seen in cancer patients. Culture of T cells in TGFβ has also been demonstrated to induce Treg; this may also be a means by which tumors elicit Treg. Treg and Tr1 disrupt anti-tumor immune responses via several mechanisms. Through their ability to secrete IL-10 and TGFβ, Treg/Tr1 dramatically suppress Th1 and CTL function[151]. In addition, Treg are able to modulate DC and macrophage function, thereby interrupting T cell activation. In this way, Treg are able to downmodulate not only immune responses to that antigen to which they are reactive, but also to "bystander" antigens presented by the same antigen presenting cell; thus, tolerance can be transferred from one antigen to another, leading to broad immunosuppression.

Changes in dendritic cell function: As DC are the principal means by which tumor-specific T cells, including CTL, T helper cells and regulatory T cells become activated, much of the adaptive immune response to tumors is controlled through the regulation of dendritic cell function. Tumors suppress proinflammatory DC functions at multiple checkpoints in DC development and activation. This leads to both a reduction in the number of DC, as well as a dramatic change in the proportion of DC subsets, with a shift away from mature DC and toward immature DC and immunosuppressive (regulatory) DC. Circulating DC were measured in patients with head and neck cancer and a variety of other cancers and were compared with blood DC levels in normal donors[164-166]. Cancer patients had a dramatic reduction in the number of normal circulating DC. Furthermore, among those DC present in tumor specimens, there is a high proportion of immature DC with low levels of co-stimulatory molecules[167]. However, not only do cancer patients have a paucity of mature DC and relative increase in immature DC, but they also have high levels of regulatory DC. These cells accumulate by trafficking toward tumor-produced Stromal-Derived Factor-1 (SDF-1); they are also generated by antigen uptake in the absence of endogenous TLR ligands and other pro-inflammatory signals[116]. Regulatory DC are a heterogeneous group of DC with low levels of costimulatory molecule expression that suppress CTL and T helper function while driving expansion of Treg. They do so by expressing high levels of the enzyme IDO[128], as well as by secreting IL-10 and nitric oxide[116].

Myeloid-derived suppressor cells: In addition to global changes in DC function, tumors induce a heterogeneous population of myeloid cells comprised of immature macrophages, granulocytes and other myeloid cells of early differentiation state; these are collectively known as myeloid-derived suppressor cells (MDSC). In, humans, MDSC are defined by expression of the common myeloid marker CD33 in the absence of other myeloid and lymphoid markers, including absence of HLA-DR[168]. These cells are absent or very rare in blood from healthy donors, but they accumulate in the blood of patients with advanced cancer and they decrease when tumors are surgically removed[169]. MDSC from cancer patients have been shown to inhibit IFNγ production by CTL; this inhibition occurs via a hydrogen peroxide-dependent mechanism[170].

Cytokines: Cytokines are soluble mediators of inflammation and play a wide array of roles in regulating inflammatory cell trafficking, changes in local tissues, susceptibility of cells to apoptosis and differentiation and activation of leukocytes. Both pro-inflammatory and anti-inflammatory cytokines have long been known to promote cancer growth, angiogenesis and metastasis and to regulate immune responses to tumors. Cytokines typically mediate their effects in an autocrine or paracrine manner that is tightly regulated in time and space. However, in the setting of cancer, supraphysiologic levels of numerous cytokines are present continuously throughout the circulation; this leads to a broad dysregulation of normal immune responses, both to the tumor and to other antigens.

Table 1: Leukocyte-derived cytokines involved in tumor immunoediting and immunosubversion

Immune response type	Major cytokines involved
Acute phase response	IL-1, IL-6, IL-8, IL-17[a], TGFβ[b] TNFα[c]
Th1 response	IL-12, IL-18, IFNγ[d] TNFα
Th2 response	IL-4, IL-5, IL-10, IL-13
Immunosuppressive response	IL-10, TGFβ

[a]IL: Interleukin; [b]TGFβ: Transforming growth factor beta; [c]TNFα: Tumor necrosis factor alpha; [d]IFNγ: Interferon gamma

The network of cytokine interactions associated with tumors and tumor-directed inflammation is intricately complex and is itself the subject of several review articles[14,171]. Here, the roles of several key leukocyte-derived cytokines in cancer-mediated immune dysregulation are highlighted.

Cytokines can be broadly and imperfectly divided based on the type of immune response with which they are associated: Acute phase responses, acute inflammatory responses, chronic inflammatory responses and tolerogenic responses (Table 1). Acute phase responses occur rapidly in response to tissue injury. These responses are characterized by production of IL-1, IL-6 and TNFα. IL-1 induces the expression of proinflammatory genes including cyclooxygenase type 2 (COX-2), inducible Nitric Oxide Synthase (iNOS) and matrix metalloproteinases[172]. IL-6 has many effects, including mediating resistance to apoptosis through upregulation of survival and proliferation factors[14]. Effects of TNFα range from induction of apoptosis to maintaining cell proliferation; it is critical in several inflammatory conditions including Chron's disease and rheumatoid arthritis[173]. Though their proinflammatory effects, acute phase response cytokines promote cancer formation in the context of chronic inflammation. In addition, IL-6 plays a direct role in protecting tumor cells from apoptosis and stimulating proliferation. Elevated serum IL-6 levels are seen in patients with multiple myeloma and with renal, ovarian, colon, breast and prostate cancers[174,175].

