

REVIEW

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Cancer immunotherapy: are we there yet?

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Abstract

The immune system is the built-in host defense mechanism against infectious agents as well as cancer. Protective immunity against cancer was convincingly demonstrated in the 1940s with syngeneic animal models (JNCI 18:769-778, 1976; Cancer Immun 1:6, 2001). Since then, the last century's dream has been to effectively prevent and cure cancers by immunological means. This dream has slowly but surely become a reality (Nature 480:480-489, 2011). The successful examples of immunoprophylaxis and therapy against cancers include: (i) targeted therapy using monoclonal antibodies (Nat Rev Cancer 12:278-287, 2012); (ii) allogeneic hematopoietic stem cell transplantation to elicit graft-versus-cancer effect against a variety of hematopoietic malignancies (Blood 112:4371-4383, 2008); (iii) vaccination for preventing cancers with clear viral etiology such as hepatocellular carcinoma and cervical cancer (Cancer J Clin 57:7-28, 2007; NEJM 336:1855-1859, 1997); (iv) T cell checkpoint blockade against inhibitory pathways including targeting CTLA-4 and PD-1 inhibitory molecules for the treatment of melanoma and other solid tumors (NEJM 363:711-723, 2010; NEJM 366:2443-2454, 2012; NEJM 369:122-133, 2013; NEJM 366:2455-2465, 2012); (v) antigen-pulsed autologous dendritic cell vaccination against prostate cancer (NEJM 363:411-422, 2010); and (vi) the transfer of T cells including those genetically engineered with chimeric antigen receptors allowing targeting of B cell neoplasms (NEJM 365:725-733, 2011; NEJM 368:1509-1518, 2013; Blood 118:4817-4828, 2013; Sci Transl Med 5:177ra138, 2013).

This article provides an overview on the exciting and expanding immunological arsenals against cancer, and discusses critical remaining unanswered questions of cancer immunology. The inherent specificity and memory of the adaptive immune response towards cancer will undoubtedly propel cancer immunotherapy to the forefront of cancer treatment in the immediate near future. Study of the fundamental mechanisms of the immune evasion of cancer shall also advance the field of immunology towards the development of effective immunotherapeutics against a wide spectrum of human diseases.

Introduction

Cancer immunotherapy has come a long way [1-16]. In the late 1800 s, William Coley was one of a growing number of investigators who noticed a correlation between regression of cancer and infection [17-20]. Coley expanded on this observation and became the first person to treat substantial numbers of cancer patients with a mixture of killed bacteria (known as Coley's toxin). Although not meeting the standards of today's trials, Coley achieved tumor regression in a relatively high proportion of sarcoma patients. Despite much enthusiasm, the advent of immune-suppressing radiation therapy and chemotherapy which could directly impact cancer progression diverted much attention away from immune-

based therapies [17,18]. Furthermore, as the immune system was not well understood, there was much skepticism that tumor cells could be different from self and capable of eliciting immune-mediated eradication. However, with growing understanding of how the immune system functioned, in 1957, Frank Macfarlane Burnet proposed a revolutionary concept that cancer cells may have antigenic differences allowing immune-mediated eradication [21]. This seed of great expectation raised hope that one day cancers might be routinely and effectively treated by immunological means. While there has been much optimism over the past 50 years, it is only during the last decade that this optimism has been met with true meaningful progress [22,23]. There is now no question that cancer immunology has entered into a period of renaissance [24,25], thanks largely to the affirmative and emphatic answer to several fundamental questions: (i) does cancer immunity exist? [2] (ii) can

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cancer-specific immunity lead to eradication of large established cancer? [16,26] (iii) does host immune defense exert pressure to cancer during oncogenesis? [27,28] (iv) are there tumor-specific and/or tumor-associated antigens? [29-31] (v) can immune tolerance to cancer be broken to result in therapeutic benefit? [8,10,32] Therefore, it is not a question of “if” but for many cancers “when” immunotherapy will be the main treatment modality.

