REVIEW

Current applications and future prospects of nanotechnology in cancer immunotherapy

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ABSTRACT

Cancer immunotherapy is an artificial stimulation of the immune system to recognize cancer cells and activate specific immune cells to target and attack cancer cells. In clinical trials, immunotherapy has recently shown impressive results in the treatment of multiple cancers. Thus, cancer immunotherapy has gained a lot of attention for its unique advantages and promising future. With extensive research on cancer immunotherapy, its safety and effectiveness has gradually been revealed. However, it is still a huge challenge to expand and drive this therapy while maintaining low toxicity, high specificity, and long-lasting efficacy. As a unique technology, nanotechnology has been applied in many fields, the advantages of which will promote the development of cancer immunotherapies. Researchers have tried to apply nanomaterials to cancer immunotherapy due to their advantageous properties, such as large specific surface areas, effective drug delivery, and controlled surface chemistry, to improve treatment efficacy. Here, we briefly introduce the current applications of nanomaterials in cancer immunotherapy, including adoptive cell therapy (ACT), therapeutic cancer vaccines, and monoclonal antibodies, and throw light on future directions of nanotechnology-based cancer immunotherapy.

KEYWORDS

Cancer immunotherapy; nanotechnology; therapeutic cancer vaccine; monoclonal antibody

Introduction

The rising incidence and mortality of cancer is increasingly become a global health issue, and cancer treatments are also the focus of much research. In 1891, William B. Coley used Streptococcus to exploit the patient’s natural defense mechanisms to eliminate a malignancy¹. This first success of the cancer immunotherapy program has opened a new chapter in cancer treatment research. With the development of immunotherapy, cancer treatment will no longer be limited to traditional surgery, chemotherapy, and radiotherapy. Cancer immunotherapy has gradually revealed therapeutic advantages with broad prospects and practical values. Cancer immunotherapy produces a systemic, specific, and persistent anticancer response by stimulating the host immune system or inhibiting tumor immune evasion.

Current cancer immunotherapies are often based on the use of ACT, therapeutic cancer vaccines, and monoclonal antibodies². Adoptive immunotherapy using tumor-infiltrating lymphocytes and engineered autologous immune effector cells based on chimeric antigen receptors (CAR) had striking clinical effects for patients with metastatic melanoma and acute lymphoblastic leukemia (ALL), respectively³,⁴. Therapeutic cancer vaccines consist of tumor-associated antigens and proper adjuvants that target dendritic cells (DCs) and tumor-specific T cells and awaken anti-tumor immunity. Sipuleucel-T is the first cancer vaccine approved by the FDA for metastatic castration-resistant prostate cancer⁵. Tumor-specific monoclonal antibody therapeutic strategies can be divided into tumor marker-labeled cancer cells and immune checkpoint blockade. Antibody drugs, such as trastuzumab (HER2), rituximab (CD20), and bevacizumab (VEGF)⁶-⁸, make it easier for patients to undergo cancer-specific chemotherapy. Moreover, checkpoint inhibitors, FDA approved monoclonal antibodies for cytotoxic T lymphocyte-associated protein 4 (CTLA-4, ipilimumab⁹), and programmed cell death protein 1 (PD-1,
pembrolizumab and nivolumab\textsuperscript{10,11}, can block co-inhibitory receptors and enhance T-cell activation for patients with metastatic melanoma and advanced squamous-cell non-small cell lung cancer (NSCLC).

