Meeting Report

Harnessing the immune system to cure cancer

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Abstract: As always, the 2014 American Association for Cancer Research (AACR) annual meeting highlighted the latest and most exciting discoveries covered all aspects of cancer research from around the world. This year's annual meeting theme: "Harnessing Breakthroughs-Targeting Cures" reflected the great progress being made in translating cancer immunological discoveries from bench to bedside. This meeting report briefly summarized key fundamental knowledge and cutting-edge advances in tumor immunology and immunotherapy. The most recent progression in cancer genomics supports the traditional notion that cancer is immunogenic. The dynamic interplay among malignant cells, immune cells and the immunosuppressive tumor microenvironment leads to the escape of tumor from host immune surveillance. A variety of approaches, including immune checkpoint blockers, adoptive cell transfer and cancer vaccines, have been developed to breakdown the tumor immune tolerance aiming to eliminate malignant cells. Long-term survival benefits have been reported in several cancer types, while the curative potential of cancer immunotherapies is just starting to be realized.

Keywords: Cancer immunotherapy; immune checkpoint blockers; adoptive cell transfer; tumor-associated macrophage

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Despite the major advances in diagnosis and multimodal therapy, cancer remains the leading cause of death in the world. Most of cancer death is due to the spread of malignant cells to vital organs, such as the lung, the liver and the brain. Chemotherapy is usually the standard of treatment for metastatic cancer patients. The overall survival (OS) benefit is modest. The systemic side toxicity and drug resistance further limit their long-term application. "The War on Cancer" hasn't been very promising during the last several decades. The latest breakthrough in cancer care is the approval of anti-tumor immunotherapeutic drugs-ipilimumab for metastatic melanoma in 2011. The curative potential of cancer immunotherapies is beginning to be realized. For examples, the woman with lung metastasis from melanoma has been alive and healthy for 13 years; the 6-year-old child near death from leukemia is now in third grade and the cancer remains in remission (1). Therefore, *Science* magazine ranked cancer immunotherapy as the "scientific breakthrough of 2013". In line with this progression, the theme for the 2014 American Association for Cancer Research (AACR) annual meeting was "Harnessing Breakthroughs-Targeting Cures". This is the first time ever that AACR talked about curing cancers.

Cancer is considered as a genetic disease. Recent progress in caner genome sequencing showed that different cancers carry a variable number of genetic alterations. Melanoma and lung tumors harbor many more mutations than average, which contain about 200 nonsynonymous mutations per tumor (2). Those mutations, theoretically, can be recognized as neoantigens or differentiation antigens by immune cells, which constantly patrol tissues to identify and destroy foreign invaders and abnormal cells. However, the development of clinically manifest tumors indicates that tumors are able to escape the host immune surveillance. Dr. Schreiber and his colleagues postulated a process named as "Cancer Immunoediting" to describe the dynamic interactions between immune system and tumors. Cancer immunoediting occurs in three sequential phases: elimination, equilibrium, and escape (3,4). Therefore, cancer immunotherapy is usually designed to overcome the escaped mechanisms of cancers and to resuscitate immune effector cells to eradicate malignant cells.

Strategies to induce anticancer immune response can be broadly divided into two categories: non-antigen-specific and

antigen-specific. Non-antigen-specific approaches include immune checkpoint blockers and non-specific immune cell activation, whereas antigen-specific approaches include a variety of cancer vaccines, adoptive transfer of autologous cancer-specific T cells or genetic engineered T cells. Examples of anticancer therapeutics in both categories have recently received regulatory approval, and many other agents are being evaluated in randomized phase II or III clinical trials.

Immune checkpoint blockers

Immune checkpoints are a group of T cell co-inhibitory molecules, which regulate the duration and amplitude of the immune response of T cells. Thus, under normal physiological conditions, immune checkpoints are crucial for the maintenance of self-tolerance and to protect tissues from damage during pathogenic infection. It is now clear that tumors co-opt certain immune checkpoint pathways as a major mechanism of immune resistance. A growing body of evidences suggest that unleashing the brake on immunity can elicit T-cell mediated anticancer immune response and provide therapeutic benefits in advanced cancer treatments. Dr. Allison and his colleagues found that cytotoxic T-lymphocyte antigen 4 (CTLA4) acts as a negative regulator to suppress T cell activation and proposed that blockade of CTLA4 can restore anti-cancer T cell immunity (5). In a landmark phase III clinical trial in patients with previously treated metastatic melanoma, ipilimumab, a monoclonal antibody that blocks CTLA4, significantly prolonged OS compared to gp100 vaccination therapy alone (median OS in gp100, ipilimumab, ipilimumab plus gp100 cohorts are 6.4, 10.0, 10.1 months, respectively) (6). More importantly, the long-term follow-up analysis showed that five-year OS ranges from 13.8% to 49.5% in a variety of clinical trials with different doses of ipilimumab treatment (7). This is a milestone in advanced melanoma cancer patient treatment.

Another immune checkpoint that has attracted lots of attention is the PD1/PD-L1 signaling pathway. PD-1 is often expressed on activated T cells that dampens the T cell immune response. PD-1's endogenous ligands, PD-L1 and PD-L2, are expressed in a number of cell types, including tumor cells (8). Blockade of PD-1 or PD-L1 has achieved impressive clinical benefit in renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC) and melanoma in several initial clinical trials (9-11). PD1/PD-L1 blockers seem to possess milder side effect profile than anti-CTLA4 antibody treatment. Furthermore, PD-1 has distinct immune regulatory mechanism and acts in a different stage of T cell activation, compared to CTLA4. These properties suggest that the blockade of both simultaneously might offer better anti-tumor activity. Besides CTLA4 and PD1/PD-L1, several other immune regulatory molecules have been identified and their therapeutic potentials are being tested in both pre-clinic and clinic settings (12).

