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Review

Nanomaterials for cancer immunotherapy

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ABSTRACT

Cancer immunotherapy is quickly growing to be the fourth most important cancer therapy, after surgery, radiation therapy, and chemotherapy. Immunotherapy is the most promising cancer management strategy because it orchestrates the body's own immune system to target and eradicate cancer cells, which may result in durable antitumor responses and reduce metastasis and recurrence more than traditional treatments. Nanomaterials hold great promise in further improving the efficiency of cancer immunotherapy - in many cases, they are even necessary for effective delivery. In this review, we briefly summarize the basic principles of cancer immunotherapy and explain why and where to apply nanomaterials in cancer immunotherapy, with special emphasis on cancer vaccines and tumor microenvironment modulation.

1. Introduction

1.1. Basic concepts in cancer immunotherapy

The clinical suppression or activation of the immune system with the goal of treating a disease is referred to as immunotherapy. For example, immunosuppressive immunotherapy is used to reduce overactive inflammation in allergic reactions, chronic inflammatory bowel disease, and organ transplantation. On the other hand, cancer growth and metastasis is often mediated by immunosuppression and immune evasion, and the field of cancer immunotherapy developed to activate the immune system against malignant cells.

Since the approval of ipilimumab in 2011, cancer immunotherapy is experiencing an explosive development [1]. Ipilimumab is a monoclonal antibody that activates the immune system by targeting cytotoxic T-lymphocyte-associated protein 4 (CTLA4), which is a protein receptor constitutively expressed on regulatory T cells (Tregs) and functions as an immune checkpoint for "off" switch of the immune responses [2]. After that, monoclonal antibodies against programmed death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) were also approved for melanoma and non-small cell lung cancer treatment [3,4]. The most impressive feature of these therapies is their long-term control of the disease in the response population, which has never seen before in other treatments. There have been many good reviews on the basic principles of cancer immunotherapy [5–7]. Briefly, cancer immunotherapy can be classified as systematically- or locally-based, depending on whether the therapy is inducing a systemic immune activation for cancer or local immune status changes. In most occasions, the former refers to systemic cytokine administration, cancer vaccines, or adoptive cell transfer (ACT) [8–12], and the latter refers to modulation of the immunosuppressive tumor microenvironment (TME), like immune checkpoint inhibitors or some small molecular inhibitors [13,14]. Combinations of systemic and local immunotherapies or of immunotherapies and more traditional clinical therapies have proven quite meaningful and powerful in cancer management [15–18].

1.2. Cancer-immunity cycle

It is important to understand that the generation of an effective anti-cancer immune response necessitates a series of stepwise events which proceed and expand iteratively. This process is termed the "cancer-immunity cycle" [19] (Fig. 1). Briefly, necrotic or apoptotic tumor cells release tumor-derived antigens. These antigens are captured by dendritic cells (DCs) and presented extracellularly on major histocompatibility complex class I (MHCI) and major histocompatibility complex class II (MHCII) molecules. In the draining lymph nodes, activated DCs prime and activate immature

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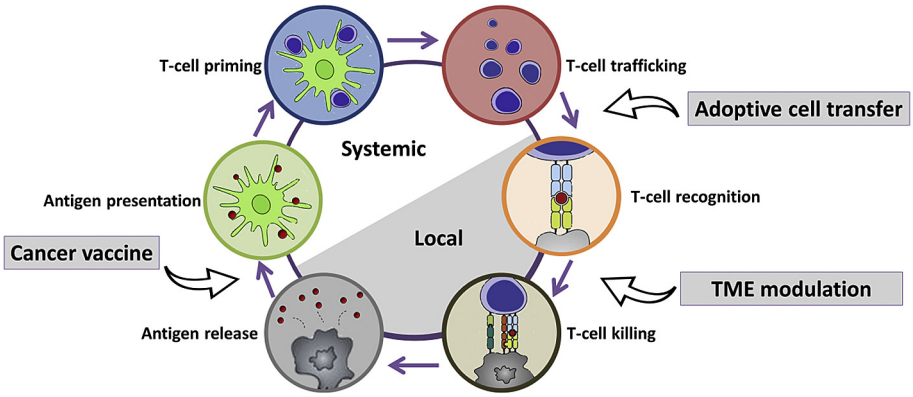

Fig. 1. The cancer-immunity cycle. The generation of an effective anti-cancer immune response necessitates a series of stepwise events. Cancer immunotherapy aims to initiate or re-implement the self-sustaining cancer-immunity cycle. Modified from Ref. [19], with permission from Elsevier.

