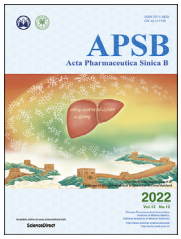
Acta Pharmaceutica Sinica B 2022;12(12):4327–4347

Chinese Pharmaceutical Association
Institute of Materia Medica, Chinese Academy of Medical Sciences

Acta Pharmaceutica Sinica B

www.elsevier.com/locate/apsb
www.sciencedirect.com



REVIEW

Targeted nanomedicines remodeling immunosuppressive tumor microenvironment for enhanced cancer immunotherapy

Yanyan Xu[a,†], **Jingyuan Xiong**[b,†], **Xiyang Sun**[c,*], **Huile Gao**[a,*]

[a]*Key Laboratory of Drug-Targeting and Drug Delivery System of the Education Ministry, Sichuan Engineering Laboratory for Plant-Sourced Drug and Sichuan Research Center for Drug Precision Industrial Technology, West China School of Pharmacy, Sichuan University, Chengdu 610041, China*
[b]*Healthy Food Evaluation Research Center, West China School of Public Health and West China Fourth Hospital, Sichuan University, Chengdu 610041, China*
[c]*Hongqiao International Institute of Medicine, Tongren Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200336, China*

Received 1 September 2022; received in revised form 3 October 2022; accepted 17 October 2022

KEY WORDS

Cancer immunotherapy;
Immunosuppressive tumor microenvironment;
Tumor microenvironment normalization;
Targeted nanomedicines;
Drug delivery;
Environment-responsive nanoparticles;
Combinational therapy;
Tumor treatment

Abstract Cancer immunotherapy has significantly flourished and revolutionized the limited conventional tumor therapies, on account of its good safety and long-term memory ability. Discouragingly, low patient response rates and potential immune-related side effects make it rather challenging to literally bring immunotherapy from bench to bedside. However, it has become evident that, although the immunosuppressive tumor microenvironment (TME) plays a pivotal role in facilitating tumor progression and metastasis, it also provides various potential targets for remodeling the immunosuppressive TME, which can consequently bolster the effectiveness of antitumor response and tumor suppression. Additionally, the particular characteristics of TME, in turn, can be exploited as avenues for designing diverse precise targeting nanomedicines. In general, it is of urgent necessity to deliver nanomedicines for remodeling the immunosuppressive TME, thus improving the therapeutic outcomes and clinical translation prospects of immunotherapy. Herein, we will illustrate several formation mechanisms of immunosuppressive TME. More importantly, a variety of strategies concerning remodeling immunosuppressive TME and

*Corresponding authors. Tel./fax: +86 28 85502532 (Huile Gao).
E-mail addresses: 732003356@shsmu.edu.cn (Xiyang Sun), gaohuile@scu.edu.cn (Huile Gao).
†These authors made equal contributions to this work.
Peer review under responsibility of Chinese Pharmaceutical Association and Institute of Materia Medica, Chinese Academy of Medical Sciences.

https://doi.org/10.1016/j.apsb.2022.11.001

strengthening patients' immune systems, will be reviewed. Ultimately, we will discuss the existing obstacles and future perspectives in the development of antitumor immunotherapy. Hopefully, the thriving bloom of immunotherapy will bring vibrancy to further exploration of comprehensive cancer treatment.

1. Introduction

Anticancer immunotherapy, which has been confirmed effective in clinical trials, presents a promising cancer regimen compared with conventional chemotherapy and radiotherapy. Initially, the approval of recombinant versions of the cytokine interferon-α ushered in an era full of innovation and possibility for oncology treatment in 1986[1]. Then the following decades witnessed numerous advances and setbacks during the development of immunotherapy, especially the emergence of immune checkpoint inhibitors (ICIs) and chimeric antigen receptor (CAR) T cell therapies, which were highlighted as milestones for cancer immunotherapy despite nonnegligible adverse effects[1−4]. To date, dozens of cancer immunotherapies, such as durvalumab[5], tisagenlecleucel[6], and axicabtagene ciloleucel[7], have been approved by the medical products administration.

The last 40 years of immuno-oncology research have firmly proved that the innate immune system is of great effect for specifically recognizing, destroying, and memorizing tumor cells without side effects to normal tissue, which is termed cancer immunosurveillance[8]. But the immune system was found to be a double-edged sword in carcinogenesis. It does suppress tumor growth, but it also plays a critical role in promoting tumor progression and metastasis by supporting chronic inflammation, shaping tumor immunogenicity, and restraining antitumor immunity[9]. More specifically, the immunologic sculpting of the immune system leads to the elimination of high immunogenicity clones and the development of multiple immune evasion mechanisms, which subvert the normal immune regulation and ultimately form an immunosuppressive tumor microenvironment (TME)[10]. The above-mentioned phenomenon is accurately described as "cancer immunoediting", which conduces to unsatisfactory therapeutic outcomes of clinical treatment. In addition, the tumor immune heterogeneity also obstructs the universal application and effectiveness of immunotherapy[11]. Therefore, there is an urgent need to develop strategies targeting diverse tumor escape mechanisms and reversing the immunosuppressive TME for enhanced immunotherapy.

Primary tumors consist of cancerous cells and stromal cells, such as lymphatic cells, endothelial cells, fibroblasts, and various bone marrow-derived cells (BMDCs), which include tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), mesenchymal stem cells (MSCs), and dendritic cells (DCs), etc[12]. It is well demonstrated that the stroma is a crucial participant in tumorigenesis, cancer growth, metastasis, and therapy resistance[13]. Moreover, adaptive immunoediting greatly alters the original signaling pathways of cancer cells and stromal cells, endowing them with more powerful resistance to immunotherapies. With a further understanding of oncology, remodeling the immunosuppressive TME as well as restoring antitumor immunity has emerged as an essential part of cancer immunotherapies. Among these, rehabilitating immune recognition[14], decreasing immunosuppression-associated cytokines[15−17], modulating immunosuppressive cells[13,18−21], and impeding inhibitory co-stimulatory molecule-related pathways[22], are intensively studied (Fig. 1).

Of equal importance, a variety of nanoparticles (NPs) have been developed for precise and timely delivery of immunotherapies[23−26]. Nanocarriers can not only shelter the therapeutic cargoes and improve the pharmacokinetics and bioavailability, but also possess the enhanced permeability and retention (EPR) effect to achieve passive accumulation in the tumor region. Furthermore, targeting moieties (*i.e.*, monoclonal antibodies, antibody fragments, peptides, growth factors, etc.) can be decorated to NPs to accomplish active targeting, thereby reducing non-specificity and increasing uptake[27]. More significantly, NPs exhibit several unique advantages: 1) Stimuli-responsiveness to internal TME stimulus (*i.e.*, pH, redox environment, enzymes, and hypoxic, etc.) and external environmental stimulus (*i.e.*, light, heat, ultrasound, and magnetism field, etc.)[28,29]; 2) novel delivery strategies to promote treatment efficiency, such as the shape conversion of NPs[30,31], cell-mediated biomimetic NPs[32,33], and functional ligand modified NPs[34,35], etc.; 3) intrinsic properties of different NPs may facilitate in tumor cells killing effects, such as cuproptosis[36]; and 4) feasible implementation of a synergetic combination of multiple therapies[37,38].

In this review, we first illustrate the broadly studied formation mechanisms of immunosuppressive TME. Subsequently, we summarize diverse strategies for remodeling the immunosuppressive TME and rewiring host immune responses. We then present the existing obstacles that impede the development and clinical translation of immunotherapy. Ultimately, conclusions and future perspectives on immunotherapy are discussed.

2. Formation mechanisms of immunosuppressive TME

Cancer immunoediting is composed of three phases: elimination, equilibrium, and escape[39]. The immune system eliminates tumor cells through specific recognition of tumor antigens *via* a series of stepwise events, which is termed the "tumor-immunity cycle", which basically includes the generation and release of tumor-associated antigens (TAAs), the capture and processing of the neoantigens by antigen-presenting cells (APCs), the activation of effector T cells, the TME infiltration of activated tumor-specific T cells through T cell receptor (TCR) and cognate antigen-bound MHC complex, and the eventual recognition of target cancer cells, thereby inducing apoptotic pathways for tumor-killing effects as well as initiating a new round of cancer-immunity cycle[40]. However, if growing tumor cells are not eradicated, cancer tends to enter the equilibrium phase[41]. Then under the impact of immunologic sculpting, one or more steps in the tumor-immunity cycle might be blocked and become dysfunctional, along with

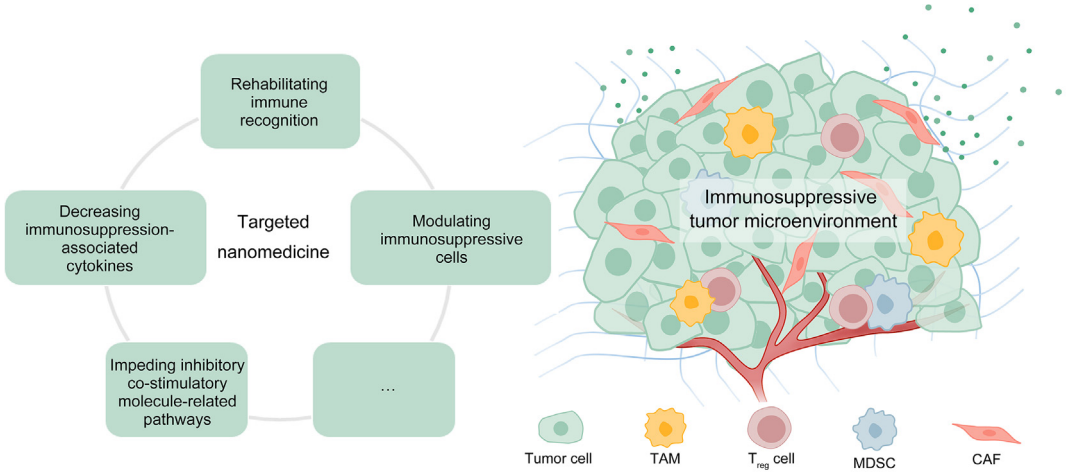


Figure 1 Main strategies for remodeling immunosuppressive tumor microenvironment. The focus is on current advances in tumor targeting nanomedicines for enhanced cancer immunotherapy.

other factors that contribute to the establishment of immunosuppressive TME, resulting in the tumor escape[40,41]. The following sections will introduce the most acknowledged formation mechanisms of immunosuppressive TME, which are the key elements of cancer immuno-resistance (Fig. 2). Of note, TME and the immune system are of great intricacy, so each mechanism described below is not separate and independent. Instead, all of the mechanisms interact mutually and thus form the dynamic immunosuppressive TME.

