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Review article

Nanotechnology based therapeutic modality to boost anti-tumor immunity and collapse tumor defense

Xiaomeng Hu[a], Tingting Wu[a], Yuling Bao[a,b], Zhiping Zhang[a,c,d,*]

[a] Tongji School of Pharmacy, PR China
[b] Department of Pharmacy, Tongji Hospital, PR China
[c] National Engineering Research Center for Nanomedicine, PR China
[d] Hubei Engineering Research Center for Novel Drug Delivery System, HuaZhong University of Science and Technology, Wuhan 430030, PR China

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ABSTRACT

Cancer is still the leading cause of death. While traditional treatments such as surgery, chemotherapy and radiotherapy play dominating roles, recent breakthroughs in cancer immunotherapy indicate that the influence of immune system on cancer development is virtually beyond our expectation. Manipulating the immune system to fight against cancer has been thriving in recent years. Further understanding of tumor anatomy provides opportunities to put a brake on immunosuppression by overcoming tumor intrinsic resistance or modulating tumor microenvironment. Nanotechnology which provides versatile engineered approaches to enhance therapeutic effects may potentially contribute to the development of future cancer treatment modality. In this review, we will focus on the application of nanotechnology both in boosting anti-tumor immunity and collapsing tumor defense.

1. Introduction

Over the past few years, immunotherapy has been developing vigorously and become the fourth modality pillar of cancer treatment after surgery, chemotherapy and radiotherapy [1]. Exploitation of the immune system in cancer therapy was proposed over a century ago. In 1894, the surgeon William Coley demonstrated that heat-killed bacterial products (Coley toxins) can be used to inhibit tumor growth [2]. This kind of crude vaccine ignited the interest in developing cancer immunotherapy. However, the serious side effects and subsequent achievements in radiotherapy rapidly shielded the silver lining from the cloud. Cancer immunotherapy wandered around the edge for almost a half century.

Even so, scientists continuously made breakthroughs to illustrate the essential role of the immune system. It was presumed that tumor cells can be specifically recognized by immune cells. In 1943, being inspired by the work of Clowes and Baeslack [3], the virologist Ludwik Gross suggested the existence of tumor-specific antigens which were preferentially expressed on tumor cells [4]. While the process of specifically inducing anti-tumor effect *via* antigens was unclear until the dendritic cells (DCs) were found as the initiators of the immune system by the Nobelists Ralph Steinman and Zanvil A. Cohn in 1973 [5]. Lately, the discovery of interaction between T cell receptors (TCRs) and major histocompatibility complex (MHC) ultimately provided an integral interpretation about the processing of antigen [6]. During the same period, using interleukin-2 (IL-2) for lymphocytes activation ignited the motion of immunologist to investigate cytokine in various tumor types, such as breast cancer, renal cell cancer, glioblastoma, lymphoma, and melanoma [7–10]. Another cytokine, interferon-α (IFN-α), was approved by the United States Food and Drug Administration (FDA) for immunotherapy in hairy cell leukemia in 1986, and then IFN-α2 was approved as the adjuvant treatment in 1995 [11,12]. In1998, IL-2 was approved by the FDA to treat metastatic melanoma. Generally, tumor cells are opportunistic to trigger T cell tolerance, which provides great convenience for tumor to escape from immune surveillance. Major progresses have been made on the immune checkpoint pathways to regulate the negative feedback of T cell. The FDA approved Ipilimumab, the anti-cytotoxic T lymphocyte antigen-4 (CTLA-4) antibody for advanced metastatic melanoma in 2011. In 2014, the first anti-programmed death receptor-1 (PD-1) antibody, Pembrolizumabanti was approved. Another anti-PD-1 immune checkpoint inhibitor, Nivolumab, was approved by FDA for treating patients with advanced squamous-cell non-small-cell lung cancer in 2015. Treatments based on checkpoint blockade have been prosperously investigated in many clinical trials [13–15] (Fig. 1).

Cancer is one of the top three killers of human. The ideal cancer

* Corresponding author at: Tongji School of Pharmacy, PR China.
E-mail address: zhipingzhang@hust.edu.cn (Z. Zhang).

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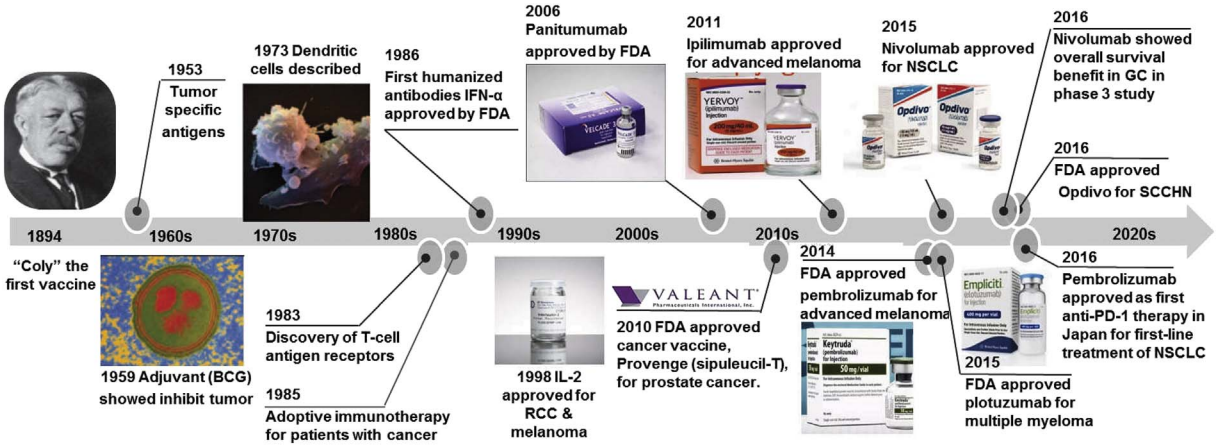