Despite these encouraging advances in cancer therapy, there are still some shortcomings in cancer immunotherapy. The complexity and heterogeneity of tumors, especially the immunosuppression of the tumor microenvironment (TME), hinders the efficacy and success rate of immunotherapy. At the same time, these therapies can also produce significant systemic side effects\textsuperscript{5,12,13}. In order to solve these tricky problems, researchers need new breakthroughs\textsuperscript{14}. Nanotechnology is an interdisciplinary field that emerged in the late 1980s and has penetrated many subject areas. The development and applications of nanotechnology, especially nanomaterials, has many advantages over conventional drug development methods. The expanding applications of nanotechnology in the medical field have also brought novel design concepts to cancer immunotherapy\textsuperscript{15}. Nanoparticles (NPs) with good biocompatibility have made noteworthy contributions to targeted drug delivery and biodistribution. Importantly, NPs coated with drugs can improve their stability and bioavailability, protect drugs from degradation, and prolong their half-life\textsuperscript{16-18}. In addition, the specific physiochemical properties of NPs (Figure 1) are suited to the delivery of antigens, vaccines, adjuvants, cytokines, and antibodies\textsuperscript{19-21}, and allow them to preferentially accumulate in key antigen-presenting cells (APCs), such as DCs in the draining lymph nodes. In turn, this accumulation activates the downstream effector CD8$^+$ cytotoxic T lymphocytes (CTLs) that recognize and kill tumor cells through T cell receptors and MHC interactions, thereby modifying the TME and awakening the immune system\textsuperscript{22}. Nowadays, nanotechnology provides an excellent opportunity for the improvement of cancer immunotherapeutic strategies. Herein, we will review the basic principles and the current status of the application of nanotechnology in cancer immunotherapy to demonstrate the broad prospects of nanotechnology applications.

Classification of nanomaterials for cancer immunotherapy

Nanomaterials are defined as materials with at least one dimension between 0.1 and 100 nm and have been successfully used in cancer immunotherapies. Compared to the biological size of some immune cells, nanomaterials have the advantage of facilitating the intake of immune cells. Moreover, drug-loaded nanomaterials generally have much longer blood retention times and enhance the production of

![Figure 1](image-url)  

**Figure 1** Typical structures of nanomaterials applied to cancer immunotherapy. Different nanomaterials with special structures have been used in cancer immunotherapy, including polymeric NPs, such as (A) stepwise branching dendrimer and (B) core-shell structure micellar; (C) liposome with lipid bilayer; (D) solid gold NP; (E) CNT consists with cylindrical models composed of carbon; (F) honeycomb-like porous structure MSN and (G) VLP derived from virus without genetic material.
cytokines that mediate humoral and cellular immunity\textsuperscript{23-25}. Currently, many types of nanomaterials are used in cancer immunotherapy and can be classified into polymeric NPs, liposome, exosome, metal NPs, mesoporous silica NPs (MSNs), carbon nanotubes (CNTs), and virus-like particles (VLPs)\textsuperscript{25-31} (Table 1).

**Polymeric NPs**

Polymeric NPs, such as poly(lactic-co-glycolic acid) (PLGA), dendrimers, micelles, and hydrogels, have been widely used in several drug delivery and targeting vehicles. PLGA, which is highly biocompatible and biodegradable, has been approved by the FDA and can encapsulate a range of biologically active compounds. PLGA microspheres as delivery tools can reach the processing pathways for MHC class I and class II molecules and increase the maturation of DCs\textsuperscript{48}. Over the last few years, research has utilized PLGA NPs with cytokine agonists, siRNAs, or CpG-coated tumor antigens to increase the DC uptake of antigens and activation of both CTL (CD8+) and Th (CD4+) immune responses\textsuperscript{32,49,50}. Dendrimers are synthesized around a focal point following stepwise branching and offer unique physical characteristics. Dendrimers, loaded with MHC class II-targeting peptides or dendritic cell-specific ICAM-3-grabbing non-integrin (DC-SIGN), can be used for antigen presentation and effective targeting of DCs\textsuperscript{34,51}. Micellar NPs have inner amphiphilic polymers and external hydrophilic residues, while hydrogels are made up of three dimensional polymeric networks\textsuperscript{36,52-54}. Both have been applied to antigenic peptide-based vaccine delivery and could potentially enhance cancer immunotherapy.