Established practice of immunotherapy of cancer

Cancer immunotherapy has already entered the mainstream of oncology [23]. Existing strategies focus on enhancing immune destruction of cancer cells by a variety of means (Table 1). One of the most successful and longstanding forms of cell-based immunotherapy is allogeneic stem cell transplant for the treatment of hematological malignancies. Although stem cell transplantation was initially thought to enhance cancer cure by allowing myeloablative therapy in the forms of high dose chemotherapy and total body irradiation [33], it has become clear that allogeneic immune response against tumor cells is a key mechanism of action [5]. The antibody-based strategy against cancer continues to make impact in cancer care, as antibodies can eliminate cancer cells via immunological means (through antibody or complement-dependent cytotoxicity) as well as via other biological means (e.g., blocking key oncogenic signals) [22,34,35]. In addition, immunomodulating cytokines remain important in the treatment of selected tumor types, such as the use of type I interferon as an adjuvant therapy for high-risk melanoma [36]. One significant milestone in the field of cancer immunology was the 2010 FDA-approval of sipuleucel-T (Sip-T), an autologous dendritic cell preparation, loaded with recombinant fusion protein between GM-CSF and prostate-specific acid phosphatase, for the treatment of metastatic prostate cancer [12]. Sip-T represents the first of its kind of therapeutic vaccine against cancer using dendritic cell-based platform [37]. In 2011, the FDA approved ipilimumab injection for the treatment of unresectable or

metastatic melanoma. Ipilimumab represents a new class of cancer immunotherapeutics based on blockage of negative T cell check-point signal [3,38]. Tumor-specific T cells can be activated by professional antigen presenting cells through engagement of T cell receptor and co-stimulatory molecules such as CD28. However, to maintain immune homeostasis, activated T cells have to be temporally turned off via engaging inhibitory receptors on T cells such as CTLA-4 [39,40]. Ipilimumab is a fully human monoclonal antibody that binds and blocks CTLA-4 to sustain T cell activity, and it has been shown to improve overall survival of patients with advanced melanoma [8]. Importantly, maximizing T cell co-stimulation was demonstrated to be an effective anti-tumor strategy as early as 1992 when stable expression of the B7 molecule in tumor cells was shown to result in T-cell specific tumor eradication [41].

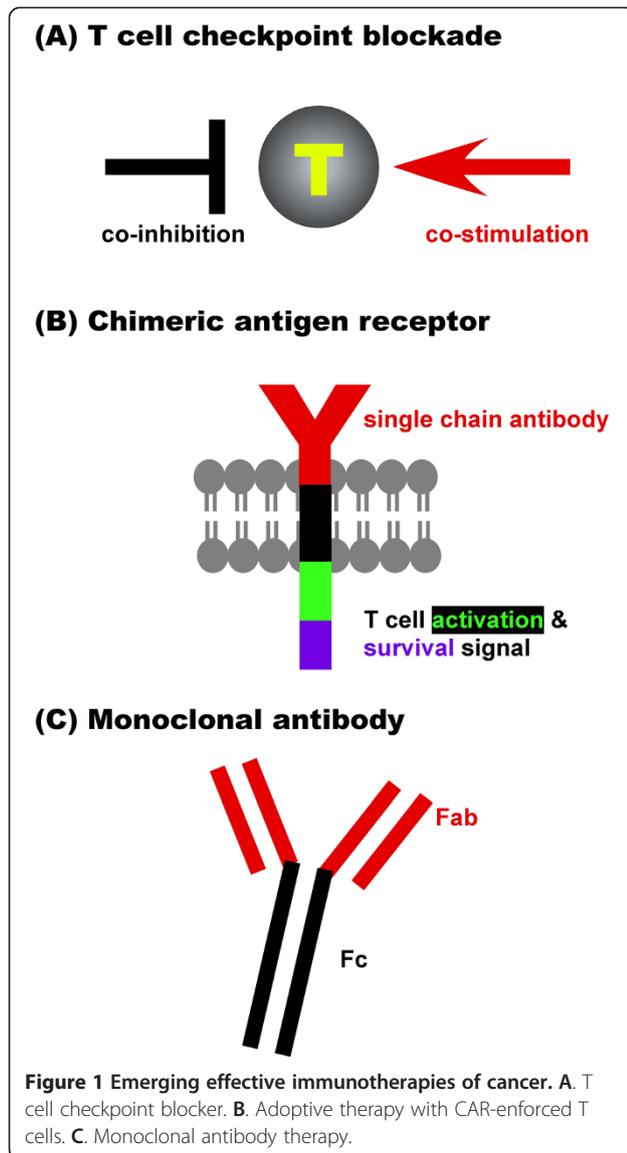
What is hot in cancer immunotherapy in 2013?

Three kinds of cancer immunotherapeutics have emerged as key breakthroughs in clinical cancer care in 2013. These advances include T cell checkpoint blockers (Figure 1A), adoptive therapy with T cells genetically modified with chimeric antigen receptor (CAR) (Figure 1B), and targeted monoclonal antibody therapy (Figure 1C).

