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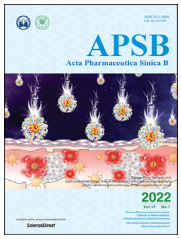

REVIEW

Symphony of nanomaterials and immunotherapy based on the cancer−immunity cycle

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Radio sensitizer

Abstract The immune system is involved in the initiation and progression of cancer. Research on cancer and immunity has contributed to the development of several clinically successful immunotherapies. These immunotherapies often act on a single step of the cancer−immunity cycle. In recent years, the discovery of new nanomaterials has dramatically expanded the functions and potential applications of nanomaterials. In addition to acting as drug-delivery platforms, some nanomaterials can induce the immunogenic cell death (ICD) of cancer cells or regulate the profile and strength of the immune response as immunomodulators. Based on their versatility, nanomaterials may serve as an integrated platform for multiple drugs or therapeutic strategies, simultaneously targeting several steps of the cancer−immunity cycle to enhance the outcome of anticancer immune response. To illustrate the critical roles of nanomaterials in cancer immunotherapies based on cancer−immunity cycle, this review will comprehensively describe the crosstalk between the immune system and cancer, and the current applications of nanomaterials, including drug carriers, ICD inducers, and immunomodulators. Moreover, this review will provide a detailed discussion of the knowledge regarding developing combinational cancer immunotherapies based on the cancer−immunity cycle, hoping to maximize the efficacy of these treatments assisted by nanomaterials.

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1. Introduction

Cancer, one of the most fatal diseases, threatens the lives of about 20 million people worldwide currently[1]. Traditionally, surgery, chemotherapy, and radiotherapy have been the main theranostics for patients with cancer. However, systemic toxicity, cancer recurrence and metastasis affect patients' prognosis[2]. As our understanding of the interaction between oncology and immunology has increased, it has become feasible to utilize patients' immune systems to defend against cancer. Cancer immunotherapies that can induce immunological memory have demonstrated a lasting inhibitory effect on cancer growth, recurrence, and metastasis[3]. Cancer immunotherapies, such as immune checkpoint blockade (ICB)[4–7] and chimeric antigen receptor T (CAR-T)[8–10] cell therapy, have improved overall survival in a subset of patients, especially in those with hematological cancers. However, these treatments induce limited responses in solid tumors[11] and are associated with systemic inflammation[12]. After the clinical success of ICB and CAR-T therapy, numerous immunotherapeutic agents and combinatorial strategies have been developed. Immunotherapy is redefining cancer theranostics and is not limited to the treatment of *in situ* or existing cancers. However, incomplete immunological knowledge as well as technical limitations still restricts the development of more efficient cancer immunotherapies. Novel immunological targets, drug delivery methods, and synergistic therapies are likely to lead to new breakthroughs in cancer immunotherapy.

Recently, discoveries in cancer immunology have broadened the horizon of cancer immunotherapy. Neoantigens, derived from mutations arising during the rapid proliferation of cancer cells, significantly increase the immunogenicity of tumor antigens[13]. Neoantigen vaccines have been shown to activate cytotoxic T ($CD8^+$ T) cells[14]. In addition, a high cancer mutation burden is an important prognostic indicator of cancer immunotherapy[15,16]. During ICB therapy, the amount of tumor-infiltrating $CD8^+$ T cells is directly linked to the therapeutic effect[17]. "Hot tumors", with higher numbers of infiltrating $CD8^+$ T cells against tumor antigens, present a greater response to ICB therapy[18]. In addition to activating an immune response against cancer cells, regulation of the tumor immunosuppressive microenvironment is also necessary. Various cytokines and immune cells are involved in the development and maintenance of tumor immunosuppressive microenvironments. These include interleukin (IL)-10, transforming growth factor (TGF)-β, immune checkpoints overexpressed on the surface of cancer cells, regulatory T (Treg) cells, and M2-type tumor-associated macrophages (TAMs)[19]. Recently, cancer–immunity cycle that describes the interaction of cancer tissues and immune system has been come up, and this concept is constantly being updated and improved[20–22]. Basically, cancer–immune cycle describes the process how tumor antigens that are released from damaged cancer cells are captured by APC cells and primed to $CD8^+$ T cells, and how $CD8^+$ T cells infiltrate into cancer tissues and kill cancer cells. For cancer immunotherapy, every step of the cancer–immunity cycle should be well considered**.** Moreover, optimizing the temporal and spatial activation of the immune response is the basis for achieving a safe and long-lasting anticancer effect[20].

Cancer immunotherapy is generally administered systemically to ensure that it reaches all potential tumors. However, this can be accompanied by severe immune-related adverse events, such as colitis, diarrhea, and endocrinopathy[23,24]. Therefore, targeting and specifically activating cancer-related immune cells are critical. Due to the concerted efforts of clinicians, biologists, chemists, and material scientists, nanomaterials now play important and diverse roles in cancer immunotherapy[25–28]. Nanomaterials can be enriched in cancer tissues compared to free small molecular drugs, which is termed an enhanced permeability and retention (EPR) effect[29]. The EPR effect was originally believed to result from the hyperpermeable tumor vasculature and impaired lymphatic drainage[30]. Recent reports have suggested that most nanomaterials enter tumor tissues *via* active trans-endothelial pathways[31,32]. A more detailed study on the mechanism of EPR will enable nanomaterials to be optimized for more efficient enrichment within cancer tissues. As an ideal platform, nanomaterials have the capacity to integrate multiple drugs for combination or synergistic treatment strategies[33,34], meanwhile a part of them possessing their own functionality, including photothermal[35], photodynamic[36] and magnetic response capabilities[37]. In addition, some nanomaterials can stimulate the immune system, partially by inducing antigen uptake and presentation by APCs[38]. These properties of nanomaterials make it possible to simultaneously activate several steps in the cancer–immunity cycle with spatial and temporal accuracy, which helps in controlling immune-related adverse events and effectively amplifies the anticancer immune response by synergistically activating different stages of the immune process. Current applications of nanomaterials in cancer immunotherapy include use as drug carriers (delivery of apoptosis inducer, immunostimulants, photothermal or photodynamic molecules, ICB antibodies), functional materials (induction of photothermal or photodynamic processes), and immunomodulators. This review summarized the immune mechanisms and knowledge about the cancer–immunity cycle, meanwhile discussing in detail the application of nanomaterials to promote cancer immunotherapies based on cancer–immunity cycle. Finally, we hope to identify a breakthrough to further promote the combination and application of nanomaterials in cancer immunotherapy.

2. Game between cancer and immunity

Cancer immunotherapy is a complicated interdisciplinary field, involving the interaction and crosstalk between tumors and the immune system at various stages of cancer development. It was initially believed that there was no clear association between immune processes and cancer development. In the past few decades, an increasing amount of evidence has been published to support the involvement of immune processes in cancer[39,40]. Additionally, cancer has been shown to influence immune processes and lead to immune escape or immune suppression[41]. Based on these discoveries, numerous studies have focused on activating patients' immune systems or adopting powerful immune cells to monitor, inhibit, and reverse cancer growth[42]. However, the effects of cancer immunotherapy against a single component of the immune process can be compromised by blocking other parts of the immune process induced by cancer. Therefore, there is an urgent need to elucidate a detailed understanding of immune responses associated with the development and treatment of cancer.

2.1. *Cancer–immunity cycle*

Cancer–immunity cycle was first summarized by Chen et al.[20] in 2013. Basically, it describes the cellular immunity process against cancer tissues. It includes several steps. Step 1, tumor antigens are

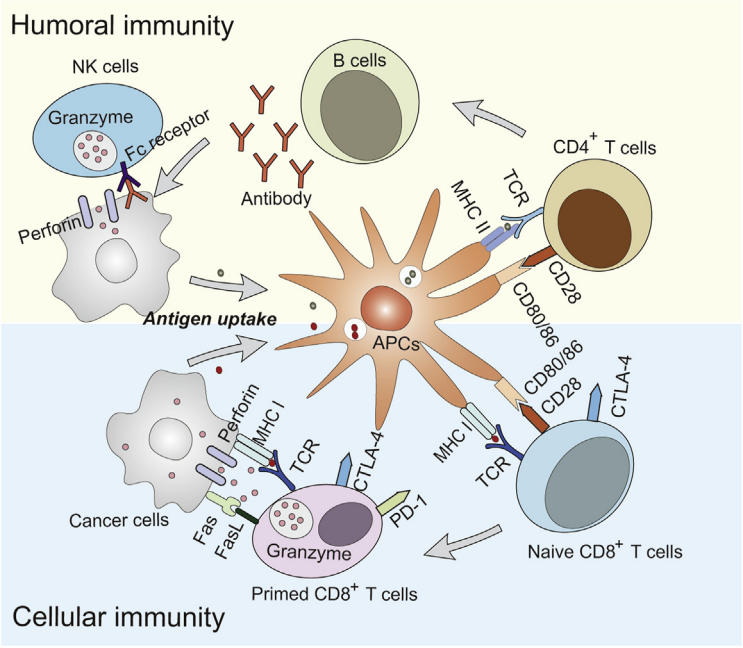

Figure 1 Adaptive immunity in cancer therapy. Humoral immunity: APCs take up and present antigens by MHC II molecules to activate CD 4^+ T cells; $CD4^+$ T cells present antigens to B cells, resulting in the secretion of antigen-specific antibodies; antibodies associate with antigens and co-precipitate for digestion by macrophages or induce ADCC effect mediated by NK cells. Cellular immunity: cancer cells are engulfed by APCs; APCs cross-present antigens to naïve $CD8^+$ T cells by MHC I molecules, which is accompanied by CTLA-4 expression on primed $CD8^+$ T cells; primed $CD8^+$ T cells recognize cancer cells *via* an MHC I/antigen complex and kill cells *via* the perforin, granzyme and Fas/FasL pathway; however, the association of CTLA-4 or PD-1 with their ligands can induce the dysfunction of primed $CD8^+$ T cells.

released from damaged cancer cells and captured by dendritic cells (DCs) for processing; Step 2, DCs present tumor antigens to MHCI and MHCII molecules on T cells; Step 3, the priming and activation the effector T cell response; Step 4, effector T cells circulate to tumors; Step 5, effector T cells infiltrate into tumor tissues; Step 6, effector T cells recognize cancer cells by TCR and MHC I complex; Step 7, effector T cells kill cancer cells. The final step of killing cancer cells contribute to the release of tumor antigens to initiate a new round of cancer−immunity cycle. Therefore, the cancer−immunity cycle has the capacity to self-sustain upon initiation. The original cancer−immunity cycle emphasizes the critical function of cellular immunity in cancer therapy. However, lots of evidence proves that humoral immunity and innate immunity play important roles in inhibiting cancer development[43]. As described in Fig. 1, the tumor antigens from cancer cells are captured by APCs. As exogenous antigens, tumor antigens that are endocytosed into the endosome−lysosome system usually bind MHC II molecules that are rich in the endosome, which further induce the priming and activation $CD4^+$ T cells. This pathway is classical humoral immunity, which kill cancer cells by antibody−antigen co-precipitation or antibody-dependent cell-mediated cytotoxicity (ADCC) mediated by NK cells. However, specific DCs, like $CD8\alpha^+$ DCs[44], or special circumstances, like endosome leakage of tumor antigens[45], induce the cross-presentation of tumor antigens. In the situation of cross-presentation, tumor antigens that exist in the cytoplasm are transported by the transporter of antigenic peptides (TAP) to the endoplasmic reticulum (ER), and are associated with newly assembled MHC I molecules. The presentation of MHC I/antigen complex eventually leads to the activation of $CD8^+$ T cells.

Therefore, we reorganized and amplified the content of cancer−immunity cycle in this review (Fig. 2). We described the cancer−immunity cycle as following steps. (1) Release of tumor antigens from damaged or dying cancer cells; (2) uptake and presentation of tumor antigens by APCs; (3) priming and activation of $CD4^+$ and $CD8^+$ T cells to trigger anticancer humoral and cellular immunity; (4) trafficking of NK cells, tumor antigen-specific antibodies, and $CD8^+$ T cells; (5) infiltration and enrichment of NK cells, tumor antigen-specific antibodies, and $CD8^+$ T cells into cancer tissues; (6) recognition and eradication of cancer cells *via* the cytotoxicity of $CD8^+$ T cells and ADCC effect mediated by NK cells.

2.2. *Immune escape and immunosuppression in cancer tissues*

The relationship between cancer and immunity is extremely complicated. Recent research has suggested that chronic inflammation contributes to the initiation and growth of cancer. Gene mutations or metabolite variations occur in cancer cells during tumorigenesis. $CD8^+$ T cells recognize and destroy cancer cells by monitoring the abnormal antigens presented by MHC I molecules on cancer cells, which ensures a low frequency of cancers considering that mutations occur in approximately 10^7−10^9 human cells every day. Commonly, the killing process of $CD8^+$ T cells on cancer cells could start up the cancer−immunity cycle and efficiently inhibit the occurrence of cancer. However, $CD8^+$ T cells sometimes are blind to a subset of mutated cells, which is termed the immune escape of cancer cells[46]. Moreover, the tumor immunosuppressive macroenvironment also impede the operation of cancer−immunity cycle. The main reasons of immune escape and immunosuppression are summarized as follows (Fig. 3).

(1) Immune selection allows tumors with relatively weak immunogenicity to escape immune surveillance and

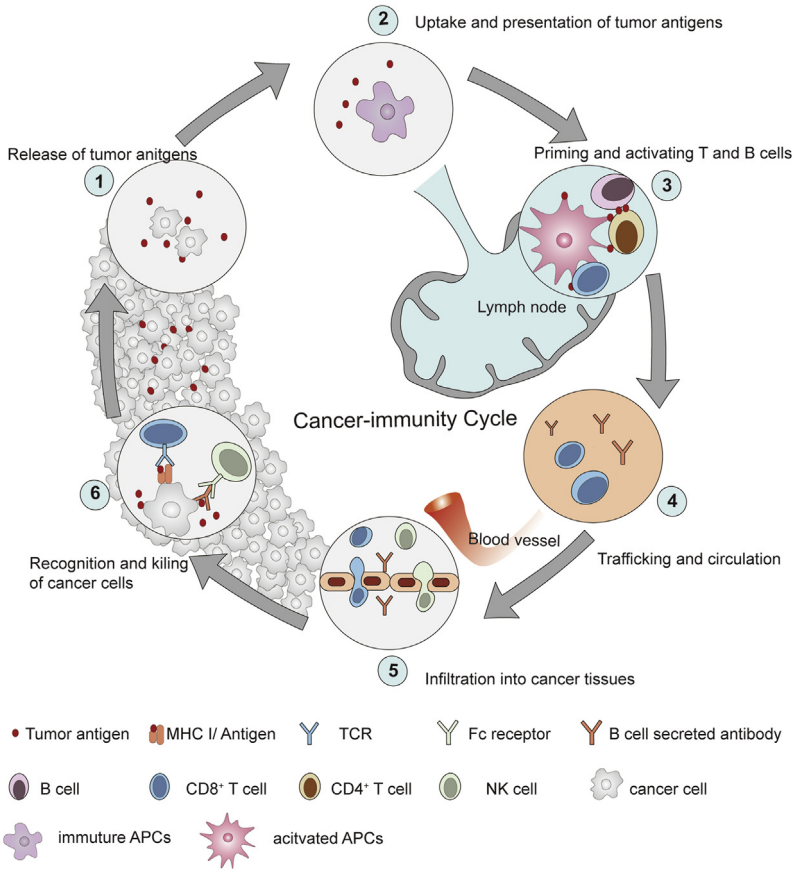

Figure 2 Cancer-immunity cycle. (1) Release of tumor antigens from damaged or dying cancer cells; (2) uptake and presentation of tumor antigens by APCs; (3) priming and activation of $CD4^+$ and $CD8^+$ T cells to trigger anticancer humoral and cellular immunity; (4) trafficking of NK cells, tumor antigen-specific antibodies, and $CD8^+$ T cells; (5) infiltration and enrichment of NK cells, tumor antigen-specific antibodies, and $CD8^+$ T cells into cancer tissues; (6) recognition and eradication of cancer cells *via* the cytotoxicity of $CD8^+$ T cells and antibody-dependent cell-mediated cytotoxicity (ADCC) mediated by NK cells. The design of Fig. 2 was inspired by Fig. 1 of Ref. 20 with the copyright permission. Copyright © 2013 Elsevier Inc.

selectively proliferate[47]. Cancers induced by oncogenic viruses and chemical carcinogens are highly immunogenic and easily cleared by the immune system, while spontaneous cancers of animals bear weak immunogenicity and tend to be retained[48].

(2) Antigen blockade or burying on the surface of cancer cells affects the recognition and attack by immune cells[49]. Some cancer cells overexpress mucopolysaccharides[50], such as sialic acid[51] or glycoproteins[52], preventing $CD8^+$ T cells from recognizing antigens presented by MHC I. Clearing sialic acid was found to enhance the anticancer immune response[53,54].

(3) Reduced expression of MHC I molecules on the surface of cancer cells can limit primed $CD8^+$ T cell recognition[55,56]. However, MHC I molecules also inhibit NK cells by binding killer-cell inhibitory receptors (KIR) on NK cells. A lack of MHC I molecules activates NK cells to mediate the lysis or apoptosis of cancer cells[57]. Therefore, cancer cells express non-classical MHC I molecules (HLA-E and HLA-G) to associate with KIR and inhibit the activity of NK cells[58].

(4) Disordered Fas expression on the surface of cancer cells limits the ability $CD8^+$ T cells to induce cancer cell apoptosis *via* the Fas/FasL pathway[59]. Moreover, some cancers overexpress and secrete FasL to bind Fas molecules on T cells and induce the death of T cells[60].

(5) Cancer cells secrete inhibitory factors, such as IL-10 and TGF-β to suppress the host immune response[61,62]. These inhibitory molecules accumulate in cancer tissues, forming a strong immunosuppressive microenvironment, which inactivates and kills infiltrating immune cells[63]. In addition, in cancer tissues, stromal cells secrete indoleamine-2,3-dioxygenase (IDO) to inhibit the proliferation of T cells[64]. IDO is the rate-limiting enzyme for tryptophan metabolism and exhausts tryptophan in the microenvironment to inhibit effector T cell proliferation[65]. Common cancer-related cytokines are listed in Table 1 [66–77].

(6) Suppressive immune cells exist in tumor tissues, including cancer-associated fibroblasts (CAFs), regulatory T (Treg) cells, myeloid derived suppressor cells (MDSCs), and M2 type tumor-associated macrophages (TAMs). Cancer, which can be considered a non-healing wound, can induce an injury-like response, including the continued activation of fibroblasts. During cancer progression, cancer cells secrete vascular endothelial growth factor (VEGF), and recruit fibroblasts, endothelial cells, and inflammatory cells.

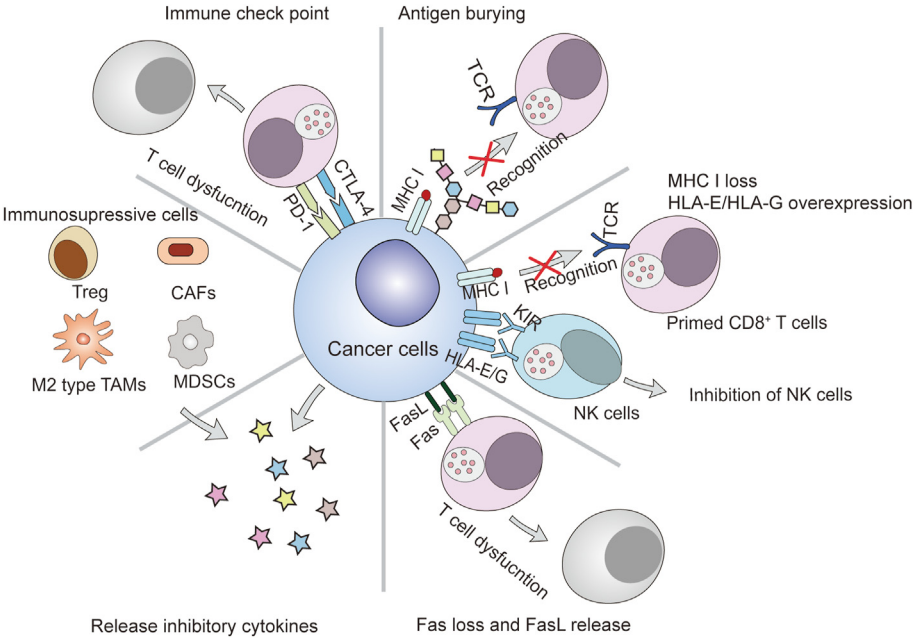

Figure 3 Immunosuppression in cancer tissues.

Fibroblasts and inflammatory cells are the main resources of host-derived VEGF, which forms an autocrine circuit in cancer tissues[78]. However, the reduced fibroblast and inflammatory cell activity observed after wound healing does not occur in cancer.

(7) Immune checkpoints

T cell activation requires the binding of antigen-bound MHC I molecules to TCRs, and is regulated by costimulatory or inhibitory signals, or an immunity checkpoint (Table 2). Immune checkpoint pairs are important strategies to achieve self-tolerance and prevent the immune system from damaging the surrounding normal tissue during anti-pathogen immunity. Immune checkpoints transmit "self" and "do not eat me" signals to T cells. Cancer cells escape immune surveillance by upregulating immune checkpoint signals. ICB strategies provide powerful therapies to facilitate anticancer immunity.