**Liposomes and exosomes**

It is reported that liposomes with hydrophilic heads and hydrophobic tails were an important class of electrostatic drug carrier used in gene therapy\textsuperscript{55}. Liposomes were used to encapsulate cGAMP, thereby facilitating its cytosolic delivery into orthotopic melanoma tumors, which improved the agonist activity of the immune adaptor protein STING and facilitated immunological memory in mice\textsuperscript{39}. Kranz et al.\textsuperscript{40} designed RNA-liposomes to protect RNA from extracellular ribonuclease interference by adjusting the net charge, thereby mediating the efficient expression of the encoded antigen by DCs. Alternatively, another strategy based on liposomes, a combined liposome-lipoplex, can promote the infiltration of CTLs to tumors at an early stage of treatment\textsuperscript{56}. A variety of cells secrete exosomes in both normal and pathological conditions. They are mainly derived from multivesicular bodies formed by intracellular lysosomal microparticles. It has been reported that exosomes released by immune cells play a role in activating immune suppression\textsuperscript{57,58}. Romagnoli et al.\textsuperscript{41} treated human breast adenocarcinoma cells (SK-BR-3) with DC-derived exosomes, which stimulated the secretion of interferon-\(\gamma\) (IFN-\(\gamma\)) and stimulated T cell activation. The immunomodulatory effect of exosomes suggests that they may be another tool for cancer immunotherapy.

**Metal NPs**

Metal NPs have been explored in biomedical imaging, diagnostics, and treatment due to their versatile surface chemistry and tunable size and shape. AuNPs are safe and improve the delivery of immunotherapeutic agents\textsuperscript{42}. For

| Table 1: Nanomaterials used for cancer immunotherapy |
|-----------------|-----------------|-----------------|
| Types           | Size (nm)       | Applications                     | Target          | Reference |
| Polymeric NPs   | PLGA            | 100-200 Vaccine carrier, adjuvant | DCs             | 32, 33    |
| Dendrimer       | 1-20            | Vaccine carrier                   | DCs             | 34        |
| Micellar        | 25-50           | Vaccine carrier                   | DCs             | 35, 36    |
| Hydrogel        | 80-600          | Vaccine carrier                   | DCs             | 37, 38    |
| Liposome        | 100-160         | Adjuvant/Vaccine carrier          | DCs/macrophage  | 39, 40    |
| Exosome         | 40-100          | Vaccine carrier                   | T cells         | 41        |
| Metal NPs       | AuNPs           | Vaccine carrier, adjuvant         | DCs             | 42        |
|                 | IONPs           | Antibody carrier                  | Tumor cells     | 43        |
| MSNs            | 50-300          | Vaccine carrier                   | T cells         | 44, 45    |
| CNTs            | 100-200 length  | Vaccine carrier, adjuvant         | DCs             | 30, 46    |
| VLPs            | 20-100          | Immunotherapy agent, Vaccine carrier | DCs/macrophage | 25, 47    |
example, the use of AuNPs in combination with modified CpG attenuates side effects and stimulates macrophages and DCs to significantly inhibit tumor growth59. Cho et al.60 designed Fe3O4-ZnO core-shell NPs to deliver carcinoembryonic antigens into DCs. These complexes, which can also be used as imaging agents, can be rapidly and efficiently taken up by DCs, and enhance the tumor antigen-specific T cell responses in mice.

MSNs and CNTs

MSNs and CNTs are classic examples of inorganic nonmetallic NPs (Figure 1). MSNs consist of a honeycomb-like porous structure with hundreds of empty mesopores which are able to absorb large amounts of bioactive molecules.45 Their special structures have attracted considerable attention for applications in cancer immunotherapy. Drugs and siRNAs, transferred into the particles through apertures, can be co-delivered into the body and induce the secretion of cytokines.44,61 CNTs are cylindrical models composed of carbon and exhibit multiple unique functions in immunomodulation. Moreover, research has found that CNTs in combination with anti-CTLA-4 antibodies could prevent the development of tumor metastasis.