2.1. *Reduction of immune recognition*

In terms of cancer cells, they are of great genome instability, generating random gene mutations or metabolite variations, some of which support tumor progression and develop resistance to tumor therapies[42]. During the equilibrium phase, tumor cell variants that survived the elimination process are deemed to be in a state of functional dormancy, which may last for years and even decades[10,39,43]. The progression of tumors is constrained. At the

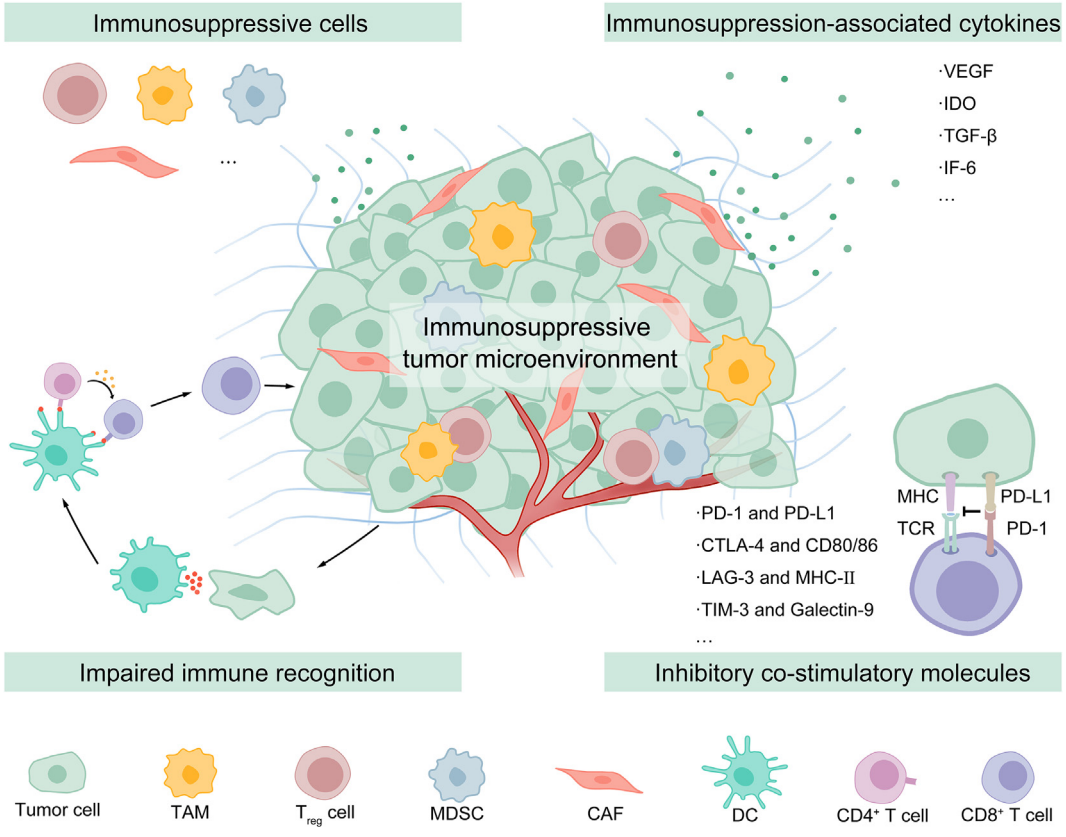


Figure 2 Main formation mechanisms of the immunosuppressive TME, serving as potential targets for TME remodeling-based antitumor immunotherapy.

same time, the Darwinian selection destroys many original variants except those that exert higher resistance to immune attack[10]. Then the accumulation of tumor cell variants with dampened immunogenicity or attenuated immune response sensitivity will proliferate and lead the tumor to escape phase, thus indicating the formation of clinically apparent malignant tumor[44].

Loss of major histocompatibility complex/human leukocyte antigen class I (MHC/HLA I) is one of the mechanisms that account for immunogenicity attenuation. The MHC/HLA I is a membrane-bound protein complex that presents the antigenic information on the surface of tumor cells, which can be specifically recognized by cytotoxic $CD8^+$ tumor-infiltrating lymphocytes (TILs), thereby triggering cancer cell lysis[45,46]. However, to avoid the control and elimination by $CD8^+$ T lymphocytes, genetically unstable cancer cells are likely to downregulate or shut down MHC/HLA I antigen presentation through transcriptional regulation, post-transcriptional/pre-translational regulation, post-translational regulation, or/and altered signaling mechanisms and extrinsic stimuli from the TME, which has no adverse impact on tumor viability or growth[47]. Intriguingly, natural killer (NK) cells, the second line of defense against lesions, can detect and kill abnormal-MHC/HLA I low cells *via* killer-cell inhibitory receptors (KIR)[48]. But cancers can dodge NK cell-mediated elimination by expressing non-classical MHC/HLA I molecules HLA-G and HLA-E, not to mention the hurdles posed by TME for NK cells to infiltrate into MHC/HLA I negative tumors[47–49]. Together, immunosurveillance is hampered. MHC/HLA I loss is commonly seen in cancers and responsible for unsatisfactory clinical outcomes, because it not only enables cancers to escape immune destruction, but also endows malignant tumor cells, such as breast cancer[50], endometrial carcinoma[45], HPV-associated cervical, and vulvar neoplasia[51], etc., with resistance to immune checkpoint therapies[47]. However, although a vast diversity of molecular mechanisms are relevant to MHC/HLA I loss and any silence in assembly steps of MHC/HLA I can generate MHC/HLA I loss, certain cancers are considered to share common characterized mechanisms and can be treated precisely[49]. Therefore, much work is required to distinguish different tumor phenotypes. Other alterations, such as loss of antigen processing ability within tumor cells, are also liable for decreased immunogenicity of tumor cells[52].

DCs are highly specialized APCs, initiating and regulating the innate and adaptive immune responses against tumors, without which the immune recognition would be incomplete[53]. DCs go through maturation when elicited by danger signals released by dying cancer cells, such as damage-associated molecular patterns (DAMPs)[54]. Nonetheless, immunosuppressive TME greatly impedes the maturation of DCs in various facets, which is remarkably adverse for antigen presentation, thereby leading to immunological ignorance[55]. Theoretically, the blockade of any participant in the tumor-immunity cycle may lead to the failure of the host defense against cancer.

2.2. *Production of immunosuppression-associated cytokines*

During tumor development, immunosuppression-associated cytokines that are secreted by cancer cells, stromal cells, and tumor-infiltrating immune cells convolutedly participate in immune reactions and provoke tremendous TME conversion, eliciting immunosuppressive TME that is resistant to cancer immunotherapy[56,57].

To meet the requirement for a slew of oxygen and nutrients for tumor progression, pro-angiogenic factors such as vascular endothelial growth factor (VEGF) are overexpressed under the stimulation of many growth factors and hypoxia, leading to the tortuous, disorganized, and inordinately branched vasculature[58,59]. The vasculature exhibits excessive leakage and higher permeability, then the following elevated interstitial fluid pressure (IFP) and maladjusted lymphatic drainage will make it hard for the entrance of immune cells and nanomedicines[58,60,61]. Furthermore, VEGF can downregulate immunity due to its nature of tissue repair[62]. For example, it was certified that VEGF hindered the differentiation of $CD34^+$ hematopoietic stem cells into DCs, weakening the presentation of tumor antigens[63]. Besides, VEGF can also directly suppress T-cell proliferation and considerably lower the cytotoxicity of T cells *via* VEGFR-2[64]. In addition, it is reported that VEGF stimulation increased the B-cell lymphoma 2 (BCL-2) expression in human microvascular endothelial cells (HMVECs) in a prostate cancer model, and in turn, the up-regulated BCL-2 improved the intratumoral microvascular survival and density as well as tumor growth[65,66].

Indoleamine 2,3-dioxygenase (IDO) is an essential enzyme that catalyzes tryptophan degradation, generating an array of immunosuppressive tryptophan metabolites, some of which were verified to be capable of curbing the T cell proliferation *in vitro* or causing T cell apoptosis[67]. Furthermore, local depletion of tryptophan brings about cellular stress, accordingly inhibiting the mechanistic target of the rapamycin (mTOR) kinase pathway and triggering the kinase activity of general control nonderepressible 2 (GCN2)[68]. Thus, the T-cell proliferation is further suppressed, and the naive $CD4^+$ T cells are biased toward differentiation into regulatory T (Treg) cells, thereby resulting in severe immunosuppression[16].

Transforming growth factor β (TGF-β) produced by various tumor types has dual functions in the advance of tumor[69]. TGF-β acts as a tumor suppressor during the early stage of cancer, inhibiting the cell cycle progression, inducing apoptosis, suppressing growth factor expression, etc., while in the later period, TGF-β promotes angiogenesis, alters cytoskeletal architecture, dysregulates cyclin-dependent kinase inhibitors, etc., which greatly fuel the tumor invasiveness and metastasis[69,70]. Another cytokine, interleukin-6 (IL-6), can set off signal transducer and activator of transcription 3 (STAT3) and nuclear transcription factor (NF-κB) pathways simultaneously, forming chronic inflammatory TME and propelling the tumor growth, metastasis, anti-apoptosis, etc[71].

In general, there are a host of cytokines that play an active role in shaping immunosuppressive TME and they collaboratively form a sophisticated interactional net with various cells in TME.

2.3. *Infiltration of immunosuppressive cells*

The functions of the host immune system are remarkably repressed in cancer patients, mainly on account of reduced homing of immune cells to the tumor tissues as well as enlarged protumor immunosuppressive cell populations[72]. In addition to immunomodulatory capacity, regulatory immune cells also act as inflammatory cells, contributing to the formation of chronic inflammatory TME and the promotion of immunosuppressive effects[15].

Treg cell has proven to be a major suppressor at tumor sites, which is defined as adaptive or inducible (i) Treg or Tr1[73]. Unlike forkhead box protein 3^+ ($FOXP3^+$) naturally occurring (n)

Tregs that prevent the host from autoimmune diseases, the tumor-infiltrating iTregs significantly suppress effector T cells through various mechanisms, generate immunosuppressive cytokines (*e.g.*, TFG-β, IL-10, prostaglandin E2, and adenosine), enhance resistance to apoptosis or anti-cancer therapies[73]. Several main immunosuppression mechanisms of iTregs lie in 1) The expression of high-affinity IL-2 receptor and extreme dependency on exogenous IL-2, hampering the IL-2 exploitation of conventional T (Tconv) cells and thus resulting in the impediment of Tconv cells activation and proliferation; 2) The constitutive expression of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), repressing the co-stimulatory signal transmission from APCs to Tconv cells; 3) The secretion of immunosuppressive cytokines and other substances, contributing to the direct death of Tconv cells or APCs, degradation of adenosine triphosphate (ATP) to immunosuppressive adenosine and suppression of most immune cells[74].

