Cancer immunotherapy in progress—an overview of the past 130 years

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Abstract

Since the first approval of an immune checkpoint inhibitor, we have witnessed the clinical success of cancer immunotherapy. Adoptive T-cell therapy with chimeric antigen receptor T (CAR-T) cells has shown remarkable efficacy in hematological malignancies. Concurrently with these successes, the cancer immunoediting concept that refined the cancer immunosurveillance concept underpinned the scientific mechanism and reason for past failures, as well as recent breakthroughs in cancer immunotherapy. Now, we face the next step of issues to be solved in this field, such as tumor heterogeneity, the tumor microenvironment, the metabolism of tumors and the immune system, and personalized approaches for patients, aiming to expand the population benefitted by the therapies.

Keywords: CAR-T therapy, immune checkpoint inhibitor, tumor heterogeneity, tumor immunology

Introduction

Here, I provide an overview of the 130-year history of the clinical development of cancer immunotherapy as well as basic science that has been trying to understand tumor immunology. I follow the long history of cancer immunotherapy and aim to reveal the reasons for the success of immune checkpoint inhibitors (ICIs) and chimeric antigen receptor T (CAR-T) cell therapy in the last 20 years. I discuss how a basic understanding of the interplay between tumors and the immune system has helped in the clinical development of cancer immunotherapy.

I also discuss the issues associated with recent cancer immunotherapy. I will try to reveal what we need to improve in future cancer immunotherapy to expand the number of patients benefitting from these endeavors.

The hypothesis that the immune system protects the host from tumor development

Paul Ehrlich might be one of the first who described the concept that the immune system may protect the host from tumor development. He was famous as a founder of chemotherapy but also had deep knowledge in many fields, including hematology and immunology. In 1909, he envisaged that the immune system would attack not only infectious agents, but also tumor cells to protect the human body (1) (Fig. 1).

From the 1950s to the 1960s, the existence of tumor antigens was experimentally demonstrated in syngeneic mice by many tumor immunologists, including Old, Foley, Prehn, Main, and Klein (2-5). The establishment of syngeneic mice made it possible for these researchers to examine whether tumor tissues could be recognized by immunity as antigenic objects, which is different from the manner in which the immune system recognizes allogeneic cells. Using syngeneic mice and chemical carcinogen-induced tumors in these mice, they found that mice treated with surgical resection of tumor A were resistant to rechallenge with tumor A. However, these mice were susceptible to challenge with independently established tumors B or C (Fig. 2). A series of experiments revealed the existence of an immune system that recognizes the tumor as a foreign agent. They also found that every tumor has a different antigenicity, i.e. the existence of tumor-specific antigens.

By these days, clinical attempts to treat cancer patients had reported the use of Coley's bacterial toxin (in 1893) (6), hormonal therapy and radiotherapy (in 1896) (7), chemo-therapy (in 1942) (8), and bone marrow transplantation (in 1957) (9, 10) (Fig. 1). Currently, the contribution of immuno-logical mechanisms to each of these treatments is known.

Frank Macfarlane Burnet and Lewis Thomas postulated the cancer immunosurveillance concept in 1957 (11–13). They suggested that T cells might be the pivotal sentinel in the immune system's response to cancer cells and protect the host



Figure 1. History of clinical cancer immunotherapy development and our understanding of basic tumor immunology.



Figure 2. Experimental demonstration of tumor-specific antigens in syngeneic mice. A series of tumor transplantation experiments utilizing syngeneic mice revealed the existence of an immune system that recognizes and rejects the tumors as foreign agents. It was also found that every tumor has a different antigenicity, i.e. the existence of tumor-specific antigens.

from cancer development (Fig. 1). This concept has created debates that lasted for more than half a century. The debates on the existence of efficient immunity against tumor development lasted a long time because very limited successes on the clinical development of immunotherapy of cancer had been achieved before the 2010s.

In conjunction with the increased recognition of the importance of soluble factors such as cytokines in immune responses, interferon- α (IFN- α) was used clinically for several malignancies including chronic myeloid leukemia (14) and was approved by the Food and Drug Administration (FDA) in 1986 (15). Interleukin-2 (IL-2), which was reported as a "T-cell

growth factor" in 1976 (16), was also used to treat cancer patients (17) and was approved by the FDA in 1992. However, these cytokine therapies did not improve the treatment results dramatically, and the application did not expand to various tumor types.

The first success in using a monoclonal antibody (mAb) in the treatment of patients with malignancy was achieved with the anti-CD20 mAb rituximab in patients with B-cell lymphoma (18). Rituximab was approved by the FDA for the treatment of B-cell non-Hodgkin lymphoma (B-NHL) in 1997, and later for other diseases including chronic lymphocytic leukemia (CML). Although rituximab appeared to be quite effective in these diseases, CD20 is not a tumor-specific antigen and the application of mAb therapy did not expand to other tumor types.

