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BIOCHEMICAL ASPECTS OF TUMOR IMMUNITY

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ABSTRACT

The immune system is an important determinant of the tumor microenvironment. Indeed, the complex interplay between cancer cells and the host immune response has been extensively investigated. The immuno-editing theory suggests that the immune system is able to recognize and eradicate subclinical tumors, but at some point equilibrium is reached and the tumor remains *in situ*, in a state of balance with a partially efficacious response. Despite the recognition of distinct phases in cancer immune surveillance, clinically, single agent efficacy of most cancer vaccines is less obvious, with objective clinical responses rarely detected. The limited success of cancer immunotherapy to date is multifactorial. Future research is likely to have realistic implications in immune-based multifaceted anticancer therapy.

KEYWORDS: Cancer, Surveillance, Tumor, Immunity, Therapy.

INTRODUCTION

The tumor microenvironment consists of cancer cells, stromal tissue and extracellular matrix. The immune system is an important determinant of the tumor microenvironment. Indeed, the complex interplay between cancer cells and the host immune response has been extensively investigated in the past few decades. Several immunological deficiencies have been linked with enhanced tumor development in mouse models as well as in humans.[1] The persistent inflammation associated with chronic infections may also encourage new tumor formation.[2] Expression of various immunological gene products during ongoing inflammation thus appears to create a favorable microenvironment for tumor growth and progression.[3]

The immune system is able to distinguish self from non self and is able to vigorously attack non self and infected self tissues. This is the basis for antimicrobial responses. The immune-editing theory suggests that the immune system is able to recognize and eradicate subclinical tumors, but at some point equilibrium is reached and the tumor remains in situ, in a state of balance with a partially efficacious response.[4] The innate immune response functions to eradicate invasive pathogen; limit the spread of infection; initiate adaptive immune responses involving T and B cells; and to initiate tissue repair. Immune responses and inflammation are generally advantageous for the host and may include suppressing growth of smaller tumors. Interestingly however, inflammation can also promote neoplastic transformation and tumor progression. For example, in a genetically engineered lung cancer model using mice with a mutation in K-ras, cigarette smoke induced inflammation and tumor development through the activation of myeloid cells.[5] In a preclinical model of squamous cell carcinoma related to HPV E6/E7, chronic inflammation caused by lymphocytes and Fc Gamma Receptor signaling on myeloid cells was responsible for malignant transformation, and tumorigenesis could be abrogated via lymphocyte depletion or Fc Gamma Receptor blockade.[6]

Cancer immunity cycle

The generation of immunity to cancer is a cyclic process that can be self propagating, leading to an accumulation of immune stimulatory factors that in principle should amplify and broaden T cell responses. The cycle is also characterized by inhibitory factors that lead to immune regulatory feedback mechanisms, which can halt the development or limit the immunity. This cycle can be divided into seven major steps, starting with the release of antigens from the cancer cell and ending with the killing of cancer cells (Fig. 1).

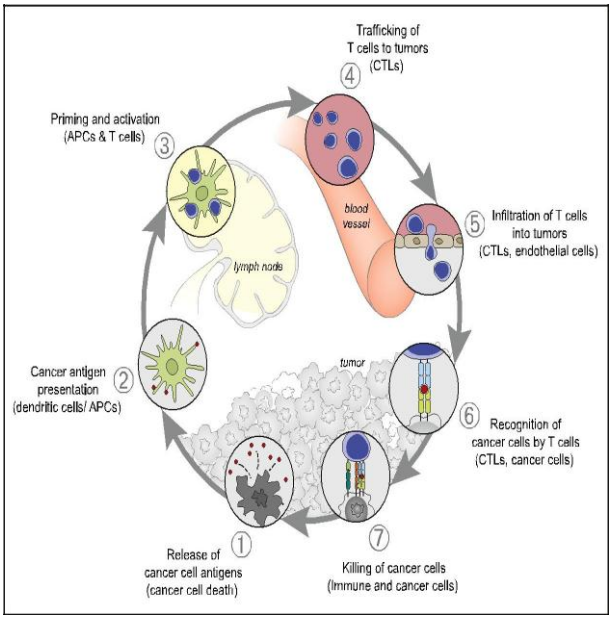

Fig. 1. Cancer immunity cycle.