VLPs

VLPs (20–100 nm in size) are artificial nanostructures resembling viruses without the ability to replicate. VLPs are immunogenic and can stimulate immune responses, which provides a new means for cancer immunotherapy. VLP-based vaccines can target immune cells and improve vaccine efficiency. At present, new cancer vaccines are developed mainly through engineering and combination of VLPs. Lizotte et al.47 first reported that a VLP-based NPs generated from cowpea mosaic virus could be directly used as a cancer immunotherapeutic agent, rather than a delivery vesicle. This method specifically targets and activates neutrophils within the TME and coordinates the downstream anti-tumor immune response, killing multiple tumor cells, including lung, ovarian, colon, and breast cancers. VLPs not only serve as nanocarriers for tumor antigens, drugs, and immunological adjuvants, but also demonstrate the effectiveness of monotherapy. Such applications have opened up fresh possibilities for VLPs to improve cancer immunotherapy.

Applications of nanotechnology in adoptive immunotherapy

ACT is an ex vivo therapeutic manipulation in which high efficacy autologous immune cells are transferred to a recipient in order to elicit an anti-neoplastic effect. The adoptive transfer of tumor-infiltrating lymphocytes62 and genetic modification of normal peripheral blood lymphocytes mediate cancer regression in some patients with metastatic melanoma. Over the past number of years, another promising ACT approach has been realized. As ACT with autologous effector T or natural killer (NK) cells would be the ideal personalized immunologic therapy, CAR-T, targeting CD19, and CAR-NK cells hold great promise as novel cellular immunotherapeutics against refractory malignancies. In reality, the generation of autologous CAR-T/NK cells for each individual patient often takes a number of weeks and the financial costs makes it restrictive for patients. Additionally, therapeutic efficacy against solid tumors is limited, and this type of treatment can cause severe toxicity, leading to organ damage. The complexity and safety of ACT is a barrier to broader clinical applications. Therefore, a combination of ACT and nanotechnology may create more effective treatments.

Compared with the application of nanotechnology in adoptive immunotherapy targeting T cells, the application of targeting NK cells is limited. There have been several breakthroughs in viral vectors and non-viral approaches aimed at genetically reprogramming NK cells to substitute the treatment of T cells. Currently, researchers have assembled scaffolds that mimic the TME, to improve adoptive T cell immunotherapy for inoperable tumors. The application of nanotechnology to T cell-based ACT has also been extensively studied. The mainstream strategy is still focused on enhancing the treatment efficiency of cancer via the conjugation of cytokines, antibodies, and adjuvant loaded NPs to the surfaces of therapeutic cells. Nanogels designed for backpacking large quantities of interleukin-15 (IL-15) super-agonist complex can attach directly to T cells, ensuring that the drug is released only in primary tumor sites, and activates T cells in situ. Drug-loaded liposomes decorated with antibodies and cytokines can target unique cell surface antigens and activate markers on T cells, respectively. Zheng et al.73 synthesized IL-2-Fc-liposomes and anti-Thy1.1-liposomes to stimulate and track ACT T-cells, both of which demonstrate repeated functional targeting of T-cells in vivo. Furthermore, drug-loaded synthetic NPs can directly couple to T cell plasma membranes, thereby enabling continuous pseudo-autocrine
stimulation of transferred T cells and increased tumor clearance\textsuperscript{72}. These NPs provide a good strategy to avoid the rapid decline in viability and function of therapeutic engineered-T cells. However, an alternative design, established for the first time, reveals that synthetic NPs can be engineered to quickly program antigen-recognition into lymphocytes\textsuperscript{74}. These NPs find T cells through the targeting molecule CD3, carrying the internally entrapped DNA into the T cells, transforming them to a CAR structure for the tumor. In this way, genetically edited T cells efficiently kill tumor cells and CAR-T gradually become apoptotic, avoiding more serious systemic toxicities. This method offers an important idea for the clinical transformation of CAR-T, including shortening the treatment cycle and the ability to spontaneously reprogram within the body without private customization for each patient. Hence, finding practical, low-cost, and broad approaches for cancer treatment has become the core aim of nanotechnology in adoptive immunotherapy applications.