T cells to effector T cells. These effector T cells traffic to the tumor site and specifically recognize tumor cells through T cell receptor (TCR) and MHC interactions. Upon recognition, effector T cells kill their target cancer cells by inducing apoptotic pathways. The killing of cancer cells releases additional tumor-derived antigens, and further strengthened the subsequent revolutions of the cycle.

In many occasions, the cancer-immunity cycle may be blocked at one or more of these steps, resulting in dampened anti-cancer immune responses or even immune escape. Factors leading to the immune escape may be failure to detect tumor antigens, Tregs expansion from DC priming, or suppression of T-cell function in tumors by factors in the TME [20]. Cancer immunotherapy aims to initiate or re-implement the cancer-immunity cycle (Fig. 1). For example, cancer vaccines are designed to promote cancer antigen presentation in DCs and facilitate more robust effector T-cell production [21]. TME modulation aims to release the "brake" for cytotoxic T cells (CTLs) in the immunosuppressive TME, improving the ability for killing their targeted cancer cells [22]. In ACT, antigen-specific CTLs are generated and expanded *ex vivo* and administered back to patients for antigen-specific tumor cell killing [23]. Still, while meeting the objective of an intact cancer-immunity cycle may require only monotherapy approaches in some patients, others may require combined therapies.

1.3. Nanomaterials for cancer immunotherapy

Nanomaterials are defined as materials with at least one dimension between 1 and 1000 nm, but in practical use may be anywhere from 1 to 200 nm. The past thirty years have viewed great success in the application of various nanomaterials for cancer diagnosis and therapy [24–27]. Due to rapid growth and irregular vascular structure, nanomaterials with a size of 10–200 nm avoid kidney clearance while selectively penetrating tumor tissues. Therefore, drugs loaded inside nanomaterials generally have much longer blood retention time and enhanced tumor distribution and reduced toxicity, which results in a higher tolerated dose [28–32]. In addition, nanomaterials are easily modified, and targeting ligands preloaded on the surface will help nanomaterials to be readily taken up by specific cells [33–36].

The application of nanomaterials to delivering cytotoxic drugs or imaging agents will also benefit immunotherapy. Delivery of tumor antigens is a critically important part of cancer vaccination, and it remains a clinical challenge [37–39]. For checkpoint inhibitors blocking the interactions between negative regulators and T cells, the lack of selectivity may result in significant immune-related toxicities [40–42]. Compared to delivering cytotoxic drugs to kill tumor cells, immunomodulation within the tumor may be a more efficient and thorough method of tumor eradication [43]. Additionally, some nanomaterials can inherently modulate the immune response due to some specific physiochemical characteristics [44–46]. In the past several years, a lot of pioneer works have been reported, and the number of publication is growing quickly (Fig. 2). There have been several good reviews summarizing the progresses in this field [47–53]. In this review, we will not list all of the innovative pioneer works, but explain some of the basic principles for applying nanomaterials in cancer immunotherapy. We will divide our discussion into two parts, cancer vaccination and immunosuppressive TME modulation (Fig. 3).

2. Application of nanomaterials for cancer vaccine design

2.1. Basic concepts in cancer vaccine

The term "cancer vaccine" can refer either to a prophylactic vaccine, given to prevent cancer, or to a therapeutic vaccine, given to eradicate an existing tumor. Representative cancer vaccines in the clinic include Gardasil® and Cervarix® against the HPV virus for preventing cervical cancer, and Sipuleucel-T as a therapeutic vaccine for metastatic prostate cancer [54]. Normally, a cancer vaccine contains a desired tumor antigen and an adjuvant capable of generating an immune response. Adjuvants act as the "danger

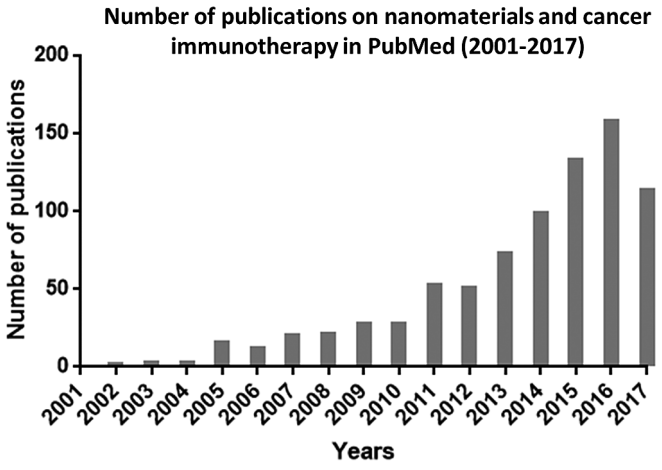

Fig. 2. Number of publications on nanomaterials and cancer immunotherapy in PubMed from 2001 to 2017.