Abbreviations: IL, interleukin; TNF, tumor necrosis factor; IFN, interferon; CDN, cyclic dinucleotide; ATP, adenosine triphosphate; HMGB1, high-mobility group protein B1; TLR, Toll-like receptor; HVEM, herpes virus entry mediator; GITR, glucocorticoid induced TNFR family related gene; CTLA4, cytotoxic T-lymphocyte antigen-4; PD-L1, programmed death-ligand 1; CXCL/CCL, chemokine motif ligands; LFA1, lymphocyte function-associated antigen-1; ICAM1, intracellular adhesion molecule 1; VEGF, vascular endothelial growth factor; IDO, indoleamine 2,3-dioxygenase; TGF, transforming growth factor; BTLA, B- and T lymphocyte attenuator; VISTA, V domain Ig suppressor of T cell activation; LAG-3, lymphocyte activation gene 3 protein; MIC, MHC class I polypeptide-related sequence protein; TIM-3, T cell immunoglobulin domain and mucin domain-3.

Each step of the cancer immunity cycle requires the coordination of numerous factors, both stimulatory and inhibitory in nature. Stimulatory factors promote immunity, whereas inhibitors help keep the process in check and reduce immune activity and/or prevent autoimmunity. Immune checkpoint proteins, such as CTLA4, can inhibit the development of an active immune response by acting primarily at the level of T cell development and proliferation (step 3). These are distinguished these from immune rheostat (‘‘immunostat’’) factors, such as PD-L1 and may have an inhibitory function that primarily modulates active immune responses in the tumor bed (step 7). Examples of such factors and the primary steps at which they can act are shown in Table 1. It is important to note that intra-tumoral T regulatory cells, macrophages and myeloid derived suppressor cells are key sources of many of these inhibitory factors.[7]

Table. 1. Cancer-Immunity Cycle: Examples of Positive and Negative Regulators.

S.No.	Steps	Stimulator	Inhibitor
1	Release of cancer Antigen	Immunogenic or necrotic Cell death	Tolerogenic or apoptotic Cell death
2	Cancer antigen presentation	Proinflammatory cytokines (e.g., TNF-α, IL-1, IFN-γ) Immune cell factors: CD40L/CD40; Endogenous adjuvants released from dying tumors: CDN (STING ligand), ATP, HMGB1 Gut microbiome products: TLR ligands	IL-10, IL-4, IL-13
3	Priming and activation	CD28:B7.1, CD137 (4-1BB)/CD137L, OX40:OX40L, CD27:CD70, HVEM, GITR, IL-2, IL-12	CTLA4:B7.1, PD-L1:PD-1 PD-L1:B7.1, prostaglandins
4	Trafficking of T cells to tumors	CX3CL1, CXCL9, CXCL10, CCL5	-
5	Infiltration of T cells into tumors	LFA1:ICAM1, selectins	VEGF, endothelin B receptor
6	Recognition of cancer cells by T cells	T cell receptor	Reduced peptide-MHC expression on cancer cells
7	Killing of cancer cells	IFN-g, T cell granule content	PD-L1:PD-1, PD-L1:B7.1, TIM-3:phospholipids, BTLA, VISTA, LAG-3, IDO, Arginase, MICA:MICB, B7-H4, TGFβ

Characteristics of tumor environment

The tumor microenvironment is made up of several important components (Table 2).

Table 2. Components of tumor microenvironment

- Tumor parenchyma cells
- Fibroblasts
- Mesenchymal cells
- Blood

- Lymph vessels
- Tumor infiltrating immune cells
- Chemokines
- Cytokines

Among these non-immune components, tumor associated fibroblasts are responsible for the formation and remodeling of the extracellular matrix and constitute a source of growth factor which promotes the growth of carcinoma cells.[8] The immune components of tumor microenvironment have gained attention in the recent decades for their critical role in tumorigenesis and tumor control. Tumorinfiltrating immune cells including myeloid derived suppressor cells (MDSC), tumor associated macrophages (TAM) and cytotoxic lymphocytes are critical determinants of cancer outcomes. Many studies have shown that increased densities of MDSC and TAM promote tumor progression via multiple suppressive mechanisms.[3]