CTLA-4 is expressed dominantly in primed $CD8^+$ T cells and shares the B7 ligand with CD28. The association of B7 with CD28, accompanied by antigen presentation, activates naïve T cells. Conversely, the binding of B7 to CTLA prevents T cell activation. The up-regulation of CTLA-4 on primed $CD8^+$ T cells prevents the overaction of cellular immunity[79]. Although CTLA-4 is mainly expressed on primed $CD8^+$ T cells, it has also been found on Th and Treg cells[80]. The engagement of CTLA-4 on Th cells reduces Th activity, while the expression of CTLA-4 on Treg cells enhances their immunosuppressive effect[81]. The principal function of PD-1 is to limit T cell activity in peripheral tissues in anti-pathogen inflammatory response. Nevertheless, it has an immunosuppressive function during cancer progression. PD-1 is expressed in many tumor-infiltrating lymphocytes (TILs), including $CD8^+$ T, Treg, B, and NK cells[82]. The common ligands of PD-1 are PD-L1 and PD-L2, which are commonly overexpressed on cancer cells[83]. The association between PD-1 and its

Table 1 Cancer-related cytokines.

Cytokine	Main source	Function	Ref.
IL-6	Macrophages Endothelial cells	Participates in acute inflammation and promote tumorigenesis	66–68
IL-10	Th2 cells Monocytes	Inhibits activated monocytes to produce cytokines Inhibits the production of Th1 cytokines	69
TGF-β	Monocytes T cells	Regulates the differentiation of Treg and Th17 cells Inhibits the proliferation and differentiation of most immune cells and the production of cytokines Promotes the healing of damaged tissue	61,63
TNF-α	Monocytes Macrophages DCs	Pathogenic mediator of several autoimmune diseases; chronic exposure to TNF-α promotes tumor growth by mediating activation-induced cell death of effector T cells	70
IL-2	Th1 cells	Activates T cells, NK cells, and macrophages	71
IL-12	DCs Macrophages	Activates NK cells and induces Th1 differentiation	72,73
IL-15	Activated myeloid cells	Activates T cells and NK cells	74
IFN-γ	Activated T cells NK cells	Activates macrophages and MHC expression Induces the differentiation of Th1 cells and inhibits Th2 cells	75
GM-CSF	Macrophages T cells	Induces the proliferation and differentiation of DCs Activates macrophages	76,77

Table 2 Immune regulatory pairs.

Regulator	Ligand	Source of ligand	Function
CTLA-4	CD80 CD86	APCs cancer cells	Limit T cell activity
PD-1	PD-L1 PD-L2	T and B cells cancer cells	Induce T cell exhaustion
BTLA	HVEM	T cells and APCs cancer cells	Inhibit T cell proliferation
TIM3	GAL9	Tregs cancer cells	Inhibit T cell proliferation
TIGHT	PVR PVRL2	DCs	Inhibit T cell activation
LAG3	MHC complexes	APC cells	Induce T cell exhaustion
CD40L	CD40	APCs	Induce CTL priming
OX40	OX40L	APCs	Promote T cell division and survival
CD27	CD70	DCs	Induce T cell priming
CD28	CD80 CD86	APCs	Induce T cell priming of
ICOS	B7RP1	B cells macrophages	T cell co-stimulation

ligands can induce the dysfunction of $CD8^+$ T and NK cells. However, PD-1 enhances the proliferation of Treg cells in the presence of ligands[84]. In solid cancers, PD-L1 is the major ligand of PD-1. However, the level of PD-L1 expression is heterogeneous in different cancers, which may be important when considering the feasibility of therapeutic strategies against PD-1 and PD-L1. The anticancer effects of CTLA-4 or PD-1 blockade arise from the synergistic effect of $CD8^+$ T and NK cell activation and Treg cell inhibition.

2.3. *Cancer immunotherapy restoring cancer−immunity cycle*

The role of the immune system during cancer initiation, development, and metastasis has received increasing attention. The identification of cancer−immunity cycle involved in cancer has supported the use of immunotherapies in patients. As immunotherapies have become more targeted, the clinical outcomes of patients receiving anticancer immunotherapies are gradually improving, meanwhile the safety profile is improving. Commonly, the cancer immunotherapies that directly reinitiate the cancer−immunity cycle or relief the immunosuppressive effect on cancer−immunity cycle, show great potentials to eradicate cancer. Because the cancer−immunity cycle has the capacity to self-sustain, any immunotherapies that promote any steps of cancer−immunity cycles may achieve self-amplified anticancer effect. Currently used cancer immunotherapies restoring cancer−immunity cycle include non-specific immunotherapy, monoclonal antibody therapy, adoptive cell therapy (ACT), and anti-tumor vaccine therapy.

2.3.1. *Non-specific immunotherapy (cytokines and immunostimulants)*

Non-specific immunotherapy, mainly including cytokines and immunostimulants, usually systematic activate immune response against cancer cells. Non-specific immunotherapy usually has diverse mechanisms of promoting cancer−immunity cycle, including inducing the tumor antigen uptake of APCs, promoting the activation of $CD8^+$ T cells and easing the tumor immunosuppressive environment by stimulatory cytokines.

Coley[85] first administered bacterial extracts (Coley's toxins) as adjuvants in patients with cancer at the end of the nineteenth century. Coley's toxins altered cytokine levels and leaded to tumor clearance in some patients. Subsequently, numerous cytokines have been demonstrated to possess anticancer effects, including IL-2, IFN-γ, and GM-CSF[86]. IL-2 and IFN-γ have demonstrated promising anticancer potential. However, the clinical application of IL-2 and IFN-γ are hindered by severe toxicity following systemic administration[87]. Fusing cytokines with targeting proteins was shown to increase the accumulation in tumors and improve the subsequent outcomes, while reducing systematic toxicity[88]. Nevertheless, fusion strategies have distinct effects on different cytokines. The combination of transgene technology and cytokines provides a novel treatment strategy. Cancer cells modified with cytokine genes have been evaluated based on the protective effect against subsequent challenges with wild-type cancer cells[89,90]. Except for stimulatory cytokines, immunostimulants, such as agonists of TLRs or STING protein, are widely utilized to activate the function of APCs[91−93].

2.3.2. *Monoclonal antibodies (mAbs)*

In cancer immunotherapy, monoclonal antibodies (mAbs) constitute a substantial proportion of US Food and Drug Administration (FDA)-approved drugs. mAbs associate with targets at high affinity, which ensures the accuracy and efficiency of these agents. Moreover, mAbs have the capacity to mediate ADCC of NK cells, which further supports the anticancer effects of mAbs. The mAbs targeting on cancer−immunity cycles are mainly divided into two categories: immune checkpoint inhibitors for relieving the immunosuppression on cancer−immunity cycle and antibody−drug conjugates (ADCs) for inducing the death and antigen release of cancer cells.

The existence of immune checkpoints on cancer cells significantly limits the effectiveness of cancer immunotherapy. To restore the function of primed $CD8^+$ T cells, antibodies that inhibit the association of CTLA-4 or PD-1 with respective ligands have been widely studied. Clinical data promote the commercialization of mAbs against CTLA-4 (ipilimumab), PD-1 (nivolumab, pembrolizumab), and PD-L1 (atezolizumab)[94]. Compared with CTLA-4 and PD-1 mAbs, PD-L1 mAbs have demonstrated lower toxicity.

Recently, ADCs have attracted attention, and three types of ADCs have been commercialized since 2019. Traditional chemical drugs have no selectivity and require a relatively high dose to achieve curative effects. High-affinity antibodies can be accurately associated with their targets. ADCs, composed of an antibody "warhead", a cleavable linker, and a cytotoxic drug, combine the advantages of antibody and chemical drugs. Currently approved ADCs target biomarkers that are overexpressed on cancer cells, such as HER-2, CD30, CD33, and CD22[95]. The development of ADC technologies has expanded the indications for these therapies from leukemia to solid malignancies. Enhertu, a newer ADC, has been used in patients with HER-2 positive breast, stomach, and non-small cell lung cancers, with an objective response rate

(ORR) of approximately 60%[96]. The FDA-approved ADCs are summarized in Table 3.

2.3.3. ACT

ACT involves the activation and expansion of autologous immune cells *in vitro*, which are then reintroduced into the patient to enhance the anticancer capacity of the immune system. ACT directly carries out the identification and killing of cancer cells and reinitiates the cancer−immunity cycle by supplying a large amount of tumor antigens.

The effector cells of ACT are mainly lymphokine-activated killer (LAK) cells[97], cytokine-induced killer (CIK) cells[98], tumor-infiltrating lymphocytes (TIL), DC, NK, TCR-T, and CAR-T[99]. In non-specific ACT therapy, the effector immune cells, including LAK, CIK, DC, and NK, do not recognize specific tumor antigens and have no MHC I restriction. Although non-specific ACT therapy has demonstrated excellent anticancer activity against cancer cells lacking MHC I molecules, the potential toxicity to normal tissue cannot be ignored. The effector immune cells in specific ACT therapy, including TIL and TCR-T, can recognize tumor antigens. The recognition and subsequent lethal effect in cancer cells are dependent on MHC I molecules. Due to the MHC I restriction, TIL- and TCR-T-based specific ACT therapies are ineffective against cancer cells lacking MHC I. Nevertheless, CAR-T utilizes an antibody-antigen recognition model to replace the association of TCR-CD3 with MHC I/antigen complex, which avoids the MHC I restriction. However, CAR-T can only target cancer cells with surface antigens, and not those with internal antigens. CAR-T therapies approved by the FDA, such as Kymriah and Yescarta, mainly target lymphomas. The application of CAR-T to solid tumors remains challenging. Identifying better cancer biomarkers and the rational design of CAR are the main determinants for the success of CAR-T therapy. Moreover, similar technologies have been utilized in CAR-NK cells, which have been utilized in many preclinical studies[100].

Patients bearing with cancer often have a weak immune system, with limitation of number and activity of self-lymphocytes. Therefore, the development of lymphocytes from other sources is considered a breakthrough. Recently, induced pluripotent stem cell (iPSC) technology has expanded the sources and doses of primary lymphocytes. Perhaps due to epigenetic memory, compared to somatic cells, iPSCs from cord blood or peripheral blood lymphocytes increase the efficiency of $CD4^+$ $CD8^+$ lymphocyte production[101]. CAR-T or CAR-NK therapies based on iPSCs have demonstrated significant curative effects in patients with B-cell malignancies and ovarian cancer[102]. Furthermore, universal CAR-T overcomes the limitations associated with cell source, providing widely applicable ACT without HLA-matching. Thus, MHC I, MHC II, and TCR molecules are eliminated to avoid transplant rejection or graft−*versus*−host reactions through mature gene editing. Furthermore, HLA-E or HLA-G is introduced to avoid immune attack by patients' NK cells[103]. Clinical trials investigating iPSC-derived ACT or universal CAR-T therapies are currently ongoing.

2.3.4. Anticancer vaccines

Tumor initiation and progression are commonly accompanied by genetic mutations, which generate unique antigens that differ from those on normal autologous cells. The release of tumor antigens is supposed to start up the cancer−immunity cycle. However, the inability of APCs in tumor macroenvironment or low immunogenicity of tumor antigens impedes the capture and presentation of tumor antigens. Cancer vaccines, which are composed of tumor antigens and adjuvants, aim to overcome the tumor immunosuppressive environment, enhance the immunogenicity of tumor antigens, activate autologous cellular and humoral immunity, and thereby control or eliminate cancers[104]. Traditionally, cancer vaccines have included whole cell (cancer cell vaccines and DC vaccines), peptide, and nucleic acid vaccines.

With recent developments in gene sequencing and bioinformatics, personalized tumor neoantigens can be rapidly identified[105]. Relative to tumor-associated antigens, neoantigens are derived from cancer cell mutations and are therefore, completely new antigens. These neoplastic neoantigens are usually polypeptide fragments that possess a certain binding capacity with HLA; however, their immunogenicity is uncertain, and should be determined *in vivo* experiments. Peptide vaccines and mRNA vaccines based on neoantigens can induce anticancer humoral and cellular immunity[14,106].

An in-depth study of cancer cell death found that some cancer cells can cause an immune response after death, which is termed immunogenic cell death (ICD). When cancer cells die normally, their antigens and immunostimulatory components are degraded *via* the apoptosis pathway. During ICD, cancer cells expose their antigens and release damage-associated molecular patterns (DAMPs), including ATP, high-mobility group protein 1 (HMGB1), and calreticulin[107]. These DMAPs induce the uptake and presentation of tumor antigens by APC cells, thereby producing anticancer effects[108]. *In situ* cancer vaccines based on the ICD process have revealed new anticancer mechanisms of

Table 3 FDA-approved ADCs for cancer therapy.

Product	ADC	Approval date	Target	FDA-approved indication
Adcertris	Brentuximab vedotin	2011	CD-30	Hodgkin's lymphoma
Kadcyla	Trastuzumab emtansine	2013	HER-2	HER2-positive advanced breast cancer
Besponsa	Inotuzumab ozogamicin	2017	CD22	Relapsed or refractory CD22-positive acute lymphoblastic leukemia
Mylotarg	Gemtuzumab ozogamicin	2017	CD33	CD33-positive newly diagnosed acute myeloid leukemia
Lumoxiti	Moxetumomab pasudotox-tdfk	2018	CD22	Adult patients with relapsed or refractory hairy cell leukemia
Policy	Polatuzumab vedotin-piiq	2019	CD-79 b	Adult patients with relapsed or refractory diffuse large B-cell lymphoma
Padcev	Enfortumab vedotin-ejfv	2019	Nectin-4	Patients with locally advanced or metastatic urothelial cancer
Enhertu	Fam-trastuzumab Deruxtecan-nxki	2019	HER-2	Adult patients with HER2-positive unresectable or metastatic breast cancer

traditional chemotherapeutic drugs, such as doxorubicin (DOX)[109]. Furthermore, several external cancer therapies, such as photothermal therapy, photodynamic therapy, and radiotherapy, have been shown to induce ICD in cancer cells. However, the effect of the *in situ* vaccine strategy is not guaranteed, and it depends directly on the immunogenicity of the tumor antigens. Cancers with greater mutation burden present a greater response to *in-situ* vaccines. Moreover, cancer vaccines that efficiently activate cellular immunity have good anticancer outcomes. The cross-presentation of APCs for exogenous tumor antigens is critical for activating cellular immunity. The cancer vaccines that could target CD8α^+ DCs in lymph nodes or release tumor antigens from endosome−lysosome system to cytoplasm, provoke cross-presentation of APCs and better anticancer cellular immunity.

3. Nanomaterials provoking cancer–immunity cycle

Nanomaterials have versatile advantages, such as controllable size, high biocompatibility, and excellent load capacity. As the mechanisms underlying cancer immunology are gradually elucidated, nanomaterials are expected to have potential to optimize many aspects of cancer immunotherapy based on cancer−immunity cycle. The targeting capacity of nanomaterials can ensure that the different steps of the cancer−immunity cycle are activated with temporal and spatial precision, which minimizes side effects while ensuring an anti-tumor immune response. The identification of EPR effects makes nanomaterials (20−200 nm) a suitable partner for cancer-targeted drug delivery[110]. Applying nanomaterials as carriers may enrich immune regulatory compounds in cancer tissues to enhance the immune response and reduce systemic toxicity. In addition, nanomaterials with a size of about 25 nm are more likely to target lymph nodes, resulting in the potent immune activation induced by cancer vaccines[111,112]. In addition to participating in cancer immunotherapy as drug carriers, an increasing number of nanomaterials are indicated to mediate external anticancer treatments, including photothermal and photodynamic therapies, which induce ICD in cancer cells to form an *in-situ* anticancer vaccine and reinitiate cancer−immunity cycle. In addition, partial nanomaterials have demonstrated unique adjuvant effects, which can stimulate the body to produce a stronger immune response and relieve the suppression of cancer−immunity cycle. The following will introduce in detail how nanomaterials as drug carriers, ICD inducers and immune adjuvants enhance cancer immunotherapy based on cancer–immunity. The versatile functions of nanomaterials raise up the possibility of developing combinatorial cancer immunotherapy for simultaneously targeting several steps of cancer−immunity cycle to achieve more potent anti-cancer outcome (Fig. 4).

3.1. Drug delivery platform

In cancer immunotherapy, nanomaterials are used widely to target and enrich immune stimulatory compounds or cancer vaccines in cancer tissues or immune tissues (such as lymph nodes). The enriched drugs enhance immune system activation because of the increased concentration, and also limit damage to normal tissue caused by a systemic immune response. Nanomaterials that target cancer tissues and lymph nodes can be divided into passive and active targeting agents, according to the mechanism used. Passive targeting relies on the uptake of specific-sized nanomaterials by cancer tissues or lymph nodes, while active targeting predominantly relies on the overexpression of receptor molecules. For example, αv-integrins or folate receptors are overexpressed in some cancer tissues, and the αv-integrin ligand (iRGD) or folic acid can be modified on the surface of nanomaterials to achieve active targeting. Mannose receptors are overexpressed on the surface of APCs in lymph nodes. Therefore, mannose can be modified on nanomaterials to actively target APCs. Cancer-targeted nanomaterials are usually loaded with immune activators that can overcome the immune suppressive microenvironment, including cytokines, immune stimulants, and ICB antibodies. Nanomaterials that target lymph nodes are usually loaded with tumor antigens to promote the processing and cross-presentation of antigens by DCs, and to activate cancer-specific CD8$^+$ T cells in the lymph nodes. The identification and development of ICD inducers have led to the use of nanomaterials to transport these agents to cancer tissues. In addition, the rational combination of different immunomodulators in nanomaterials will further improve the efficacy of cancer immunotherapy.

3.1.1. Cytokines and immunostimulants

Systemic administration of free cytokines and immunostimulants leads to an uncontrollable immune storm. Cancer-targeted nanomaterials can restrict immune activation occurring inside cancer tissues. Following the assembly of low molecular-weight polyethyleneimine (600 Da), linkage with β-cyclodextrin and the *IL-2* gene, and association with folate, polymeric nanoparticles about 100 nm in diameter, were shown to induce the activation of CD4$^+$ T cells, CD 8$^+$ T cells and NK cells, resulting in the regression of B16−F1 melanoma grafts[113]. A combination of the *IL-2* gene, *IL-12* gene, endosomally cleavable lipid, and endosomally cleavable RGD peptide generated nanoparticles approximately 100 nm in size, which led to increased leukocyte infiltration and necrotic cancerous areas[114]. In addition, loading IL-2-fused Fc proteins and an agonistic CD137 antibody on liposomes could retain the potent anticancer effects of IL-2 and an agonistic CD137 antibody, while significantly reducing systemic toxicity caused by circulating leukocytes[115] (Fig. 5).

Except for cytokines, nanomaterials combined with immunostimulants ensure the local activation of tumor-infiltrating leukocytes. Intravenous administration of cyclic-di GMP-loaded cationic lipids was shown to efficiently trigger the production of interferon (IFN) and the activation of NK cells, which inhibited lung metastasis in a B16-F10 xenograft mouse model[116]. In addition, immunomodulator-loaded nanomaterials have the potential to target cancer-related leukocytes. For example, nanoparticles loaded with a TLR7/8 agonist specifically targeted DCs in cancer tissues and draining lymph nodes through passive targeting due to the size effects[117]. PLGA-PEG polymeric nanomaterials associated with an anti-PD-1 antibody (aPD1) or a CD8 antibody were shown to specifically bind to PD-1 positive CD8$^+$ T cells. These PLGA-PEG polymeric nanomaterials were shown to deliver TGF-β inhibitors, reversing the suppressive effect of TGF-β on CD 8$^+$ T cells[118]. Similar nanoparticles decorated with aPD1 were used to deliver a NF-κB inhibitor to PD-1 positive TILs to reduce the production of IL-10 and TGF-β, thereby easing the immunosuppressive conditions[119].

3.1.2. mAbs

ICB, the most successful mAb therapy used in cancer immunotherapy, acts on both TIL and circulatory leukocytes, which induce anticancer effects along with autoimmune inflammation. Nanomaterials can transport ICB antibodies to cancer tissues and ameliorate toxicity. Self-degradable microneedles encapsulating aPD1 were shown to release aPD1 to melanoma tissues and significantly inhibit

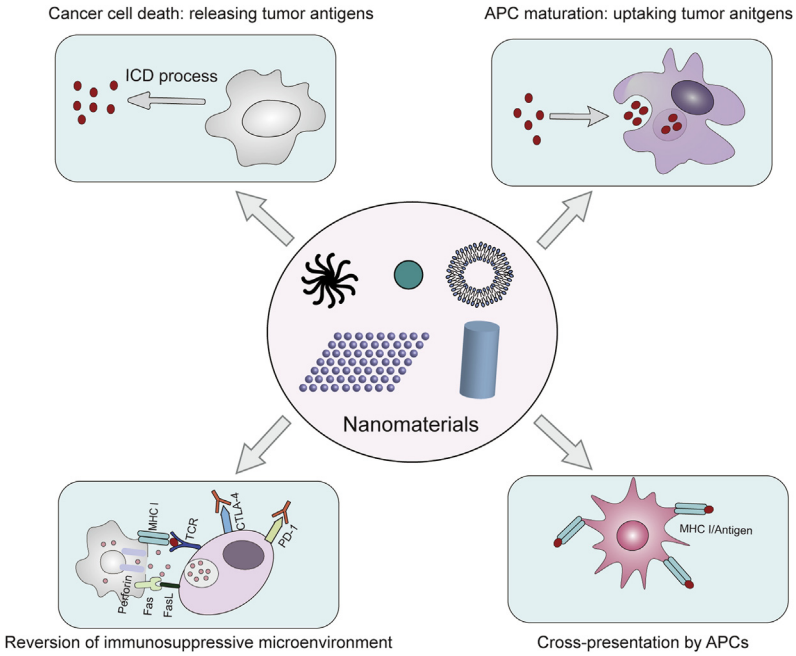

Figure 4 Nanomaterials target different stages of the cancer−immunity cycle individually or simultaneously. Currently used nanomaterials mainly induce the ICD of cancer cells, promoting the antigen uptake and maturation of APCs, enhancing the cross-presentation of APCs, and regulating the immunosuppressive microenvironment of cancer tissues.

cancer progress[120]. In addition to controlled release, nanomaterials also endow ICB antibodies with multivalent effects, which strengthens the interaction between antibodies and their targets. Construction of a multivalent anti-PD-L1 antibody (aPD-L1) by conjugating aPD-L1 with hyperbranched poly-(amidoamine) dendrimers, enhanced the binding avidity with PD-L1 six-fold compared with free aPD-L1[121]. Moreover, fusion of recombinant scFv of aPD1 with immune-tolerant elastin-like polypeptide (iTEP) resulted in the self-assembly of aPD1 nanoparticles, which blocked the PD-1 immune checkpoint *in vitro* and *in vivo*[122]. Furthermore, nanoparticles co-loaded with different mAbs, such as aPD1 and anti-OX40 antibody (aOX40) demonstrated synergistic and improved anticancer outcomes compared to the two free antibodies[123] (Fig. 6).

