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POSITION PAPER

2011: the immune hallmarks of cancer

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Abstract Ten years after the publication of the position paper "The hallmarks of cancer" (Hanahan and Weinberg Cell 100:57–70, 2000), it has become increasingly clear that mutated cells on their way to giving rise to a tumor have also to learn how to thrive in a chronically inflamed microenvironment, evade immune recognition, and suppress immune reactivity. Genetic and molecular definition of these three immune hallmarks of cancer offers the opportunity to learn how to deploy specific countermeasures to reverse the situation in favor of the immune system and, eventually, the patient. This new information could be channeled to address what seem to be the three major hallmarks for the immune control of cancer progression: effective procedures to activate immune reactivity; characterization of not-disposable oncoantigens; and counteraction of immune suppression.

Keywords Cancer · Inflammation · Immune surveillance · Immune suppression · Oncoantigens · Tumor vaccine · Antitumor antibodies

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The immune hallmarks of cancer

In an important position paper published in January 2000, Hanahan and Weinberg listed six alterations essential for malignant growth: self-sufficiency in growth signals, insensitivity to antigrowth signals, limitless replicative potential, ability to evade apoptosis, sustained angiogenesis, and ability to invade the tissues and metastasize [1]. The ability to deal with immune mechanisms, however, was not included among these essential capabilities, but may be supposed to be acquired by most—and perhaps all—tumors. Because of the authoritative impact of this paper, these six hallmarks are usually quoted as the starting ground for new anticancer strategies, while the addition of other critical features of malignant tumors as hallmarks is often urged [2].

In the 10 years since the publication of the paper, it has become increasingly clear that both exploitation of immune mechanisms and evasion of immune surveillance are skills that cancer cells should acquire on their way to giving rise to a tumor. A comprehensive cellular, molecular, and genetic interpretation of the initially somewhat fuzzy evidence of the importance of such acquisition has also been worked out. Three such immune hallmarks are certainly required:

1. Ability to thrive in a chronically inflamed microenvironment
2. Ability to evade immune recognition
3. Ability to suppress immune reactivity

These three capabilities and acquisition of the genetic changes required to put them into practice are constant and essential features of natural and experimental cancers. Their strength, however, may vary from one kind of tumor to another, and even more variable are the mechanisms

through which the various types of cancer undertake these activities. Acquisition of a specific genome change, therefore, is not important, whereas acquisition of these capabilities is crucial, irrespective of the mechanisms involved.

Ability to thrive in a chronically inflamed microenvironment

Genetically modified mouse models show the intrinsic carcinogenic potency of inflammation [3–5] and permit molecular definition of several of the mechanisms whereby an incipient tumor takes advantage of an inflammatory microenvironment. Continual activation of leukocyte populations, triggered by unrelenting infections, tissue damage or the anomalous behavior of the mutated cells, contributes to the progression of neoplastic transformation with multiple mechanisms that range from reactive oxygen species to growth and angiogenic factors [6]. The balance between immunity and inflammation is constantly altered during aging, with inflammation holding the center of the stage in old age when tumor incidence peaks [7, 8].

The importance of an inflammatory microenvironment is so strong that even the time frame within which an oncogene-addicted cell population gives rise to a tumor in transgenic mice is modulated by the reactive stroma that surrounds the cancer lesion [9]. Inflammation and carcinogenesis are linked even in the absence of external inflammatory stimuli. Oncogene-driven signals activate intrinsic pro-inflammatory pathways that affect the time frame within which a carcinoma appears and progresses [6, 10]. Genome-wide microarray analysis in transgenic mice identifies cytokine genes whose increased expression in the tumor microenvironment is naturally induced by the transformed cells and required for their progression [11]. The inflammatory cytokines produced can be both involved in autocrine loops directly fueling tumor cell proliferation [12] and released by immune/inflammatory cells recruited to the site of epithelial transformation [13]. Inhibition of the NF-kB pathway in these immune cells modifies stroma cell components and limits tumor expansion [14, 15].

Murine molecular data are directly endorsed by many epidemiological studies in humans that link extrinsic and intrinsic inflammatory pathways with an increased risk of cancer [16]. The increased risk of gastric cancer in the setting of bacterial infections is linked to the polymorphisms in genes coding for pro-inflammatory cytokines [17]. These findings show how extrinsic and intrinsic inflammatory pathways conspire along the road to cancer. Molecular definition of the ways in which chronic inflammation contributes to viral, chemical, and intrinsic carcinogenesis in humans is opening up novel prospects for immunoprevention.