TAMs also play a prominent role in facilitating the establishment of immunosuppressive TME[75]. Immature macrophages will differentiate and polarize into different subsets based on the microenvironmental conditions[76]. There are two main categories, which are proinflammatory classically activated (M1) phenotype and anti-inflammatory alternatively activated (M2) phenotype, respectively[77]. With the progression of tumors, infiltrating macrophages are increasingly prone to differentiate into M2 phenotype, resulting from the stimulation of enzymes, cytokines, and chemokines in TME[76,77]. The M2-like TAMs secret a mass of pro-angiogenic mediators, proteolytic enzymes, and immunosuppressive cytokines such as IL-10 and TGF-β, assisting the formation of immunosuppressive TME and fostering tumor invasion and migration[76]. Studies also have demonstrated that the M2-like TAMs promote tumor metastasis by prompting the epithelial-mesenchymal transition (EMT) through the TGF-β/Smad2 signaling pathway[78,79]. In addition, high TAMs densities are considered to be an indicator of poor prognosis and unfavorable overall survival rates[80].

The term "myeloid derived suppressor cells (MDSCs)" was first brought up to describe the heterogeneous cluster of immature myeloid cells in a pathological environment, which consist of mononuclear phagocytes (M-MDSCs) and granulocytes (G-MDSCs or PMN-MDSCs)[81]. MDSCs stay immature under the influence of multiple factors in TME and are manipulated to become immunosuppressive phenotype, generating ROS and immunosuppressive cytokines (*e.g.*, IL-10, TGF-β)[82]. It is now well substantiated that MDSCs suppress adaptive antitumor immunity by depressing T-cell activation and function (*e.g.*, T-cell receptor down-regulation, T-cell cell cycle repression, immune checkpoint blockade) and recruiting immunosuppressive cells like Tregs, at the same time, the innate immunity is also restricted by polarizing macrophages to M2-like TAMs and inhibiting the cytotoxicity of NK cells[82]. Similar to MDSCs, cancer-associated fibroblasts (CAFs) are another core components of immunosuppressive TME. By suppressing and deleting $CD8^+$ T cells, inhibiting T cells *via the* CXCL12-CXCR4 axis, reducing the antigens-presenting ability of DCs, secreting CXCL12 and Chitinase-3 like 1 (Chi3L1) to maintain M2-like TAMs, etc., CAFs remarkably support the immunosuppression of TME[83]. Simply stated, various immunosuppressive cells have significant negative impacts on TME, which, to some extent, contribute to the unsatisfied efficacy of therapeutic outcomes of anticancer immunotherapies.

2.4. *Overexpression of inhibitory co-stimulatory molecules*

Aside from MHC-presented antigen signal, co-stimulatory molecules on APCs are indispensable for delivering another key signal for T cell activation, without which will cause T cell death or exhaustion (a state of dysfunction)[22]. The inhibitory co-stimulatory molecules (also known as immunity checkpoint) are intrinsic mechanisms against autoimmune diseases, but tumors malignantly harness the mechanism and upregulate immune checkpoint signals to escape immunosurveillance[84]. Moreover, the inhibitory signals are greatly associated with altered TME. For example, once the inhibitory co-stimulatory ligands on tumor cells bind to receptors, the metabolic phenotype of T cells will be shifted from glycolysis to fatty acid oxidation (FAO), thus blunting the metabolic processes for activating effector function as well as stabilizing immunosuppressive Treg cells[85]. Moreover, the expression of inhibitory co-stimulatory receptors will also be upregulated in exhausted T cells, thereby further depressing the function of effector T cells (Teffs)[85].

CTLA-4 is expressed mainly in Teffs, which competitively binds to CD80/CD86 on the APCs with CD28, inhibiting the production of IL-2 and the activation of T cells[86]. Simultaneously, CTLA-4 induces IDO[86]. Nonetheless, FDA-approved anti-CTLA-4 antibodies are proven to be inadequate for cancer immunotherapy, with inferior efficacy and high toxicity[87]. Programmed death receptor-1 (PD-1) is expressed on the surface of many TILs, while its ligands, PD-L1, and PD-L2, are mainly overexpressed in many solid tumors and hematologic malignancies[88]. When engaged with PD-L1 or PD-L2, PD-1 is phosphorylated at tyrosine residues, with the recruitment of Src homology 2 (SH2) domain-containing tyrosine phosphatase 2 and the dephosphorylation of the proximal TCR signaling molecules, thereby leading to the inhibition of T-cell activation, survival, and cytolytic function as well as the promotion to cancer growth[89,90]. In comparison with CTLA-4, the blockade of the PD-1/PD-L1 pathway has captured more attention due to its lower rates of immunotherapy-related adverse events and better cancer immunotherapeutic effect in clinical trials[87]. Similarly, T cell immunoglobulin and mucin domain-containing protein 3 (TIM-3) bind to galectin-9 and the adhesion molecule carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1), triggering the release of BAT3, the suppression of tyrosine kinase LCK recruitment and eventually the anergy or apoptosis of $CD8^+$ T cells[91]. Lymphocyte activation gene-3 (LAG-3), the inhibitory co-stimulatory receptor of MHC-II, inhibits Teffs *via* the KIEELE motif, enabling Treg cell-mediated immunosuppression[92]. LAG-3 is recognized to have synergistic effects with PD-1 in the tumor immune escape, making it effective for co-blocking LAG-3 and PD-1 in cancer treatments[93]. Despite the prospects of ICIs, it has been noted that there exists cross-regulation between multiple checkpoint molecules[94]. For example, the co-blockade of PD-1 and PD-L1 led to the upregulation of TIM-3 and LAG-3 on $CD4^+CD25^+$ T cells and $CD4^+CD25^+FoxO3^+Helios^+$ Tregs in triple-negative breast cancer[95]. Likewise, the combination of TIM-3 and PD-1 mAbs also increased the expression of LAG-3 and GITR (a co-stimulatory receptor) in TILs[94]. For the past decade, combining ICIs with other therapeutics, such as chemotherapeutics[96] and anti-angiogenic agents[97], has drawn fierce attention and has been broadly investigated both in preclinical testing and clinical trials.

Additionally, glyco-immune checkpoints are under extensive exploration. Aberrant glycosylation is a universal hallmark of

cancer cells, commonly characterized by anomalous expression and glycosylation of mucins, abnormal branching of N-glycans, and increased expression of sialoglycans on proteins and lipids[98,99]. Sialic acid-binding immunoglobulin-like lectins (Siglecs) expressed on most immune cells are receptors for tumor-cell-derived sialoglycans, and the signaling through the sialoglycan-Siglec axis is similar to the PD-1/PD-L1 signaling, which stifles the anti-tumor immunity and brings about immunosuppressive TME[100−102]. Hitherto few targeted nanomedicines interfering with the sialoglycan-Siglec immune checkpoint have been brought up, it is a potential approach for enhancing cancer immunotherapy.

3. Strategies for remodeling immunosuppressive TME

The immunosuppressive TME, which is shaped under the cooperative effect of tumor cells with poor immunogenicity and various immune cells, dramatically retards the response rates of immunotherapies (*e.g.*, CAR T-cell therapies and ICIs) in recent clinical investigations[103,104]. Apart from seeking predictive therapeutic biomarkers, rejuvenating the immunosuppressive TME and rehabilitating patients' inherent immunological systems have emerged as promising approaches in the evolving field of immunotherapy. Inspiringly, abnormalities also represent potential therapeutic targets. Nanomedicine is deemed a potent therapeutic strategy, attributed to its design flexibility[105], ease of decoration, and versatility (*e.g.*, spatiotemporally controlled drug delivery and release[106], biodegradability[107], and the ability to overcome drug resistance[108]). Moreover, inspiring insights into the *in vivo* fate of nanoparticles have also fueled the investigation of nanomedicine-based antitumor immunotherapy[109]. Combined the understanding of the formation mechanisms of immunosuppressive TME with the advantages of nanomedicines, it is of immense promise to develop effective and precise nanomedicines for remodeling immunosuppressive TME and enhancing the efficiency of anticancer immunotherapies[20,110,111]. Of note, due to the sophisticated interactional net formed by the intricate immune system and TME, researchers prefer combinatorial therapy for ameliorated feasibility, so the strategies elucidated beneath will be classified based on the main effect of combinatorial therapy.

3.1. *Rehabilitating immune recognition*

As described above, any impairment of steps in the tumor-immunity cycle will contribute to the failure of cancer eradication by adaptive immunity. Tactics that target rejuvenating the dysfunctional tumor-immunity cycle for remodeling the immunosuppressive TME have continuously emerged, especially immunogenic cell death (ICD). Under the enormous cellular stress provoked by antitumor therapy, ICD is induced, which encompasses the release of TAAs, DAMPs as well as inflammatory cytokines and the activation of tumor-specific immune responses, thus addressing the poor immunogenicity of edited tumors and eliminating tumors by both anticancer drugs and antitumor immunity[112,113]. There is a wide range of nanomedicine-mediated ICD triggering approaches. Potent approaches, such as chemotherapeutics (*e.g.*, doxorubicin[114], paclitaxel[115], 7-ethyl-10-hydroxycamptothecin[116]), photothermal therapy (PTT)[117−120], photodynamic therapy (PDT)[121] and oxidative stress amplifiers[122,123], have been intensively applied. In the work of Ding et al.[124], reactive oxygen species (ROS)-sensitive nanoparticles loaded with copper chaperone inhibitor DC_AC50 and cisplatin(Ⅳ) prodrug were fabricated. Along with the chemotherapeutic effect of cisplatin, massive ROS generated from DC_AC50 spurred on synergistic ICD, thereby restoring the cancer immunogenicity. Chen et al.[125] put forward GSH-depleting second near-infrared (NIR-II) photothermal and photoacoustic agents (denoted as TTF-F4TCNQ) based on the small molecular organic metal adjuvants (OMAs), contributing to elevating immune responsiveness by the ICD effect elicited by PTT and ROS. With the optimized combination of commercially available donors and acceptors, TTF-F4TCNQ exhibited advanced efficiencies, such as broader substrate scope, higher accessibility, and flexibly tuned optical characteristics. Moreover, TTF-F4TCNQ possessed the ability to deplete GSH and cysteine, thus interrupting intracellular redox homeostasis as well as augmenting ROS accumulation. The multifunctional TTF-F4TCNQ had a synergistic impact on arousing abundant ICD and enhancing immune responses to eradicate cancer cells. In addition, the administration of PD-1 antibody assisted the antitumor immunotherapy *via* increasing T cell infiltrations. Together, both the primary and distant tumors were inhibited in 4T1 tumor-bearing mice due to the suppressed tumor immune evasion and enhanced immune responses (Fig. 3).