3.1.3. *Cancer vaccines*

Tumor antigens and adjuvants are required for cancer vaccines. Auxiliary ingredients, such as immunostimulants, could further improve the immunogenicity of cancer vaccines. Nanomaterials are multifunctional platforms that provide versatile advantages for the construction of cancer vaccines, as follows[124,125]: (1) the capacity to simultaneously deliver different vaccine components to the same APCs to boost an specific immune response; (2) enrich cancer vaccines to APCs in lymph nodes or cancer tissues by passive or active targeting; (3) mediate size and multivalence effects of cancer vaccines to trigger a potent immune response; (4) the controlled and sustainable release of tumor antigens ensuring long-term activation of the immune system; (5) cytosolic delivery of tumor antigens to promote cross-presentation of APCs to efficiently prime naïve $CD8^+$ T cells.

Tumor-associated antigens (TAAs) and model antigens have been widely utilized for the primary identification and development of cancer vaccines, since identification of tumor-specific antigens is relatively difficult. Based on TAAs and model antigens (such as ovalbumin, OVA), numerous nanoparticles have been used to develop cancer nanovaccines. For example, biodegradable PLGA[126], lipid−calcium−phosphate (LCP) nanoparticles[127], glutathione-depletion mesoporous organosilica nanoparticles[128] and protein nanoparticles[129] have successfully loaded TAAs and model antigens, and shown to mediate tumor antigen-specific immunity. Following the discovery that DCs play important roles in the uptake and handling of cancer vaccines, an increasing number of cancer nanovaccines have been designed to target DCs[130]. For example, golden nanoparticles approximately 14 nm in size were used to load red fluorescent protein (RFP) as a model antigen and CPG-ODN as adjuvants. The formulation resulted in the enrichment of nanoparticles in draining lymph nodes, a high titer of anti-RFP antibody, and the regression of RFP-expressing B16-F10 tumors[131]. In addition, DC-targeting molecules, such as mannose or CD40 antibodies, are commonly modified on nanoparticles to deliver cancer nanovaccines to DCs. For example, PLGA-nanoparticles containing Pam_3CSK_4, Poly (I:C), and OVA, were associated with anti-CD40 antibody, which resulted in efficient vaccine delivery to DCs and the potent activation of $CD8^+$ T cells[132].

Under normal circumstances, DCs present antigens to $CD4^+$ T cells to induce humoral immunity after engulfing exogenous antigens. However, cellular immunity facilitated by the cross-presentation of DCs with the aid of MHC I molecules represents a more efficient anticancer immune response. Nanomaterials that have the capacity to deliver tumor antigens into the cytoplasm greatly improve the probability and efficiency of cross-presentation. Positively charged nanomaterials, such as polyethyleneimine (PEI) and chitosan/calcium phosphate nanosheets, have been shown to trigger the endosomal escape of cargos *via* a proton sponge effect[45,133]. Nanomaterials loaded with endosomal-disrupting agents, such as pore-forming peptides, can mediate the escape of co-delivered cargos. For example, Kong and Liu et al.[134] constructed nanovaccines by loading PLGA with OVA and hydroxychloroquine (HCQ). HCQ induced

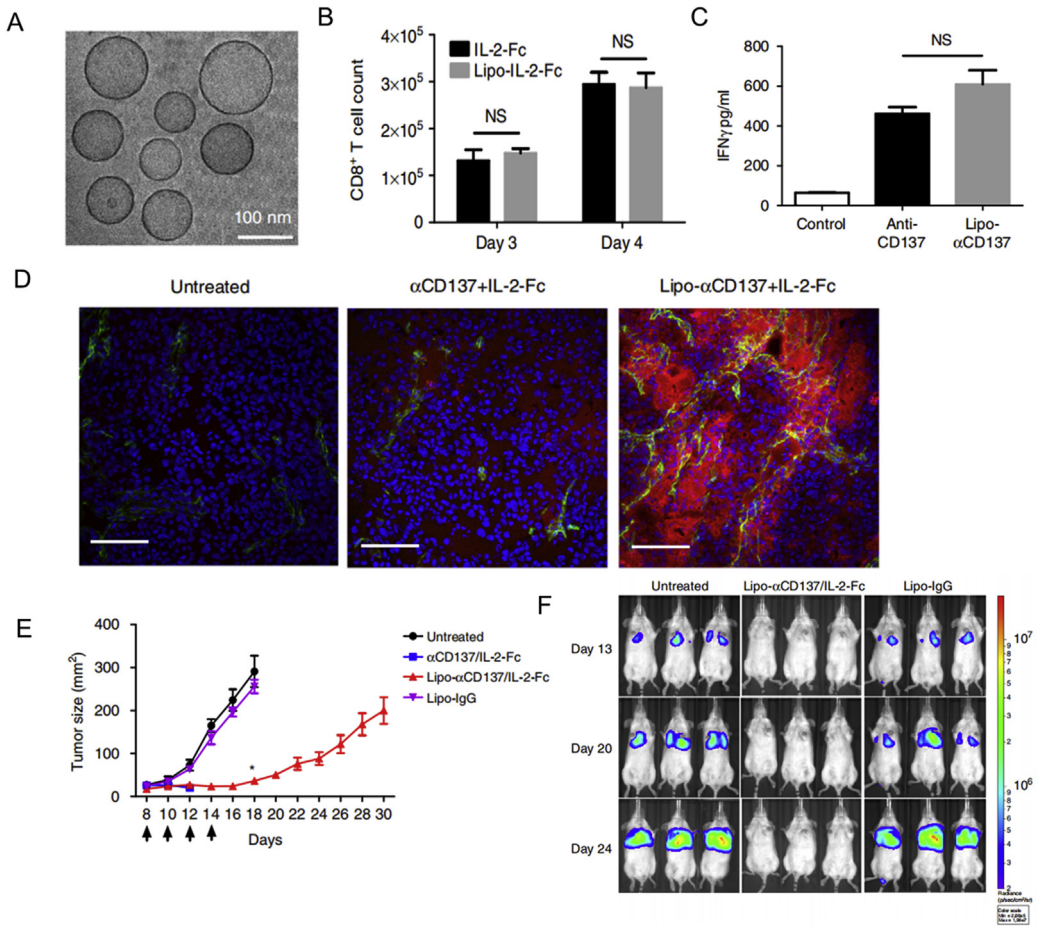

Figure 5 Liposomes anchoring IL-2-fused Fc and an agonistic CD137 antibody resulted in anticancer immunity without systemic toxicity. (A) Cryo-TEM image of a IL-2-Fc-liposome (anti-CD137 liposomes were similar). (B) $CD8^+$ T cell counts were determined following the treatment of polyclonal T cells from C57Bl/6 mice with soluble or liposomal IL-2-Fc (10 ng/mL of protein). (C) secreted IFN-γ was analyzed and then activated T cells were incubated with soluble anti-CD137 or Lipo-αCD137 (final αCD137 concentration: 10 μg/mL). (D) frozen sections of tumor after injections of Alexa-568-labeled αCD137 and IL-2-Fc and Lipo-αCD137 + Lipo-IL2-Fc. (E) tumor sizes in C57Bl/6 mice following treatment with αCD137 + IL-2-Fc, Lipo-αCD137 + Lipo-IL-2-Fc, or Lipo-IgG. (F) Bioluminescence images of C57BL/6 mice carrying luciferase-expressing B16F10 tumors, after treatment with Lipo-αCD137 + Lipo-IL-2-Fc or Lipo-IgG. Reprinted with the permission from Ref. 115. Copyright © 2019 Nature Publishing Group.

membrane permeabilization of the endosome and facilitated the release of OVA. Compared to PLGA/OVA nanoparticles, nanovaccines enhanced the expression of MHC-I and the costimulatory molecule CD86 of BMDCs, increased the frequency of IFN-γ^+ $CD8^+$ T cells, IFN-γ^+ $CD4^+$ T cells, and central memory T cells, and promoted the significant regression of tumors. In 2019, Xu et al.[135] constructed another nanovaccine facilitating cross-presentation by loading OVA and CpG-ODN on a polyamidoamine dendrimer modified with guanidinobenzoic acid (DGBA). This nanovaccine induced potent antigen-specific cellular immunity and prevented the re-challenge of B16-OVA melanoma. Moreover, this nanovaccine demonstrated robust anticancer efficacy against B16-OVA melanomas when combined with the ICB strategy of aPD-1.

Following the maturation of identification technology for neoantigens, cancer neoantigens are now being utilized to formulate cancer nanovaccines. Nanodiscs coated with neoantigens and CPG-ODN were demonstrated to enriched in lymphoid organs, and induced up to 47-fold more neoantigen-specific CTLs than soluble vaccines[136]. In addition, the use of T7 bacteriophages as nanocarriers for the expression of neoantigens could obtain nanovaccines containing diverse neoantigens. These nanovaccines elicited high titers of anti-neoantigen antibodies and B cell responses[137]. In addition, the construction of cancer nanovaccines by the self-assembly of neoantigens and immunostimulants ensured efficient codelivery and high loading capacity. Conjugation of neoantigen peptides with an imidazoquinoline-based TLR-7/8 agonist could self-assemble into nanoparticles about 20 nm in size. Administration of this nanoparticles elicited functional $CD8^+$ T cells against approximately 50% of neoantigens and led to enhanced tumor clearance[138].

Neoantigens are specific for different tumor types, making them ideal antigen sources for cancer vaccines. Nevertheless, common neoantigen cancer vaccines are difficult to include all tumor antigens owing to the heterogenicity and frequent mutation of cancer cells. Therefore, cancer cell lysis and membrane structures have attracted attention for being rich in antigens. Polydopamine nanoparticles (PDA NPs) conjugated with cancer cell lysates with a high loading capacity were demonstrated to efficiently inhibit cancer progression[139]. In addition, cancer biofilms may be a suitable antigen donor for developing cancer vaccines. In

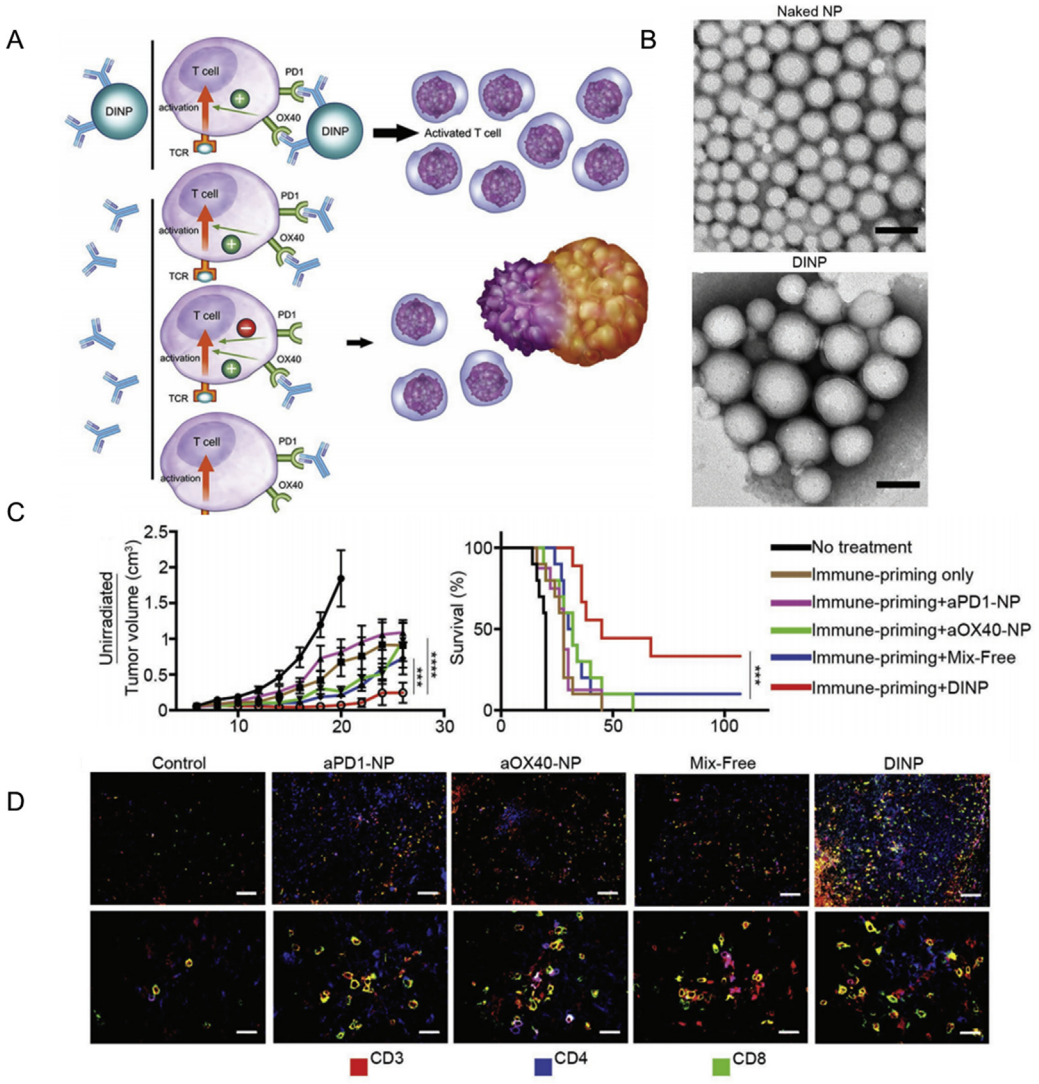

Figure 6 A dual immunotherapy nanoparticle targeting PD-1 and OX40 improved anticancer immunity. (A) Schematic of DINP-facilitated enhancement of combination immunotherapy. (B) images of nanoparticles before and after antibody conjugation (scale bar: 100 nm). (C) tumor size and survival curves of C57BL/6 mice with B16F10 tumors following treatment with different drugs. (D) immunofluorescent images of tumors after treatment of different drugs. Reprinted with the permission from Ref. 123. Copyright © 2018 WILEY-VCH Publishing Group.

2014, Fang et al.[140] utilized PLGA as the core material, encapsulated within cancer cell membranes derived from murine melanoma cells, and monophosphoryl lipid A (MPLA) as an adjuvant. This PLGA-membrane system retained most of the membrane-bound protein antigens and potently activated DCs with the aid of MPLA. Notably, the PLGA−membrane system without MPLA rarely induced DC activation, which might result from the low immunogenicity of the membrane alone.

In addition, the cell membrane from murine melanoma after PEGylation and association with CPG-ODN as an adjuvant, was found to induce a 3.7-fold greater antigen-specific cytotoxic $CD8^+$ T cell response, compared to cancer cell lysates. Moreover, the PEGylated cancer vaccine combined with aPD-1 potently inhibited melanoma development[141]. Cancer vaccines derived from the cell membrane elicited a more efficient anticancer effect when combined with DC targeting. For example, PLGA loaded with the TLR7 agonist R837 significantly triggered DCs activation, IL-12 release, and TNF-α production after coating with cancer cytomembrane and mannose[142]. Fusion cell membranes from cancer cells and DCs have provided new insights into the construction of biofilm-based cancer vaccines. The fused cell membrane presented both tumor antigens and costimulatory molecules of DCs, producing potent DC-mimicking nanoparticles to directly present tumor antigens to T cells, and protect against re-challenge by cancer cells[143]. However, the fusion efficiency and stability of fused cells should be optimized.

Theoretically, ICD inducers cause the release of tumor antigens and DAMPs, which function as *in situ* vaccines to activate APCs[107]. However, the immunogenicity of *in situ* vaccines is usually not strong, and depends on the mutation burden of cancer cells. Nanomaterials can target cancer tissues to deliver ICD inducers and co-load versatile immunostimulants to enhance the immunogenicity of *in situ* cancer vaccines. In addition to traditional chemotherapy drugs that induce ICD in cancer cells, such as DOX, oxaliplatin, and mitoxantrone, other types of molecules have also been shown to induce ICD, including photothermal and

photodynamic agents[144]. Indocyanine green (ICG) is an FDA-approved dye used to assess liver function and blood flow, and is widely utilized as a photothermal agent in cancer immunotherapy. For example, PLGA loaded with ICG and R837 was found to mediate local tumor regression after irradiation with near-infrared light, and further inhibited tumor recurrence *via* the activation of cellular immunity against cancer cells[145] (Fig. 7). A similar strategy was used to carry ICG and R837 on magnetic nanoparticles. With the aid of a magnetic field, the nanoparticles could be efficiently enriched in cancer tissues for MRI imaging. Moreover, the magnetic nanoparticles potently inhibited the progression of localized cancer and metastasis[146].

Photofrin and seven other photosensitizers have been approved by the FDA for use in photodynamic therapy. New-generation photosensitizers with longer excitation wavelengths and improved light stability are currently under development. Chlorin e6 (Ce6), which efficiently produces singlet oxygen, has attracted significant attention in basic research. As photosensitizers, O_2 and light are necessary for the effective production of singlet oxygen and other reactive oxygen species (ROS). Nanomaterials are commonly used to co-deliver photosensitizers and O_2 to cancer tissues to overcome the hypoxic environment. For example, hemoglobin (Hb) covalently bound to Ce6 and loaded with sorafenib (SRF, ferroptosis promotor) was shown to recruit immune cells to secrete IFN-γ and mediate potent anticancer effects[147]. Recently, nanomaterials were applied as antigen capture carriers *in vivo* for the construction of *in situ* cancer nanovaccines[148]. After the release of tumor antigens induced by radiotherapy, different surface-modified PLGA nanoparticles were injected intratumorally and their ability to capture tumor antigens and activate DC and $CD8^+$ T cells was assessed. Screening demonstrated that maleimide polyethylene glycol PLGA (Mal AC-NPs) could elicit potent cellular immunity and a subsequent anticancer outcome[149].

In addition, nanomaterials are designed to recruit and associate cancer cells with immune cells such as APCs. For example, Yuan et al.[150] constructed a bi-specific nanobioconjugate engager equipped with an antibody against HER2 on cancer cells and CRT proteins to recruit APCs. This nanoparticle induced HER-2-mediated phagocytosis and resulted in a durable anticancer response against HER2-positive cancer cells.

3.2. *Functional material as an ICD inducer*

The types and functions of nanomaterials are diverse. They can be used as drug carriers (such as liposomes, mesoporous silicon, and polymers), and also have various other functions, such as photothermal effects, photo dynamic effects, chemical kinetic effects, magnetothermal effects, and radiation enhancement effects. A part of nanomaterials with these functions have been shown to induce ICD in cancer cells, thereby releasing tumor antigens and DMAPs[151]. The combination of these nanomaterials with traditional immunotherapy, such as immunostimulants and immune checkpoint therapy, has the potential to efficiently promote several steps of cancer−immunity cycle and eventually achieve better anticancer effect. The following part of this review will introduce photothermal, photodynamic, radiotherapeutic, chemodynamic, and other functional nanomaterials, and discuss their applications in cancer immunotherapy based on cancer−immunity cycle.

3.2.1. *Photothermal nanomaterial*

Photothermal agents (PTAs) transform light energy into thermal energy. PTA nanomaterials are usually divided into metal-based inorganic agents, carbon-based inorganic agents, phosphorene-based agents, polymeric agents, and other new PTAs[152−154]. Metal-based inorganic PTAs include conventional noble metal materials (including Au, Ag, Pd, and Pt) and semiconductor materials (containing CuS, MoS_2, and WS_2). Metal-based inorganic PTAs are easily synthesized with adjustable sizes and shapes, but have disadvantages such as slow metabolism rate and unclear long-term toxicity profiles. Carbon-based inorganic PTAs are mainly composed of graphene, carbon nanotubes, and fullerene. While carbon-based inorganic PTAs have high photothermal conversion efficiency and stability, they have potential to induce pneumonia and are difficult to produce on a large-scale. Phosphorene-based PTAs, newly developed nanomaterials, contain two-dimensional black phosphorene and black phosphorous quantum dots. Phosphorene-based PTAs have high photothermal conversion efficiency and excellent biodegradation properties. Nevertheless, issues with stability, large-scale production, and storage capacity remain to be resolved. Moreover, the acute toxicity and immune effects associated with phosphorene-based PTAs are still unclear. Polymeric PTAs, including polypyrrole (PPy) and polydopamine (PDA), are easily synthesized with adjustable molecular weights. Regarding other novel PTAs, several two-dimensional materials have been generated with high photothermal conversion efficiency, such as C_3N_4 and MXenes with the general formula $M_{n+1}X_n$. In $M_{n+1}X_n$, M indicates a transition metal (Ti, V, Ta, Nb, Mo, and Zr) and X represents C or N.

The PTAs suitable for PTT in cancer immunotherapy should satisfy the following requirements: (1) relatively high photothermal conversion efficiency to avoid laser damage to normal tissue; (2) excellent biocompatibility and biodegradation to avoid systemic toxicity; and (3) light absorption in the NIR region, which is optimal in the second NIR (NIR-II) window (1000−1350 nm). To date, photothermal therapies function as two models: high-temperature PTT and low-temperature PTT. For high temperature PTT, cancer tissues are ablated at temperatures exceeding 50 °C[155]. High temperature and heat transduction may damage adjacent normal tissue[156]. Normally, mammalian cells respond to heat shock by overexpressing heat shock proteins (HSPs), such as HSP70 and HSP90. Therefore, research has focused on sensitizing cancer cells for low-temperature PTT by inhibiting the expression and activity of HSPs[157].