In 1991, Boon *et al.* cloned MAGE-1 as the first human tumor-associated antigen known to be recognized by T cells (19) (Fig. 1). Subsequently, many tumor-associated antigens have been identified. The identification of tumor-associated antigens in humans has made it possible to develop tumor-specific immunotherapies, such as cancer vaccines and cell therapy for cancer, targeting the identified antigens. However, except for the approval of Provenge in the USA as a therapeutic cancer vaccine for patients with prostate cancer in 2010 (20), a continuous failure of therapeutic cancer vaccines in clinical trials has been reported (21). The reason for the discrepancy between the significant amount of basic research results that support the existence of an immune response to cancer and difficulties in the clinical development of effective immunotherapy is largely unclear.

The cancer immunoediting concept

One attractive clue to understanding this discrepancy came from a series of basic studies on carcinogenesis in immunodeficient mice. Schreiber *et al.* performed chemical carcinogen-induced tumor development experiments in lymphocyte-deficient RAG2 KO (recombinase-activating gene 2 knockout) mice as well as interferon- γ (IFN- γ)-insusceptible IFNGR KO (IFN- γ receptor knockout) and STAT1 KO (signal transducer and activator of transcription 1 knockout) mice (22). They observed earlier tumor formation and a higher incidence of tumor development in lymphocyte-deficient and IFN- γ -insusceptible mice compared with immunocompetent wild-type (WT) mice. They also observed an increased incidence of spontaneous tumor formation in aged RAG2 KO and RAG2 STAT1 double-KO mice.

These results showed that cancer immunosurveillance does exist. However, this was not the end of the story. They harvested tumors from carcinogen-treated WT and RAG2 KO mice groups. Tumor cells were then transplanted into WT and RAG2 KO mice. In RAG2 KO hosts, tumors derived from WT mice and RAG2 KO mice grew progressively in an equivalent manner. However, in WT hosts, 60% of the RAG2 KO mouse-derived tumors grew progressively, whereas the remaining 40% of the RAG2 KO mouse-derived tumors failed to grow and were rejected. One hundred percent of WT mousederived tumors grew successfully in the WT mice. These results suggested that tumors formed in the RAG2 KO host had never encountered immunological pressure; therefore, 40% of these tumor cells were eliminated when transferred into an immunocompetent environment. The immune system protects the host from highly immunogenic tumors, leaving behind less immunogenic ones.

Schreiber et al. revealed the paradoxical effect of the immune system in selecting and facilitating the progressive growth of tumors in immunocompetent hosts. They called this process cancer immunoediting to describe the interaction between developing tumors and the immune system more precisely. They proposed three phases of cancer immunoediting: elimination, equilibrium, and escape (23) (Fig. 3). They envisaged that many of the developing tumors were eliminated by the innate and adaptive immune systems in the elimination phase. Sometimes, tumor cells are not eliminated completely but are not able to progress soon after being checked by immune cells in the equilibrium phase (24). Meanwhile, genetic instability allows tumor cells to acguire additional characteristics. When acquired alterations help tumor cells escape or suppress the immune system, they enter the escape phase, where they grow progressively without immunological pressure to form massive tumor tissue. On the basis of this concept, we can understand that many clinically evident tumors are in the escape phase, where the tumor has already acquired immunosuppressive and/or immune-escaping phenotypes. These tumors were selected to be resistant to immunological attack. In many cases, the problem is not the lack of tumor antigen, but the existence of escape mechanisms from immunological attacks. Therefore, it is difficult to develop effective cancer vaccines.

Chen and Mellman proposed the cancer-immunity cycle describing the process that is needed for the effective elimination of cancer by the immune system in 2013 (25) and updated this in 2023 (26) (Fig. 4). They divide the cycle into seven steps. Step 1 is the release of cancer cell antigens from dead cancer cells. Step 2 is cancer antigen presentation to antigen-presenting cells (APCs), such as dendritic cells (DCs). Step 3 involves the priming and activation of T cells by APCs, mainly in the lymph nodes. Step 4 involves the trafficking of T cells to tumor sites via the blood. Step 5 involves extravasation and infiltration of T cells into tumors. Step 6 involves the recognition of cancer cells by T cells via the T-cell antigen receptor (TCR). Step 7 involves killing cancer cells using the cytotoxic machinery of T cells. When the cancerimmunity cycle proceeds to Step 7, it initiates a new Step 1 as a positive feedback of cancer destruction. However, they showed that there are many inhibitory factors found in every step that can stop the progression of the cancer-immunity cycle, again making us understand that we need to fight against tumors in the escape phase in a clinical setting.