Ability to evade immune recognition

The immune surveillance theory was put forward in the 1960s. It defined the ability to identify and destroy nascent tumors as a central asset of the immune system [18, 19], but later received an apparently deadly blow when no increase in tumor incidence was observed in athymic nude mice [20, 21]. Work in the last 10 years, however, has shown that these mice are not an appropriate model for the investigation of immune surveillance, while the employment of genetically modified mice to generate defined and stable immune defects has fully vindicated this theory. Mice with genetic alterations leading to complete T- and B-cell deficiencies are more prone to spontaneous and chemical carcinogenesis than wild-type mice [22]. Additional gene defects affecting natural immune responses increase the risk of more aggressive and precocious tumors [22]. Moreover, immune mechanisms hold occult cancer at bay for periods equivalent to the natural life span of the mouse, while temporary immunodepression allows it to progress [23].

Immune surveillance mechanisms limit cancer development, but are not completely efficient. Tumors that eventually arise are those that are poorly or not-immunogenic [24]. A critical feature that distinguishes occult neoplastic lesions from overt cancer is thus their susceptibility to immune control. The ability to evade is another hallmark of cancer.

Data from patients with acquired immune deficiencies such as AIDS and post-transplant immune suppression show a dramatic increase in the incidence of several tumor types, including lung cancer, lymphoid tumors and tumors related to viral infections, such as Kaposi's sarcoma (human herpes virus-8) and anogenital carcinomas (human papilloma virus, HPV) [25].

In the last 10 years, it has become evident that a tumor becomes aware of its susceptibility to immune attack and elaborates many defenses against it. These have now been defined in both cellular and molecular terms.

The increasing instability of the genome of precancerous cells favors the emergence of clones of different immunogenicity. The poorly immunogenic ones are those that sneak through the meshes of immunosurveillance. The stealthiness of clinical tumors can be seen as one of the results of an effective immunosurveillance [24]. The loss or rarefaction of the expression of the glycoproteins of the major histocompatibility complex (MHC) on the cell membrane is one of the mechanisms by which tumor stealthiness is acquired. In addition, it may result from the subversion of cell physiology as a consequence of the overexpression of oncogene-coded proteins [26, 27], and alteration of antigenic peptide-processing machinery [28, 29].

Poor MHC glycoprotein expression and hampered antigenic peptide expression on the tumor cell surface frustrate direct recognition of tumor antigens by T cells and impede direct priming of an immune response by a tumor. Moreover, they make the effector phase of the T-cell reaction against tumor-associated antigens worthless. Blockage of these two functions is a crucial issue in tumor development since T-cell-mediated cytotoxicity is an effective mechanism of tumor inhibition.

Ability to suppress immune reactivity

As their growth hidden from immune recognition is not enough to allay their obsession with attacks on the part of the immune system, most—all?—tumors acquire the ability to release a series of factors and cytokines to subvert normal reaction mechanisms. When a tumor acquires the ability to release significant amounts of the colony-stimulating factors [30] or the vascular endothelial growth factor [31], it causes the expansion of a population of myeloid immature cells that may not only help tumors to suppress immune reaction but also aid in the construction of new blood vessels for tumor growth [32, 33].

Yet even this is not enough. Through direct release of transforming growth factor (TGF)-beta, IL-10, and indoleamine 2,3-dioxygenase (IDO), or through the activation of such secretions in myeloid-derived suppressor cells, tumor-associated macrophages and dendritic cells, a tumor converts naïve T cells into adaptive regulatory T (T_{Reg}) cells. Expansion of these cells is another way by which a tumor holds back host reactivity [34].

Tumors also exploit the physiologic role of natural T_{Reg} cells to block immune reactions. These cells recognize with high affinity self-antigens and block the induction of autoimmunity. The overexpression of a few tolerated self-antigens, as happens during the expansion of tumor cells overexpressing oncogene products, leads to the activation of natural T_{Regs}. Thus, both through the exploitation of a physiologic safeguard mechanism to control autoimmunity and the ability to convert naïve T cells into a suppressor population, a growing tumor biases the immune response toward immunosuppression. The activation of adaptive and natural T_{Reg} cells is triggered by specific activation of their T-cell receptor. The T_{Reg} suppressor mechanisms thus turned on are mediated by different functions:

(a) Exposure on the cell membrane of molecules delivering negative signals (CTLA4 and LAG3) to dendritic cells. These signals inhibit the maturation of dendritic cells, block their expression of MHC and co-stimulatory molecules (CD80 and CD86) [35], activate their ability to produce IDO that leads to the generation of the immunosuppressive mediator kynurenine, and indirectly suppress genes encoding IL-6 and TNF [36].
(b) Release of adenosine and the secretion of TGF-β, IL-10, and IL-35 that interfere with the activation and effector functions of T cells [35, 37].
(c) Secretion of granzymes and perforin that might have cytolytic effects on target T cells, as well as on dendritic cells [35].

The same group of signals triggers the activation and maintenance of anomalous functions of tolerogenic dendritic cells and tumor-associated macrophages. In this way, a growing tumor orchestrates a web of distinct but integrated suppressive activities.