Recent studies have confirmed that PTT can induce ICD in cancer cells[144]. The higher temperature induced by irradiation resulted in more efficient cell death. However, ICD biomarkers did not increase with raising temperature. ICD markers, such as ATP release, HMGB1 release, and calreticulin expression, emerged more frequently at 63.3−66.4 °C than at higher (83.0−83.5 °C) and lower (50.7−52.7 °C) temperatures. Moreover, subsequent vaccination with different PTT-treated neuroblastomas confirmed *in vitro* findings. Challenging immunized mice with neuroblastoma cells within an optimal temperature window resulted in improved long-term survival compared to higher or lower temperature groups[158].

However, it is difficult to elicit a potent anticancer immune response only depending on antigen immunogenicity resulting from PTT-induced ICD. Therefore, PTA nanomaterials are frequently combined with other traditional immune strategies to improve the outcome of cancer immunotherapy. Utilization of carbon nanotubes as PTAs, combined with systemic administration of an anti CTLA-4 antibody effectively inhibited distant cancer and cancer metastasis under irradiation[159]. Hollow CuS nanoparticles coated with chitosan and CpG-ODN

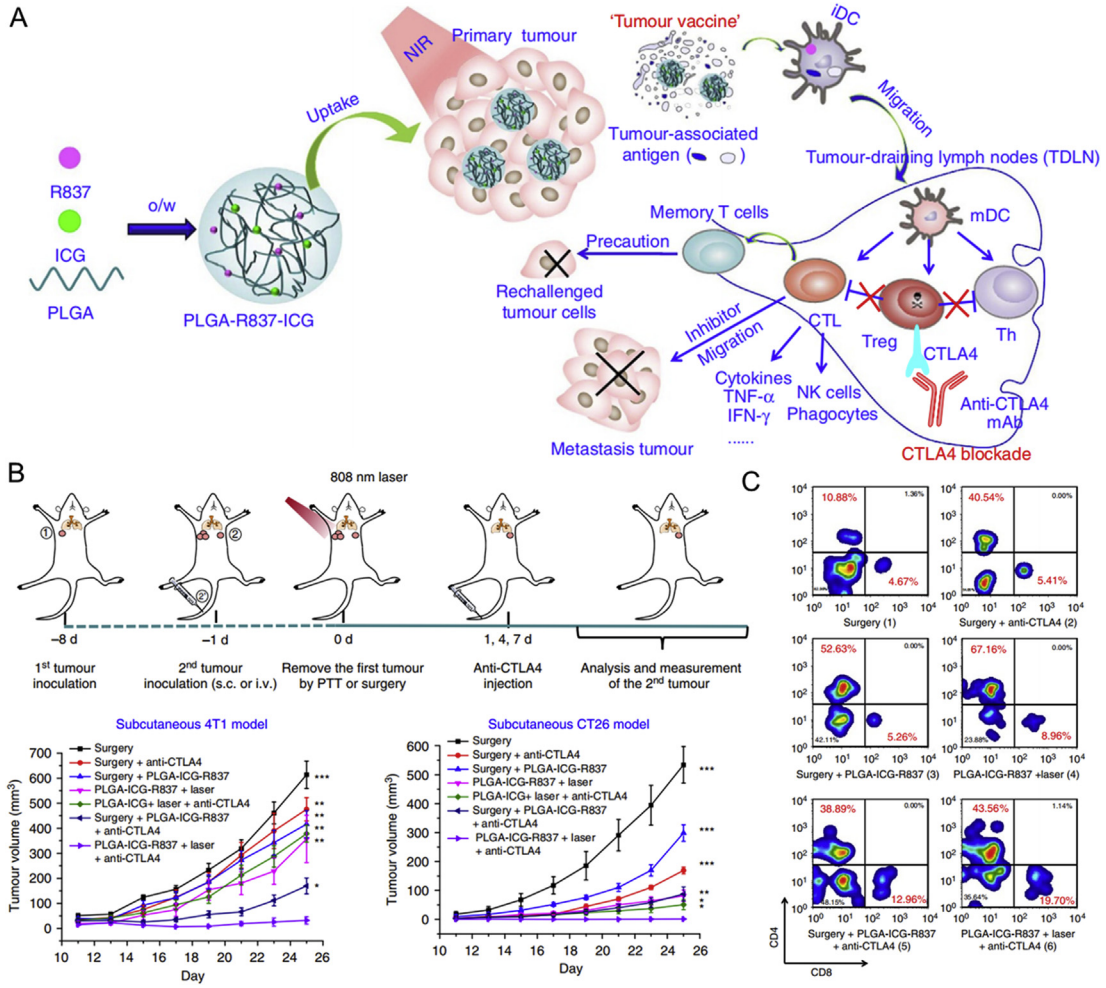

Figure 7 Photothermal therapy with immune-adjuvant nanoparticles induced anticancer immunity. (A) Schematic of immune-adjuvant nanoparticle constructed by PLGA loaded with ICG and R837 and its effect on immune system. (B) tumor volume of 4T1 and CT26 distant tumors following the indicated treatment of the primary tumor. (C) $CD4^+$ and $CD8^+$ T cells counts of distant tumors following the indicated treatment of the primary tumor. Reprinted with the permission from Ref. 145. Copyright © 2016 Nature Publishing Group.

were found to activate NK cells and DCs in cancer tissues and draining lymph nodes, leading to the inhibition of localized and distant cancer[160]. Recently, mammalian cells have been utilized for the *in situ* generation of PTAs, Au nanoparticles (AuNPs). Treatment of B16F10 cells with $HAuCl_4$ induced the intracellular generation of AuNPs. After exocytosis, AuNPs were encapsulated in B16F10 membranes containing diverse tumor antigens. Then, the AuNP@B16F10 cells were incubated with DC2.4 cells to further decorate the DC membrane and form AuNP@DC_{B16F10}. Administration of AuNP@DC_{B16F10} to B16F10-bearing mice significantly inhibited cancer development and activated DCs and $CD8^+$ T cells after irradiation[161] (Fig. 8).

Although nanomaterial-mediated PTT has been used widely in basic research for its non-invasive feature, there are still no successful clinical applications. The obstacles of nanomaterial-mediated PTT in clinical transformation can be summarized into six categories. (1) The limitation derived from the material features of most nanomaterials, including poor blood stability and dispersion, limited long circulation capacity, liver enrichment and inflammation, and unclear pharmacokinetic process. (2) The limitation of nanomaterial-based PTAs, including low photothermal efficiency and poor photo stability, especially for gold-based PTAs. (3) The obstacles derived from the irradiation process of light, including light toxicity and superficial tissue penetration. (4) What temperature is beneficial to the ICD process? Is there general principle for all nanomaterials-based PTAs (5) The limitation of knowledge about ICD process induced by nanomaterials-assisted PTT, for example, whether all the nanomaterials-assisted PTT cause ICD of cancer cells and how to evaluate and predict the capacity of nanomaterial-based PTAs to induce ICD process. (6) The intensity of ICD process induced by nanomaterials-assisted PTT is not enough to potently reinitiate the cancer−immunity cycle, and the combination of nanomaterials-assisted PTT with other cancer immunotherapy is necessary, which increases the complexity of the treatment system.

3.2.2. *Photodynamic nanomaterial*

In PDT, photosensitizers (PSs) can absorb photons and transform them from a ground state to an excited state. Under an excited state, the PS is usually unstable and easily transfers high-energy electronics to other substrates. In type I reactions, PS in an excited state, reacts with the cell membrane or other biomolecules to form

radicals, which further react with O_2 to generate oxygenated products. In type II reactions, PS in an excited state directly reacts with O_2 to form singlet oxygen, which is a highly active ROS[162] (Fig. 9). Therefore, the PDT output is closely related to O_2 concentration. Under a hypoxic tumor environment, it is difficult to demonstrate high efficiency with PDT. Although PDT emerged in the 1970s and was successfully used to treat superficial cancers, PDT-mediated immune activation was confirmed in the late 20th century, and therapies are still under development[163−165]. In more recent studies, PDT has been shown to be an effective method of inducing ICD in cancer cells[166,167]. Notably, it appears that ROS are required for ICD, because the immunogenicity of the process is largely inhibited in the presence of antioxidants. The PS of PDT includes organic dyes and nanomaterials. Organic dyes have several intrinsic drawbacks, including hydrophobicity, low penetration depth, and low specificity for cancer cells. Utilizing nanomaterials as carriers for organic PSs can overcome their several shortcomings, and related content have been introduced in Section 3.1.3. Herein, we will introduce nanomaterials that have an intrinsic capability to elicit photodynamic processes and their application in cancer immunotherapy.

Common PDT nanomaterials include noble metallic nanomaterials, carbon-based nanomaterials, black phosphorene, and nanoscale metal−organic frameworks (MOFs)[168]. Briefly, noble metallic nanomaterials are represented by gold and silver nanoparticles. Gold nanorods, for example, were reported to produce singlet oxygen under NIR light at 915 nm, which destroyed B16F0 melanoma tumors in a mouse model. In addition, these gold nanorods induced an increase in temperature around cancer tissues following irradiation with NIR light at 780 nm[169]. The switch in excitation light could transform the therapeutic model between PTT and PDT. Carbon-based PS nanomaterials contain carbon nanotubes, fullerenes, and graphene quantum dots. Native carbon-based PS produces limited singlet oxygen under NIR irradiation. However, doping and surface modification can endow carbon-based PS with excellent quantum conversion efficiency under NIR irradiation[170−172]. Black phosphorene with a tunable band gap, excellent biocompatibility, and biodegradation was first applied as PS in 2015. Black phosphorene demonstrated an approximately 0.91 quantum yield of singlet oxygen upon 660 nm irradiation, and caused significant cell death and tumor suppression[173]. MOFs assembled with organic PSs as ligand, and metal ions (Hf, Fe, Zn, and Zr ions) as metal centers, were shown to function as a PS nanomaterial[174,175]. For example, a new porphyrin derivative, 5,15-di (*p*-benzoato) porphyrin (H_2DBP) was reacted with $HfCl_4$ through a solvothermal reaction to generate a DBP-UiO MOF structure. The DBP-UiO-O MOF showed enhanced PDT efficacy and eliminated cancer in approximately half of mice following a single administration, and once exposure of 640 nm irradiation[176]. Subsequent research developed chlorin-based MOF by replacing H_2DBP with 5,15-di (*p*-benzoato)-chlorin (H_2DBC) to obtain DBC-UiO, which had red shift excitation and an 11-fold greater extinction coefficient compared to DBP-UiO[177]. Compared to PTAs, the types and application potentials of current PS nanomaterials are limited. Most PS nanomaterials are excited under visible light or the NIR-I region, which limits the depth of tissue penetration. Two-photon excitation PDT nanomaterials provide a solution of NIR-II irradiation[178]. Conventional one-photon excitation of PSs absorbs a single photon to trigger PSs. However, two-photon excitation PSs are capable of absorbing two low-energy photons simultaneously to achieve the band-gap energy of PSs by the sum of the two photon energies. Two-photon excitation allows for deeper tissue penetration and reduced photobleaching of PSs. For example, CdSe QDs were used as two-photon excitation nanomaterials that could be excited under an 1100 nm laser and emit photons with a wavelength of 635 nm. The silicon phthalocyanine 4 (Pc 4) conjugated on CdSe QDs was able to absorb 635 nm photons and functioned as a PS *via* a fluorescence resonance energy transfer (FRET) process between QD and Pc 4[179]. Although current PS nanomaterials can potently inhibit localized cancers, the prevention of distant and metastatic cancers are dependent on the combination with other cancer immunotherapies. For example, Fe-TBP MOF was constructed from [Fe_3O(OAc)$_6$(H_2O)$_3$] OAc and the 5,10,15,20-tetra (*p*-benzoato) porphyrin (TBP) ligand. Fe^{3+} can interact with H_2O_2, which is abundant in cancer tissues, to generate O_2 and ease hypoxia in cancer tissues, resulting in improved PDT efficiency. Fe-TBP combined with aPD-1 inhibited both localized primary cancers and distant cancers *via* abscopal effects[180]. Recently, poly (γ-glutamic acid) @glucose oxidase @carbon dot nanoparticles were constructed and combined with aPD-1. This nanomaterial generated O_2 from H_2O_2 under Mn^{2+} catalysis and mediated carbon dot-based PDT, which further induced an anticancer immune response against treated and untreated distant tumors[181].

Compared to conventional organic PSs, functional nanomaterial-mediated PDT is relatively rare. Development of NIR-II-elicited PDT nanomaterials with excellent biocompatibility and biodegradation may provide new opportunities for PDT. Except for the general limitations of nanomaterials, nanomaterials-assisted PDT owns its unique obstacles. First, it has photo toxicity and poor tissue penetration depth, which are common problems in photo irradiation therapy. Secondly, better intracellular uptake of PDT nanomaterials is necessary, for the ROS produced in PDT is active and only effective in the nanometer range. Thirdly, it should achieve a balance between PTT and PDT process induced by nanomaterials, for many nanomaterials have the ability to convert photons into heat and high-energy free radicals at the same time. Fourthly, O_2 is necessary in PDT and hypoxia in cancer tissues impedes the efficiency of PDT. However, delivery of O_2 with nanomaterial-based PS complicates the drug system and is not sustainable.

3.2.3. *Radiotherapy nanomaterial*

Radiotherapy is a mature treatment for cancer. Some nanomaterials are believed to enhance the effect of radiotherapy. Combined with its cancer-targeting ability, nanomaterial-based radiotherapy can reduce the damage to surrounding normal tissue[182]. Radiotherapy-enhanced nanomaterials are usually composed of high-Z elements[183]. The most prevailing radiosensitizers are gold-based nanoparticles[184]. Other studied radiosensitizers include lanthanide-based NPs[185,186], Bi_2Se_3 nanoparticles[187] and Hf-based MOF nanomaterials[188,189]. These radiosensitizing nanoparticles have been shown to improve the efficacy of radiotherapy by enhancing the photoelectric and Compton effects, which further increase the emission of secondary electrons and the production of ROS. During radiotherapy, DNA radicals need to react with O_2 to induce DNA double-strand breaks. Therefore, the hypoxic environment of cancer tissues weakens the anticancer effects of radiotherapy. To circumvent the hypoxic microenvironment, radiosensitizers are usually accompanied by O_2 delivery molecules, such as MnO_2 nanoparticles or perfluorocarbons. For example, core−shell Au@MnO_2-PEG was constructed to combine radiosensitizer high-Z atoms and O_2 generators. The Au core, a well-known radiosensitizer, can enhance the production of DNA radicals. MnO_2 has the capacity to decompose H_2O_2 to O_2 to overcome hypoxia-mediated resistance to

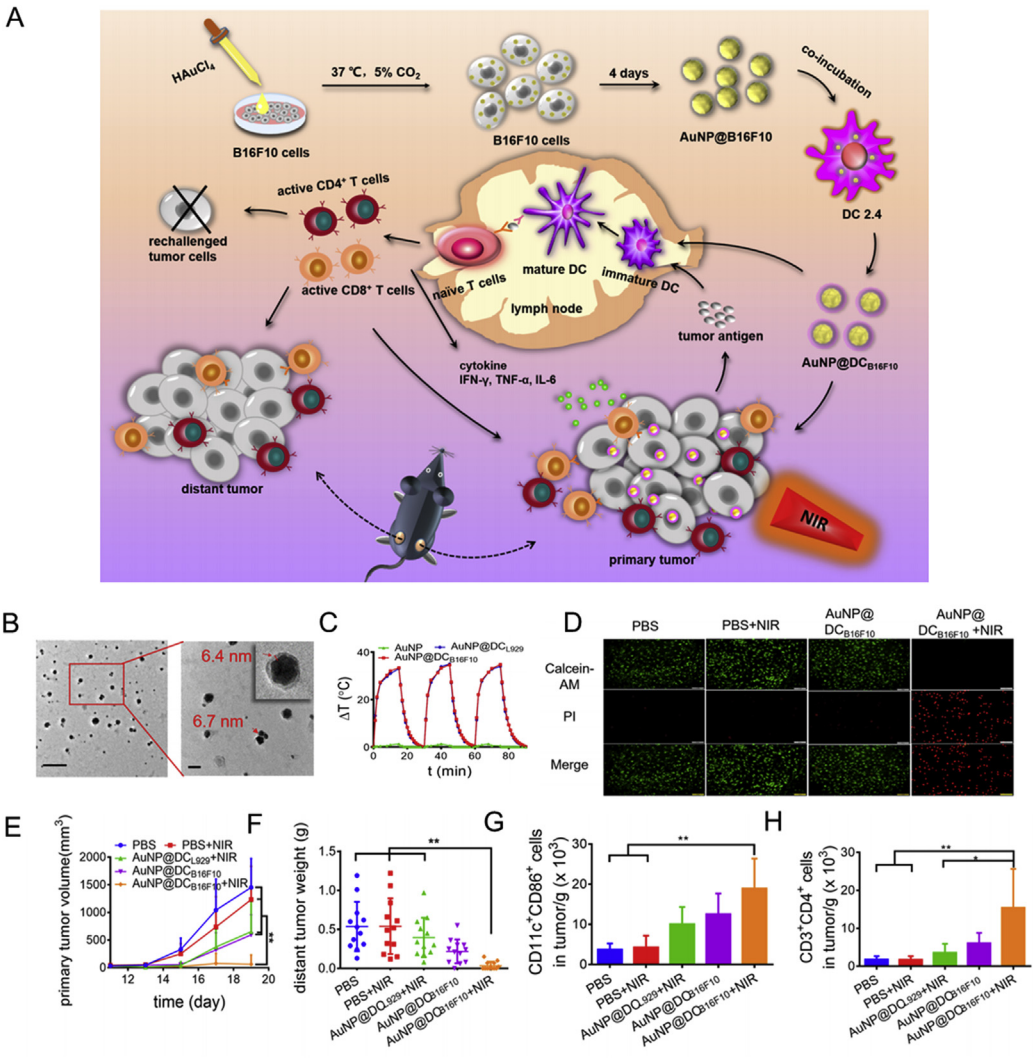

Figure 8 Gold nanoparticles *in situ* generated in B16F10 and DCs for the combination of PPT and immunotherapy. (A) Schematic of construction and immunological functions of AUNP@DC_{B16F10}. (B) TEM images of AUNP@DC_{B16F10}. (C) temperature change (ΔT) of AuNP, AuNP@DC_{L929}, and AuNP@DC_{B16F10}. (D) images presenting live/dead cells after treatment with AuNP@DC_{B16F10} or/and laser. (E) primary tumor volume following the indicated treatment. (F) distant tumor weight following the indicated treatment. (G) DC maturation following the indicated treatment. (H) $CD4^+$ T cell count after the indicated treatment. Reprinted with the permission from Ref. 161. Copyright © 2019 ACS Publishing Group.

radiotherapy[190]. In addition, perfluorocarbon-coated hollow Bi_2Se_3 nanoparticles were shown to enhance the efficacy of radiotherapy *via* three mechanisms: perfluorocarbon, as an O_2 carrier, reduced the hypoxic condition in solid tumors; Bi_2Se_3 nanoparticles, as radiosensitizers with high Z atom Bi, efficiently enhanced the photoelectric effect of RT; Bi_2Se_3 absorbed NIR light and produced a photothermal effect to increase the intertumoral blood flow, thus enhancing the concentration of O_2 in tumor tissues[191].

The abscopal effect, first proposed in 1953, hints at the evolution of the immune system under radiotherapy[192]. Subsequent studies found that radiotherapy could upregulate the expression of MHC I molecules and TAAs, thereby inducing the antigen presentation of DCs and the activation and trafficking of $CD8^+$ T cells[193]. Further studies demonstrated that radiotherapy enhanced the immune response *via* ICD[194]. Combining radiotherapy with other immunotherapeutic strategies strengthens the immune response and induces synergistic anticancer efficacy. For example, Hf-based nMOFs with radiosensitizing effects induced potent CRT exposure and activation of immune effector cells (including DC, $CD4^+$ T, $CD8^+$ T, and NK cells), which further inhibited the growth of primary and distant tumors. Moreover, combining Hf-based nMOFs with aPD-L1 clearly improved the immune response and almost eradicated primary and abscopal tumors[188].

Radiotherapy achieves deeper tissue penetration than photo irradiation. The immune elicitation mediated by radiotherapy is relatively well documented compared with photo irradiation. However, the tumor's hypoxic microenvironment is an obstacle for radiotherapy to produce enough ROS. Moreover, radiotherapy resistance mechanisms in cancer cells, like up-regulating DNA repair enzyme, reduce the anticancer outcome of radiotherapy. Besides, it is necessary to carefully evaluate the anti-cancer effect brought by the enhanced immune response and the cost of nanomaterial. Moreover, the general limitations of nanomaterials cannot be ignored in radiotherapy.

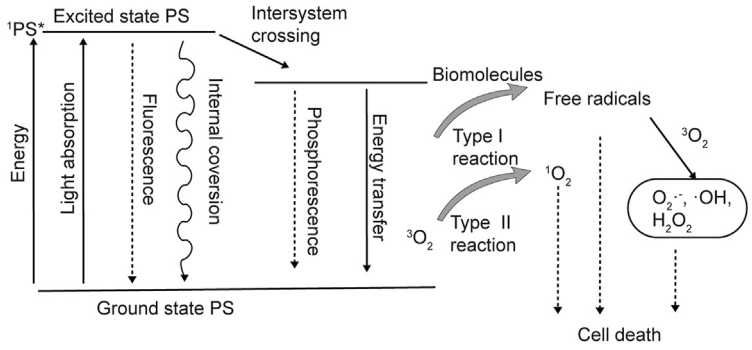

Figure 9 ROS generation in photodynamic therapies.