**Applications of nanotechnology in cancer therapeutic vaccines**

Vaccine development is one of the most important events in the history of public health, protecting the lives of millions of people. The cancer vaccines TheraCys\textsuperscript{®}, Provenge\textsuperscript{®}, and Imlygic\textsuperscript{®} have achieved FDA approval for the treatment of some cancers\textsuperscript{25}. The continuous development of vaccines has also greatly improved their safety. However, most of the new generation vaccines, including cancer vaccines, are poor immunogenic subunit vaccines. Nanotechnology, especially the use of nanomaterials, has had a major impact on the delivery of vaccines and adjuvants (Table 1), providing valuable conditions for improving the immunogenicity of cancer vaccine formulas\textsuperscript{76,77}.

### Antigen delivery

The difficulty in vaccine development lies in the immune escape and efficient delivery of antigens such that the antigen dose is reduced or APCs are not recognized. Therefore, the use of nanomaterials with numerous functions provides a foundation for new vaccines that produce high and broad immune responses\textsuperscript{78} (Figure 3). Hamdy et al.\textsuperscript{79} utilized a poorly immunogenic melanoma antigen, tyrosinase-related protein 2 (TRP2), along with a toll-like receptor (TLR) ligand (7-acyl lipid A) co-encapsulated into PLGA NPs. After injection of the vaccine, it was found that CD8+ T cells in mice bearing melanoma B16 tumors were activated to kill the melanoma cells, and the levels of pro-inflammatory factors continued to rise. Vaccines comprising NPs and antigens are conferred antigen-targeting properties by protective antigens which are release when the target cells are reached. Based on DC-based cancer immunotherapy, Au and Fe\textsubscript{3}O\textsubscript{4} NP carriers can rapidly and efficiently deliver tumor antigens to DCs\textsuperscript{60,60}. Subsequently, DCs that acquired antigenic information further present antigens to cytotoxic T lymphocytes to produce anti-tumor immune responses. The efficiency of
antigen presentation ultimately determines the extent of the immune response, and NPs can be used to increase antigen presentation efficiency. Li et al. solved this problem with α-Al₂O₃ NPs. They found that such particles can reduce the delivery of DC-targeted antigens, allowing the use of limited antigens to stimulate T cell immune responses. Additionally, NPs have an antigen adjustable pulse release, which can prolong the local action time of the vaccine and enhance the immune system by continuously stimulating it.

NPs as carriers can not only present tumor-associated antigens, leading to DC maturation to activate tumor-specific T cells in lymph nodes, but also present other types of antigens, such as cytokines, nucleic acids, adjuvants, and soluble molecules. Cytokines regulate immune responses by modulating cell growth, differentiation, and their effects. Although cytokines have been approved by the FDA for the treatment of cancer, safety and the loss of blood circulation are still challenges. Many types of cytokines have been loaded into NPs and delivered to immune cells to enhance antitumor responses. Curnis et al. used AuNPs to deliver tumor necrosis factor and the CD13 ligand, Asn-Gly-Arg, to mice with fibrosarcomas, providing a new platform for single- or multi-cytokine delivery. In the development of immunotherapy for solid tumors, Wang et al. used systemic administration of NPs coated with IL12 and polymeric materials to reverse tumor-associated macrophage phenotypes in the TME and exert immunomodulation for cancer treatment.

Nucleic acid antigens, including DNA and RNA, that encode antigenic proteins, allow the vaccine to be delivered to the tumor site before antigen synthesis. However, nucleic acids, especially RNA, are easily degraded by nucleases, reducing the immunogenicity of the vaccine. The use of NPs for antigen delivery can protect nucleic acids. Liposome NPs can be used to encapsulate mRNA encoding tumor-associated antigenic proteins, and target DC cells that reach the spleen and lymph nodes and present them to T cells. CD8+ T cells that obtain antigenic information then begin to destroy the tumor cells. This design idea can also solve the selective restriction of different types of antigens on nanomaterials. Further, nucleic acid antigens may only need to change nucleic acid sequences to achieve diverse tumor elimination effects, which greatly reduces the difficulty of drug development. Researchers have designed NPs for the

Figure 3 Schematic of nanomaterials applied in antigen or vaccine/adjuvant delivery. Nanomaterials loaded TAA, vaccine and adjuvant can target DCs or T cells in response to activate CTLs for killing tumor cells.
delivery of siRNA. They used cationic lipid-assisted PEG-PLA-based NPs to deliver CTLA-4 siRNA (NP-siCTLA-4) and demonstrated anti-tumor immune responses.