How to counteract the immune hallmarks of cancer

The knowledge gained in the last 10 years offers the opportunity to learn how to deploy specific countermeasures to reverse the situation in favor of the immune system and, eventually, the patient. This new information could be channeled to address what seem to be the three major hallmarks for the immune control of cancer progression:

1. Effective procedures to activate immune reactivity
2. Characterization of not-disposable oncoantigens
3. Counteract immune suppression.

Effective procedures to activate immune reactivity

Chronic inflammation can be dampened with anti-inflammatory drugs, which in some cases reduce the risk of cancer (sulindac, aspirin) [38]. However, a more sensitive strategy is to re-orient inflammation from tumor promotion to a tumor-preventive reaction [39–41]. Both passive (antibodies) and active (vaccines) immunization effectively protect the host from tumor onset [42, 43]. However, a much larger body of evidence favors active immunization.

The high efficacy of vaccines in the prevention of infection by carcinogenic viruses and other infectious agents causing cancer is currently getting an extraordinary social impact. Vaccines aimed at removing an infective risk factor are being commonly used.

Hepatocellular carcinoma accounts for more than 4% of all human cancers, and 80% of cases are associated with viral infection. Vaccination against hepatitis B virus (HBV) markedly reduced the incidence of post-hepatitis hepatocellular carcinoma [44]. Since chronic inflammation plays a significant role in the onset of liver cancer that follows HBV infection, this vaccine can be viewed as a form of primary prevention of a carcinogenic chronic inflammation.

HPV causes neoplastic disorders ranging from benign warts to malignant cervical and anogenital carcinomas [45]. The worldwide implementation of vaccination programs against HPV began only a few years ago, and their long-term efficacy in the prevention of cervical carcinoma is not yet completely assessed. Initial results are extremely favorable, and almost complete prevention of carcinogenesis is foreseen [46]. Current HPV vaccines are effective in cancer prevention but devoid of therapeutic efficacy. Vaccines able to cure cervical carcinomas are actively studied [47].

The Epstein–Barr virus (EBV) is implicated in a variety of diseases worldwide: infectious mononucleosis in Western countries, nasopharyngeal carcinoma in Asia, Burkitt's lymphoma in Africa, and lymphoproliferative diseases in immunodeficient patients. The use of some promising candidate vaccines is being actively pursued [48, 49].

While vaccines to prevent tumors related to an infectious agent are becoming a medical reality, a large series of studies on genetically engineered mice suggest that vaccines to prevent tumors not related to an infectious agent may also be a new form of prevention [50, 51]. Numerous data on healthy mice carrying oncogenes that predestine to lethal cancer show that vaccines addressing oncogene products block the onset of neoplastic lesions. Repeated boosts of the vaccine afford a persistent protection that may last as long as the natural murine life span.

Somewhat surprisingly, the T-cell-mediated cytotoxic response plays a minor role in the protection afforded by several of these vaccines. Since the target oncogene products are self molecules, they elicit a kind of split-tolerance that mainly causes the disappearance of high-affinity $CD8^+$ T cells [52]. In addition, this response is inhibited by the expansion of natural T_{Reg} cells that recognize the target antigen as a self-protein [53]. Therefore, most of the antitumor action elicited by preventive vaccines rests on the multiple direct and indirect antitumor activities of antibodies [54–56].

Characterization of not-disposable oncoantigens

Vaccines that must elicit and sustain a virtually lifelong immune response carry the risk of downmodulation or loss of the target antigen by neoplastic cells. A suitable target antigen that preempts the loss of immune recognition should

(a) have an essential role in tumor growth or progression;
(b) be a target of cytotoxic cells and antibodies.

We have chosen the term "oncoantigens" for tumor antigens that fulfill these two requirements [50]. When carcinogenesis is driven by an oncoantigen, antigen-loss variants can occur, but their tumorigenic potential would be markedly impaired [57, 58]. In the later course of tumor progression, the driving role of the targeted oncogene can be taken by different genes [59, 60], whose products, in turn, will offer further oncoantigen targets.

Tumors evade T-cell recognition through the downmodulation of antigen-processing machinery and MHC glycoprotein expression. However, antibody recognition of accessible molecules is not affected, and antibodies still ensure a functional inhibition of the target oncoantigen together with the activation of complement-mediated cytotoxicity and ADCC. Class I oncoantigens expressed on the cell surface can be attacked by both antibodies and cell-mediated immunity and are probably the best target for a preventive vaccine [50]. Class II oncoantigens are tumor-secreted molecules or molecules in the tumor microenvironment that play essential roles in tumor expansion [61]. These can be targeted by antibodies but not by T-cell-mediated immunity. Class III oncoantigens are tumor molecules that cannot be reached by antibodies because of their intracellular localization, and thus can only be targeted by T cells [62, 63].