Recent findings demonstrate that a variety of functionally non-overlapping co-inhibitory receptors can be expressed by T cells to turn off their effector function [3,42]. These inhibitory receptors include CTLA-4, PD-1, TIM-3, BTLA, PD-1H (VISTA) and LAG-3. While in theory, blocking any of these inhibitory receptors could lead to increased activation of tumor-reactive T cells, systemic activation of T cells does not necessarily lead to more effective anti-tumor activity. Blockade of CTLA-4 with antibody led to tumor regression in 10-15% patients with advanced melanoma whereas severe autoimmune toxicity was evident in >30% of patients. Therefore, a strategy to selectively manipulate tumor microenvironment rather than systemic promotion of T cell immunity is desirable. It is particularly promising as many tumor cells express ligands for the co-inhibitory receptors, such as PD-L1 (also known as B7-H1), the ligand for PD-1

Table 1 Examples of FDA-approved cancer immunotherapeutic agents

Modality	Principle
Hematopoietic stem cell transplantation (e.g., leukemia and myeloma)	1. Reset the immune system
Antibody (e.g., rituximab, trastuzumab)	2. Allo-antigen response (graft versus tumor effect)
Cytokines (e.g., type I interferon, interleukin-2)	1. Eliminate cancer cells
Dendritic cells (e.g., Sip-T for prostate cancer)	2. Block key signaling pathways
T cell checkpoint blockade (e.g., ipilimumab for melanoma)	Boost both innate and adaptive immunity
Microbes (e.g., BCG for the transitional bladder cancer)	Enhance tumor-specific T cell priming
	Block/reverse immune tolerance
	Enhance innate and adaptive immunity



whereas there is minimal expression of this molecule in normal tissues [43]. Indeed, 9 of 25 patients (36%) with PD-L1-positive advanced tumors had an objective response to anti-PD-1 antibody therapy [9]. Surprisingly, when nivolumab (anti-PD-1 antibody) and ipilimumab were given to patients with advanced melanoma concurrently every 3 weeks for 4 doses, followed by nivolumab alone every 3 weeks for 4 doses, 53% of patients had an objective response, all with tumor reduction of 80% or more [10]. This study demonstrated the potential to combine multiple T cell checkpoint blockade to maximize anti-cancer immunity, with acceptable toxicity. Because this type of immunotherapy depends on a healthy immune system, conventional cancer treatments including chemotherapy and radiation therapy often impair immune system and could decrease the efficacy of this therapy. The field is

waiting with anticipation of data of frontline therapy with T cell checkpoint blockade of cancer patients.

Several proof-of-principle studies have demonstrated the huge potential of utilizing synthetic immunology to engineer CAR-expressing or TCR-expressing T cells for the adoptive therapy of select cancers including lymphocytic leukemia [44-46]. Building off work from Steven Rosenberg's group [47], Carl June and his colleagues successfully engineered a CD19-reactive CAR composed of a fusion protein between extracellular single chain anti-CD19 antibody, the transmembrane domain, 4-1BB (CD137) survival signal, and the CD3 ζ chain signaling motif [48]. Autologous T cells transduced with the CD19-reactive CAR were shown to have potent clinical activity against CD19⁺ tumors after infusion in three of three patients with advanced chronic lymphocytic leukemia (CLL) [13]. In April 2013, it was reported that two children with relapsed and refractory pre-B-cell acute lymphocytic leukemia received infusions of T cells transduced with CD19-reactive CAR [14]. In both patients, these T cells expanded to a level that was more than 1000 times as high as the initial engraftment level, and the cells were identified in bone marrow. In addition, the CAR⁺ T cells were observed in the cerebrospinal fluid. More importantly, complete remission was observed in both patients and is ongoing in one patient at 11 months after treatment at the time of the report. The other patient had a relapse, with blast cells that no longer expressed CD19, approximately 2 months after treatment. Thus, CAR-modified T cells are capable of killing even aggressive, treatment-refractory acute leukemia cells *in vivo*. Indeed, Michel Sadelain's group treated five relapsed acute B cell lymphocytic leukemia subjects with autologous T cells expressing a CD19-reactive CD28/CD3 ζ second-generation dual-signaling CAR [16]. All patients with persistent disease upon T cell infusion demonstrated rapid tumor eradication and achieved complete molecular remissions as assessed by polymerase chain reaction, therefore, this therapy appears to be very promising in treating hematopoietic malignancies. It will be interesting to see whether the same approach could also be applied successfully for the treatment of solid tumors.