Cancer immunotherapies break through the clinical limitations

The journal *Science* selected cancer immunotherapy as "breakthrough of the year" for 2013 (27). This selection was based on the success of ICIs and adoptive T-cell therapy. Immune checkpoint molecules are receptors that deliver co-stimulatory or inhibitory signals that modulate the main signal through the TCR in T cells. Blocking the inhibitory signals from CTLA-4 (28–30) and PD-1 (31–33) showed



Figure 3. Cited from reference (65) with modifications. Cancer immunoediting concept. Many of the developing tumors were envisaged to be eliminated by the innate and adaptive immune systems in the elimination phase. Sometimes, it progresses to the equilibrium phase where tumor cells are not eliminated completely but are not able to progress. Meanwhile, genetic instability allows tumor cells to acquire additional characteristics that help tumor cells escape or suppress the immune system to enter the escape phase.

significant anti-tumor effects in patients with various types of tumors. In 2011, an anti-CTLA-4 mAb was approved by the US FDA as the first checkpoint inhibitor for the treatment of melanoma (34, 35). In 2014, an anti-PD-1 mAb was approved for the treatment of melanoma (36) and later for the treatment of non-small cell lung carcinoma (NSCLC), renal cell carcinoma, Hodgkin's lymphoma, and head and neck squamous carcinoma (Fig. 1). ICIs are currently used to treat many tumor types, including melanoma, NSCLC, renal cell carcinoma, Hodgkin lymphoma, head and neck carcinoma, gastric carcinoma, malignant mesothelioma, Merkel cell carcinoma, hepatocellular carcinoma, mammary carcinoma, and microsatellite instability high (MSI-H) solid tumors. T-cell exhaustion is an important obstacle in the cancer immunity. ICIs are suggested to inhibit and/or invert the exhaustion of tumor-specific T cells in the tumor microenvironment. The success of checkpoint inhibitors in the clinical treatment of cancer eloquently emphasizes the importance of overcoming the immunosuppressive and/or immune-escaping phenotype of clinical tumors in the escape phase.

Following the success of ICIs, adoptive cell therapy with T cells engineered to express a CAR gene that consists of a single-chain Fv region (scFv) of an antibody that is specific to the tumor cell surface molecule and the intracellular signal domains of CD3 ζ and co-stimulatory molecules such as CD28 or 41-BB showed remarkable clinical responses. CD19-CAR-T cell (CD19-specific chimeric antigen receptor T cell) therapy was approved for the treatment of acute lymphocytic

leukemia and diffuse large B-cell lymphoma in 2017 (37-40) (Fig. 1). B-cell maturation antigen (BCMA) CAR-T cells were approved by the FDA for the treatment of patients with multiple myeloma in 2021 (41-43). Blinatumomab. a CD19-CD3 bispecific antibody, exerts its anti-leukemic effect by engaging leukemia cells and host T cells in a manner that resembles a CAR-T attack. Blinatumomab was approved for the treatment of B-cell acute lymphocytic leukemia in 2014 (44). TCR-T cell therapy that utilizes T cells engineered to express TCR α and β genes derived from T-cell clones specific to tumor antigens has shown a significant tumor response in clinical trials for synovial cell sarcoma patients, targeting the NY-ESO-1 antigen (45-47). MAGE-A4-specific TCR-T cell therapy was approved by the FDA as a treatment of patients with synovial cell sarcoma in 2024. These adoptive cell therapies are effective, presumably because they can bypass several steps in the cancer-immunity cycle, where inhibitory factors may have limited the generation of a large number of effector T cells in patients. Again, this reminds us of how to fight malignancy in the escape phase.

Issues in current cancer immunotherapy

Although ICI therapies are currently used in many kinds of cancer types including hematopoietic malignancies and solid tumors, as mentioned above, the patients who benefited from the therapies remain between 10% and 30% in most of the tumor types. The expansion of the population that can be

treated by ICI is an urgent issue. Development of therapies targeting new molecules including LAG3, TIM3, and TIGIT is in progress. Combination therapy with other therapy such as cytotoxic agents and molecular targeted-based agents, or multiple ICI may expand the application.

Selection of appropriate patients is also an important issue in ICI therapy. Although biomarkers such as PD-1 ligand 1 (PD-L1) and tumor mutation burden have been used, more indicators are needed for the precise selection of patients that can be benefited. In addition, adverse events should be prevented, diagnosed early, and treated effectively with new technologies.

Although CAR-T cell therapy is starting to benefit patients with hematopoietic malignancies, especially lymphoid malignancies, the development of effective CAR-T cells against solid tumors has been largely hampered (44, 48). Table 1 highlights the problems that must be solved for the development of effective CAR-T cells against hematopoietic malignancies and solid tumors.