**Adjuvant delivery**

Adjuvants are substances that are capable of directly or indirectly activating immune cells and enhancing immune responses with no toxicity or few side effects. Additionally, they can enhance the immunogenicity of antigens; mixing the adjuvant with antigens can reduce the decomposition rate of the antigens, slowing their release into the lymphatic system to achieve sustained immune stimulation. In addition to being carriers for conventional adjuvants, nanomaterials have an inherent immunological regulatory function that allows them to act as adjuvants to stimulate the host immune response. Nanomaterials used as adjuvants can also generally be referred to as nanoadjuvants. The use of nanoadjuvants enhances the phagocytosis of APCs and the presentation of antigens, thereby improving the vaccine. In addition, compared with traditional adjuvants, nanoadjuvants are better for antigen stability and have less toxic side effects. Similar to antigen delivery, adjuvant delivery or antigen and adjuvant co-delivery based on nanomaterial carriers, play a superior role in cancer immune activation. Polymeric NPs coated with cancer cell membranes coupled with immunological adjuvants can be used in vaccines to promote tumor-specific immune responses. Moreover, Morishita et al. proposed a highly efficient exosome-based tumor antigen-adjuvant co-delivery system. Pulmonary metastasis of B16BL6 cells was significantly reduced after tumor-bearing mice were intratumorally immunized with exosomes containing endogenous tumor antigens and immunostimulatory CpG DNA adjuvants, when compared to simple co-administration of antigens and adjuvants. Lymphatic trafficking of NPs is also dependent on the particle size. Studies have shown that VLPs or polymeric NPs with diameters under 50 nm target lymph nodes more effectively than larger particles. 20-40 nm is the optimal size range for NP-based vaccines to enter the lymph nodes. Therefore, nanoadjuvants are efficient and ideal biomaterials for antigen presentation and cancer immunotherapy.

**Applications of nanotechnology in monoclonal antibodies**

Compared with traditional cancer drugs, cancer immunotherapy drugs can kill tumors through active or passive immune reactions, reduce the side effects of drugs, and stimulate the host sustained immune response, which significantly improves their therapeutic effects. However, cancer immunotherapy drugs face drawbacks, such as monoclonal antibodies triggering a series of cytokine releases that can cause cytokine storms. Toxic side-effects and treatment efficiencies are problems associated with such drugs, and nanomaterials are playing an active role in solving these problems.

Pioneering hybridoma technology has become a significant success in the clinical trials of monoclonal antibodies. Nanomaterials have an inherent advantage for tumor-targeted drug delivery, known as the EPR effect (enhanced permeability and retention effect). Choi et al. used iron oxide NPs and DOX-encapsulated multifunctional particles to act on tumor cells with anti-human epidermal growth factor receptor 2 (HER2) antibody drug Trastuzumab, and found that NPs also eliminated the anti-cancer drug DOX delivery. The NPs conjugated with Au and CD44v6 monoclonal antibodies have noticeable effects on 44-expressing gastric cancer stem cells (GCSCs), which is an ideal strategy to improve the prognosis of gastric cancer and reduce recurrence. Recent research on in situ sprayed immunotherapeutic bioresponsive gels has received extensive attention. Chen et al. used a fibrinogen solution containing anti-CD47 antibody-loaded calcium carbonate NPs for inhibiting tumor recurrence post-surgery.