Nonetheless, ICD-induced TAAs themselves are not sufficient to elicit potent antitumor immunity owing in large part to the lack of activated APCs, which are responsible for taking in the cancer neoantigens and cross-presenting them to prime naive $CD4^+$ and $CD8^+$ T cells, thereby triggering immunogenic T helper 1 (Th1) and cytotoxic T lymphocyte (CTL) responses[53,126]. Hence, effective activation of APCs is a prerequisite for TAAs to trigger the tumor-immunity cycle. For DC maturation, various methods have been brought up, such as nucleic acid-based vaccine[127,128], calreticulin[129], and toll-like receptor (TLR) agonists[130,131], which all manifest great prospects. Moreover, Liu et al.[132] proposed that Ca^{2+}-assisted surface polydopamine engineering of DC could effectively relieve the suppressed state and promote DC maturation under 808 nm laser irradiation, offering a potential approach for the elevation of antigen presentation. Furthermore, artificial APCs (aAPCs) have emerged as a powerful alternative to natural APCs, indirectly overcoming the difficulty that APCs are suppressed in TME. Xu et al.[133] developed biomimetic nanoaggregates of aggregation-induced emission photosensitizers (AIEgens) coated with DC cell membranes (DC@AIEdots). Leveraging DC cell membranes, the nano-photosensitizers were capable of crossing the biological barrier of blood vessels to accumulate around the tumor by hitchhiking on T cells, and then artificially presenting antigens to mediate T cell proliferation and activation. AIE photosensitizers could specifically target lipid droplets accumulated in cancer cells, without interference with surrounding immune cells in complex TME. Among a series of synthesized AIE photosensitizers, MeTIND-4 was selected for its longest NIT emission and highest ROS generation. The levels of tumor necrosis factor (TNF-α) and interferon (IFN-γ) in DC@AIEdots-treated T cells were 14-fold and 11-fold superior to cells treated with PBS buffer or bare AIEdots. T cell numbers in DC@AIEdots-treated groups were also increased by more than five times, in comparison to the control groups. *In vivo* experiments also exhibited abundant activated T cell infiltration, apparent tumor size reduction, and distant tumor inhibition, with long-term effects and biocompatibility (Fig. 4).

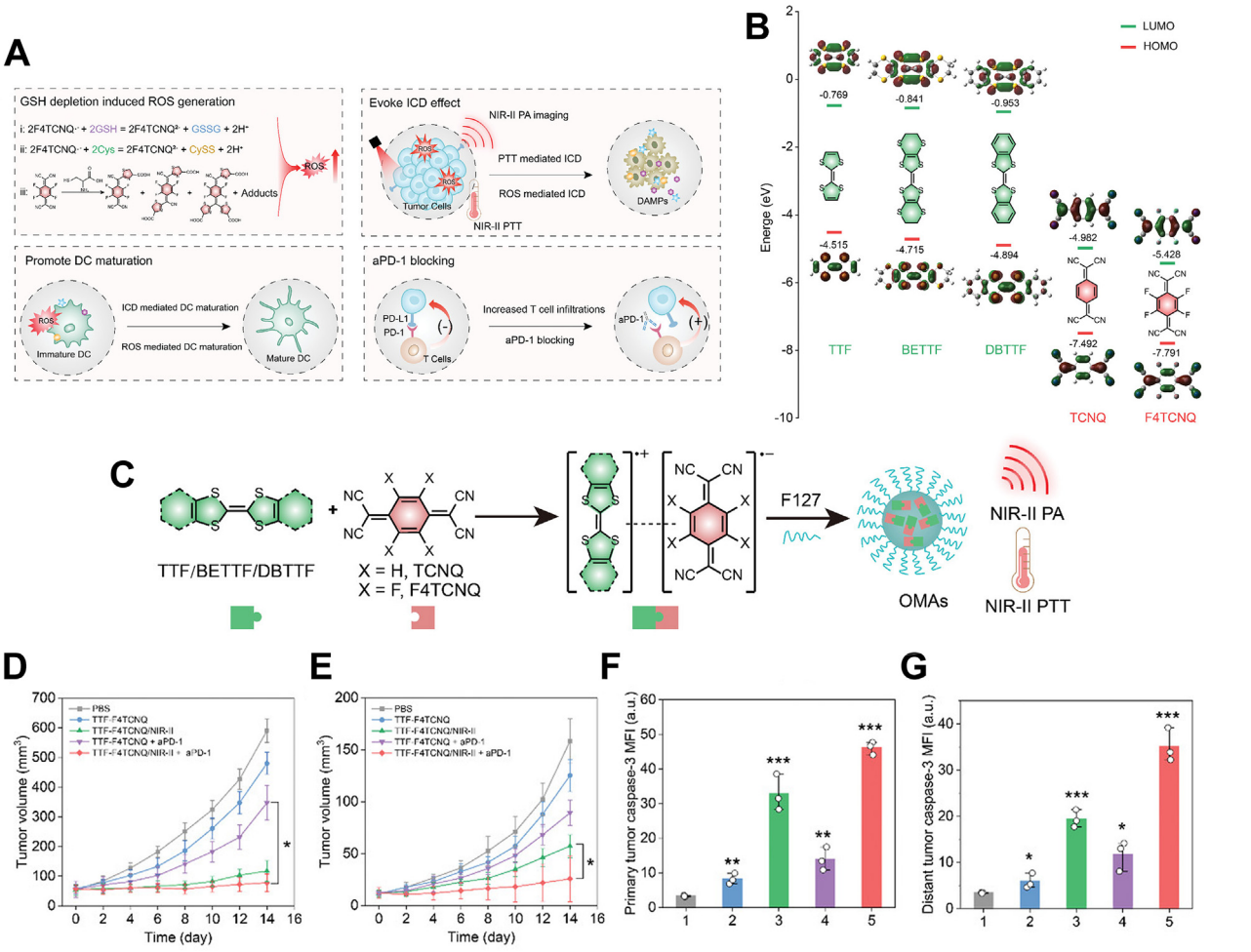


Figure 3 OMA-mediated NIR-II photothermal immunotherapy for potentiating immunogenicity and immune responses. (A) Mechanisms of OMAs. (B) Energy levels of donors and acceptors. (C) Preparation process of OMAs. (D) Growth curves of primary tumors and (E) distant tumors following different treatments ($n = 5$). (F) Quantitative analysis of caspase-3 levels in primary tumors and (G) distant tumors after different treatments ($n = 3$). Treatment groups: 1, PBS; 2, TTF-F4TCNQ; 3, TTF-F4TCNQ/NIR-II; 4, TTF-F4TCNQ + aPD-1; 5, TTF-F4TCNQ/NIR-II + aPD-1. *P* values were calculated by two-tailed Student's *t*-test (D and E) and measured *via* ANOVA with Tukey *post-hoc* test (F and G). Data are presented as mean ± SD, $*P < 0.05$, $**P < 0.01$, and $***P < 0.001$ *vs.* indicated. Reproduced with the permission from Ref. 125. Copyright © 2022, Wiley-VCH GmbH.

3.2. *Decreasing immunosuppression-associated cytokines*

In terms of previous illustrated mechanisms, decreasing the expression or/and the secretion of immunosuppression-associated cytokines is of great prospect for immunosuppressive TME reversal. Among these, VEGF, IDO, TGF-β, and IL-6 have been the most investigated. Song et al.[134] introduced a dual pH-responsive nanocarrier for the co-delivery of VEGF siRNA (siVEGF) and placental growth factor (a homolog of VEGF) siRNA (siPIGF) to breast cancer cells and M2-like TAMs. Based on the ionic gelation between a cationic polyethylene glycol (PEG) and mannose modified-trimethyl chitosan conjugate (PEG = MT) and an anionic poly-(allylamine hydrochloride)-citraconic anhydride (PAH-Cit, PC), PEG = MT/PC/siVEGF/siPIGF NPs were formed. Interestingly, the NPs underwent two stages to overcome biological barriers and achieve on-demand release. First, the benzamide bond between PEG and MT cleaved upon arriving at weakly acidic tumor sites (pH 6.0−7.0), leading to the exposure of mannose ligands and positively-charged groups, which accelerated the active uptake by mannose receptors-overexpressed M2-like TAMs as well as passive uptake by negatively charged tumor cells. Second, a more acidic endosomal or lysosomal environment (pH 4.5−5.5) led to PC hydrolyzation, contributing to charge reversal, endosomal/lysosomal escape, and cytoplasmic release of siRNA. As a result of silencing immunosuppressive VEGF, the combinatorial therapy not only inhibited the proliferation of breast cancer cells but also re-educated M2-TAMs to proinflammatory M1 phenotypes, sharing a synergistic effect on TME remodeling and immunotherapy sensitization. Recently, two monoclonal antibodies (*i.e.*, anti-VEGF-A antibody Bevacizumab and anti-VEGFR2 antibody Ramucizumab) have been approved for clinical application[135]. However, some concerns are raised that VEGFR-2 inhibitors may interfere with other receptors of the tyrosine kinase family, on account of structural resemblance[136]. Modi et al.[136] took advantage of structure-based drug design (SBDD) approaches (*i.e.*, docking and molecular

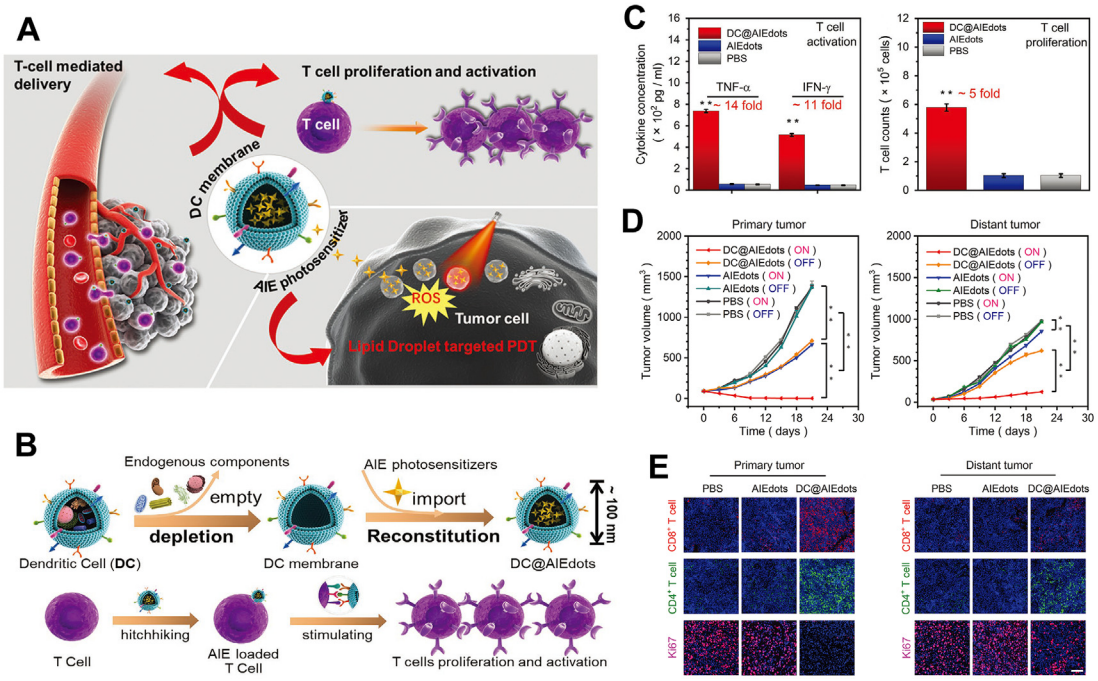


Figure 4 Artificial antigen-presenting NPs with lipid droplet targeting function for cancer photodynamic immunotherapy. (A) Schematic illustration of DC@AIEdots. (B) Preparation process of DC@AIEdots, and the interaction between DC@AIEdots and T cells. (C) The levels of T cell activation and proliferation after incubation with different preparations. (D) The tumor volume of primary and distant tumors in different treatments groups. (E) CLSM images of $CD8^+$, $CD4^+$ T cells and tumor cell proliferation after incubation with different preparations (scale bar = 200 μm). *P* values in (C) and (D) were calculated by two-tailed Student's *t*-test or one-way ANOVA. Data are presented as mean ± SD ($n = 3$), $^{**}P < 0.01$, *vs.* indicated. Reproduced with the permission from Ref. 133. Copyright © 2021, Wiley-VCH GmbH.