Inflammation has been implicated in the development of cancers since the seminal observation made by Virchow in 1863[9-10] that chronic inflammation creates a microenvironment conducive to tumorigenesis. The inflammation associated with chronic infections such as *Helicobacter pylori* or hepatitis B virus promotes the respective development of gastric and liver cancers.[3] Proinflammatory cytokines such as IL-6, IL-1α and IL-8, as well as various chemokines, re known to favor tumor growth and progression.[9-10] The inappropriately named tumor necrosis factor (TNF)-α has also been linked to several aspects of tumorigenesis including cellular transformation, proliferation, invasion and metastasis.[9] Molecular mechanism linking chronic inflammation to cancer progression involves a transcription factor known as STAT3 (signal transducer and activator of transcription 3). Tumors can also cause systemic immunosuppression as noted in preclinical models demonstrating an increase in splenic myeloid suppressor cells, which are a specialized population of innate myeloid cells.[6]

Tumor antigens and immunogenicity

Dendritic cells (DC) link the innate immune system to the adaptive immune response. These cells dwell in the tissues, continually sampling the microenvironment and taking up antigens primarily through pinocytosis. When the innate immune system is activated in their vicinity, DCs sense this as "danger"[11], cease antigen uptake and travel to local lymph nodes, where their role is to present antigen to specific T lymphocytes. In mice, a subset of DCs that express CD8 is primarily responsible for priming anti tumor immune responses.[12] Their human equivalent is thought to be CD141+ DCs.[13-16] These subsets are known to produce IL-12 and cross present antigens to lymphocytes. The other major strategy under study is to target antigens specifically to DCs in vivo. This routinely involves the use an adjuvant (e.g. TLR agonist) in combination with signaling antibodies (e.g. anti-CD40, anti-DC-SIGN, anti-MMR, anti-DEC-205) and tumor-specific antigen.[6]

In patients with metastatic melanoma, the expression of T cell markers and chemokines correlated with response to a DCbased vaccine.[13] Likewise, a proinflammatory gene expression profile within the tumor microenvironment was associated with survival following administration of a protein based vaccine in patients with metastatic melanoma. T cell activation is clearly influenced by the spectrum of cytokines present during antigen recognition, and several cytokines exert their immunologic effects by modulating the function of STAT proteins during T cell activation. In that regard, STAT4 has thus far been demonstrated to be crucial to T cell mediated anti tumor immune responses. IL-12 activates STAT4, which in turn skews T cells toward a Th1 phenotype and IFN-γ production.[6] Multiple processing pathways exist for proteolysis of antigen and presentation in MHC molecules.[14] Determinants of a peptide's ability to induce an immune response (i.e. its "antigenicity") include its affinity to the MHC, as well as the affinity of the peptide/MHC complex for a given T Cell Receptor (TCR). A critical facet of this interaction is a set of amino acids which are integral to MHC binding, so called MHC-anchor residues. To induce more robust immune responses, it is possible to modify antigenic peptides in several ways. MHC variable peptides (MVP), for example, are peptides designed with amino acid point changes involving MHC contact residues, usually optimized for improved MHC affinity. Conversely, altered peptide ligands (APL) are peptides with amino acid substitutions designed to optimize interactions with the TCR. These altered peptides have been used in an attempt to augment immune response against a specific antigen.[15]

Immune mechanisms to distinguish tumor cells from normal cells

Memory cells can be divided into
(1) Effectormemory having more cytotoxic function
(2) Central memory cells, which likely represent the more classic quiescent memory cell with high proliferative capacity once re-stimulated
(3) Tissue resident memory associated with an organ-specific distribution *in vivo.*[6]

Accordingly, question concerns how cells of the immunosurveillance network distinguish nascent transformed or established tumor cells from normal cells. Work over the last decade has begun to reveal the molecular basis of this crucial distinction particularly within the adaptive immune compartment. Specifically, $CD4^+$and $CD8^+$T cells recognize tumor antigens in the context of MHC class II and class I proteins, respectively. Since the first human tumor antigen was identified in 1991[16], many tumor antigens have been cloned and can be segregated into five categories: (1) differentiation antigens, e.g., melanocyte differentiation antigens, Melan-A/MART-

1, tyrosinase, and gp-100; (2) mutational antigens, e.g., abnormal forms of p53; (3) over expressed/amplified antigens, e.g., HER-2/ neu; (4) cancer-testis (CT) antigens, e.g., MAGE and NY-ESO-1; and (5) viral antigens, e.g., EBV and HPV. The molecular definition of tumor antigens has revolutionized the field of tumor immunology by providing a firm basis for how the adaptive immune system discriminates between normal and neoplastic cells.[17]