Th1 immune responses are were classically described as acute responses to microbial pathogens such as viruses and some bacteria. Hallmarks of Th1 responses include enhanced antigen presentation and induction of cytotoxic mechanisms driving target cell apoptosis. Th1 responses often involve TNFα, but also involve IL-12, IL-18 and IFNγ. IL-12 is produced by mature DC and induces T cell differentiation to Th1 cells. IFNγ is secreted by Th1, CTL and NK cells and it promotes macrophage activation, upregulation of MHC presentation and increased target cell susceptibility to immune-mediated apoptosis. IL-18 serves to stimulate CTL and NK cells and augments IFNγ production[176]. Th1 immune responses have frequently been shown in animal models to eradicate tumors. As such, they are used to monitor immune responses in cancer immunotherapy trials[177]. However, uncontrolled systemic Th1 cytokines can be harmful in the setting of cancer, in that IL-18 is often secreted by cancer cells themselves and IL-18 has been shown to promote tumor angiogenesis, proliferation and metastasis[176].

Immune responses driven by Th2 cytokines are involved in immunity to helminths and other large parasites, as well as in allergic hypersensitivity responses. Th2-mediated inflammation is characterized by induction of antibody production and by stimulation of eosinophils and mast cells. These serve to generate a chronic inflammatory environment such as is seen in chronic parasitic infections and in asthma. In addition, Th1 and Th2 cytokines serve as negative regulators of one another, thus polarizing immune responses toward one type or the other[178]. IL-4 serves as a control cytokine for Th2 immune responses; it is a growth factor for Th2 cells and drives antibody production by B cells. IL-4 also opposes IL-12 in that it skews immune responses away from a Th1 phenotype. IL-5 primarily serves to induce eosinophil-based inflammatory responses, while IL-10 is a highly potent negative regulator of Th1 immune responses. IL-13, which shares homology with IL-4, also suppresses Th1 immunity[179]. Some investigators have described effective anti-tumor responses driven by Th2 cytokines, particularly implicating eosinophils as an effective anti-tumor mediator[180]. However, because of their potent suppression of Th1-based immunity, Th2 cytokines are generally regarded as harmful to anti-tumor immunity. Unfortunately, Th2 dominance is often seen in advanced cancer patients, as patients with metastatic cancer have elevated levels of multiple Th2 cytokines systemically[181] and elevation in plasma levels of IL-10[182,183] predict poor clinical outcomes.

While IL-10 is considered by many to be a Th2 cytokine, its principal effect is to suppress cytotoxic immune responses and it is produced by Tr1 regulatory T cells in addition to Th2 cells. TGFβ, while it has broad effects on differing cells and tissues, is also considered to be primarily an immunosuppressive cytokine with regard to inflammation in that it suppresses both Th1 and Th2 immune responses[184]. TGFβ has both protective and tumor-promoting roles. In responsive epithelial tissues TGFβ promotes cytostasis, differentiation and apoptosis[185]. However, once tumor cells lose responsiveness to TGFβ, its immunosuppressive effects, along with its ability to promote angiogenesis and metastasis serve to promote tumor progression.

Vascular growth factors: The isoforms of Vascular Endothelial Growth Factor (VEGF) and other related growth factors such as Placental Growth Factor (PlGF) are well-known by tumor biologists and oncologists for their importance in mediating tumor angiogenesis. Many solid tumors overproduce VEGF and VEGF overproduction is closely associated with poor outcomes[186]. While VEGF concentrations are highest in the tumor microenvironment, marked plasma elevations in VEGF are frequently seen in patients[187]. As tumors must synthesize their own blood vessels to grow beyond a certain size, interruption of vasculogenesis by blockade of vascular growth factors has proven to be an effective means of controlling growth. Agents that bind VEGF or block signaling from VEGF receptors have been proven efficacious in patients with many tumor types.

It has been observed that *in vitro* DC maturation from CD34+ progenitors isolated from umbilical cord blood is impaired by incubation with tumor cell culture supernatants[188]. Additionally, IFNγ production by Peripheral Blood Mononuclear Cells (PBMC) is abrogated in the presence of patient plasma; responses to non-specific T cell stimuli were skewed from Th1 to Th2 dominance[181]. In both DC maturation and PBMC stimulation, addition of VEGF to cell cultures reproduced the immune inhibitory function of tumor cell supernatants or cancer patient plasma. This indicates that VEGF, which is nearly ubiquitous in tumors and is often present systemically in cancer patients, is involved in global immune dysregulation and in altering anti-tumor immunity.

CONCLUSION

While the debate over the importance of the immune system in preventing and controlling tumor growth has now gone on for over a century, accumulating clinical evidence now strongly supports the relevance of both tumor immunosurveillance in preventing clinical tumorigenesis and immunoediting in controlling tumor growth. Clinical evidence now also demonstrates the ability of cancers to prevent, evade, or disrupt anti-tumor immune responses by a variety of mechanisms. Immunosubversion appears to begin within the tumor microenvironment, but ultimately leads to systemic dysregulation via both cellular and soluble mediators of immunosuppression. As the means by which tumors inhibit anti-tumor immunity are both diverse and redundant, it is likely that successful immune modulation will require simultaneous targeting of multiple immunosuppressive pathways in order to achieve consistent clinical benefit.

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