dynamics simulations) to conceive VEGFR-2, which shed light on the way ahead for smarter and more specific drug design.

For IDO, recent efforts unveiled many synergetic treatments in combination with IDO inhibitors (*e.g.*, 1-methyl-D-tryptophan (1-MT)[137–139], NLG919[140], Epacadostat[141]) and other therapeutic modalities, such as chemotherapy, PDT, PTT and radiotherapy, which all demonstrated relieved immune suppression and enhanced therapeutic effects, offering vast clinical prospects. Our group[142] designed laser-responsive and size-changeable NPs [(C/I)BP@B-A(D)&M1m] decorated with M1-macrophage membranes. M1-macrophage membranes enabled delayed mononuclear phagocyte system clearance and tumor-homing effect *via* membrane proteins. The NPs were comprised of PEGylated bilirubin with hydrophobic Ce6 and IDO inhibitor indoximode (IND) co-loaded [(C/I)BP] and DOX-embedded and BSA-protected gold nanoclusters [B-A(D)], which could be disrupted in response to laser irradiation. Then the (C/I)BP would reaggregate into "Caterpillar-like" NPs to facilitate retention and sustained drug release, and the small-sized B-A(D) would penetrate into the deep tumor region, thereby reinforcing cytotoxicity. The combination of chemotherapeutic drug, PDT therapy, and reversing tumor immunosuppression by IDO1 pathway exerted great suppression of primary tumor growth and metastasis (Fig. 5). To further bolster the specificity of the nanomedicine, our group fabricated shape-transformable nanomicelles (Ce6/BR-FFVLK-PEG) with macrophage membrane to co-deliver thioketal-linked paclitaxel dimer and disulfide-linked 1-MT dimer (denoted as I-P@NPs@M)[143]. Upon laser irradiation, the spherical nanomicelles turned into nanofibers when stimulated by massive ROS generated by Ce6, thus bolstering retention and cellular internalization in tumor[144]. With nanomicelles being destroyed, the drug dimers loaded in the hydrophobic core were consequently released and activated to monomeric drugs by ROS and GSH, respectively. Notably, 1-MT blocked the IDO pathway to reduce immune inhibition, thus amplifying ICD triggered by PDT and chemotherapy and synergistically suppressing both *in situ* breast cancer and lung metastasis (Fig. 6). Additionally, researchers have been engaged in discovering potent and safe IDO inhibitors that derived from small-molecule compounds by virtual screening and kinetic method for enzymatic analysis[145]. Scientists found lead compounds that exerted potential IDO inhibitory activity from PQAs (the natural alkaloids in *Picrasma quassioides*), which were verified more potent than 1-MT, thereby enriching the diversity and availability of natural anti-tumor agents[145].

As for TGF-β, it has been authenticated to be a critical promoter of epithelial-mesenchymal transition (EMT), which allows the metastasis of cancer[146]. Guo et al.[147] constructed a fucoidan-functionalized DOX-loaded micelle (FD/DOX) to reestablish TME and achieve potent antitumor immune responses for metastatic cancer treatment. Fucoidan, a highly sulfated polysaccharide, had a nanomolar affinity for P-selectin, which supported the hypothesis that fucoidan-functionalized micelle can track tumor cells precisely by hitchhiking on activated platelet. More importantly, fucoidan not only inhibited TGF-β in the liver fibrosis model but also displayed immunostimulatory function to boost adaptive immune responses, thus having the potential to reverse the immunosuppressive TME. Attributed to the addition of chemotherapy, the micelle was expected to exhibit more potent anti-cancer efficacy. The therapeutic effects of FD/DOX were successfully observed in both *in vitro* and *in vivo* experiments,

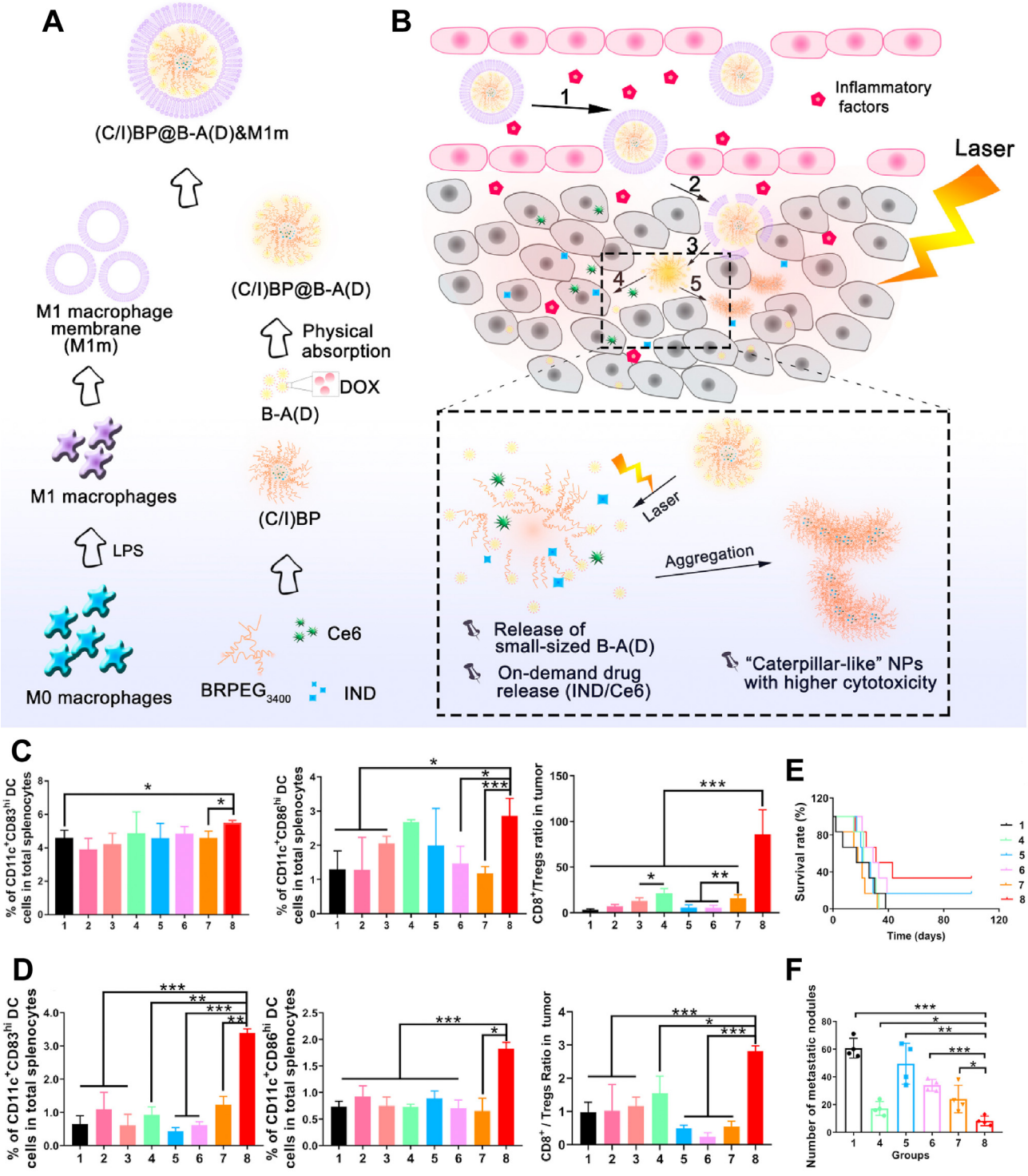


Figure 5 Phagocyte-membrane-coated and laser-responsive NPs for combinatorial therapy of chemotherapeutics, PDT and immunosuppression modulation. (A) Preparation process of (C/I)BP@B-A(D)&M1m. (B) Schematic illustration of (C/I)BP@B-A(D)&M1m + laser treatment. (C) Analysis of immune cells in the B16F10-tumor-bearing mice and (D) 4T1-tumor-bearing mice treated with various NPs. (E) Survival curve of the 4T1-bearing mouse models after removing primary tumors by treatment or surgery. (F) Number of lung metastatic foci determined grossly. Treatment groups: 1, PBS; 2, IND; 3, DOX/Ce6 + laser; 4, DOX/Ce6/IND + laser; 5, (C/I)BP + laser; 6, (C/I)BP@B-A(D); 7, (C/I)BP@B-A(D) + laser; 8, (C/I)BP@B-A(D)&M1m + Laser. *P* values were calculated by two-tailed Student's *t*-test (C, D and F) and one-way ANOVA test (C and D). Data are presented as mean ± SD ($n \geq 3$), $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$ *vs.* indicated. Reproduced with the permission from Ref. 142. Copyright © 2020, Elsevier Ltd.

