Cell Research (2017) 27:1-2.

www.nature.com/cr

EDITORIAL

A special issue on cancer immunotherapy

Cell Research (2017) **27**:1-2. doi:10.1038/cr.2017.1; published online 6 January 2017

A century ago, Paul Ehrlich postulated that cancer would be quite common in long-lived organisms if not for the protective effects of immunity. Harnessing the immune system to treat cancer can be traced back to William Coley, a surgeon at Cornell University, who treated cancer patients with live bacteria in 1896. In 1980s, Steven Rosenberg and his colleagues developed adoptive cell therapy (ACT) using tumor-infiltrating lymphocytes (TILs) for the treatment of melanoma cancer patients [1], providing the first direct evidence that the immune system can be manipulated to achieve therapeutic efficacy in cancer treatment. Despite significant progresses made before 2010, many clinical studies were met only with sporadic success, leading to the disbelief in most people that cancer immunotherapy can effectively treat cancer. However, this view of cancer immunotherapy has been completely changed since 2010. The US Food and Drug Administration (FDA) approved the first blood cell-based vaccine for the treatment of patients with metastatic prostate cancer in 2010. In following year, FDA approved the first checkpoint inhibitor drug (anti-cytotoxic lymphocyte antigen-4 (CTLA-4) antibody) for treating metastatic melanoma. Meanwhile, clinical trials using CD19-chimeric antigen receptor (CD19-CAR) and NY-ESO-1-specific T cell receptor (NY-ESO-1 TCR) engineered T cell therapies have also shown promising clinical responses and impressive benefits [2-5]. As results, cancer immunotherapy was named as the "Breakthrough of the Year" in 2013 by *Science* [6]. Since then, we have witnessed an explosion of the cancer immunotherapy field.

However, it should be noted that today's success of cancer immunotherapy is largely built on major discoveries made in the 1990s. Firstly, the first human cancer antigen was identified in 1991, providing direct evidence that tumor-reactive T cells recognize targets expressed on cancer cells [7]; this led to the first wave of cancer antigen discovery, including the discovery of NY-ESO-1, one of the best targets for cancer immunotherapy [8, 9], and MHC class II-restricted neoantigens recognized by T cells [10]. Secondly, the concept of co-stimulatory and co-inhibitory signaling of T cell activation was also proposed in 1990s. CTLA-4 was demonstrated as a negative regulator of T cell activation and its blockade with anti-CTLA-4 led to tumor regression in mice [11], providing a rationale for human clinical trials. Similarly, PD-1 (programmed death 1) and its ligand PD-L1 (also known as B7-H1) were identified in 1990s [12, 13]. Lieping Chen and his colleagues demonstrated the importance of PD-1/PD-L1 signaling in cancer immunotherapy. These discoveries and subsequent clinical trials have led to the recent approval of anti-CTLA-4, anti-PD-1 and anti-PD-L1 antibody blockade therapies. Thirdly, the first generation of CAR technology was reported in 1993 [14]. Finally, Regulatory T (Treg) cells were also re-discovered in 1995 [15]. Thus, these early discoveries provide the basis for scientific breakthrough and clinical success of cancer immunotherapy, which has now been applied for the treatment of both immunogenic and non-immunogenic cancers. In this special issue on "cancer immunotherapy", six review articles contributed by experts in the field summarize recent advances of cancer immunotherapy and our understanding of molecular mechanisms underlying immune recognition, cell-based immunotherapy and vaccines, innate immune signaling, and immune suppression, and discuss future paths towards the goal of therapeutic cures of cancer.