Contingent to the physiological roles of immune checkpoints, blockade of immune checkpoints generated immune-related adverse events, such as fatigue, fever, chills, rash, diarrhea, colitis and pneumonitis (6,7,9,10). Although early applications of immune checkpoint blockers caused a small portion of patient deaths, life-threatening complications have been minimized by using mechanism-based algorithms (7). For example, the administration of systemic corticosteroids can effectively and rapidly reverse the symptoms of colitis in the majority of patients (6,7). Therefore, the safety profiles of cancer immunotherapies are often milder and more manageable, compared to traditional or targeted cancer therapies.

Adoptive cell transfer and chimeric antigen receptor (CAR) T cells

Adoptive T cell therapy (ACT) involves the isolation and reinfusion of *in vitro* expanded and activated tumor-antigen specific T cells into patients, aiming to eliminate malignant cells (13). Dr. Rosenberg and his colleagues pioneered the application of autologous ACT for treatment of patients with advanced melanoma (13). ACT immunotherapies were reported to achieve 20-50% cure rates in metastatic melanoma (14,15). The high curative potential of ACT in melanoma has inspired the attempts to explore this regimen in other cancer types, unfortunately the efficacy hasn't been very promising. Cancer genomic data suggested that melanoma harbors higher mutation rates than other cancers, which may explain, at least in part, why melanoma often responses well to cancer immunotherapies, including ACT and immune checkpoint blockers, but not other epithelial cancers (2,15). The limitations of conventional ACT include the low affinity to tumor-specific antigens, central tolerance and the potent immunosuppressive microenvironment. Subsequently, genetically engineered T cells, such as CAR T cells, were developed, aiming to overcome those shortcomings (16). A distinct CAR T cells contain three modules: an extracellular target binding domain derived from an antibody fragment, a transmembrane module and an intracellular signal module providing costimulatory signals (16). CARs have shown spectacular outcomes in several hematological malignancies, such as B cell malignancies, and are now being evaluated for solid tumors. These approaches also face many disadvantages, including the availability of specific tumor antigens, the

persistence of infused T cells, the trafficking of effector cells into tumor sites, and the negative regulators to T cell activity in the tumor bed.

Cancer vaccines

Vaccines represent a traditional approach with enormous medical success, especially in the prevention of infection diseases. Therapeutic cancer vaccines are designed to activate and boost the body's immune cells to attack growing malignant cells (17). Numerous approaches have been developed to stimulate anti-cancer immunity, including dendritic cells, whole tumor cells, proteins, peptides, viral vectors, bacteria, nucleic acids (DNA and RNA), and a variety of adjuvant. US FDA approved the first therapeutic cancer vaccine sipuleucel-T for advanced prostate cancer in 2010 (18). However, the clinical benefits of cancer vaccine therapy remain modest and are usually difficult to predict (15). A recent advance in cancer vaccination is to employ tumor cells as a type of endogenous vaccine under cytotoxic therapies. Chemotherapy, radiotherapy, and targeted therapy are able to cause cancer cell death in a fashion to induce anti-cancer immune responses, but achieving it requires specific chemotherapeutic agents and appropriate doses (19).

Targeting tumor-associated macrophages (TAMs)

TAMs are one of the major cellular components within the tumor microenvironment. However, instead of acting as immune defenders that fights cancer, macrophages are often hijacked by cancers to suppress host immune responses and facilitate tumor progression. Within solid tumors, TAMs typically compose of a heterogeneous cell population that has M1, M2 and intermediate phenotypes (20). M1-like TAMs have anti-tumor activity, while M2-like TAMs promote tumor progression and metastasis. The tumor microenvironment consists of various immune inhibitory cytokines and growth factors that polarize TAMs to pro-tumoral and immunosuppressive M2-like phenotype (20,21). Therefore, converting TAMs to their natural immune surveillance status provides a powerful approach to promote immune mediate anti-cancer response and inhibit tumor growth. Targeting CSF-1R signaling or reduce tumor tissue hypoxia has been shown to alter TAM phenotypes and suppress tumor progression (22,23).

Combinational therapy

Although durable monotherapy responses are being constantly reported for several different immunotherapeutic agents in a broad range of metastatic human cancers, the response rates are still low. Curing cancer is an extremely challenging task. Tumors are highly heterogeneous, including interpatients, intertumors, intratumor and intercellular heterogeneity (24). This cellular and molecular heterogeneity is difficult to overcome with single target. Furthermore, cancer has developed multiple mechanisms to escape host immune surveillance, such as immune checkpoints, central tolerance, and the immunosuppressive tumor microenvironment. Therefore, multimodal immunotherapy as well as combinational therapy to simultaneously overcome intrinsic and extrinsic tumor immune tolerance seems to be necessary to achieve optimal clinical benefits. The combination of anti-CTLA4 and anti-PD-1 increase the response rate and improve anti-cancer efficacy, compared to monotherapies (25). The combination of vaccine therapy and immune checkpoint blockers showed better tumor growth inhibition. Many different combinational cancer immunotherapies are being tested in various cancer models (26,27).

Concluding remarks

Active cancer immunotherapy is in the limelight of cancer treatments. Its long-term survival benefit with curative potential is attracting more and more attentions from oncologists, patients, cancer researchers and pharmaceutical companies. However, the overall response rate remains low. To fully realize the potential of cancer immunotherapies in the future will rely on the new insight into the key immune tolerant mechanisms, the identification of reliable immune biomarkers to stratify cancer patients and perform personalized immunotherapy, and the development of more effective and safer combinational regimens to maximize anticancer efficacy.

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Footnote

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Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related

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