A historical but ongoing issue is the lack of appropriate antigens to be targeted by CAR-T cells. Success has been achieved in targeting CD19 and BCMA; however, both are not tumor-specific but are lineage-associated antigens that are expressed in both malignant and healthy cells. Because B cells and plasma cells are dispensable, at least tentatively, the CAR-T cells against these targets effectively kill almost all tumor cells in a very efficient manner. It is difficult to identify these antigens in non-lymphoid hematopoietic malignancies. Recently, attempts to target non-lymphoid hematopoietic malignancies by CAR-T cells have been reported using CAR-T cells against the pan-leukocyte marker CD45 or myeloid markers such as FLT3, CD123, or KIT, combined with transplantation of hematopoietic stem cells that were protected from CAR-T cells by epitope base editing technology (49, 50). Identification of dispensable target antigens is also very difficult in solid tumors. Claudin 18.2-specific CAR-T cells were suggested to show tumor response in patients with gastrointestinal cancers with acceptable safety, presumably because of the polar localization of Claudin 18.2 molecule in the tight junction of the lateral side of normal epithelial cells (51).

In solid tumors, it is difficult to identify cancer-specific or cancer-associated antigens that are ubiquitously expressed in all tumor cells, reflecting the second issue of tumor heterogeneity. Tumor heterogeneity is more evident in solid tumors than in hematopoietic malignancies (52, 53). In solid tumors, tumor cells may lack or downregulate the expression of antigens and/or antigen-presenting machinery, such as β 2-microglobulin.

Among other issues, a lack of sensitivity to cytokines such as IFN- γ or tumor necrosis factor- α (TNF- α) and the expression of suppressive molecules such as PD-L1 are also reported frequently. The microenvironment of solid tumors is often immunosuppressive (54, 55), as it is often infiltrated by regulatory T cells (Tregs), tumor-associated macrophages (TAMs), and myeloid-derived suppressor cells (MDSCs) (56). The metabolic environment is often severe for effector T cells (57) and preferable for cancer cells and Tregs. The vascular environment in solid tumors is not conducive to T cells. To reach a solid tumor, CAR-T cells also require homing/migration capacity to tumor sites that requires appropriate migration mechanisms and interactions between chemokines and chemokine receptors (58).



Figure 4. Cited from reference (65) with modifications. Cancer-immunity cycle. Chen and Mellman proposed the cancer-immunity cycle describing the process that is needed for the effective elimination of cancer by the immune system (25, 26).

Table 1. Current issues in CAR-T c	ell therapy
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Issue	Solid tumors	Hematopoietic malignancy
Lack of appropriate antigens	+++	++ Non-lymphoid malignancy
Tumor heterogeneity	+++ Lack of antigen/antigen presentation Cytokine sensitivity	+
Tumor microenvironment	Suppressive molecule expression +++ Suppressive cell populations (Treg, MDSC, etc.) Metabolism Vascular environment	+
Homing/migration T-cell fitness/function/persistence Adverse events	+++ ++ ++	+ ++ ++

T-cell exhaustion is an important issue. As CAR-T cells and TCR-T cells can utilize non-exhausted T cells derived from patients or a third party, these modalities may have advantages compared to other therapies that rely on heavily exhausted patients' tumor-specific T cells. Nevertheless, exhaustion of CAR-T cells has been reported as one of the obstacles in failure of the therapy. Preventing or inverting the exhaustion of CAR-T cells is an important future challenge. CAR-T cells may acquire improved fitness/function/persistence when genetically engineered or when their culture system is modulated (59).

The personalization of immunotherapy will be an important issue not only in CAR-T cell therapy but also in all cancer immunotherapies. Heterogeneity and differences always exist not only within tumors but also between individuals. Every tumor in different individuals differs in its environment, microbiota, host immune system, escape mechanism of the tumor, and style of tumor heterogeneity. How can we approach and overcome the issue of personalization? The precision medicine approach is one way to go (56, 60–62). The usefulness of the immunoscore classification has been reported (63, 64) (Fig. 1). Combination immunotherapy is an attractive method for improving the effects in some patient fractions. However, the immune system does not always assist patients. Recently, immune-based metastasis and cancer evolution have been reported (Fig. 1).

What more can we do for patients with cancer? As outlined in this article, lessons from history reveal the importance of intercommunication between basic science and clinical testing. We hope that continuous and enthusiastic communication between basic and clinical attempts will help in the development of novel and effective cancer immunotherapies that will benefit patients in the future.

Conclusions

History tells us the importance of intercommunication between the development of clinical cancer immunotherapy and the basic understanding of tumor immunology. The next issues to be addressed in this field are tumor heterogeneity, tumor microenvironment, metabolism, and personalized approaches to patients aiming to expand the population benefitted by the therapy.

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Conflict of interest statement

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