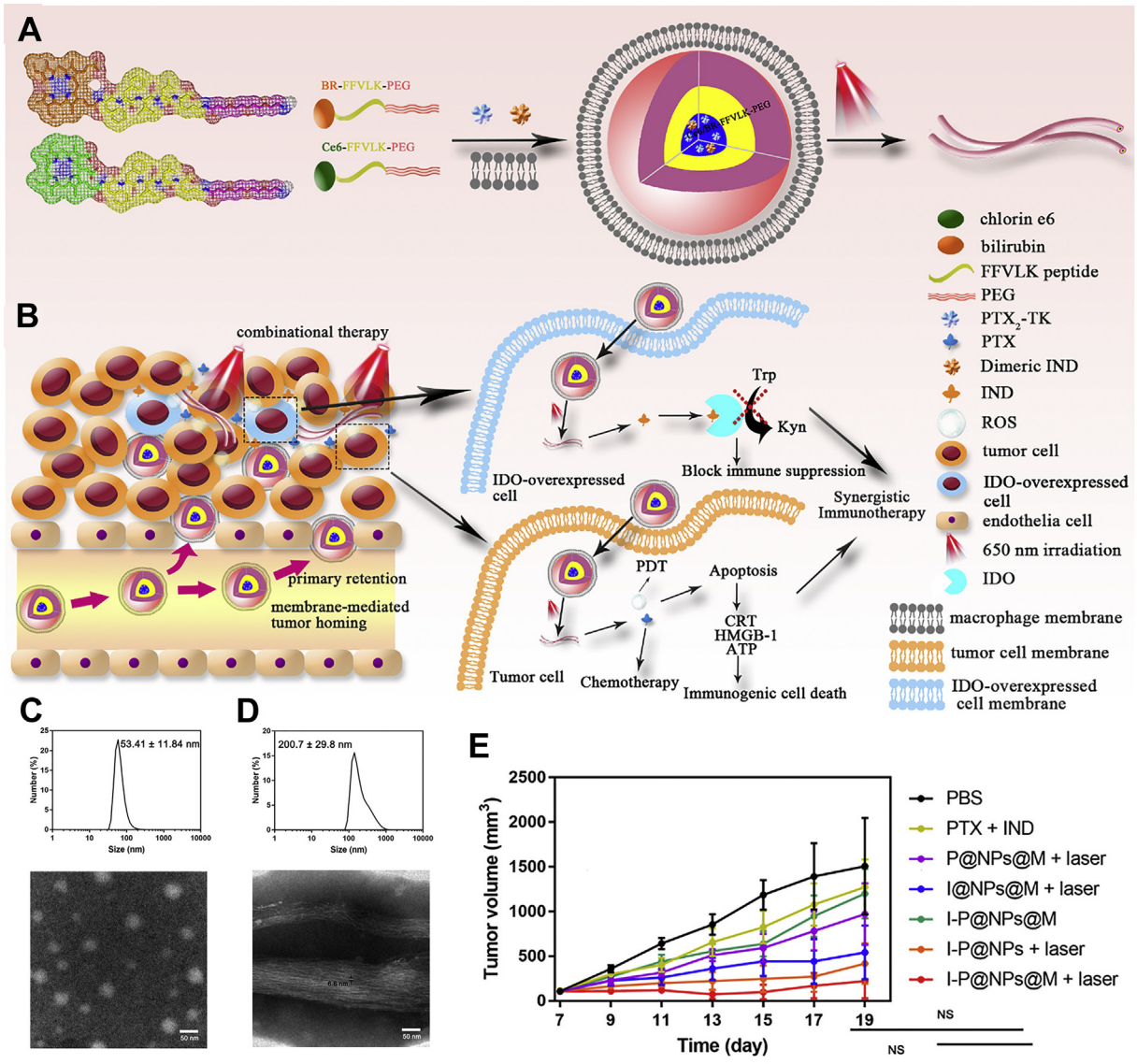


Figure 6 Macrophage-mimic and shape-transformable NPs for multimodal breast cancer therapy. (A) Schematic illustration of the construction of I-P@NPs@M. (B) Schematic illustration of anticancer functions of I-P@NPs@M. (C) The DLS measurements and TEM images of I-P@NPs@M and (D) I-P@NPs@M + laser (scale = 50 nm). (E) The tumor volume of *in situ* tumors in different treatment groups. Reproduced with the permission from Ref. 143. Copyright © 2020, Elsevier B.V.

thus providing a simple but valuable paradigm of cancer treatment. Other approaches aiming at TGF-β inhibition were also brought up, such as BIX02189[148].

3.3. *Modulating immunosuppressive cells*

3.3.1. *Regulatory T cells*

It is universally acknowledged that immunosuppressive Treg cells have to be depleted or attenuated, or else immunological treatments such as vaccination and checkpoint blockade will be disabled[74]. Maneuvers for selectively targeting Treg cells can be divided into three categories, including depletion of effector Treg cells in tumor sites, agonistic antibody affecting Treg suppression, and small molecular inhibitors for Treg depletion or modulation. When it comes to depleting effector Treg cells in tumor tissues, CCR4 is a representative target, which is the receptor for chemokines CCL22 and CCL17 that mainly from DCs and macrophages[149]. The interaction is crucial for Treg migration and metastasis of $CCR4^+$ lymphoma cells, which simultaneously provides an ideal target for blockade[149]. But current researches are mostly concentrated on the development of novel anti-CCR4 antibodies rather than targeted nanomedicines, which, therefore, will not be covered in this review. Glucocorticoid-induced TNFR-related gene (GITR) is expressed by Treg cells, acting as a potential target for suppressing Treg[150]. Sun et al.[151] developed an immunomodulating nanosystem based on the combination of phototherapy and immunotherapy, which was denoted as PDA-ICG@CAT-DTA-1. Catalase (CAT) and anti-GITR antibody (DTA-1) were co-loaded to nanoparticles comprised of photothermal agent polydopamine (PDA) and photosensitizer

indocyanine green (ICG). With the aid of the EPR effect, the PDA-ICG@CAT-DTA-1 tended to accumulate in cancer regions and then endocytosed *via* the vesicle transport pathway by tumor cells. It was worth noting that the nanosystem offered a Tregs targeting vehicle for DTA-1, which facilitated the abrogation of tumor immune suppression and the effects of ICD induced by phototherapy, thereby fostering antitumor immunotherapy. ICG@CAT-DTA-1 showed potent antitumor effects in mice models, with an inhibition ratio of 95.1% for primary cancers and 68.7% for abscopal cancers, highlighting the great prospects of this versatile nanosystem. As for small molecular inhibitors for Treg depletion or modulation, low-dose cyclophosphamide (CTX) is one of the most broadly utilized agents, which selectively depletes $CD4^+CD25^+$ Treg cells[152,153]. Yet, the application of CTX is still restricted to its original role of chemotherapeutic, and articles on both Treg inhibiting function and nanomedicines are rare.

3.3.2. *Tumor-associated macrophages*

Reprogramming TAM towards anti-tumoral phenotype, namely M1-like TAMs, is perceived as significantly beneficial in remodeling immunosuppressive TME[75]. The approaches can be generally classified into two types, one is re-educating tumor-promoting M2-like TAMs to M1-like TAMs, and the other is directly hindering the formation and survival of M2-like TAMs. In studies from our group[154,155], we constructed a furin-responsive aggregated nanoplatform encapsulating DOX and hydroxychloroquine (HCQ). The HCQ was a typical autophagy inhibitor, which not only diminished the chemo-resistance of tumor cells but also enhanced NF-κB nuclear translocation and activated the NF-κB pathway to reprogram tumor-promoting TAMs to pro-inflammatory M1-like phenotype, thus reversing immunosuppressive TME. He et al.[156] fabricated binary-drug liposomes modified with lactoferrin (LF) for targeting immune-inactive colorectal tumor cells and immunosuppressive M2-like TAMs. The drugs capsulated were FDA-approved histone deacetylase inhibitor panobinostat (Pano) and bromodomain and extra-terminal (BET) proteins inhibitor JQ1, which were effective in M2-like TAMs reeducation and PD-1/PD-L1 pathway suppression, respectively. LF modification equipped the liposomes with colorectal tumor cells and TAMs targeting ability, for the high expression of low-density lipoprotein receptor-associated protein 1 (LRP-1) on the surface of those cells, which possessed superior binding affinity to LF. Moreover, the liposomes would absorb endogenous albumin and then form albumin corona *in situ*, endowing the liposomes with binding ability to the albumin-binding proteins such as SPARC that were overexpressed in tumors. The dual-targeting and dual-drug loaded liposomes displayed efficient TME reversion function and potent antitumor effects. In addition, numerous studies have demonstrated various effective TAMs reprogramming agents, such as paclitaxel[157], extracellular vesicles derived from ginseng[158], monoamine oxidase A inhibitor[159], etc. Otherwise, directly hindering the formation and survival of M2-like TAMs is conducive. It was reported[160] that STAT3 and STAT6 pathways contributed to the M2 differentiation, providing various potential candidates for depressing the formation of M2-like TAMs. For example, Yang et al.[161] constructed a BRD4 decorated amphiphilic micelle carrying ARV-825 for glioma treatment, which suppressed M2-like TAMs polarization through the inhibition of interferon regulatory factor 4 (IRF4) promoter transcription and phosphorylation of STAT3, STAT6 and protein kinase B. Other inhibiting agents, such as zoledronic acid and hispanolone derivative 8,9-dehydrohispanolone-15,16-lactol, were proved effective as well[162,163].

3.3.3. *Myeloid-derived suppressor cells*

MDSCs not only impede antitumor immunity presented by T cells but also propel angiogenesis and metastasis of cancer, resulting from quantities of both direct and indirect crosstalk with various cells in tumor region[164]. Wang et al.[165] proposed a self-assembled nano-filament system through the conjugation of MDSCs repressor curcumin and a self-assembled peptide FFE-ss-EE (denoted as Nano-Cur) for lung cancer. Given that Cur was verified to have potential inhibitory capacities on MDSCs but was restricted by its poor bioavailability and tumor accumulation, researchers exploited self-assembled peptide-based nano-filaments to improve the loading capacity and retention effect of curcumin[166]. At the same time, nano-filaments exert better tumor retention ability than common nanoparticles because different nanoplatform shapes exhibit different properties. Moreover, curcumin was incorporated into the peptide, making it possible for persistent drug release. Under Nano-Cur treatment, dramatical suppression of the number and immunosuppressive function of MDSCs was witnessed both in *in vitro* and *in vivo* models, indicating an effective approach for lung cancer treatment. Extensive investigations on suppressing immunosuppressive functions and inhibiting the recruitment of MDSCs have yielded various strategies, such as Neobavaisoflavone nanoemulsion[167], multilayer polyarginine nanocapsules loaded with chemokine CCL2 and two different RNAi sequences modulating the CCAAT/enhancer-binding protein beta (C/EBPβ) pathway[168], micellar hypotoxic low molecular weight heparin-tocopherol succinate nanoparticle[169], etc. Additionally, repolarizing MDSCs is another valid avenue. Wu et al.[170] introduced a magnetic nanoparticle-based platform with polyethylenimine modification to complement the effect of radiotherapy for glioma therapy, which could manipulate the repolarization of MDSCs to a pro-inflammatory phenotype that was capable of generating a substantial amount of TNF-α and inducible nitric oxide synthase (iNOS) as well as recognizing and attacking glioma cells.