One could imagine that in the future, vaccines to prevent cancer will be administered to the general population, as is happening now to prevent infectious tumors. In a more realistic perspective, there are several human groups at risk of cancer that could benefit from specific vaccines, especially in the case of genetic risk, preneoplastic syndromes, cohorts of individuals previously exposed to environmental carcinogens, and cancer survivors with increased risk of a new primary tumor. Of particular interest appears the finding that a vaccine against ERBB2, an archetypal class I oncoantigen, impairs chemical carcinogenesis in hamsters since it may open a new way to treat healthy persons with a specific risk of a chemically induced cancer for whom no active therapeutic option exists at present [64].

Counteraction of immune suppression

The efficacy of vaccines is diminished by the tumor-driven expansion of immunosuppressive cells, including T_{Reg} and myeloid-derived suppressor cells (MDSC) [50], that results in both a far less significant immune response and suppression of its effector arm [65, 66]. Strategies that counteract suppression during vaccination can make the difference between a poorly effective vaccine and a sterilizing one. T_{Reg} cells accumulate in both human and mouse tumors, as well as in secondary lymphoid organs, and are recruited [67] and expanded by either the proliferation of preexisting T_{Reg} cells [68] or the conversion of CD25-negative T cells [34, 69]. Tumor-driven T_{Reg} cell expansion also changes the tumor-specific T-cell repertoire [53, 70] and inhibits the reaction of low-avidity T cells against tumor antigens [53, 69].

When vaccination is coupled with T_{Reg} depletion by the administration of anti-CD25 monoclonal antibody, a long-lasting tumor immunity is induced, and the antibody response is enhanced. In addition, the low-avidity CTL response against the immunodominant peptide is restored, due to the freeing of $CD8^+$ T cells from T_{Reg} constraints [53]. These effects of T_{Reg} depletion render the vaccination efficacious at tumor stages at which vaccination alone is ineffective [53]. Similarly, T_{Reg} cell functional inhibition, by means of OX40 triggering, protects mice from subsequent tumor challenge and induces a complete rejection of already-established nodules [71].

T_{Reg} are not the sole suppressive cells than can be attacked to counteract immune suppression. Myeloid-derived suppressor cells (MDSC) are an underdeveloped target of growing importance [72–74]. It has been shown that powerful vaccines inhibit MDSC [41, 75]; however, a more direct strategy can be more effective. Four lines of attack were outlined in a recent review [76]: induction of MDSC maturation, inhibition of MDSC generation, accumulation, and suppressive function.

The clinical use of antisuppressive approaches will benefit all cancer patients, in particular more advanced ones, who frequently display higher levels of immune suppression and suppressive cells. As novel immunotherapies are first tried in advanced patients, we think that the success rate of such clinical trials would be significantly enhanced by the simultaneous implementation of counter-suppression approaches.

Conclusions and perspectives

Can these three hallmarks lead to the formulation of immune procedures effective in tumor therapy? The emerging evidence shows that immune maneuvers can control cancer. This evidence is still scattered, but a series of recent reports suggest that immunotherapy is becoming a real option in the management of cancer patients. Vaccines of various kinds, in fact, have provided results equal or better than the most successful conventional treatments in a range of neoplastic diseases such as lymphomas [77], melanomas [78], prostate, and lung cancer [79]. These results along with the approval by US FDA of an initial vaccine for cancer therapy [80] will certainly spur fresh and even more rational strategies for vaccines in cancer therapy. It is thus predictable that new vaccines based on innovative technologies will progressively reach the efficacy of most conventional cancer therapies and spare patients from the devastating side effects of chemotherapy. In some cases, the cure afforded by a vaccine may prove to be even more effective, more persistent than chemotherapy.

It is noteworthy that current preclinical and clinical results converge on the relevance of antibodies in antitumor immune responses [63, 81, 82]. In the last 10 years, Herceptin and other mAbs have become efficacious new drugs that are commonly used and provide incredibly high revenues [83].

The mechanism of antitumor activity of mAb is complex and depends on the targeted antigen. mAb against Class I and Class II oncoantigens not only functionally inhibit the activity of their targets and recruit antibody-dependent killer mechanisms and complement-dependent reactions but also recruit the host adaptive response and act to some extent as a vaccine [84, 85]. Despite these important clinical results, most antitumor vaccines are still designed to trigger only cell-mediated immunity. It is remarkable that a clinical trial of the first approved vaccine revealed significant correlations between patient survival and specific antibody titers, but not T-cell responses [80]. Probably, the time is ripe to integrate such "humoral" concepts in the design of new therapeutic cancer vaccines.

In conclusion, appraisal of the immune hallmarks of cancer, and of the possible countermeasures, opens the doors not only to widespread cancer immunoprevention but also to innovative and more efficacious cancer immunotherapies.

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