3.2.4. Other functional nanomaterials

In addition to improving the efficiency of PTT, PDT, and radiotherapy, nanomaterials also present other functionalities, including chemodynamic effect, inducing ferroptosis and magnetic hyperthermia (MHT) effects. The chemodynamic effect is mainly derived from the Fenton reaction, which primarily describes the reaction of Fe^{2+} with H_2O_2 to produce Fe^{3+} and hydroxyl radicals (·OH) with high oxidizing ability. High concentrations of ·OH are lethal to cancer cells. Except for ferrous ions, other cations, such as Cu^{2+}, Mn^{2+}, V^{2+}, and Cr^{4+}, are capable of catalyzing Fenton-like reactions[195]. Compared to stable Fe_3O_4 nanoparticles that only utilize surficial Fe^{2+} to catalyze the Fenton reaction, amorphous Fe nanoparticles (AFeNPs), which would be more efficiently ionized under an acidic tumor microenvironment and release active Fe^{2+}, enhanced the inhibition of cancer development[196]. Although H_2O_2 is present at much higher levels in cancer cells compared with in normal cells, endogenous H_2O_2 seems not enough to mediate a lethal chemodynamic effect on cancer cells *in vitro*. For many CDT therapies, the supply of additional H_2O_2 is necessary to induce cancer cell death and tumor regression[197]. Therefore, CDT is usually combined with other cancer therapies. For example, our group[36] developed a Z-scheme heterojunction with a FeS_2 core and Fe_2O_3 shell. The novel 2D thermally oxidized pyrite nanosheets (TOPY NSs) were able to kill cancer cells through glutathione consumption, the Fenton reaction, heterojunction-mediated PDT, and PTT. Moreover, TOPY NSs almost eradicated HepG2 xenograft tumors under irradiation at 650 and 808 nm. As CDT generates ROS as PDT does, it may induce ICD in cancer cells as well. However, the interaction between CDT and the immune system requires further study.

Ferroptosis is a new type of programmed cell death. Under the action of divalent iron or ester oxygenase, it catalyzes the high expression of unsaturated fatty acids on the cell membrane to cause lipid peroxidation, thereby inducing cell death. The ROS production in ferroptosis and non-apoptotic nature of ferroptosis imply its ability to modulate the immune system. Ferroptocide, a newly identified natural product, was proved to induce ferroptosis *via* covalent conjugation on thioredoxin, a critical component of the antioxidant system. The ferroptocide induced 40% tumor retardation in 4T1 bearing BALB/c mice but had rare inhibition in 4T1 bearing nude mice, which suggested the participation of T and B cells in ferroptocide meditated *in vivo* tumor inhibition[198]. The nanomaterials inducing chemodynamic effects could start up the ferroptosis process, because Fenton reaction can initiate liposome peroxidation[199]. However, several nanomaterials that not contain divalent iron show the potential to induce ferroptosis. PEGylated untrasmall silica nanoparticles (about 6 nm) were demonstrated to induce ferroptosis in nutrient-deprived cancer cells. The cell death induced by silica nanoparticles was inhibited by treatment of scavengers of lipid ROS (liproxstatin-1) or glutathione repletion *via* the addition of glutathione or *N*-acetylcysteine (NAC). Moreover, intravenous injection of the silica particles (12 nmol per dose) significantly inhibited the growth of 786-O and HT-1080 xenograft tumors in nude mice. And intraperitoneal doses of liproxstatin-1 significantly reduced the particle induced tumor inhibition[200]. Recently, arginine-rich manganese silicate nanobubbles (AMSNs) have been proved to induce ferroptosis by highly efficiently depletion of glutathione (GSH) and thereby inducing the inactivation of glutathione-dependent peroxidases 4 (GPX4). Manganese in AMSNs mediated the depletion of GSH, and ariginine modification provide tumor targeting ability. The AMSNs induced tumor inhibition by ferroptosis mechanism *in vitro* and *in vivo*[201]. Recently, a hybrid core–shell vesicles (HCSVs) was constructed by utilizing ascorbic acid (AA) as core and PLGA as shell decorated with iron oxide nanocubes (IONCs). HCSVs induced the exposure of calreticulin *via* Fenton reaction and ferroptosis-like cell death after magnetic field treatment. Moreover, intratumoral injection of HCSVs boosted significant proliferation of splenocytes, DC activation in inguinal LNs, and T cells activation in tumors and LN[202].

MHT mainly depends on superparamagnetic materials, which can achieve magnetic targeting and transform electromagnetic to thermal energy under an alternating magnetic field. Compared to PDT and PTT, MHT has a deeper penetration capacity and is associated with lower toxicity to surrounding tissue[203]. Fe_3O_4 nanoparticles are the most widely applied superparamagnetic nanomaterials, which can heat tumors above 43 °C and trigger the activation and proliferation of $CD4^+$ and $CD8^+$ T cells. The inhibition of distal and secondary tumors by Fe_3O_4 nanoparticles suggests the involvement of the immune system[204]. Utilizing Fe nanoparticles (FeNPs) as MHT agents, local administration of PLGA-R837 and systemic administration of aCTLA-4 checkpoint blockade were found to efficiently prevent cancer metastasis[205].

In conclusion, functional nanomaterials that induce photothermal, photodynamic, radiosensitizing, chemodynamic, ferroptotic and magnetic hyperthermia effect, show great potentials to induce the ICD process of cancer cells in which dying cancer cells could release tumor antigens and present immunostimulatory signals to activate the APCs. The potential ICD nano-inducers are summarized in Table 4. For many functional nanomaterials, whether they induce ICD of cancer cells and whether ICD strength is sufficient to restart cancer–immunity cycle remains to be

Table 4 Potential ICD nano-inducers.

Nanomaterial	Component	Function	ICD biomarker	Ref.
FAL-ICG-HAuNS	ER-targeting pardaxin (FAL) peptides-modified, ICG-conjugated hollow gold nanospheres	PTT PDT	ROS generation and CRT exposure Increased $CD8^+$ T cells, reduced $CD4^+$ T cells and Tregs in tumor, increased TNF-α and IFN-γ in blood	144
Prussian blue nano-particles	Coordination compound between Fe^{2+}, Fe^{3+} and CN	PTT	ATP release, HMGB1 release and CRT exposure, vaccination mediated prevention of tumor challenge	158
Single-walled nanotubes (SWNTs)	PEG-grafted amphiphilic polymer-decorated SWNTs	PTT	DC maturation and the expression of pro-inflammatory cytokines, no direct ICD biomarkers are evaluated, primary and metastatic tumor inhibition through combination of CTLA-4 mAbs	159
Fe-TBP MOF	Solvothermal synthesis from $[Fe_3O(OAc)_6(H_2O)_3]$ OAc (OAc = acetate) and H4TBP	PDT	Exposure of calreticulin, proliferation of tumor-antigen Specific cytotoxic T cells and $CD4^+$ T cells, inhibition of distal tumors, better anticancer outcome combined with α-PD-L1	180
PGA@glucose oxidase@carbon dot nanoparticles	Poly (γ-glutamic acid)@glucose oxidase@carbon dot nanoparticles	PDT PTT	No direct ICD biomarkers are evaluated, inhibition of distal tumors, better anticancer outcome combined with α-PD-L1	181
Hf-based nMOF	Hf6-DBA with a formula of $Hf_6(\mu3\text{-}O)_4$ ($\mu3$-$OH)_4$ $(DBA)_6$ and Hf12-DBA with a formula of $Hf_{12}(\mu3\text{-}O)_8$ ($\mu3$-$OH)_8$ ($\mu2$-$OH)_6$ $(DBA)_9$	RT	Exposure of calreticulin, release of HMGB1, proliferation of $CD8^+$ and $CD4^+$ T cells, inhibition of distal tumors, prevention of tumor challenge	188
A hybrid core–shell vesicle (HCSVs)	Ascorbic acid (AA) in the core and poly (lactic-*co*-glycolic acid) shell incorporating iron oxide nanocubes (IONCs)	CDT ferroptosis	CRT exposure, GPX4 downregulation, the maturation of DCs, proliferation of $CD8^+$ T cells in DLN, inhibition of primary tumor	202
Ferrihydrite nanoparticles	PEGylation of ferrihydrite nanoparticles	Ferroptosis	Glutathione peroxidase 4 (GPX4) inhibition, increasing of ROS level, TAM polarization from M2 to M1, inhibition of tumor metastasis	199
Iron oxide nanoparticles	Iron oxide nanoparticles	MHT	Activation of DCs and $CD8^+$ T cells in LN, production of cytokines and chemokines, inhibition of distal tumor, prevention of tumor challenge	204
FeNPs	Pure iron nanoparticles functionalized with polyethylene glycol (PEG)/dopamine (DA) -cografted polymer	MHT	Increase of $CD8^+$ T cells in secondary tumor, slight inhibition of secondary tumor, better anticancer effect after combination with R837 and α-CTLA-4	205

studied. In addition, a small number of reports on functional nanomaterials inducing ICD are difficult to explain that all functional nanomaterials of the same type can induce ICD. However, lack of standardized characterization and research on the ICD process mediated by nanomaterials impede the rational optimization of ICD nano-inducers.

3.3. *Immunomodulatory adjuvants*

Adjuvants are essential components of modern vaccines, which strengthen and/or shape the immune response against pathogens or malignancies. In the field of cancer vaccines, it is critical to trigger potent cellular immunity against tumor antigens. Nanomaterials with various sizes, shapes, and surface modifications may function as adjuvants *via* the following mechanisms[206]: delivery and consistent release of antigens, targeting APCs in a passive or active way, the cytosolic delivery of antigens to enhance the cross-presentation of APCs, and modulate the immune response. The use of nanomaterials as delivery platforms to transport tumor antigens to immune organs and the cytoplasm of DCs is described in Section 3.1.3. Herein, we will discuss the immunomodulatory effects of nanomaterials and their application in cancer immunotherapy.

The immunomodulatory effects of nanomaterials mainly include inflammasome activation, complement system activation, and the recruitment of immune cells[207]. Alum adjuvants, which are widely used clinically, have been shown to induce NLPR3 inflammasome activation. Upon exposure to danger, such as pathogens, DAMPs or PAMPs, NLPR3, and other related proteins will self-interact to form high-molecular-weight complexes that induce the autocleavage of caspase-1. This further regulates the secretion of IL-β and IL-18[208]. In addition to alum, numerous nanomaterials have been shown to induce NLRP3 inflammasome activation, including carbon black nanoparticles[209], SiO_2[210,211] and TiO_2 nanoparticles[212]. Inflammasomes are activated in response to the danger signal provided by nanoparticles, such as lysosomal destabilization and ROS production. Complement proteins exist in the serum and tissue fluid in humans and vertebrates. Complements can be activated by antigen−antibody complexes or microorganisms, leading to the lysis or phagocytosis of pathogenic microorganisms. Recent studies have demonstrated that

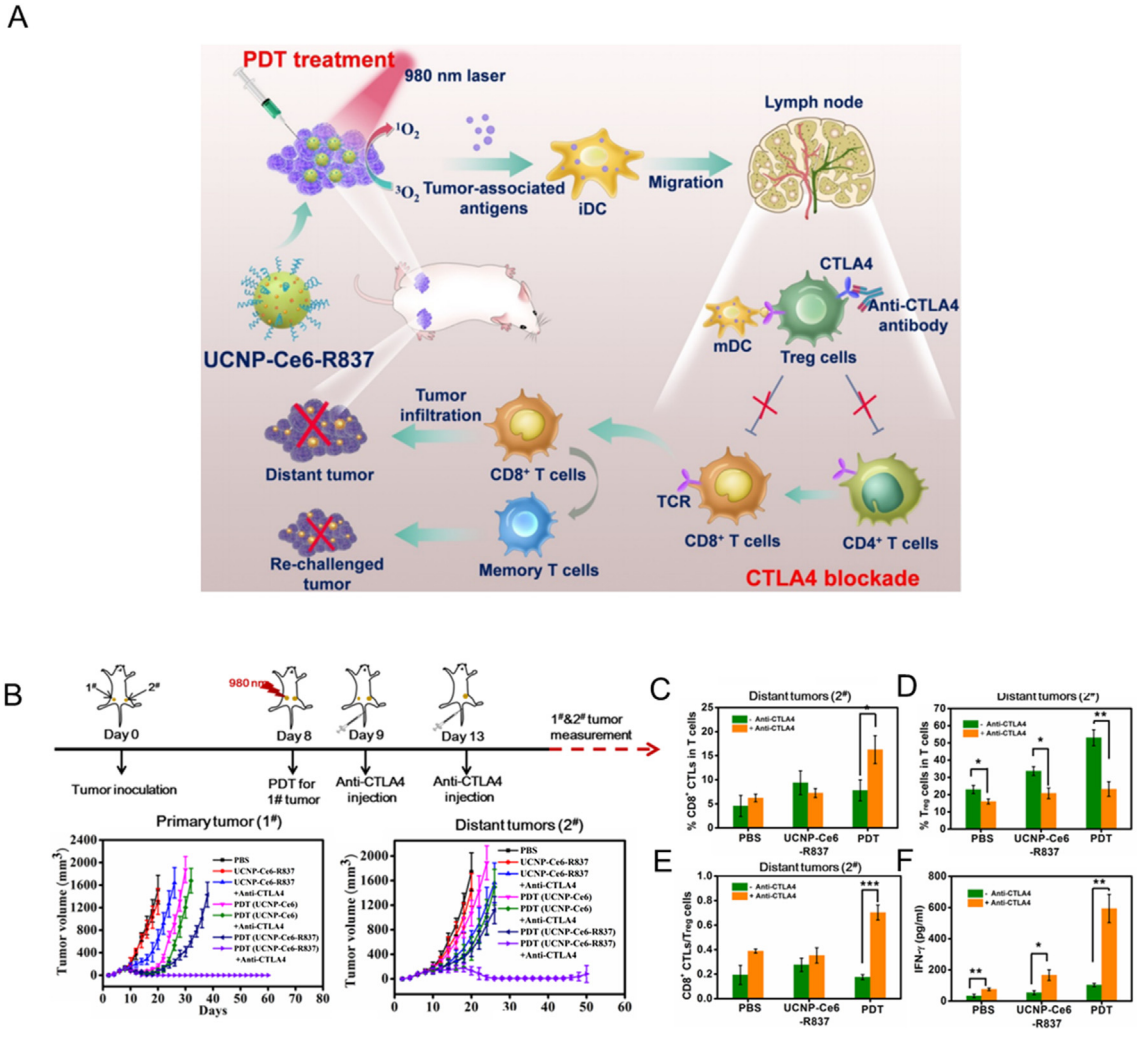

Figure 10 NIR triggered PDT combinatorial therapy with immune checkpoint blockade. (A) Schematic showing the anticancer function of UCNP-Ce6-R837. (B) tumor volume of primary and distant CT26 tumors following the indicated treatment; the level of $CD8^+$ CTL cells (C), Treg cells (D) and the $CD8^+$ CTL/Treg ratio (E) in distant tumors, and IFN-γ cytokine levels in sera (F) from mice following the indicated treatment. Reprinted with the permission from Ref. 215. Copyright © 2017 ACS Publishing Group.

opsonin, a type of complement, could adsorb onto nanoparticles to mediate the recognition and endocytosis of particles by phagocytic cells. After ingestion by phagocytes, nanomaterials may induce phagocytes to synthesize and secrete proinflammatory cytokines and chemokines to recruit immune cells, such as macrophages, DCs, and T cells. For example, in 2010, Yang et al.[213] reported an $[Gd@C_{82}(OH)_{22}]_n$ nanoparticles, which induced cytokine production (including IL-12p70), co-stimulatory molecule expression, and MHC molecule expression in DCs. Furthermore, mice immunized with OVA and $[Gd@C_{82}(OH)_{22}]_n$ presented a robust Th1 immune response. In 2017, Luo et al.[214] constructed novel polymeric PC7A nanoparticles, which were ultra-pH sensitive and had diameters of 20−50 nm for lymph node targeting. Using PC7A as a carrier without other immunostimulatory agents to deliver tumor antigens to lymph nodes potently inhibited the growth of melanoma and colon cancer. These PC7A nanoparticles were shown to regulate the immune response, including the promotion of DC maturation through the STING pathway.

The immunoregulatory function of nanomaterials is usually ignored in application of nanomaterials as drug delivery. Recently, consensus that lots of nanomaterials affect immune system has been reached. The influence on immune response of nanomaterials is diverse. Although we mainly introduced the immunostimulatory effect of nanomaterials, other nanomaterials that provoked inflammation or immunosuppression were reported. Large amount of immune evaluation of nanomaterials should be accumulated. The relationship between structure of nanomaterials and immunoregulatory function remains to be uncovered.

3.4. Combinatorial cancer immunotherapy enabled by nanomaterials

Based on the cancer−immunity cycle, successful cancer immunotherapies should focus on the following aspects.

(1) Making tumor antigens available for DCs. Apoptosis of cancer cells removes most antigens, and *in situ* ICD or exogenous cancer vaccines can retain or provide tumor antigens.
(2) Enhancing the immunogenicity of tumor antigens. Usually, tumor antigens have relatively low immunogenicity, making it difficult to trigger an antigen-specific immune response. Therefore, immunostimulatory agents such as CpG-ODN, R837, CDG, and Pam_3CSK_4 are necessary to enhance the immunogenicity of tumor antigens and increase the antigen-uptake of DCs.
(3) Co-delivery of tumor antigens and immunostimulatory agents to DCs. The simultaneous uptake of both tumor antigens and immunostimulatory agents by APCs will enhance the strength of antigen-specific immune responses.
(4) Enhancing the cross-presentation of tumor antigens by DCs. Targeting lymph nodes and the cytoplasmic delivery of tumor antigens in DCs are essential for enhancing cross-presentation efficiency, which is directly related to the strength of the cellular immune response.
(5) Overcoming the immunosuppressive microenvironment of cancer tissues. After activating and recruiting antigen-

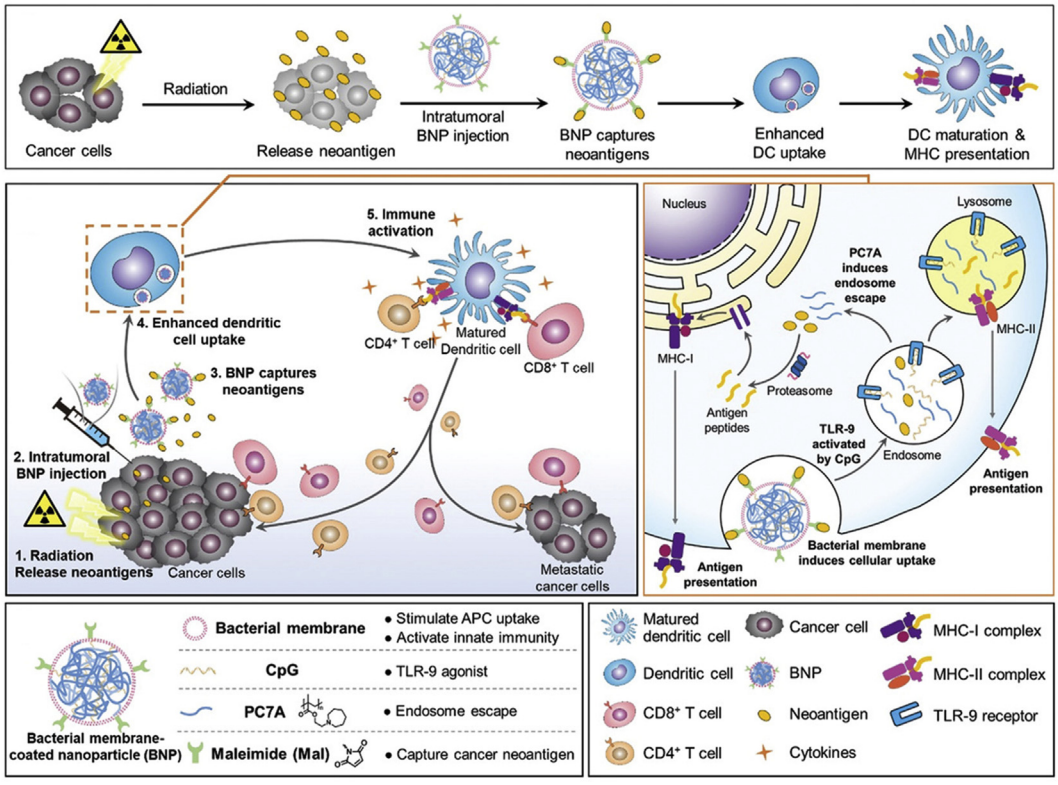

Figure 11 *In situ* vaccine elicited by combined RT + BNP. Reprinted with the permission from Ref. 217. Copyright © 2019 John Wiley and Sons Group.

specific CD8$^+$ T cells, the immunosuppressive microenvironment tends to trigger the dysfunction or exhaustion of CD8$^+$ T cells. Therefore, ICB inhibitors, IDO inhibitors, or other agents that can overcome the immunosuppressive microenvironment, have potential in cancer immunotherapy.

(6) Combination therapies may lead to additional or synergistic anticancer effects. However, the toxicity of combination therapies should be carefully evaluated and controlled.

Combination immunotherapies that act simultaneously on the different components detailed above, or on different steps of the cancer−immunity cycle, have an increased possibility of triggering robust antigen-specific cellular immunity. Nanomaterials, which act as carriers, ICD inducers, and immunomodulatory agents, have the potential to integrate different anticancer functions into a single platform and to achieve relatively efficient anticancer outcome.

Initially, nanomaterials were used to co-deliver tumor antigens and immunostimulatory agents for the development of potent anticancer vaccines in combination immunotherapies. For example, Xu et al.[127] in 2013 constructed lipid-calcium-phosphate (LCP) nanoparticles modified with mannose to target DCs, which were co-loaded with tyrosinase-related protein 2 (Trp 2) peptide as melanoma antigens and CPG ODN as an adjuvant.