3.3.4. *Cancer-associated fibroblasts*

As the most abundant stromal cells in TME, CAFs secret a host of regulatory factors and remodel the extracellular matrix (ECM), thus facilitating the formation of the immunosuppressive TME and tumor progression[171]. CAFs depletion or inactivation plays a potential role in developing more powerful cancer therapies. Lang et al.[172] developed cell-penetrating peptide (CPP, nine-arginine, R9)-based self-assembly nanoparticles loaded with CXCL12 silencing siRNA (si*CXCL12*), with fibroblast activation protein-α monoclonal antibodies (anti-FAP-α mAb) absorbed on the surface. The nanosystem actively targeted to CAFs *via* a specific binding effect between anti-FAP-α mAb and FAP-α, then knocked down the expression of the CXCL 12 gene in CAFs, which inhibited the CXCL12-CXCR4 axis and hindered the maintenance of the tumor-promoting phenotype of CAFs. Therefore, the malignantly immunosuppressive TME was reshaped under the influence of the inactivation of CAFs, thereby hampering the tumor growth and migration for orthotopic prostate tumors. However, compared with CAFs inhibition monotherapy, combinatorial therapy may be more sufficient. Li et al.[173] integrated PTT with CAFs regulator to achieve better therapeutic outcomes. A vitamin-D receptor ligand named Calcipotriol (Cal) can transcriptionally deactivate CAFs to a quiescent state with increased lipid droplet storage and reduced

expression of fibroblast activation marker α-smooth muscle actin (α-SMA), which was co-loaded with a typical photosensitizer ICG to tumor cell-derived microparticles (denoted as Cal/ICG@MPs), thus forming an innovative tumor-targeted nanosystem with superb stability, high biocompatibility, low immunogenicity, and target-homing capability. With the assistance of Cal, the depressed CAFs and reduced tumor ECM led to the enhanced accumulation and penetration of ICG, thereby igniting a more potent PTT effect. The synergetic therapy can trigger strong systemic antitumor immune responses and long-lasting immunological memory, realizing excellent tumor eradication effect. Similarly, Nicolás-Boluda et al.[174] proposed multifunctional iron oxide nanoflowers decorated with gold nanoparticles (GIONF) as nanoheaters to deplete CAFs for reversing immunosuppressive TME, highlighting a spatiotemporally controlled physical strategy for cholangiocarcinoma treatment. Up to now, many CAFs inactivators have been leveraged to counteract the immunosuppression in TME to a certain degree, such as salvianolic acid B[175], vismodegib[176], telmisartan[177], etc.

3.4. *Impeding inhibitory co-stimulatory molecule-related pathways*

Cancer cells activate different immune checkpoint pathways to harbor immunosuppressive functions[178]. Among various inhibitory co-stimulatory molecule-associated signaling pathways, the PD-1/PD-L1 pathway has been the most intensively investigated, which will be taken as an example in the succeeding discussion. Prohibiting strategies include blocking monoclonal antibodies(mAbs) against PD-1 or PD-L1, PD-1/PD-L1 inhibitors, genetic ablation of PD-1 or PD-L1 gene, RNA interference, etc[88].

The past several years have witnessed immense advances in clinical cancer immunotherapy, with approvals of antibodies targeting PD-1/PD-L1 (*e.g.*, nivolumab, pembrolizumab, cemiplimab, atezolizumab, durvalumab, avelumab), which can efficiently rescue T cells from exhaustion and revive immune response against tumor[179]. Aiming to promote the antitumor efficacy of immunomodulatory mAbs, Jiang et al.[180] integrated two types of mAbs targeting effector cells and tumor cells with nanoparticles to construct immunomodulating nano-adaptors (imNAs), which could facilitate the engagement of effector immune cells and tumor cells to bolster cytotoxicity. Intriguingly, rather than chemically immobilizing mAbs onto NPs, which was at high risk of hurting the valency and affinity of antibodies, the researchers employed anti-IgG (Fc specific) antibody (αFc) as an intermediary between NPs and mAbs. Given that αFc was linked to NPs through orientated conjugation and could noncovalently bind mAbs *via* specific Fc recognition, both the stability and efficacy of the nano-adaptors were guaranteed. The general applicability of αFc-NP and the therapeutic superiority of imNAs were validated in multiple murine tumor models, presenting a versatile nanoplatform for mAbs-associated treatment. However, anti-PD-1/PD-L1 antibodies also pose many drawbacks, such as a limited responding proportion of patients, innate and/or acquired resistance, and a series of immune-mediated adverse events[181−183].

In recent laboratory investigations, plenty of PD-1/PD-L1 inhibitors have been applied. Our group[184] conjugated acidic-sensitive PD-L1 inhibitor Metformin (MET) with Ce6 through matrix metalloproteinase-2 (MMP-2) cleavable peptide (GPLGVRGDK, pepA) to develop MMP-responsive self-delivery nanoparticles. Apart from type 2 diabetes, MET was also reported to be effective in degrading endoplasmic-reticulum-associated PD-L1 to reverse tumor immunosuppression. Moreover, 1,4-phthaladehyde was introduced to form an acid-sensitive imine bond between MET and pepA, thus achieving a specific release of positive charged MET in the TME (pH 6.8) and facilitating cellular uptake. The dual-sensitive NPs indicated an intelligent and simple cancer treatment paradigm based on PDT and immunotherapy. There are other approaches for inhibiting PD-1 or PD-L1, such as ^{D}PPA-1[185], PD-LYSO[186], and tubeimoside-1[187]. Notably, there exist various adaptively compensatory mechanisms that cooperatively contribute to the aggravation of immunosuppressive TME, which will be reviewed later. Intriguingly, with the emergence of diverse promising PD-1/PD-L1 inhibitors, Jin et al.[188] introduced that artificial intelligence can be elegantly exploited to assess PD-1/PD-L1 inhibitors from three perspectives, which are population screening, response prediction, and efficacy evaluation, thereby conveniently facilitating the selection of different PD-1/PD-L1 inhibitors.

For genetic ablation of PD-1 or PD-L1 gene, Deng et al.[189] designed a CRISPR-Cas9 plasmid to specifically knock out Cyclin-dependent kinase 5 (Cdk5) gene to attenuate the PD-L1 expression on tumor cells, with a biodegradable cationic polymer, poly(β-amino esters) (PBAEs) as the carrier (denoted as aPBAE/Cas9-Cdk5). CRISPR-Cas9 genome editing system is characterized by simplicity, highly targeting ability, and great knockout efficiency. Compared with PEI 25K and HP reagent, aPBAE/Cas9-Cdk5 showed higher transfection efficiency in various cell lines. *In vivo*, both the melanoma and triple-negative breast cancer models exhibited obvious PD-L1 downregulation, with modulated immunosuppressive TME, enhanced antitumor immunity, and suppressed tumor progression. Based on nanotechnology and genome engineering, aPBAE/Cas9-Cdk5 enriched the options of immunotherapy, providing an innovative candidate for antitumor treatment.

Equally, RNA interference plays a promising role in PD-1/PD-L1 checkpoint blockade. Guo et al.[190] employed a PD-L1 small interfering RNA (siRNA) cross-linker and a pheophorbide A (PPA) photosensitizer-bearing DNA tetrahedral framework to fabricate a supramolecular nucleic acid nanogel (denoted as siRNA/PPA-NG). PPAs were grafted onto the backbones of four component DNA strands at the phosphorothioate modification sites to obtain water-soluble PPA-DNA conjugates, which would assemble into a DNA tetrahedral framework. Then, a sticky end was introduced at each vertex of the PPA-bearing DNA tetrahedron, enabling the overhangs predesigned on the siRNA linker. Eventually, two structural units were successfully cross-linked through the sticky end association to form siRNA/PPA-NG, in which the PPAs can homogeneously dissolve in an aqueous solution under the assistance of hydrophilic DNA. In addition, siRNA was deemed more effective than mAb inhibitors because it suppressed immune checkpoint proteins from the intracellular source, permitting a more thorough PD-1/PD-L1 blockade and an enhanced T-cell mediated cancer elimination. The synergetic combination with PDT further augmented antitumor effects, and the nanogel served as a highly desirable co-packaging vehicle, with satisfactory drug loading capability, great siRNA compression efficiency, and biocompatibility. This nanosystem felicitously exemplified the significance of rational design in combining varied therapeutic agents (Fig. 7). Likewise, Kim et al.[191] engineered a polymeric nanoconjugate consisting of siPD-L1-based polyplexes, PEGylated hyaluronic acid and model foreign antigen ovalbumin, which achieved vigorous rejection towards tumor cells, TME reprogramming, and long-term protective immunity.