In addition to tumor antigens presented on MHC molecules, transformed cells may over express other molecular sign posts that can function as recognition targets in the immunosurveillance process. Several studies have pointed to the NKG2D activating receptor, expressed on NK cells, µ6 T cells and CD8 aþ T cells[18-19], as one important component that is used by both adaptive and innate immune cells to distinguish cancer cells from normal cells. Functional NKG2D receptors complexes consist of the NKG2D ligand binding polypeptide and either the DAP10 or DAP12 signaling polypeptide.[17] In humans, NKG2D binds to the MHC class I chain related proteins A and B(MICA/B), as well as the UL16 binding proteins (ULBPs)[20-21] and the recently discovered lymphocyte effectors cell toxicity activating ligand (Letal) first reported as RAET1E and also termed ULBP4. The MICA/B proteins are highly polymorphic, non classical MHC cell surface glycoproteins that do not associate with þ2m or require TAP1 for expression.[17] Interestingly, while MIC expression in normal tissues has only been documented on the gastrointestinal epithelium of the stomach and large intestines, MICA/B proteins are often expressed in primary carcinomas of the lung, kidney, prostate, ovary, colon[22] and liver, as well as in melanomas. In addition, ULBPs and Letal are also frequently expressed on tumor cells. In mice, NKG2D binds to there tinoic acid early transcript 1 (Rae-1) family proteins Rae 1a c, the minor histocompatibility antigen H60 and mouse UL16 binding protein like transcript (MULT-1) NKG2D[17] ligand expression has been observed on a wide range of murine tumors[23] and ectopic expression of Rae-1, H60, or MULT-1 was sufficient to induce the rejection of several progressively growing, transplant able tumors.[17] It will be important to characterize the regulation of NKG2D ligand expression in both human and murine cells. These molecules are often described as"stress molecules," but to date no cancer relevant signaling pathways have been causally linked to their expression. In human cells, MICA/B gene expression has been induced in several non transformed human cell lines by heat shock at 42°C[22], infection with human cytomegalo virus, or exposure to *E. coli*, although in dendritic cells MICA/B is up regulated by type I interfereon or *M.tuberculosis* infection. However, it remains unclear how these conditions overlap the molecular cascades that underlie neoplastic transformation. In mice, Rae-1 is up regulated by retinoic acid in F9 cells (Nomura et al., 1994) and is also expressed early in development.[17] In addition, one study assessed the expression of the NKG2D ligands H60 and Rae-1 after topical application of DMBA and TPA.[23] While no expression of these molecules was observed by RT-PCR in normal skin, Rae-1 and H60 expression became detectable 24 hr after carcinogen treatment. Strikingly, expression of both molecules was significantly increased in papillomas and carcinomas generated by DMBA/TPA treatment. It is possible that the transformation process itself induces molecules such as the NKG2D ligands so that the genomic upheaval of tumorigenesis is directly translated into enhanced immune recognition. Further study on the immunology of transformation will be necessary to detail when and how in the course of tumorigenesis a cancer cell becomes immunogenic.[17]

Phases of immune surveillance

Normal cells subject to common oncogenic stimuli ultimately undergo transformation and become tumor cells. Even at early stages of tumorigenesis, these cells may express distinct tumor specific markers and generate pro inflammatory "danger" signals that initiate the cancer immune editing process. In the first phase of elimination, cells and molecules of innate and adaptive immunity, which comprise the cancer immunosurveillance network, may eradicate the developing tumor and protect the host from tumor formation. However, if this process is not successful, the tumor cells may enter the equilibrium phase where they may be either maintained chronically or immunologically sculpted by immune "editors" to produce new populations of tumor variants. These variants may eventually evade the immune system by a variety of mechanisms and become clinically detectable in the escape phase (Fig. 2).[17]