More recently, nanomaterials equipped with inducers of ICD and immunostimulatory agents have been used in combination with ICB therapies. For example, in 2017, Chen et al.[145] prepared a nanosystem composed of PLGA loaded with ICG and R837. ICG generated a strong photothermal effect, which mediated the release of tumor antigens. R837, a robust TLR-7 agonist, potently activated DCs. Utilization of PLGA to co-deliver ICG and R837 was shown to induce the strongest effect on DC maturation and TNF-α production under 808 nm irradiation. Following combination treatment with aCTLA-4, PLGA-ICG-R837 with laser irradiation almost eradicated 4T1 and CT26 distant xenograft tumors, and efficiently inhibited the metastasis and recurrence of tumors. The inhibition of cancer growth, metastasis, and recurrence was enhanced by the activation and proliferation of CD4$^+$ and CD8$^+$ T cells, and a reduction of Treg cells. Thereafter, Xu et al.[215] constructed a multifunctional nanosystem combining upconversion nanoparticles (UCNPs), Ce6, R837, and aCTLA-4. The UCNPs were modified with amphiphilic polymers to load Ce6 and R837. UCNPs were able to absorb light at 980 nm and emit light at 550 nm to activate Ce6 and produce ROS. UCNP-Ce6-R837 was shown to potently induce DC maturation and pro-inflammatory cytokine secretion under 908 nm irradiation. Furthermore, UCNP-Ce6-R837 combined with systemic administration of aCTLA-4 robustly inhibited the growth of primary, distant, and metastatic tumors (Fig. 10).

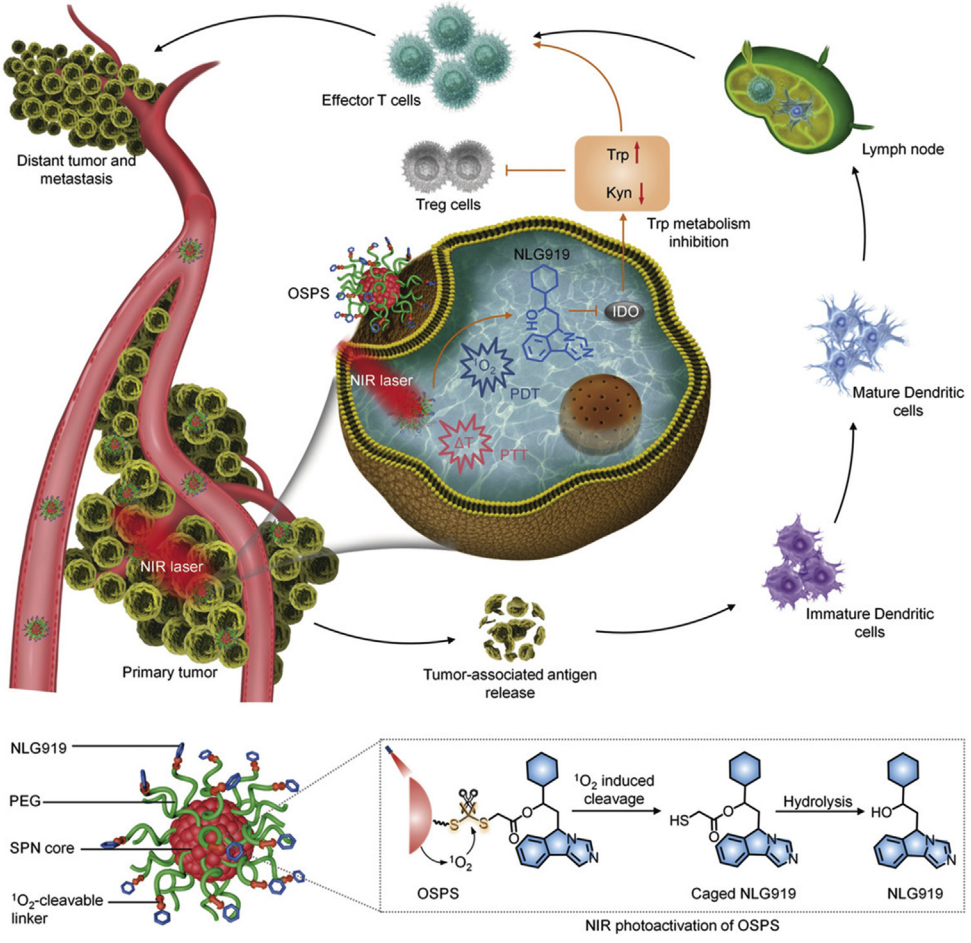

Figure 12 The scheme of OSPS mediated combinatory cancer therapy. Reprinted with the permission from Ref. 218. Copyright © 2019 John Wiley and Sons Group.

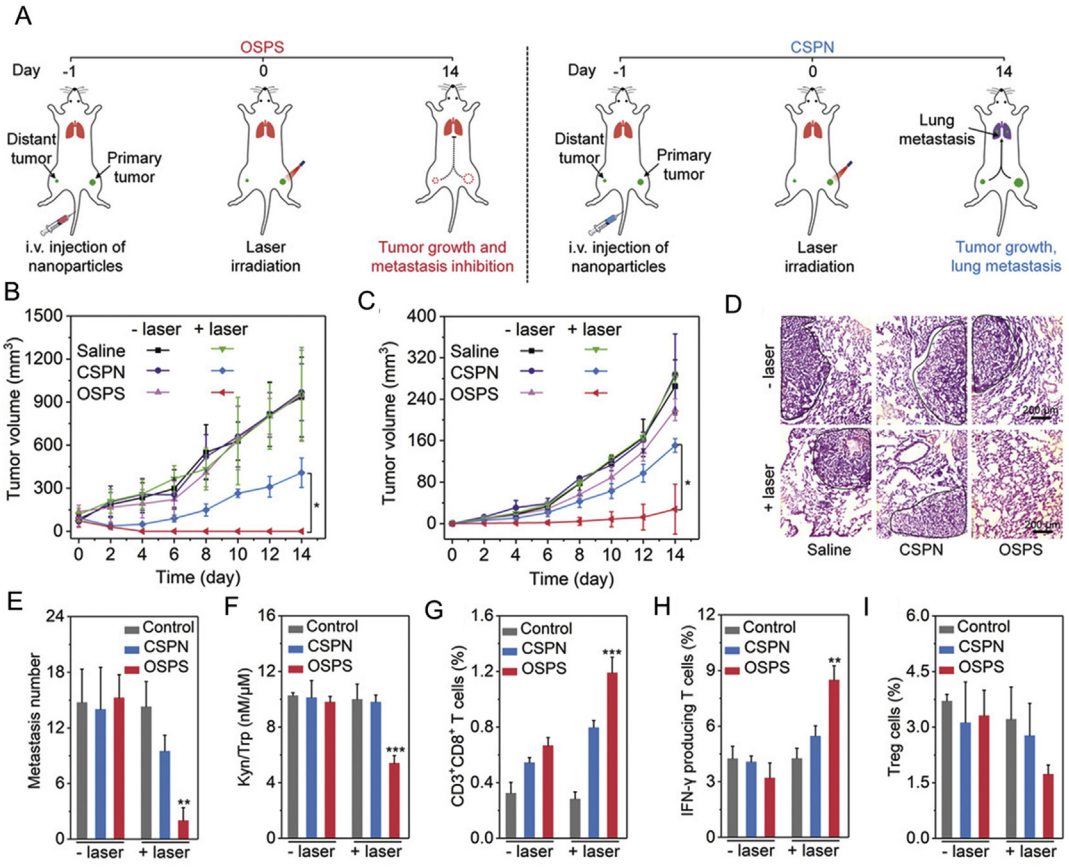

Figure 13 Anticancer immune response induced by OSPS. (A) OSPS-mediated tumor inhibition and lung metastasis. (B) Growth curves of primary tumors in 4T1 tumor-bearing mice. (C) Growth curves of distant tumors in 4T1 tumor-bearing mice. (D) H&E staining of lung metastasis in 4T1 tumor-bearing mice. (E) Number of metastatic nodules in 4T1 tumor-bearing mice (F) The Kyn/Trp ratio in primary tumors in 4T1 tumor-bearing mice. (G) Population of $CD3^+CD8^+$ T cells in distant tumors. (H) IFN-γ producing T-cells in distant tumors. (I) Treg cells in distant tumors. $^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, $n = 5$. CSPN, nanoparticles without NLG919. Reprinted with the permission from Ref. 218. Copyright © 2019 John Wiley and Sons Group.

Furthermore, Chen et al.[216] in 2019 combined enhanced radiotherapy, immunostimulatory agents, and aCTLA-4. PLGA was used to encapsulate R837 and catalase, which could convert tumor-rich H_2O_2 to O_2, thereby ameliorating the hypoxic environment of cancer tissues. PLGA-R837@cat nanoparticles under X-ray irradiation induced ICD and reverted the immunosuppressive environment, which further contributed to the therapeutic efficacy against cancer growth, metastasis, and recurrence. Recently, Patel et al.[217] constructed BNP nanoparticles by using PC7A nanoparticles as carriers to load CpG and bacterial membranes, meanwhile capturing tumor antigens released during radiation *via* a maleimide modification on bacterial membranes. This combination enhanced the antigen uptake and cross-presentation of DCs and robustly activated effector T cells to induce clear tumor regression (Fig. 11). Qin et al.[148] constructed cyclodextrin (CD)-based gel system, DOX/ICG/CpG-P-ss-M/CD, which was load with DOX, ICG and CpG-P-ss-M. CpG-P-ss-M was indicated polyamidoamine (PAMAM) dendrimer decorated with reductive 4-aminophenyl-α-D-mannopyranoside (MAN)−polyethylene glycol (PEG) chain and CpG. The DOX/ICG/CpG-P-ss-M/CD released tumor antigens by DOX treatment and PTT, meanwhile capturing the tumor antigens by CpG-P-ss-M nanoparticle to form *in situ* vaccine for inducing antigen uptake of DCs. Furthermore, DOX/ICG/CpG-P-ss-M/CD system induced the activation of DCs in spleen and the proliferation of $CD8^+$ T cells, and eventually inhibited the growth of primary and distant tumors.

In addition, nanomaterials that induce ICD are combined with immunostimulants. For example, Li et al.[218] developed an organic semiconducting pro-nano-stimulant (OSPS) with a semiconducting polymer nanomaterial as the core and an immunostimulant (NLG919) as the coating layer (Fig. 12). This OSPS showed excellent photothermal and photodynamic efficiency, which ensured the potent activation of $CD8^+$ T cells and inhibition of primary and distant tumors (Fig. 13).

4. Conclusions

The interaction of cancer with the immune system is complicated. Tumor formation usually requires long-term immune screening and an immune-tolerant microenvironment. Therefore, an individual's immune system may not be sufficient by itself to eliminate cancer cells. The use of external agents that reinitiate the cancer−immunity cycle at one or multiple steps is the basis of cancer immunotherapy. Restoring the cancer−immunity cycle includes the following key steps: making tumor antigens available for APCs, inducing the maturation of APCs, promoting the cross-presentation of APCs, and ameliorating the immunosuppressive microenvironment. Targeting multiple key points simultaneously

is an effective means to overcome compensation mechanisms and promote potent anticancer immunity.

Nanomaterials are used widely in the fields of diagnostics and drug delivery because of their controllable size, shape, and surface properties. Development and in-depth research on nanomaterials show that nanomaterials can not only be used for drug delivery, but also have versatile properties, such as their photothermal effect, photodynamic effect, ability to enhance radiotherapy, magnetic hyperthermia effect, and immunomodulatory effect. These properties allow nanomaterials to be used as a comprehensive platform to integrate diverse drugs or strategies focusing on different steps of cancer−immunity cycle, which promotes additional, or even synergistic anticancer outcomes. As excellent drug delivery platform, nanomaterials have the capacity to load and sustainably release of multiple immunomodulators simultaneously to cancer tissues or lymph nodes to potently activate the different processes of cancer−immunity cycle, like supply of tumor antigens, activation of APCs and inhibition of immune checkpoint or immunosuppressive regulatory immune cell. As functional nanomaterials, nanomaterials are able to trigger the ICD process of cancer cells, thereby inducing the uptake of immunogenic tumor antigens by APCs and the activation of APCs. As for immunomodulators, nanomaterials could function as adjuvant and directly induce the activaiton of inflammasome and production of stimulatory cytokines for activation of immune system and ease of immunosuppression. The three faces of nanomaterials make them excellent candidate for manually regulating cancer−immunity cycle. Moreover, nanomaterials can possess multiple roles at the same time, for example, functional nanomaterials are able to deliver small molecular immunomodulators.

5. Challenges and future perspectives

Nanomaterials have unique advantages in promoting cancer immunotherapy. In recent years, many basic scientific studies have been performed in this field. However, nanomaterial-assisted immunotherapy is still rarely used clinically. The main limitations include unclear mechanisms underlying the toxicity of nanomaterials, pharmacokinetics, and interactions with the immune system. Although the cytotoxicity and acute toxicity of nanomaterials have been systematically studied, the chronic toxicity of nanomaterials is often not addressed. Some nanomaterials easily accumulate in tissues, such as the liver and lungs, causing chronic inflammation. The pharmacokinetics of nanomaterials also need to be studied. For example, for how long are they retained in the body? Will they cause damage to metabolic organs? In addition, the relationship between nanomaterials and immunity remains unclear. Some nanomaterials promote inflammation, and some suppress immune responses. Therefore, each nanomaterial should be systematically evaluated to determine its toxicity, pharmacokinetics, and mechanisms of immune regulation before application. In addition, the stability of nanomaterials is also an important aspect that restricts their clinical applications. Many nanomaterials, especially inorganic nanomaterials, have poor stability in saline or serum and aggregate easily, which is unfavorable for clinical applications. Besides, the protein corona of nanomaterials has significant effects on the drug releasing capacity, stability, tissue distribution and pharmacokinetics. The different species of nanomaterials and diverse surface modifications on nanomaterials lead to different components of protein corona.

Except for these general limitations of nanomaterials, ICD nano-inducers possess their own problems. The most important issue of ICD nano-inducers is lack of standardized characterization and research on the ICD process mediated by nanomaterials. Currently, lots of nanomaterials-based PTAs, PSs and radiosensitizers are combined with immunotherapies, like ICBs, IDO inhibitors or immunostimulatory molecules. Although, these combinations achieve enhanced proliferation of $CD8^+$ T cells and significant inhibition of primary, distant and metastatic tumors, the immune related mechanisms are roughly studied. It's hard to differentiate the main cause of the activation of anticancer immune response. Is it derived from the ICD process induced by functional nanomaterials or because of the introduction of ICBs or immunostimulatory molecules? We are cautious about whether all nanomaterials-based PTAs or PSs can induce ICD. Detailed experimental evaluation needs to be performed to explain the structure−activity relationship of nanomaterials and ICD inducing capacity. Besides, currently designed nanomaterials targeting on several steps of cancer−immunity cycle often need complex composition and several steps of modifications or drug loading, which seriously hinders the clinical application of these systems. The multifunctional nanomaterials that could simultaneously possess better cancer targeting ability, ICD inducing capacity and immune regulatory potential should be identified and designed.

Increased knowledge of cancer immunology has resulted in the availability of several immunotherapeutic anticancer strategies, such as CAR-T and ICB therapy. However, our understanding of the immune environment in cancer tissues, and the relationship between the immune system and cancer remain incomplete. The low efficiency of CAR-T in solid tumors and the low response rate of ICB therapy remain to be solved. The identification and classification of cancer markers is likely to promote the use of cancer immunotherapy, for example, detecting the level of PD-L1 expression in cancer cells to determine the suitability of PD-L1 antibody treatments. Even though PD-L1 or PD-1 positivity is necessary for a good prognosis in response to ICB therapy, it is not a sufficient condition to guarantee its antitumor outcome. Cancer is commonly divided into "cold" or "hot" types. Hot tumors are rich in TILs, which are important biomarkers for ICB therapy. Activating these TILs may efficiently eliminate cancer cells. However, some studies have found that most of the TILs act on viruses, but not cancer cells[219]. These limitations of cancer immunotherapies highlight the need for further research, and emphasize that cancer immunotherapy is not a panacea. Some malignancies have achieved the ability to ignore immune killing during the long-term battle with the immune system. For example, the immune system is unable to identify and kill cancer cells that lack MHC I and meanwhile overexpress NK inhibitory biomarkers (such as HLA-E). Therefore, rational combinations of cancer immunotherapy with other traditional cancer theranostics, and the artificial transformation of effector immune cells may provide an efficient method of treating cancer.

Acknowledgments

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Author contributions

Under the supervision of Prof. Lin Mei and Prof. Dunwan Zhu, Qianqian Li summarized related literatures and wrote this review. Zhaoqing Shi, Zengzeng Wei and Fan Zhang helped investigate the literatures and checked the spelling and formatting errors of this review. All authors read and contributed to the manuscript.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *Ca - Cancer J Clin* 2019;**69**:7−34.
2. Liang C, Xu L, Song G, Liu Z. Emerging nanomedicine approaches fighting tumor metastasis: animal models, metastasis-targeted drug delivery, phototherapy, and immunotherapy. *Chem Soc Rev* 2016;**45**:6250−69.
3. Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. *Nature* 2011;**480**:480−9.
4. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer* 2012;**12**:252−64.
5. Sharma P, Allison JP. The future of immune checkpoint therapy. *Science* 2015;**348**:56−61.
6. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* 2010;**363**:711−23.
7. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med* 2012;**366**:2443−54.
8. June CH, O'Connor RS, Kawalekar OU, Ghassemi S, Milone MC. CAR T cell immunotherapy for human cancer. *Science* 2018;**359**:1361−5.
9. Porter DL, Levine BL, Kalos M, Bagg A, June CH. Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia. *N Engl J Med* 2011;**365**:725−33.
10. Grupp SA, Kalos M, Barrett D, Aplenc R, Porter DL, Rheingold SR, et al. Chimeric antigen receptor-modified T cells for acute lymphoid leukemia. *N Engl J Med* 2013;**368**:1509−18.
11. Newick K, O'Brien S, Moon E, Albelda SM. CAR T cell therapy for solid tumors. *Annu Rev Med* 2017;**68**:139−52.
12. Martins F, Sofiya L, Sykiotis GP, Lamine F, Maillard M, Fraga M, et al. Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. *Nat Rev Clin Oncol* 2019;**16**:563−80.
13. Schumacher TN, Schreiber RD. Neoantigens in cancer immunotherapy. *Science* 2015;**348**:69−74.
14. Ott PA, Hu Z, Keskin DB, Shukla SA, Sun J, Bozym DJ, et al. An immunogenic personal neoantigen vaccine for patients with melanoma. *Nature* 2017;**547**:217−21.
15. Rizvi NA, Hellmann MD, Snyder A, Kvistborg P, Makarov V, Havel JJ, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science* 2015;**348**:124−8.
16. Chan TA, Yarchoan M, Jaffee E, Swanton C, Quezada SA, Stenzinger A, et al. Development of tumor mutation burden as an immunotherapy biomarker: utility for the oncology clinic. *Ann Oncol* 2019;**30**:44−56.
17. Simoni Y, Becht E, Fehlings M, Loh CY, Koo SL, Teng KWW, et al. Bystander $CD8^+$ T cells are abundant and phenotypically distinct in human tumour infiltrates. *Nature* 2018;**557**:575−9.
18. Pigeon JC, Jegede O, Mahoney KM, Moreira RB, Novak J, Conen H. Impact of immune checkpoint protein expression in tumor cells and tumor infiltrating $CD8^+$ T cells on clinical benefit from PD-1 blockade in metastatic clear cell renal cell carcinoma (mccRCC). *J Clin Oncol* 2017;**35**:477.
19. Whiteside TL. The tumor microenvironment and its role in promoting tumor growth. *Oncogene* 2008;**27**:5904−12.
20. Chen DS, Mellman I. Oncology meets immunology: the cancer–immunity cycle. *Immunity* 2013;**39**:1−10.
21. Manieri NA, Chiang EY, Grogan JL. TIGIT: a key inhibitor of the cancer immunity cycle. *Trends Immunol* 2017;**38**:20−8.
22. Ellmark P, Mangsbo SM, Furebring C, Totterman TH, Norlen P. Kick-starting the cancer–immunity cycle by targeting CD40. *OncoImmunology* 2015;**4**:1011484.
23. Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American society of clinical oncology clinical practice guideline. *J Clin Oncol* 2018;**36**:1714−68.
24. Liu YH, Zang XY, Wang JC, Huang SS, Xu J, Zhang P. Diagnosis and management of immune related adverse events (irAEs) in cancer immunotherapy. *Biomed Pharmacother* 2019;**120**:109437.
25. Irvine DJ, Dane EL. Enhancing cancer immunotherapy with nanomedicine. *Nat Rev Immunol* 2020;**20**:321−34.
26. Li X, Wang X, Ito A. Tailoring inorganic nanoadjuvants towards next-generation vaccines. *Chem Soc Rev* 2018;**47**:4954−80.
27. Park W, Heo YJ, Han DK. New opportunities for nanoparticles in cancer immunotherapy. *Biomater Res* 2018;**22**:24.
28. Song W, Musetti SN, Huang L. Nanomaterials for cancer immunotherapy. *Biomaterials* 2017;**148**:16−30.
29. Fang J, Nakamura H, Maeda H. The EPR effect: unique features of tumor blood vessels for drug delivery factors involved and limitations and augmentation of the effect. *Adv Drug Deliv Rev* 2011;**63**:136−51.
30. Shi J, Kantoff PW, Wooster R, Farokhzad OC. Cancer nanomedicine: progress challenges and opportunities. *Nat Rev Cancer* 2017;**17**:20−37.
31. Sindhwani S, Syed AM, Ngai J, Kingston BR, Maiorino L, Rothschild J, et al. The entry of nanoparticles into solid tumours. *Nat Mater* 2020;**19**:566−75.
32. Price LSL, Stern ST, Deal AM, Kabanov AV, Zamboni WC. A reanalysis of nanoparticle tumor delivery using classical pharmacokinetic metrics. *Sci Adv* 2020;**6**:eaay9249.
33. Cheng W, Nie J, Gao N, Liu G, Tao W, Xiao X, et al. A multifunctional nanoplatform against multidrug resistant cancer: merging the best of targeted chemo/gene/photothermal therapy. *Adv Funct Mater* 2017;**27**:1704135.
34. Shi ZQ, Li QQ, Mei L. pH-Sensitive nanoscale materials as robust drug delivery systems for cancer therapy. *Chin Chem Lett* 2020;**31**:1345−56.
35. Ye X, Liang X, Chen Q, Miao Q, Chen X, Zhang X, et al. Surgical tumor-derived personalized photothermal vaccine formulation for cancer immunotherapy. *ACS Nano* 2019;**13**:2956−68.
36. Pan C, Ou M, Cheng Q, Zhou Y, Yu Y, Li Z, et al. Z-Scheme heterojunction functionalized pyrite nanosheets for modulating tumor microenvironment and strengthening photo/chemodynamic therapeutic effects. *Adv Funct Mater* 2019;**30**:1906466.
37. Zhang F, Li F, Lu GH, Nie W, Zhang L, Lv Y, et al. Engineering magnetosomes for ferroptosis/immunomodulation synergism in cancer. *ACS Nano* 2019;**13**:5662−73.
38. Fang RH, Kroll AV, Zhang L. Nanoparticle-based manipulation of antigen-presenting cells for cancer immunotherapy. *Small* 2015;**11**:5483−96.
39. Mantovani A, Romero P, Palucka AK, Marincola FM. Tumour immunity: effector response to tumour and role of the microenvironment. *Lancet* 2008;**371**:771−83.
40. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. *Cell* 2010;**140**:883−99.
41. Dunn GP, Bruce AT, Ikeda H, Old LJ, Schreiber RD. Cancer immunoediting: from immunosurveillance to tumor escape. *Nat Immunol* 2002;**3**:991−8.