Fig. 1. Timeline of important events in cancer immunotherapy. Adapted with permission from [1]. Copyright 2012 American Cancer Society, Inc.

immunotherapy not merely aims at strengthening anti-tumor immunity, but also possesses the ability to collapse tumor defense to the immune system. Fortunately, years of concentrated efforts in nanotechnology have given us numerous options to achieve this goal. Nanotechnology involves multidisciplinary fields, such as physics, chemistry, biology and engineering, to develop diverse devices in nanoscale. With a wide range of innovative nano-materials developed for medical application, nanotechnology can be regarded as excellent medium to promote interdisciplinary cooperation [16]. The application of nanotechnology can fulfill diverse requirements from pharmaceutical formulation, such as protecting payloads, delivering therapeutic agents to targeted area, extending the circulation in blood and so on. Especially in cancer immunotherapy, nanotechnology provides promising strategies for manipulating the immune system to fight against tumor. For vaccination, nanoparticles can be employed as delivery system to promote anti-tumor immunity of traditional vaccine, such as protecting payloads, enhancing cross-presentation and promoting DCs maturation and migration. In the field of T cell therapy, nano-engineering can be used to facilitate T cell expansion *ex vivo* or *in vivo* for effective anti-tumor immune response. In cooperation with nanotechnology, immunomodulatory therapy can effectively overturn the tumor immunosuppressive microenvironment and create more feasible conditions for the immune system to eliminate tumor cells. In this review, based on current development of immunotherapy, we will discuss the potential application of nanotechnology to enhance the anti-tumor immune response and overcome tumor immune resistance.

2. Strengthen the immune system

2.1. Dendritic cell immunotherapy

As the most professional antigen-presenting cells (APCs), DCs can act as the initiator and modulator in the immune response. They can capture and process antigens to form MHC/peptide complexes, begin to mature accompany with the expression of co-stimulatory molecules, adhesion molecules and chemokine receptors, migrate to lymphoid organ and subsequently motivate naive T cells to become cytotoxic T lymphocytes (CTLs) or helper T cells [17,18] (Fig. 2). Due to the outstanding capacities in regulating and activating the immune system, DCs have been considered as the attractive target in several immunotherapeutic approaches for cancer treatment.

2.1.1. Dendritic cell vaccine

The antigen delivery ability of DCs has been utilized to develop cellular vaccination. The therapeutic process includes isolating DCs from peripheral blood by density gradients centrifugation, *ex vivo* pulsing with tumor antigens and transfusing back to the organism. This therapy was prosperously developed from the mid 1990s. The first generation of DC vaccine involved partially mature DCs which expressed co-stimulatory molecules at a suboptimal level and constituted weaker immunogens [1,20]. To overcome the limitations of the first generation of DC vaccine, clinical trials undertook numerous approaches to obtain matured DCs for the second generation of DC vaccine [21,22]. By using cytokine cocktail that involved IL-1a, tumor necrosis factor-α (TNF-α) and IL-6, it was able to induce the maturation of DCs with high expression of co-stimulatory molecules and chemokine receptors [23,24]. Notably, the first DC vaccine, Provenge® (Sipuleucel-T) for metastatic castration-resistant prostate cancer was approved by FDA in 2010.

DC vaccine can elicit CTLs activation and expansion. The results from Leonhartsberszger et al. [25] indicated that about 77% of patients with renal cell cancer were elicited with immune responses. It was also documented that the safety of DC based immunotherapy was expected to preserve the quality of life for cancer patients. In line with low toxicity, DC vaccines are capable to sufficiently improve the overall survival, which is generally regarded as the most objective measurement of therapeutic benefit. The median survival was improved to 4.1-month for patients who received treatment with Sipuleucel-T [26]. DC vaccine can elicit adaptive and innate anti-tumor immune responses coupled with the low occurrence of immune related adverse events [27].

Although hundreds of experiments were tested on DC vaccine, some drawbacks are still existed, which restrict the application. First of all, the poor migration to the lymph nodes and low occurrence in blood after injection of DC vaccine make a huge demand for antigen modified DCs, which are the direct cause for the other limited factors. Merely 5% transferred DCs can migrate to draining lymph nodes to activate T cells [28]. Secondly, the production is labor-intensive. All the processing steps described above, including cell isolating, antigen-loading and maturation are based on a complicated process and have high requirement for professional laboratory techniques [29]. Thirdly, the production cost hinders the applicability of DC vaccine. For each individual, the preparation of cell isolation, antigen-loading and maturation need to be specific, directly increasing the medical expenditure of patients. According to the advice from the UK National Institute for Health and Care Excellence, the cost of Provenge® is more than $73,000 for per course treatment [30]. Taking all these together, there is huge promotion room in therapeutic effects, waiting for new therapies to reclaim. Due to the brilliant achievements in nanotechnology, it has sparked an interest to shift the field of DC vaccines generated *in vitro* to nano-based cancer vaccines, which can deliver antigen to DCs *in vivo* to realize *in situ* DC maturation and induce subsequent more efficient antigen-specific T cell response against cancer.