2013 continues to witness the increasing application of monoclonal antibody for cancer immunotherapy [22]. Approved monoclonal antibodies by the FDA in 2013 include Ado-trastuzumab emtansine and pertuzumab for Her2⁺ breast cancer, denosumab for giant cell tumor of the bone, bevacizumab for both first and second line therapy for metastatic colorectal cancer in combination with chemotherapy. Ever since anti-CD3 antibody was approved in 1986 for the treatment of autoimmune diseases, more than 35 antibodies have been introduced to the market with a significant portion of them indicated

for cancer therapy including rituximab (anti-CD20 antibody), Herceptin (anti-Her2 antibody), and Ipilimumab (anti-CTLA-4 antibody).

Key unanswered questions in cancer immunology

The current enthusiasm in cancer immunology raises the question of whether all cancers may be amenable by immune intervention. As a basis for addressing this question and making existing therapies more effective, there are four critical unanswered questions (Table 2). First, what is the molecular entity in cancer that triggers the initial immune response particularly during advanced disease? If we understand the antigens the immune system targets successfully in cancers known to be immune amenable, we may be able to better identify such antigens in patients with other types of cancer. Second, what determines the outcome of tumor immunity? We need to be mindful that tumors are not bacteria, virus or parasites. The quality of immune response to cancer cannot simply be viewed through the conventional immunological prisms we use to predict the immune response against infectious agents. Third, what is the mechanism of tumor evasion? In this case, the answer might have to come from the study of the tumor micro-environment rather than systemic suppression. Finally, as much as we all hope to have a universal cancer vaccine on a population basis [49], immunotherapy of established (clinically detectable) cancer may often need to be individualized. Figuring out how to combine various arsenals in the immune system in a tailored fashion to individual patients is a challenge as well as a wonderful opportunity for future research.

Goals of cancer immunotherapy and perspective: are we there yet?

Slowly but surely there has been a growing paradigm shift in the understanding of biology and immunology of cancer. This is evident from the essay by Douglas Hanahan and Robert Weinberg on the Hallmarks of Cancer (The Next Generation) in 2011

which added “avoiding immune destruction” and “tumor-promoting inflammation” as another two hallmarks of cancer to their original perspective [50]. Given that the immune system has a remarkable ability to detect, “remember” and eliminate cancer cells, it is becoming clear that immunotherapy is not simply a means of cancer treatment. Rather, establishing long-lasting, cancer-specific immunity can be a goal to allow for curative therapy. In addition, development of effective immunotherapeutic cancer strategies requires our attention to deal with both of the immunological hallmarks of cancer: “avoiding immune destruction” and “tumor-promoting inflammation”. Presently, most of the approved cancer immunotherapeutics (Table 1) focus on maximizing immune destruction of cancers. No specific modalities are available clinically to silence “tumor-promoting inflammation”, other than antibiotics and vaccines to eliminate microbes-associated cancer. We are just starting to understand how cancer cells “avoiding immune destruction”. Defining and blunting oncoinflammation will likely prove critical in the future for achieving effective anti-cancer immune responses (Table 2).

Immunotherapy of cancer is no longer a dream. Gone is the time when elimination of cancer by immunological means was anecdotal or achievable only in animal studies. Immune-based therapies have now demonstrated efficacy in a range of clinical studies and types of cancer. Adoptive transfer of tumor-reactive T cells can cure select patients with advanced metastatic disease that have exhausted all other options. Other reagents, such as selective manipulation of T cell checkpoint blockers in cancer microenvironment, offer the possibility of off-the-shelf dosing or novel combinatorial therapies. More than ever before, the field of cancer immunology is permeated with a sense of optimism [23]. The key question today is not whether immune-based therapies will transform cancer therapy, but how will these approaches transform cancer medicine in the future.

Table 2 A few key research themes in cancer immunology

Theme	Research question
Immune recognition of cancer	What are characteristics of antigens critical for immune recognition of cancer cells? Do these antigens exist for all cancers?
Fate determination of tumor immunity	Tumors are not bacteria, not viruses, and not parasites. How do differences in antigen presentation and innate immunity signals impact the ability to initiate and mediate effective anti-tumor immunity?
Mechanism of immune evasion	Are immune evasion and oncogenesis closely coupled? What is the molecular definition of oncoinflammation in the tumor environment and its impact on cancer immunity?
Immunotherapy	It is time to redefine the goals of conventional therapy to convert non-immunogenic signals to immunogenic ones. What is the best strategy to combine immunotherapy with radiation therapy, chemotherapy or targeted therapy? More innovative immunotherapeutic strategies are needed including novel targets (e.g., cancer stem cells), novel sources of antigens (subdominant antigens), novel adjuvants, novel cytokines and new ways to reset the immune system from tolerogenic status to immunogenic one.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

All authors wrote, reviewed and approved the manuscript.

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