42. Zitvogel L, Apetoh L, Ghiringhelli F, Andre F, Tesniere A, Kroemer G. The anticancer immune response: indispensable for therapeutic success?. *J Clin Invest* 2008;**118**:1991−2001.
43. Demaria O, Cornen S, Daeron M, Morel Y, Medzhitov R, Vivier E. Harnessing innate immunity in cancer therapy. *Nature* 2019;**574**:45−56.
44. Cerovic V, Houston S, Westlund J, Utriainen L, Davison E, Scott C, et al. Lymph-borne CD8 alpha$^+$ dendritic cells are uniquely able to cross-prime CD8$^+$ T cells with antigen acquired from intestinal epithelial cells. *Mucosal Immunol* 2014;**8**:38−48.
45. Chen JA, Li ZR, Huang H, Yang YZ, Ding QA, Mai JH, et al. Improved antigen cross-presentation by polyethyleneimine-based nanoparticles. *Int J Nanomed* 2011;**6**:77−84.
46. Beatty GL, Gladney WL. Immune escape mechanisms as a guide for cancer immunotherapy. *Clin Cancer Res* 2015;**21**:687−92.
47. Gavin D, Allen B, Hiroaki I, Lloyd O, Robert S. Cancer immunoediting: from immunosurveillance to tumor escape. *Nat Immunol* 2002;**3**:991−8.
48. DuPage M, Mazumdar C, Schmidt LM, Cheung AF, Jacks T. Expression of tumour-specific antigens underlies cancer immunoediting. *Nature* 2012;**482**:405−9.
49. Fukuda M. Possible roles of tumor-associated carbohydrate antigens. *Cancer Res* 1996;**56**:2237−44.
50. Paszek MJ, DuFort CC, Rossier O, Bainer R, Mouw JK, Godula K, et al. The cancer glycocalyx mechanically primes integrin-mediated growth and survival. *Nature* 2014;**511**:319−25.
51. Matsumoto A, Cabral H, Sato N, Kataoka K, Miyahara Y. Assessment of tumor metastasis by the direct determination of cell-membrane sialic acid expression. *Angew Chem Int Ed* 2010;**49**:5494−7.
52. Kufe DW. Mucins in cancer: function, prognosis and therapy. *Nat Rev Canc* 2009;**9**:874−85.
53. Chen JY, Tang YA, Huang SM, Juan HF, Wu LW, Sun YC, et al. A novel sialyltransferase inhibitor suppresses FAK/paxillin signaling and cancer angiogenesis and metastasis pathways. *Cancer Res* 2011;**71**:473−83.
54. Xiao H, Woods EC, Vukojicic P, Bertozzi CR. Precision glycocalyx editing as a strategy for cancer immunotherapy. *Proc Natl Acad Sci U S A* 2016;**113**:10304−9.
55. Paulson KG, Tegeder A, Willmes C, Iyer JG, Afanasiev OK, Schrama D, et al. Downregulation of MHC-I expression is prevalent but reversible in merkel cell carcinoma. *Canc Immunol Res* 2014;**2**:1071−9.
56. Angell TE, Lechner MG, Jang JK, LoPresti JS, Epstein AL. MHC class I loss is a frequent mechanism of immune escape in papillary thyroid cancer that is reversed by interferon and selumetinib treatment *in vitro*. *Clin Cancer Res* 2014;**20**:6034−44.
57. Vivier E, Tomasello E, Baratin M, Walzer T, Ugolini S. Functions of natural killer cells. *Nat Immunol* 2008;**9**:503−10.
58. Kochan G, Escors D, Breckpot K, Guerrero-Setas D. Role of non-classical MHC class I molecules in cancer immunosuppression. *OncoImmunology* 2013;**2**:e26491.
59. Kornmann M, Ishiwata T, Kleeff J, Beger HG, Korc M. Fas and Fas-ligand expression in human pancreatic cancer. *Ann Surg* 2000;**231**:368−79.
60. Ohta T, Elnemr A, Kitagawa H, Kayahara M, Takamura H, Fujimura T, et al. Fas ligand expression in human pancreatic cancer. *Oncol Rep* 2004;**12**:749−54.
61. Mariathasan S, Turley SJ, Nickles D, Castiglioni A, Yuen K, Wang Y, et al. TGFbeta attenuates tumour response to PD-L1 blockade by contributing to exclusion of T cells. *Nature* 2018;**554**:544−8.
62. Lamichhane P, Karyampudi L, Shreeder B, Krempski J, Bahr D, Daum J, et al. IL10 release upon PD-1 blockade sustains immunosuppression in ovarian cancer. *Cancer Res* 2017;**77**:6667−78.
63. Tauriello DVF, Palomo-Ponce S, Stork D, Berenguer-Llergo A, Badia-Ramentol J, Iglesias M, et al. TGFbeta drives immune evasion in genetically reconstituted colon cancer metastasis. *Nature* 2018;**554**:538−43.
64. Munn DH, Mellor AL. Indoleamine 2,3-dioxygenase and tumor-induced tolerance. *J Clin Invest* 2007;**117**:1147−54.
65. Uyttenhove C, Pilotte L, Theate I, Stroobant V, Colau D, Parmentier N, et al. Evidence for a tumoral immune resistance mechanism based on tryptophan degradation by indoleamine 2,3-dioxygenase. *Nat Med* 2003;**9**:1269−74.
66. Hodge DR, Hurt EM, Farrar WL. The role of IL-6 and STAT3 in inflammation and cancer. *Eur J Cancer* 2005;**41**:2502−12.
67. Kumari N, Dwarakanath BS, Das A, Bhatt AN. Role of interleukin-6 in cancer progression and therapeutic resistance. *Tumor Biol* 2016;**37**:11553−72.
68. Tsukamoto H, Fujieda K, Miyashita A, Fukushima S, Ikeda T, Kubo Y, et al. Combined blockade of IL6 and PD-1/PD-L1 signaling abrogates mutual regulation of their immunosuppressive effects in the tumor microenvironment. *Cancer Res* 2018;**78**:5011−22.
69. Llanes-Fernandez L, Alvarez-Goyanes RI, Arango-Prado MD, Alcocer-Gonzalez JM, Mojarrieta JC, Perez XE, et al. Relationship between IL-10 and tumor markers in breast cancer patients. *Breast* 2006;**15**:482−9.
70. Balkwill F. TNF-alpha in promotion and progression of cancer. *Cancer Metastasis Rev* 2006;**25**:409−16.
71. Rosenberg SA. IL-2: the first effective immunotherapy for human cancer. *J Immunol* 2014;**192**:5451−8.
72. Zitvogel L, Tahara H, Robbins PD, Storkus WJ, Clarke MR, Nalesnik MA, et al. Cancer immunotherapy of established tumors with IL-12. Effective delivery by genetically engineered fibroblasts. *J Immunol* 1995;**155**:1393−403.
73. Tahara H, Lotze MT. Antitumor effects of interleukin-12 (IL-12): applications for the immunotherapy and gene therapy of cancer. *Gene Ther* 1995;**2**:96−106.
74. Steel JC, Waldmann TA, Morris JC. Interleukin-15 biology and its therapeutic implications in cancer. *Trends Pharmacol Sci* 2012;**33**:35−41.
75. Beatty GL, Paterson Y. Regulation of tumor growth by IFN-gamma in cancer immunotherapy. *Immunol Res* 2001;**24**:201−10.
76. Dai S, Wei D, Wu Z, Zhou X, Wei X, Huang H, et al. Phase I clinical trial of autologous ascites-derived exosomes combined with GM-CSF for colorectal cancer. *Mol Ther* 2008;**16**:782−90.
77. Dranoff G. GM-CSF-based cancer vaccines. *Immunol Rev* 2002;**188**:147−54.
78. Kalluri R, Zeisberg M. Fibroblasts in cancer. *Nat Rev Cancer* 2006;**6**:392−401.
79. Alegre ML, Frauwirth KA, Thompson CB. T-cell regulation by CD28 and CTLA-4. *Nat Rev Immunol* 2001;**1**:220−8.
80. Chan DV, Gibson HM, Aufiero BM, Wilson AJ, Hafner MS, Mi QS, et al. Differential CTLA-4 expression in human CD4$^+$ *versus* CD8$^+$ T cells is associated with increased NFAT1 and inhibition of CD4$^+$ proliferation. *Gene Immun* 2014;**15**:25−32.
81. Sojka DK, Hughson A, Fowell DJ. CTLA-4 is required by CD4$^+$CD25$^+$ Treg to control CD4$^+$ T-cell lymphopenia-induced proliferation. *Eur J Immunol* 2009;**39**:1544−51.
82. Muenst S, Soysal SD, Gao F, Obermann EC, Oertli D, Gillanders WE. The presence of programmed death 1 (PD-1)-positive tumor-infiltrating lymphocytes is associated with poor prognosis in human breast cancer. *Breast Cancer Res Treat* 2013;**139**:667−76.
83. Konishi J, Yamazaki K, Azuma M, Kinoshita I, Dosaka-Akita H, Nishimura M. B7-h1 expression on non-small cell lung cancer cells and its relationship with tumor-infiltrating lymphocytes and their PD-1 expression. *Clin Cancer Res* 2004;**10**:5094−100.
84. Leung CS, Yang KY, Li XS, Chan VW, Ku MC, Waldmann H, et al. Single-cell transcriptomics reveal that PD-1 mediates immune tolerance by regulating proliferation of regulatory T cells. *Genome Med* 2018;**10**:71.
85. Coley WB. The treatment of malignant tumors by repeated inoculations of erysipelas. With a report of ten original cases. *Clin Orthop Relat Res 1991* 1893:3−11.

86. Dranoff G. Cytokines in cancer pathogenesis and cancer therapy. *Nat Rev Cancer* 2004;**4**:11−22.
87. Parton M, Gore M, Eisen T. Role of cytokine therapy in 2006 and beyond for metastatic renal cell cancer. *J Clin Oncol* 2006;**24**: 5584−92.
88. Halin C, Rondini S, Nilsson F, Berndt A, Kosmehl H, Zardi L, et al. Enhancement of the antitumor activity of interleukin-12 by targeted delivery to neovasculature. *Nat Biotechnol* 2002;**20**:264−9.
89. Dranoff G, Jaffee E, Lazenby A, Golumbek P, Levitsky H, Brose K, et al. Vaccination with irradiated tumor cells engineered to secrete murine granulocyte-macrophage colony-stimulating factor stimulates potent specific, and long-lasting anti-tumor immunity. *Proc Natl Acad Sci U S A* 1993;**90**:3539−43.
90. Cavallo F, Signorelli P, Giovarelli M, Musiani P, Modesti A, Brunda MJ, et al. Antitumor efficacy of adenocarcinoma cells engineered to produce interleukin 12 (IL-12) or other cytokines compared with exogenous IL-12. *J Natl Cancer Inst* 1997; **89**:1049−58.
91. Vacchelli E, Eggermont A, Sautes-Fridman C, Galon J, Zitvogel L, Kroemer G, et al. Trial watch Toll-like receptor agonists for cancer therapy. *OncoImmunology* 2013;**2**:e25238.
92. Wu JJ, Li WH, Chen PG, Zhang BD, Hu HG, Li QQ, et al. Targeting STING with cyclic di-GMP greatly augmented immune responses of glycopeptide cancer vaccines. *Chem Commun* 2018;**54**:9655−8.
93. Ramanjulu JM, Pesiridis GS, Yang JS, Concha N, Singhaus R, Zhang SY, et al. Design of amidobenzimidazole STING receptor agonists with systemic activity. *Nature* 2018;**564**:439−43.
94. Hargadon KM, Johnson CE, Williams CJ. Immune checkpoint blockade therapy for cancer: an overview of FDA-approved immune checkpoint inhibitors. *Int Immunopharm* 2018;**62**:29−39.
95. Abdollahpour-Alitappeh M, Lotfinia M, Gharibi T, Mardaneh J, Farhadihosseinabadi B, Larki P, et al. Antibody-drug conjugates (ADCs) for cancer therapy: strategies, challenges and successes. *J Cell Physiol* 2019;**234**:5628−42.
96. Two drugs for advanced HER2-positive breast cancer (Enhertu and Tukysa). *Med Lett Drugs Ther* 2020;**62**:182−4.
97. Margolin KA, Rayner AA, Hawkins MJ, Atkins MB, Dutcher JP, Fisher RI, et al. Interleukin-2 and lymphokine-activated killer cell therapy of solid tumors: analysis of toxicity and management guidelines. *J Clin Oncol* 1989;**7**:486−98.
98. Schmidt-Wolf IG, Negrin RS, Kiem HP, Blume KG, Weissman IL. Use of a SCID mouse/human lymphoma model to evaluate cytokine-induced killer cells with potent antitumor cell activity. *J Exp Med* 1991;**174**:139−49.
99. Rosenberg SA, Restifo NP, Yang JC, Morgan RA, Dudley ME. Adoptive cell transfer: a clinical path to effective cancer immunotherapy. *Nat Rev Cancer* 2008;**8**:299−308.
100. Rezvani K, Rouce R, Liu EL, Shpall E. Engineering natural killer cells for cancer immunotherapy. *Mol Ther* 2017;**25**:1769−81.
101. Themeli M, Kloss CC, Ciriello G, Fedorov VD, Perna F, Gonen M, et al. Generation of tumor-targeted human T lymphocytes from induced pluripotent stem cells for cancer therapy. *Nat Biotechnol* 2013;**31**:928−33.
102. Li Y, Hermanson DL, Moriarity BS, Kaufman DS. Human iPSC-derived natural killer cells engineered with chimeric antigen receptors enhance anti-tumor activity. *Cell Stem Cell* 2018;**23**: 181−92.
103. Cho JH, Collins JJ, Wong WW. Universal chimeric antigen receptors for multiplexed and logical control of T cell responses. *Cell* 2018; **173**:1426−38.
104. Rosenberg SA, Yang JC, Restifo NP. Cancer immunotherapy: moving beyond current vaccines. *Nat Med* 2004;**10**:909−15.
105. Hu Z, Ott PA, Wu CJ. Towards personalized, tumour-specific, therapeutic vaccines for cancer. *Nat Rev Immunol* 2018;**18**:168−82.
106. Sahin U, Derhovanessian E, Miller M, Kloke BP, Simon P, Lower M, et al. Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer. *Nature* 2017;**547**:222−6.
107. Krysko DV, Garg AD, Kaczmarek A, Krysko O, Agostinis P, Vandenabeele P. Immunogenic cell death and DAMPs in cancer therapy. *Nat Rev Cancer* 2012;**12**:860−75.
108. Tesniere A, Panaretakis T, Kepp O, Apetoh L, Ghiringhelli F, Zitvogel L, et al. Molecular characteristics of immunogenic cancer cell death. *Cell Death Differ* 2008;**15**:3−12.
109. Obeid M, Tesniere A, Ghiringhelli F, Fimia GM, Apetoh L, Perfettini JL, et al. Calreticulin exposure dictates the immunogenicity of cancer cell death. *Nat Med* 2007;**13**:54−61.
110. Maeda H. The enhanced permeability and retention (EPR) effect in tumor vasculature: the key role of tumor-selective macromolecular drug targeting. *Adv Enzym Regul* 2001;**41**:189−207.
111. Jiang H, Wang Q, Sun X. Lymph node targeting strategies to improve vaccination efficacy. *J Control Release* 2017;**267**:47−56.
112. Reddy ST, van der Vlies AJ, Simeoni E, Angeli V, Randolph GJ, O'Neill CP, et al. Exploiting lymphatic transport and complement activation in nanoparticle vaccines. *Nat Biotechnol* 2007;**25**: 1159−64.
113. Yao H, Ng SS, Huo LF, Chow BKC, Shen Z, Yang M, et al. Effective melanoma immunotherapy with interleukin-2 delivered by a novel polymeric nanoparticle. *Mol Cancer Therapeut* 2011;**10**:1082−92.
114. Tagalakis AD, Grosse SM, Meng QH, Mustapa MFM, Kwok A, Salehi SE, et al. Integrin-targeted nanocomplexes for tumour specific delivery and therapy by systemic administration. *Biomaterials* 2011; **32**:1370−6.
115. Zhang Y, Li N, Suh H, Irvine DJ. Nanoparticle anchoring targets immune agonists to tumors enabling anti-cancer immunity without systemic toxicity. *Nat Commun* 2018;**9**:6.
116. Nakamura T, Miyabe H, Hyodo M, Sato Y, Hayakawa Y, Harashima H. Liposomes loaded with a STING pathway ligand, cyclic di-GMP, enhance cancer immunotherapy against metastatic melanoma. *J Control Release* 2015;**216**:149−57.
117. Nuhn L, De Koker S, Van Lint S, Zhong ZF, Catani JP, Combes F, et al. Nanoparticle-conjugate TLR7/8 agonist localized immunotherapy provokes safe antitumoral responses. *Adv Mater* 2018;**30**: 1803397.
118. Schmid D, Park CG, Hartl CA, Subedi N, Cartwright AN, Puerto RB, et al. T cell-targeting nanoparticles focus delivery of immunotherapy to improve antitumor immunity. *Nat Commun* 2017;**8**:1747.
119. Xiao ZC, Su ZW, Han SS, Huang JS, Lin LT, Shoai XT. Dual pH-sensitive nanodrug blocks PD-1 immune checkpoint and uses T cells to deliver NF-kappa B inhibitor for antitumor immunotherapy. *Sci Adv* 2020;**6**:eaay7785.
120. Wang C, Ye YQ, Hochu GM, Sadeghifar H, Gu Z. Enhanced cancer immunotherapy by microneedle patch-assisted delivery of anti-PD1 antibody. *Nano Lett* 2016;**16**:2334−40.
121. Bu JY, Nair A, Iida M, Jeong WJ, Poellmann MJ, Mudd K, et al. An avidity-based PD-L1 antagonist using nanoparticle-antibody conjugates for enhanced immunotherapy. *Nano Lett* 2020;**20**:4901−9.
122. Zhao P, Atanackovic D, Dong SY, Yagita HD, He X, Chen MN. An anti-programmed death-1 antibody (alpha PD-1) fusion protein that self-assembles into a multivalent and functional alpha PD-1 nanoparticle. *Mol Pharm* 2017;**14**:1494−500.
123. Mi Y, Smith CC, Yang FF, Qi YF, Roche KC, Serody JS, et al. A dual immunotherapy nanoparticle improves T-cell activation and cancer immunotherapy. *Adv Mater* 2018;**30**:e1706098.
124. Fan YC, Moon JJ. Nanoparticle drug delivery systems designed to improve cancer vaccines and immunotherapy. *Vaccines-Basel* 2015; **3**:662−85.
125. Kapadia CH, Tian SM, Perry JL, Sailer D, Luft JC, DeSimone JM. Extending antigen release from particulate vaccines results in enhanced antitumor immune response. *J Control Release* 2018;**269**: 393−404.
126. Zhang ZP, Tongchusak S, Mizukami Y, Kang YJ, Ioji T, Touma M, et al. Induction of anti-tumor cytotoxic T cell responses through PLGA-nanoparticle mediated antigen delivery. *Biomaterials* 2011; **32**:3666−78.