Despite impressive and durable clinical responses with checkpoint blockade, CAR and TCR T cell therapy, many patients fail to respond. In particular, CAR T cell therapy does not yet work well in solid cancers, while NY-ESO-1-specific TCR therapy is suitable for only a small fraction of cancer patients due to its low frequency of expression in cancers. Rapid identification of cancer targets has been a key issue for development of immunotherapy for many cancer types. Given the relatively low cost of the new generation sequencing technology, whole-exome sequencing has become a routine practice in clinical diagnosis. Mutation-derived neoantigens might serve as potentially important targets of immunotherapy and precision medicine. The review by Wang provides a comprehensive summary of cancer antigen discovery, and discusses recent progresses on the rapid identification of neoantigens using exome sequencing in the second wave of antigen discovery, as well as their applications in personalized immunotherapy and precision medicine. With the availability of a large number of immune targets, both CAR- and TCR-engineered T cell immunotherapies have been extensively tested in clinical setting and demonstrated impressive clinical responses

[2-5], setting a stage for T cell immunotherapy against different cancers. However, affinity-enhanced TCR T cell therapy may cause severe unanticipated autoimmune effects. Similarly, CAR T cell therapy has also shown potential toxicities, including cytokine storms and unexpected immune responses. The review by June and his colleague summarizes the latest progresses of CAR- and TCR-engineered T cell immunotherapy and discusses potential toxicity associated with modified T cell therapy. Chronic inflammation induced by invading pathogens, including bacteria and viruses, contributes to cancer development. An estimated 15%-20% of cancers worldwide are associated with infections of Epstein-Barr virus (EBV), hepatitis B and C viruses (HBV and HCV), human immunodeficiency virus (HIV) and human papilloma virus (HPV). Therefore, viral antigens could serve as targets for immunotherapy. Because viral antigens function as foreign antigens and are more immunogenic than cancer antigens, these virus-associated cancer patients could be treated with viral peptide-induced T cells. The review contributed by Brenner and his colleague summarizes recent development of virus-specific T cells or TCR-engineered T cells for immunotherapy against virus-induced cancers. Immunotherapy using TCR-engineered T cells by targeting neoantigens is possible, but very costly. Therefore, development of therapeutic vaccines against neoantigens is urgently needed. Despite significant progress in our understanding of dendritic cell (DC) biology and DC-based clinical studies, current vaccines are not potent enough for eliminating cancer. The review by Bhardwaj and her colleagues summarizes our current understanding of DC-based vaccination and discusses new strategies to combine DC vaccines with checkpoint inhibitors. In addition, it is becoming clear that overcoming multiple immune suppressive mechanisms such as PD-1/PD-L1-mediated co-inhibitory signaling and Treg cell-mediated suppression is a prerequisite for cancer vaccines to work. Although many different subsets of Treg cells have been extensively studied in cancer and autoimmunity, how to best control Treg cell-mediated suppression of immune response for cancer therapy remains to be defined. The review by Sakaguchi and his colleague discusses the latest progress of Treg cell research in cancer and recent strategies to develop cancer immunotherapy by targeting Treg cells through several different mechanisms. Innate immunity has been shown to play a critical role in generating antitumor immunity through activation of NF-κB, type I interferon and inflammasome signaling pathways. Recent studies show that type I interferon production through DNA or RNA sensors could enhance or inhibit subsequent antitumor immunity. The successful development of effective innate immune activators could expand the fraction of patients in response to checkpoint blockade therapy. The review by Gajewski and his colleagues discusses recent understanding of innate immune signaling in cancer, functional interactions of innate immune signaling with commensal microbiota, and strategies of combining innate immune activation with checkpoint blockade in cancer immunotherapy.

In summary, this special issue encompasses many rapid-moving research areas and clinical studies of cancer immunotherapy, with an emphasis on immune targets, and CAR- and TCR-engineered T cell therapy for blood cancer, solid cancer as well as viral infection-associated malignancies. DC-based immunotherapy, Treg cell-mediated immunosuppression and innate immune signaling represent the fast-moving areas that offer novel ideas and strategies to further improve therapeutic efficacy and expand the coverage of cancer patients for immunotherapy. Other important research areas such as epigenetic and metabolic reprogramming of immune cells for immunotherapy are not covered in this issue, but will be presented in future issues. With review articles contributed by internationally recognized experts, this special issue provides the essential introduction and recent progresses of cancer immunotherapy for a broad readership, including immunologists, synthetic biologists, and basic and clinical cancer researchers. Cancer immunotherapy may become the mainstream treatment of many types of cancer by 2025.

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