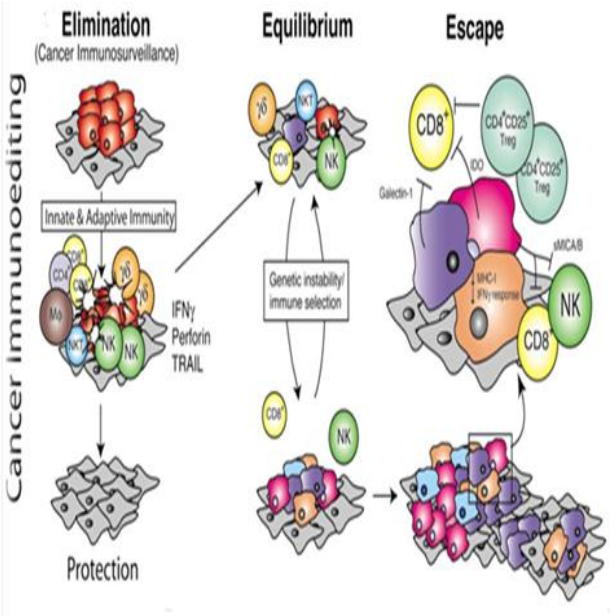

Fig. 2. The Triphasic Cancer Immunoediting Process.

Cancer Immunotherapy

Radiation

Local radiotherapy on cancer cells occasionally induces the regression of metastatic cancer at distant sites which have not been irradiated apparently through induction of adaptive immune responses. This phenomenon has been called an abscopal effect and can be attributed to the induction and enhancement of endogenous anti tumor innate and adaptive immune responses Cytokines play an important role in the abscopal effect. In one case, a Japanese patient receiving radiotherapy for thoracic vertebral bone metastasis, experienced spontaneous regression of an unrelated hepatocellular carcinoma. Pre and post analysis of serum cytokine levels revealed marked elevation of tumor necrosis factor-α following radiotherapy, suggesting that the abscopal related regression may involve such cytokines as part of the host immune response.[24] Another radiation induced cytokine, IFN-β, has been shown to enhance T cell dependent tumor regression by increasing the cross priming capacity of tumor infiltrating dendritic cells in mouse model, an effect that can be mimicked by delivery of exogenous IFN-β into the tumor tissues without radiation. That this abscopal effect is mediated by immune cells is supported by the observation that exogenous administration of chemokines following local radiation therapy can lead to enhanced killing of tumors at distal sites. This abscopal effect was tumor type independent, involving infiltration of $CD8^+$ and $CD4^+$ lymphocytes and $NK1.1^+$ NK cells into the tumor sites of mice.[25] T lymphocyte associated antigen 4 (CTLA-4), one of the negative regulators of cytotoxic $CD8^+$ T cells, has been targeted as a means to activate anti tumor immune CTLs in mouse xenografts. This effect can be attributed in part to an anti CTLA4 mAb mediated decrease in the threshold of activation among endogenous tumor reactive T cells. When immunogenic tumor cells were treated with ionizing radiation in the presence of a DNA repair inhibitor (veliparib) and then injected into tumor bearing mice, an antitumor CTL response was generated leading to elimination of established tumors. Some types of tumor cell deaths can induce a DC mediated cytotoxic T lymphocyte (CTL) response, wherein calreticulin, a Ca^{2+} binding protein, becomes exposed on the cell surface during immunogenic cell death. In cancer therapies, some notions of metastasis and recurrence may be explained using oligometastases and oligo recurrence. Oligometastases is the state capable of achieving long term survival or cure with local therapy despite active primary legions. On the other hand, oligo recurrence is the notion that metastatic and recurrent lesions could be treated with local therapy since the primary lesions have been controlled.[26]

Vaccines

A variety of vaccine approaches have been explored (Table 3).

Table 3. Anticancer vaccines

- Synthetic peptides
- Recombinant virus like particles (VLP)
- Naked/stabilized nucleic acids
- Recombinant viruses
- Recombinant bacteria
- Dendritic cells

One notable facet of cancer vaccines is that they must provide antigen (signal 1) in addition to a second signal (signal 2) to elicit full effector function. The addition of an appropriate adjuvant to a vaccine (i.e. a "danger" signal), can be important in providing signal 2. Despite a great deal of work, only two cancer vaccines have been approved for clinical use, including Oncophage (Russia, 2008) and Provenge (sipuleucel-T) (USA, 2010). The PSA targeting viral vaccine Prost Vac VF is currently in phase III trials worldwide.[6]