The Nobel Prize in Physiology or Medicine 2018 was awarded to James P. Allison and Tasuku Honjo in recognition of their contributions to cancer therapy and inhibition of negative immune regulation. Checkpoint blockade cancer immunotherapy is the forefront of immunotherapy for a variety of cancers by checkpoint inhibitors releasing T cell-mediated immunosuppressants. Checkpoint inhibitors include CTLA-4, PD-1/PD-L1, indoleamine 2,3-dioxygenase (IDO), CD47, CD40, and 4-1BB (CD137). To date, two major antibodies, aCTLA-4 and aPD-1/PD-L1 axis, have clinically been successful and have altered the prognosis of some advanced cancer patients. As with other cancer immunotherapies, the application of nanotechnology can significantly improve this therapy by reducing the side effects and enhancing anti-tumor effects.
treatment regimen for neuroblastoma in animal models. Mi et al. utilized dual immunotherapy NPs to conjugate αPD1 and antitumor necrosis factor receptor superfamily member 4 (αOX40) for treating two tumor models, inducing higher T-cell activation than free antibody immunotherapy. Wang et al. reported the preparation of microneedles (MN) consisting of hyaluronic acid integrated with pH-sensitive dextran NPs that encapsulate αPD1 and glucose oxidase (GOx). GOx can convert glucose to gluconic acid and reduce the pH, promoting the degradation of NPs and sustained release of antibodies. Following the application of MNs, researchers observed enhanced immune responses when compared to a single injection of αPD-1.

Furthermore, in face of the reality that a large fraction of patients failed to respond to checkpoint inhibitors, research into the application of nanomaterials for improving checkpoint inhibitors is urgently required. The application of NPs to immunosuppressive agents and other drugs may yield good results. As αPD-1 was ineffective in metastatic colon cancer, He et al. designed a polymer core-shell NP carrying oxaliplatin and the photosensitizer pyropheophorbide-lipid (pyrolipid). When they injected BALB/c mice bearing colorectal cancer CT26 with this NP and αPD-L1, the primary and distant tumor cells were significantly reduced when compared to those treated with αPD-L1 alone. Nanotechnology combined with chemotherapy, photodynamic therapy, and checkpoint blockade cancer therapy may provide a cure for extremely malignant cancers.

Conclusions

In this review, we summarized the principles and applications of nanotechnology in cancer immunotherapy. Although recent successes in immunotherapy have attracted the development of novel immunotherapeutics, the complexity of tumors and the TME, off-target side effects, and low immunogenicity are still challenges for effective cancer immunotherapy. Suppression of tumor-specific T cells is regulated by the activity of tumor cells, tumor-
associated stromal cells, tumor-infiltrating immune cells, and various cytokines or chemokines. How to reawaken the immune response in this complex system is a major and arduous task. Based on the current problems and technical challenges in cancer immunotherapy, the application of nanotechnology, with its unique advantages, is a boost for cancer immunotherapy research. The development of nanotechnology, especially nanomaterials, is a new era for the exploration of cancer immunotherapy. In addition to the applications discussed above, some researchers have used genetically engineered cells to obtain PD-1-expressing cellular nanocarriers to deliver small immunological molecules. These strategies are also expected to provide new ideas for personalized immunotherapy. Nanomaterials play a unique role in targeted delivery for cancer immunotherapy, however, their targeting ability is limited by the controllability of nanomaterials. Therefore, the application of nanomaterials depends on the development of measurement and characterization techniques, as well as the continuous updating of clinical data. So far, the impact of nanomaterials on human patients and clinical transformations has been insufficient. The selectivity and effectiveness of nanocarriers restrict the distribution of the delivered drug at tumor sites, which directly limits the clinical application of nanomaterials. Finally, as a drug carrier, the biosafety of nanomaterials needs to be further considered. The pharmacokinetic behavior of nanomaterials in animal models and the evaluation of host immune responses by various components need to be studied in detail. Although the clinical development of nanomaterials still has many challenges and questions, the advancement of nanotechnology, the deepening of clinical research, and the design and fabrication of nanomaterials will greatly aid the development of safe and effective cancer immunotherapeutics. The interfusion and continuation of nanotechnology and cancer immunotherapy will move forwards in the future.

**Acknowledgements**

This work was supported by the State Key Program of National Natural Science Foundation of China (Grant No. 51832001) and the National Natural Science Foundation of China for Key Project of International Cooperation (Grant No. 61420106012).

**Conflict of interest statement**

No potential conflicts of interest are disclosed.

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