127. Xu ZH, Ramishetti S, Tseng YC, Guo ST, Wang YH, Huang L. Multifunctional nanoparticles co-delivering Trp 2 peptide and CpG adjuvant induce potent cytotoxic T-lymphocyte response against melanoma and its lung metastasis. *J Control Release* 2013;**172**: 259−65.
128. Lu Y, Yang YN, Gu ZY, Zhang J, Song H, Xiang GY, et al. Glutathione-depletion mesoporous organosilica nanoparticles as a self-adjuvant and co-delivery platform for enhanced cancer immunotherapy. *Biomaterials* 2018;**175**:82−92.
129. Neek M, Tucker JA, Kim TI, Molino NM, Nelson EL, Wang SW. Co-delivery of human cancer-testis antigens with adjuvant in protein nanoparticles induces higher cell-mediated immune responses. *Biomaterials* 2018;**156**:194−203.
130. Joshi MD, Unger WJ, Storm G, van Kooyk Y, Mastrobattista E. Targeting tumor antigens to dendritic cells using particulate carriers. *J Control Release* 2012;**161**:25−37.
131. Lee IH, Kwon HK, An S, Kim D, Kim S, Yu MK, et al. Imageable antigen-presenting gold nanoparticle vaccines for effective cancer immunotherapy *in vivo*. *Angew Chem Int Ed* 2012;**51**:8800−5.
132. Rosalia RA, Cruz LJ, van Duikeren S, Tromp AT, Silva AL, Jiskoot W, et al. CD40-targeted dendritic cell delivery of PLGA-nanoparticle vaccines induce potent anti-tumor responses. *Biomaterials* 2015;**40**:88−97.
133. Pei MY, Liang JY, Zhang C, Wang XL, Zhang CNA, Ma GL, et al. Chitosan/calcium phosphates nanosheet as a vaccine carrier for effective cross-presentation of exogenous antigens. *Carbohydr Polym* 2019;**224**:115172.
134. Liu JL, Liu XX, Han YF, Zhang J, Liu D, Ma GL, et al. Nanovaccine incorporated with hydroxychloroquine enhances antigen cross-presentation and promotes antitumor immune responses. *Acs Appl Mater Inter* 2018;**10**:30983−93.
135. Xu J, Wang H, Xu LG, Chao Y, Wang CY, Han X, et al. Nanovaccine based on a protein-delivering dendrimer for effective antigen cross-presentation and cancer immunotherapy. *Biomaterials* 2019;**207**: 1−9.
136. Kuai R, Ochyl LJ, Bahjat KS, Schwendeman A, Moon JJ. Designer vaccine nanodiscs for personalized cancer immunotherapy. *Nat Mater* 2017;**16**:489−96.
137. Shukla GS, Sun YJ, Pero SC, Sholler GS, Krag DN. Immunization with tumor neoantigens displayed on T7 phage nanoparticles elicits plasma antibody and vaccine-draining lymph node B cell responses. *J Immunol Methods* 2018;**460**:51−62.
138. Lynn GM, Sedlik C, Baharom F, Zhu YL, Ramirez-Valdez RA, Coble VL, et al. Peptide-TLR-7/8a conjugate vaccines chemically programmed for nanoparticle self-assembly enhance CD8 T-cell immunity to tumor antigens. *Nat Biotechnol* 2020;**38**:320−32.
139. Wang XL, Wang N, Yang Y, Wang XX, Liang JY, Tian XX, et al. Polydopamine nanoparticles carrying tumor cell lysate as a potential vaccine for colorectal cancer immunotherapy. *Biomater Sci* 2019;**7**: 3062−75.
140. Fang RH, Hu CMJ, Luk BT, Gao WW, Copp JA, Tai YY, et al. Cancer cell membrane-coated nanoparticles for anticancer vaccination and drug delivery. *Nano Lett* 2014;**14**:2181−8.
141. Ochyl LJ, Bazzill JD, Park C, Xu Y, Kuai R, Moon JJ. PEGylated tumor cell membrane vesicles as a new vaccine platform for cancer immunotherapy. *Biomaterials* 2018;**182**:157−66.
142. Yang R, Xu J, Xu LG, Sun XQ, Chen Q, Zhao YH, et al. Cancer cell membrane-coated adjuvant nanoparticles with mannose modification for effective anticancer vaccination. *ACS Nano* 2018;**12**:5121−9.
143. Liu WL, Zou MZ, Liu T, Zeng JY, Li X, Yu WY, et al. Cytomembrane nanovaccines show therapeutic effects by mimicking tumor cells and antigen presenting cells. *Nat Commun* 2019;**10**:3199.
144. Li W, Yang J, Luo L, Jiang M, Qin B, Yin H, et al. Targeting photodynamic and photothermal therapy to the endoplasmic reticulum enhances immunogenic cancer cell death. *Nat Commun* 2019;**10**: 3349.
145. Chen Q, Xu LG, Liang C, Wang C, Peng R, Liu Z. Photothermal therapy with immune-adjuvant nanoparticles together with checkpoint blockade for effective cancer immunotherapy. *Nat Commun* 2016;**7**:13193.
146. Zhang F, Lu G, Wen X, Li F, Ji X, Li Q, et al. Magnetic nanoparticles coated with polyphenols for spatio-temporally controlled cancer photothermal/immunotherapy. *J Control Release* 2020;**326**:131−9.
147. Xu T, Ma YY, Yuan QL, Hu HX, Hu XK, Qian ZY, et al. Enhanced ferroptosis by oxygen-boosted phototherapy based on a 2-in-1 nanoplatform of ferrous hemoglobin for tumor synergistic therapy. *ACS Nano* 2020;**14**:3414−25.
148. Qin L, Cao J, Shao K, Tong F, Yang ZH, Lei T, et al. A tumor-to-lymph procedure navigated versatile gel system for combinatorial therapy against tumor recurrence and metastasis. *Sci Adv* 2020;**6**: eabb3116.
149. Min YZ, Roche KC, Tian SM, Eblan MJ, McKinnon KP, Caster JM, et al. Antigen-capturing nanoparticles improve the abscopal effect and cancer immunotherapy. *Nat Nanotechnol* 2017; **12**:877−82.
150. Yuan HF, Jiang W, von Roemeling CA, Qie YQ, Liu XJ, Chen YX, et al. Multivalent bi-specific nanobioconjugate engager for targeted cancer immunotherapy. *Nat Nanotechnol* 2017;**12**:763−9.
151. Duan XP, Chan C, Lin WB. Nanoparticle-mediated immunogenic cell death enables and potentiates cancer immunotherapy. *Angew Chem Int Ed* 2019;**58**:670−80.
152. Yang ZZ, Sun ZR, Ren Y, Chen X, Zhang W, Zhu XH, et al. Advances in nanomaterials for use in photothermal and photodynamic therapeutics. *Mol Med Rep* 2019;**20**:5−15.
153. Doughty ACV, Hoover AR, Layton E, Murray CK, Howard EW, Chen WR. Nanomaterial applications in photothermal therapy for cancer. *Materials* 2019;**12**.
154. Hu JJ, Cheng YJ, Zhang XZ. Recent advances in nanomaterials for enhanced photothermal therapy of tumors. *Nanoscale* 2018;**10**: 22657−72.
155. Zhang YJ, Zhan XL, Xiong J, Peng SS, Huang W, Joshi R, et al. Temperature-dependent cell death patterns induced by functionalized gold nanoparticle photothermal therapy in melanoma cells. *Sci Rep* 2018;**8**:8720.
156. Zhu XJ, Feng W, Chang J, Tan YW, Li JC, Chen M, et al. Temperature-feedback upconversion nanocomposite for accurate photothermal therapy at facile temperature. *Nat Commun* 2016;**7**: 10437.
157. Deng XY, Guan W, Qing XC, Yang WB, Que YM, Tan L, et al. Ultrafast low-temperature photothermal therapy activates autophagy and recovers immunity for efficient antitumor treatment. *Acs Appl Mater Inter* 2020;**12**:4265−75.
158. Sweeney EE, Cano-Mejia J, Fernandes R. Photothermal therapy generates a thermal window of immunogenic cell death in neuroblastoma. *Small* 2018;**14**:1800678.
159. Wang C, Xu LG, Liang C, Xiang J, Peng R, Liu Z. Immunological responses triggered by photothermal therapy with carbon nanotubes in combination with anti-CTLA-4 therapy to inhibit cancer metastasis. *Adv Mater* 2014;**26**:8154−62.
160. Guo LR, Yan DD, Yang DF, Li YJ, Wang XD, Zalewski O, et al. Combinatorial photothermal and immuno cancer therapy using chitosan-coated hollow copper sulfide nanoparticles. *ACS Nano* 2014;**8**:5670−81.
161. Zhang D, Wu TT, Qin XY, Qiao Q, Shang LH, Song QL, et al. Intracellularly generated immunological gold nanoparticles for combinatorial photothermal therapy and immunotherapy against tumor. *Nano Lett* 2019;**19**:6635−46.
162. Chen JM, Fan TJ, Xie ZJ, Zeng QQ, Xue P, Zheng TT, et al. Advances in nanomaterials for photodynamic therapy applications: status and challenges. *Biomaterials* 2020;**237**:119827.
163. Korbelik M. Induction of tumor immunity by photodynamic therapy. *J Clin Laser Med Surg* 1996;**14**:329−34.
164. Castano AP, Mroz P, Hamblin MR. Photodynamic therapy and anti-tumour immunity. *Nat Rev Cancer* 2006;**6**:535−45.
165. Thong PSP, Ong KW, Goh NSG, Kho KW, Manivasager V, Bhuvaneswari R, et al. Photodynamic-therapy-activated immune

response against distant untreated tumours in recurrent angiosarcoma. *Lancet Oncol* 2007;**8**:950−2.
166. Garg AD, Agostinis P. ER stress autophagy and immunogenic cell death in photodynamic therapy-induced anti-cancer immune responses. *Photochem Photobiol Sci* 2014;**13**:474−87.
167. Zheng YH, Yin GF, Le V, Zhang AL, Chen SY, Liang X, et al. Photodynamic-therapy activates immune response by disrupting immunity homeostasis of tumor cells which generates vaccine for cancer therapy. *Int J Biol Sci* 2016;**12**:120−32.
168. Hong EJ, Choi DG, Shim MS. Targeted and effective photodynamic therapy for cancer using functionalized nanomaterials. *Acta Pharm Sin B* 2016;**6**:297−307.
169. Vankayala R, Huang YK, Kalluru P, Chiang CS, Hwang KC. First demonstration of gold nanorods-mediated photodynamic therapeutic destruction of tumors *via* near infra-red light activation. *Small* 2014;**10**:1612−22.
170. Murakami T, Nakatsuji H, Inada M, Matoba Y, Umeyama T, Tsujimoto M, et al. Photodynamic and photothermal effects of semiconducting and metallic-enriched single-walled carbon nanotubes. *J Am Chem Soc* 2012;**134**:17862−5.
171. Mroz P, Xia YM, Asanuma D, Konopko A, Zhiyentayev T, Huang YY, et al. Intraperitoneal photodynamic therapy mediated by a fullerene in a mouse model of abdominal dissemination of colon adenocarcinoma. *Nanomed Nanotechnol* 2011;**7**:965−74.
172. Wang L, Shi JJ, Liu RY, Liu Y, Zhang J, Yu XY, et al. Photodynamic effect of functionalized single-walled carbon nanotubes: a potential sensitizer for photodynamic therapy. *Nanoscale* 2014;**6**:4642−51.
173. Wang H, Yang XZ, Shao W, Chen SC, Xie JF, Zhang XD, et al. Ultrathin black phosphorus nanosheets for efficient singlet oxygen generation. *J Am Chem Soc* 2015;**137**:11376−82.
174. He ME, Chen YA, Tao C, Tian QQ, An L, Lin JM, et al. Mn-porphyrin-based metal-organic framework with high longitudinal relaxivity for magnetic resonance imaging guidance and oxygen self-supplementing photodynamic therapy. *ACS Appl Mater Interfaces* 2019;**11**:41946−56.
175. Park J, Jiang Q, Feng DW, Mao LQ, Zhou HC. Size-controlled synthesis of porphyrinic metal-organic framework and functionalization for targeted photodynamic therapy. *J Am Chem Soc* 2016;**138**:3518−25.
176. Lu KD, He CB, Lin WB. Nanoscale metal-organic framework for highly effective photodynamic therapy of resistant head and neck cancer. *J Am Chem Soc* 2014;**136**:16712−5.
177. Lu KD, He CB, Lin WB. A chlorin-based nanoscale metal-organic framework for photodynamic therapy of colon cancers. *J Am Chem Soc* 2015;**137**:7600−3.
178. Secret E, Maynadier M, Gallud A, Chaix A, Bouffard E, Gary-Bobo M, et al. Two-photon excitation of porphyrin-functionalized porous silicon nanoparticles for photodynamic therapy. *Adv Mater* 2014;**26**:7643−8.
179. Dayal S, Burda C. Semiconductor quantum dots as two-photon sensitizers. *J Am Chem Soc* 2008;**130**:2890−1.
180. Lan GX, Ni KY, Xu ZW, Veroneau SS, Song Y, Lin WB. Nanoscale metal-organic framework overcomes hypoxia for photodynamic therapy primed cancer immunotherapy. *J Am Chem Soc* 2018;**140**:5670−3.
181. Zhang M, Wang WT, Wu F, Zheng T, Ashley J, Mohammadniaei M, et al. Biodegradable poly(gamma-glutamic acid)@glucose oxidase@carbon dot nanoparticles for simultaneous multimodal imaging and synergetic cancer therapy. *Biomaterials* 2020;**252**:120106.
182. Song G, Cheng L, Chao Y, Yang K, Liu Z. Emerging nanotechnology and advanced materials for cancer radiation therapy. *Adv Mater* 2017;**29**:1700996.
183. Coulter JA, Hyland WB, Nicol J, Currell FJ. Radiosensitising nanoparticles as novel cancer therapeuticspipe dream or realistic prospect?. *Clin Oncol* 2013;**25**:593−603.
184. Her S, Jaffray DA, Allen C. Gold nanoparticles for applications in cancer radiotherapy: mechanisms and recent advancements. *Adv Drug Deliv Rev* 2017;**109**:84−101.
185. Sancey L, Lux F, Kotb S, Roux S, Dufort S, Bianchi A, et al. The use of theranostic gadolinium-based nanoprobes to improve radiotherapy efficacy. *Br J Radiol* 2014;**87**:20140134.
186. Chen YY, Li N, Wang JB, Zhang X, Pan W, Yu LH, et al. Enhancement of mitochondrial ROS accumulation and radiotherapeutic efficacy using a Gd-doped titania nanosensitizer. *Theranostics* 2019;**9**:167−78.
187. Ma M, Huang Y, Chen HR, Jia XQ, Wang SG, Wang ZZ, et al. Bi2S3-embedded mesoporous silica nanoparticles for efficient drug delivery and interstitial radiotherapy sensitization. *Biomaterials* 2015;**37**:447−55.
188. Ni KY, Lan GX, Chan C, Quigley B, Lu KD, Aung T, et al. Nanoscale metal-organic frameworks enhance radiotherapy to potentiate checkpoint blockade immunotherapy. *Nat Commun* 2018;**9**:2351.
189. Retif P, Pinel S, Toussaint M, Frochot C, Chouikrat R, Bastogne T, et al. Nanoparticles for radiation therapy enhancement: the key parameters. *Theranostics* 2015;**5**:1030−45.
190. Yi X, Chen L, Zhong XY, Gao RL, Qian YT, Wu F, et al. Core-shell Au@MnO2 nanoparticles for enhanced radiotherapy *via* improving the tumor oxygenation. *Nano Res* 2016;**9**:3267−78.
191. Song G, Liang C, Yi X, Zhao Q, Cheng L, Yang K, et al. Perfluorocarbon-loaded hollow Bi_2Se_3 nanoparticles for timely supply of oxygen under near-infrared light to enhance the radiotherapy of cancer. *Adv Mater* 2016;**28**:2716−23.
192. Jeong H, Bok S, Hong BJ, Choi HS, Ahn GO. Radiation-induced immune responses: mechanisms and therapeutic perspectives. *Blood Res* 2016;**51**:157−63.
193. Reits EA, Hodge JW, Herberts CA, Groothuis TA, Chakraborty M, Wansley EK, et al. Radiation modulates the peptide repertoire enhances MHC class I expression and induces successful antitumor immunotherapy. *J Exp Med* 2006;**203**:1259−71.
194. Formenti SC, Demaria S. Systemic effects of local radiotherapy. *Lancet Oncol* 2009;**10**:718−26.
195. Ranji-Burachaloo H, Gurr PA, Dunstan DE, Qiao GG. Cancer treatment through nanoparticle-facilitated Fenton reaction. *ACS Nano* 2018;**12**:11819−37.
196. Zhang C, Bu WB, Ni DL, Zhang SJ, Li Q, Yao ZW, et al. Synthesis of iron nanometallic glasses and their application in cancer therapy by a localized fenton reaction. *Angew Chem Int Ed* 2016;**55**:2101−6.
197. Ying W, Zhang Y, Gao W, Cai X, Wang G, Wu X, et al. Hollow magnetic nanocatalysts drive starvation-chemodynamic-hyperthermia synergistic therapy for tumor. *ACS Nano* 2020;**14**:9662−74.
198. Llabani E, Hicklin RW, Lee HY, Motika SE, Crawford LA, Weerapana E, et al. Diverse compounds from pleuromutilin lead to a thioredoxin inhibitor and inducer of ferroptosis. *Nat Chem* 2019;**11**:521−32.
199. Yang Y, Tian Q, Wu S, Li Y, Yang K, Yan Y, et al. Blue light-triggered Fe^{2+}-release from monodispersed ferrihydrite nanoparticles for cancer iron therapy. *Biomaterials* 2021;**271**:120739.
200. Kim SE, Zhang L, Ma K, Riegman M, Chen F, Ingold I, et al. Ultrasmall nanoparticles induce ferroptosis in nutrient-deprived cancer cells and suppress tumour growth. *Nat Nanotechnol* 2016;**11**:977−85.
201. Wang S, Li F, Qiao R, Hu X, Liao H, Chen L, et al. Arginine-rich manganese silicate nanobubbles as a ferroptosis-Inducing agent for tumor-targeted theranostics. *ACS Nano* 2018;**12**:12380−92.
202. Yu B, Choi B, Li W, Kim DH. Magnetic field boosted ferroptosis-like cell death and responsive MRI using hybrid vesicles for cancer immunotherapy. *Nat Commun* 2020;**11**:3637.
203. Kumar CSSR, Mohammad F. Magnetic nanomaterials for hyperthermia-based therapy and controlled drug delivery. *Adv Drug Deliv Rev* 2011;**63**:789−808.
204. Toraya-Brown S, Sheen MR, Zhang PS, Chen L, Baird JR, Demidenko E, et al. Local hyperthermia treatment of tumors induces $CD8^+$ T cell-mediated resistance against distal and secondary tumors. *Nanomed Nanotechnol* 2014;**10**:1273−85.

205. Chao Y, Chen GB, Liang C, Xu J, Dong ZL, Han X, et al. Iron nanoparticles for low-power local magnetic hyperthermia in combination with immune checkpoint blockade for systemic antitumor therapy. *Nano Lett* 2019;**19**:4287−96.
206. Oyewumi MO, Kumar A, Cui ZR. Nano-microparticles as immune adjuvants: correlating particle sizes and the resultant immune responses. *Expert Rev Vaccines* 2010;**9**:1095−107.
207. Zhu MT, Wang RF, Nie GJ. Applications of nanomaterials as vaccine adjuvants. *Hum Vaccines Immunother* 2014;**10**:2761−74.
208. Li HF, Willingham SB, Ting JPY, Re F. Cutting edge: inflammasome activation by alum and alum's adjuvant effect are mediated by NLRP3. *J Immunol* 2008;**181**:17−21.
209. Reisetter AC, Stebounova LV, Baltrusaitis J, Powers L, Gupta A, Grassian VH, et al. Induction of inflammasome-dependent pyroptosis by carbon black nanoparticles. *J Biol Chem* 2011;**286**:21844−52.
210. Dostert C, Petrilli V, Van Bruggen R, Steele C, Mossman BT, Tschopp J. Innate immune activation through Nalp3 inflammasome sensing of asbestos and silica. *Science* 2008;**320**:674−7.
211. Wang XP, Li X, Yoshiyuki K, Watanabe Y, Sogo Y, Ohno T, et al. Comprehensive mechanism analysis of mesoporous-silica-nanoparticle-induced cancer immunotherapy. *Adv Healthc Mater* 2016;**5**:1169−76.
212. Morishige T, Yoshioka Y, Tanabe A, Yao X, Tsunoda S, Tsutsumi Y, et al. Titanium dioxide induces different levels of IL-1 beta production dependent on its particle characteristics through caspase-1 activation mediated by reactive oxygen species and cathepsin B. *Biochem Biophys Res Commun* 2010;**392**:160−5.
213. Yang D, Zhao YL, Guo H, Li YN, Tewary P, Xing GM, et al. [Gd@$C_{82}(OH)_{22}]_n$ nanoparticles induce dendritic cell maturation and activate Th1 immune responses. *ACS Nano* 2010;**4**:1178−86.
214. Luo M, Wang H, Wang ZH, Cai HC, Lu ZG, Li Y, et al. A STING-activating nanovaccine for cancer immunotherapy. *Nat Nanotechnol* 2017;**12**:648−54.
215. Xu J, Xu LG, Wang CY, Yang R, Zhuang Q, Han X, et al. Near-infrared-triggered photodynamic therapy with multitasking upconversion nanoparticles in combination with checkpoint blockade for immunotherapy of colorectal cancer. *ACS Nano* 2017;**11**:4463−74.
216. Chen Q, Chen JW, Yang ZJ, Xu J, Xu LG, Liang C, et al. Nanoparticle-enhanced radiotherapy to trigger robust cancer immunotherapy. *Adv Mater* 2019;**31**:1802228.
217. Patel RB, Ye MZ, Carlson PM, Jaquish A, Zangl L, Ma B, et al. Development of an *in situ* cancer vaccine *via* combinational radiation and bacterial-membrane-coated nanoparticles. *Adv Mater* 2019;**31**:1902626.
218. Li JC, Cui D, Huang JG, He SS, Yang ZB, Zhang Y, et al. Organic semiconducting pro-nanostimulants for near-infrared photoactivatable cancer immunotherapy. *Angew Chem Int Ed* 2019;**58**:12680−7.
219. Scheper W, Kelderman S, Fanchi LF, Linnemann C, Bendle G, de Rooij MAJ, et al. Low and variable tumor reactivity of the intratumoral TCR repertoire in human cancers. *Nat Med* 2019;**25**:89−94.