Cytotoxic or genotoxic agents which induce cellular stress or DNA damage could release danger signals that are sensed by Toll like receptors and activate innate immune responses. Chemotherapeutic drugs have also been found to activate the immune system despite the prevailing view that these agents induce immunosuppressive effects. For example, low doses of cyclophosphamide inhibit Treg and gemcitabine or 5-fluorouracil eliminate MDSC. Cyclophosphamide, paclitaxel, doxorubicin and vinblastine given at regular intervals normalize the tumor associated vasculature, thereby facilitating the delivery of drugs and recruitment of T lymphocytes. Gemcitabine can activate both the adaptive and humoral immunity to elicit meaningful antitumor responses in animal models.[3]

Adoptive T Cell Therapy

Adoptive cellular therapy involves the *ex vivo* isolation and expansion of tumor reactive T cells for infusion with the expectation that these T cells will traffic to tumor sites, eradicate tumor and provide long term immune protection. Adoptively transferred cells can be described as:

(1) Tumor infiltrating lymphocytes, derived from a tumor biopsy which has been disaggregated and cultured in the presence of highdose IL-2 to enrich for a population of tumor reactive T cells from the mixed tumor-T cell population.

(2) Chimeric antibody receptor (CAR) or T cell receptorengineered lymphocytes generated by transfection of a vector encoding the antibody or T cell receptor recognizing the ligand of interest.

(3) Antigen specific T cells present in very low frequency in the peripheral blood selected and enriched using specialized *in vitro* culture approaches.[26]

Monoclonal antibodies

Monoclonal antibodies are now widely utilized in the treatment of a number of tumor types; pertinent examples including trastuzumab (anti-Her-2) for the treatment of breast cancer, rituximab (anti-CD20) for the

treatment of lymphoma and the recently approved immune conjugate T-DM1, which fuses trastuzumab to a highly potent chemotherapy, emtansine (DM1 [deacetylmaytansine]) to facilitate local delivery and minimize systemic toxicity. The Fc portion of a monoclonal antibody plays a major role in determining the immune mechanisms induced, with monoclonal antibodies of the human IgG4 isotype primarily functioning as "blockers". One interesting aspect involved in the development of monoclonal antibodies for the clinic involves their affinity, while higher antibody affinity results in increased target engagement and ADCC, higher affinities can also result in decreased tumor penetration and compromised efficacy. An 11% absolute benefit in 2year survival was observed in patients with advanced neuroblastoma treated with a combination of IL-2, GM-CSF, and an antibody targeting GD2 (disialoganglioside 2) (P = 0.02).[6]

Cancer vaccines

An alternative to infusion of preformed tumor specific antibodies or T cells, known as passive immunotherapy, is active specific immunotherapy (i.e., cancer vaccines) designed to elicit or boost similar tumor antibodies and T cells in the patient. Some examples are vaccines against breast cancer (the HER2 antigen), B cell lymphoma (the tumor immunoglobulin idiotype), lung cancer (the MUC1 antigen), melanoma (dendritic cells loaded with tumor peptides or killed tumor cells), pancreatic cancer (telomerase peptides) and prostate cancer (dendritic cells loaded with prostatic acid phosphatase).[27]

The limited success of cancer immunotherapy to date can primarily be attributed to three main factors- (i) poor host responses towards tumor antigens; (ii) low infiltration of effector cells into solid tumors; and (iii) the intrinsically immunosuppressive tumor microenvironment. Tipping the balance of immune responses from tumor protection towards tumor rejection seems to be key for effective cancer immunotherapy. Cancer vaccines aim to induce immune responses against tumor associated antigens and several such vaccines are currently under development to treat various cancers. The first FDA approved therapeutic cancer vaccine Provenge (Sipuleucel-T) provides modest but significant benefits in castrate resistant prostate cancer. Alternatively, vaccines that aim to control the inflammation induced by chronic infections may serve as effective tumor prevention measures. One such example is the hepatitis B vaccination which has successfully reduced the incidence of liver cancer in Taiwan since being introduced in 1984.[3]

Conclusions and future perspectives

Originally, cancer immunosurveillance was envisaged as a binary process: the immune system either protected the host from the development or cancer, or it did not.[28] Moreover, the surveillance functions of the immune system were thought to be executed only at the earliest stages of tumorigenesis. However, recent studies have started to explain what happens when tumors develop in immunocompetent hosts, as they do in individuals with cancer and what has emerged from this is the realization that even when immunosurveillance fails, the relationship between immunity and cancer is far from over.[17] Clinically, single agent efficacy of most cancer vaccines is less obvious, with objective clinical responses rarely detected.[29]

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