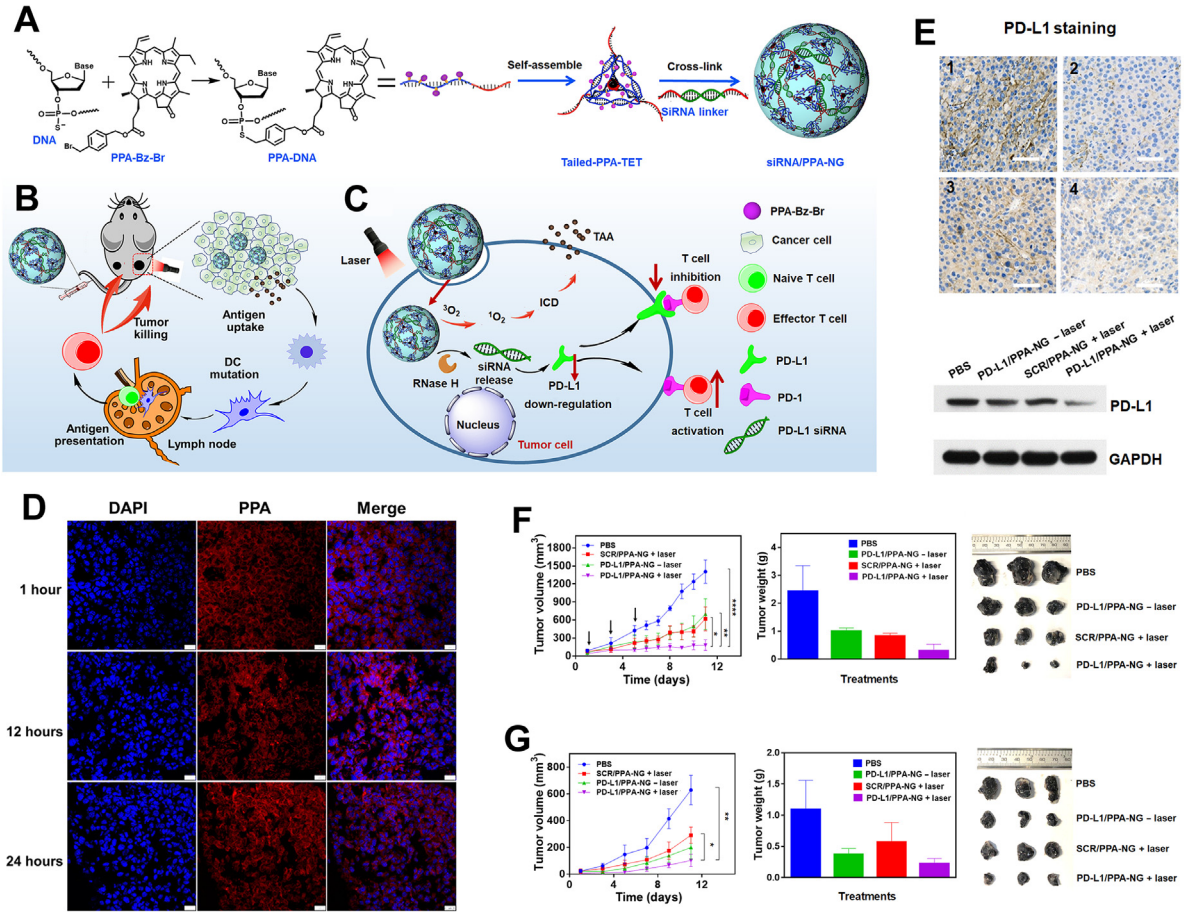


Figure 7 Photosensitizer and PD-L1 siRNA copackaged nucleic acid nanogel for synergistic cancer photoimmunotherapy. (A) Preparation process of the PPA-DNA conjugates, tailed-PPA-TET and siRNA/PPA-NG. (B) Schematic illustration of the photoimmunotherapy mediated by siRNA/PPA-NG *in vivo*. (C) Schematic illustration of the intracellular synergistic antitumor effects of siRNA/PPA-NG. (D) CLSM images of cellular uptake behaviors of siRNA/PPA-NG in tumor sections from the mice after intravenously administration (scale bar = 25 μm). (E) Immunohistochemical and Western blot analysis of PD-L1 expression in primary tumors(scale bar = 50 μm). Treatment groups: 1, PBS; 2, PD-L1/PPA-NG; 3, SCR/PPA-NG + laser; 4, PD-L1/PPA-NG + laser. (F) Growth curves, weights and images of the primary tumors and (G) the distant tumors following the indicated treatment. *P* values in (F) and (G) were calculated by ANOVA and two-tailed Student's *t*-test. Data are presented as mean ± SD, $^{*}P < 0.05$, $^{**}P < 0.01$ and $^{****}P < 0.0001$ *vs*. indicated. Reproduced with the permission from Ref. 190. Copyright © 2022, The Authors.

Despite inspiring breakthroughs made by PD-1/PD-L1 blockade in clinical practice, the therapeutic outcomes of anti-PD-1/PD-L1 antibodies are constrained due to low durable response rates and acquired resistance that results from compensatory mechanisms of immunosuppressive TME. Therefore, antitumor immunotherapies concerning inhibitory co-stimulatory molecule-related pathways are still expected to be explored and optimized.

3.5. *Other strategies*

Multiple crosstalk between cancer and immune cells collaboratively shapes the intricate immunosuppressive TME. Researchers have been dedicated to probing more strategies concerning TME remodeling, which can be potentially beneficial for antitumor immunotherapies in the clinic. Apart from the typical strategies delineated above, diverse strategies are continuously emerging.

It is noteworthy that, metabolic behaviors of cancer are of distinguishing features compared with healthy, normal tissues. Altered aerobic glycolysis (also known as the "Warburg effect") not only provides energy, building blocks, and redox potentials for uncontrollable cancer proliferation, but also generates a large amount of lactic acid and ATP and leads to hypoxia[192,193]. Therefore, with TME homeostasis being severely disrupted, manifold dysfunctions correspondingly facilitate the formation of immunosuppressive TME. For instance, Treg cells can actively absorb lactic acid produced in highly glycolytic TME, resulting in enhanced PD-1 expression in Treg cells, dampened PD-1 expression in Teff cells, and the failure of PD-1 blockade treatment[194]. Tremendous efforts have been devoted to reversing abnormal metabolic behaviors, alleviating the TME burdens, and ameliorating the efficiency of immunotherapy. Ma et al.[195] put forward bio-responsive DOX-based mannose nanogels (DM NGs), with prolonged blood circulation and reinforced tumor accumulation. The inferior bioavailability of chemo-drug was surmounted by conjugating hydroxyl-containing DOX with hydroxyl-containing mannose *via* GSH-sensitive-SS- bond linker. High GSH concentration in the tumor region would trigger the bond

cleavage and the release of drug. Mannose was engulfed by cells through glucose transporter, which could impede glucose uptake of tumor cells, thus interdicting glycolysis, regulating tumor metabolism, and ultimately resulting in the apoptosis of tumor cells[196]. Accompanied by robust DOX-induced ICD, the DM NGs manifested effective immunosuppressive TME regulating ability and amplified tumor eliminating effects both *in vitro* and *in vivo*, offering a promising combinatorial antitumor chemo-immunotherapy. For a more thorough glycolysis interdiction, Zang et al.[197] developed a biomimetic nanocarrier with chemotherapeutic paclitaxel and glycolysis inhibitor PFK15 co-loaded. The nanocarrier was endowed with a dual-targeting ability due to the capsulation of hybrid membranes of breast cancer cell membrane (4T1 cell membranes) and activated fibroblast membranes (CAFs-like NIH3T3 cell membranes), eventually yielding enhanced effects of lactate production abatement and chemo-immunotherapy. Besides, in a study from our research group[198], morpholine-modified PEGylated bilirubin nanoparticles loaded with Ce6 and diclofenac (Dc) were brought up (denoted as Ce6&Dc@MBNP), with an aim to settle the issue that PDT-induced oxygen consumption and microvascular damage could aggravate hypoxia, aerobic glycolysis, and angiogenesis. Dc, one of the non-steroidal anti-inflammatory drugs (NSAID), was a lactate dehydrogenase A (LDHA) inhibitor and exploited to interfere with lactate secretion, thereby averting hypoxia-induced resistance-glycolysis and angiogenesis[199]. Aiming to implement deep penetration in tumors, our group combined a self-propelled nanomotor (NM) with hexokinase-2 (HK-2) siRNA to synergistically reconstruct TME[200]. The NM adsorbed catalase (Cat) and glucose oxidase (GOx) to persistently generate oxygen bubbles in a cascade manner, assisting the nanomedicine to move towards deep tumor to alleviate hypoxia and the lysosome escaping of HK-2 siRNA to efficiently inhibit glycolysis. Particularly, *in vivo* results demonstrated a preeminent anti-metastasis outcome of commercially available albumin-bound paclitaxel (PTX@HSA) with NM-si pre-treated for TME modulation (Fig. 8). In general, researchers have been opening up more versatile and comprehensive strategies for addressing glycolysis-associated immunosuppression.

Additionally, hypoxic tumors activate the occurrence of an adenosinergic pathway, which emerges as a major immunosuppressive mechanism and simultaneously a prospective novel therapeutic target for cancer therapy[201]. Abundant ATP may be degraded to increase the adenosine level. Yu et al.[202] constructed an ATP-exhausted nanocomplex by the self-assembly of siRNA/PEI complex, imidazole-2-carboxaldehyde (2-ICA) and Zn^{2+}, with electrostatic adsorbed ICG and surface coated RGD-decorated polylactic acid-hyperbranched polyglycerol (PLA-HPG-RGD), which not only intervened in tumor energy metabolism to regulate TME but also depleted excessive intracellular ATP and inhibited ATP synthesis, thereby enhancing PTT-induced ICD. Mao et al.[203] contrived ROS-responsive nanoparticles loading CD39/CD73 inhibitor ARL and photosensitizer IR700, which combined ATP release from PDT-induced ICD with ATP degradation constraint to realize a durable antitumor immune response. Nucleotide derivatives such as ARL are potent ectonucleotidase inhibitors that hamper intracellular ATP degradation to adenosine, with unsatisfactory pharmacokinetic properties. Thus, boronic acids (BAs) were exploited to form ROS-responsive reversible covalent esters with ARL. More specifically, the ROS-labile nanoparticles were composed of BA-containing cationic polymer poly [(2-acrylogy) ethyl (*p*-boronic acid benzyl) diethylammonium bromide] (PDEAEA-PBA) and IR700-containing lipid polymer 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-*N*-[amino (polyethylene glycol)-2000]-IRDye 700 (DSPE-PEG_{2000}-IR700), which can precisely release ARL in response to ROS. Moreover, in addition to endogenous ROS, IR700 also generated ROS upon near-infrared irradiation, accelerating the release of ARL. Mouse tumor models confirmed that these NPs could reprogram the immunogenic landscape in tumors, and ignite tumor-specific T cell responses as well as tumor regression. Notably, immunological effects were also induced in the patient-derived organotypic tumor spheroid model, which vigorously supported the translation potential for clinical treatment. Altogether, a plethora of feasible strategies has emerged to reconstruct the immunosuppressive TME and enhance anticancer immunotherapy.

4. Obstacles encountered in remodeling immunosuppressive TME

Collectively, investigations on antitumor immunotherapy are vigorously thriving, and the significance of remodeling immunosuppressive TME to enhance therapeutic outcomes has been recognized. Nevertheless, due to the extraordinary intricacy of the immune system and oncology, various facets of the intrinsic mechanisms are still waiting to be unraveled. Moreover, limitations (*e.g.*, low response rates, therapy resistance, adverse events) have emerged in the clinical practice of immunotherapy, which greatly constrain the therapeutic benefits to cancer patients. How to elegantly balance the feasibility of clinical translation and the effectiveness of immunotherapies remains to be tackled. The discussion beneath will briefly introduce several obstacles encountered in immunosuppressive TME modulation and its clinical translation.

In order to spur more successes in immunosuppressive TME rejuvenation, it is imperative to recognize multiple adaptively compensatory mechanisms in immunosuppressive TME. For instance, immunotherapy based on immune response enhancement triggers the activation of the adenosinergic pathway in TME, which is a negative feedback mechanism that dampens TME inflammation and bolsters TME immunosuppression[201]. Likewise, compensatory inhibitory signaling, such as LAG3 and TIM3, is upregulated in the course of PD-1/PD-L1 blockade therapy, hampering the reinvigoration of $CD8^+$ T cells[204]. For the sake of complete tumor elimination and tumor relapse inhibition, a broader understanding of such latent compensatory mechanisms is required imminently to polish up existing immunotherapies.

Even though targeted nanomedicines do manifest preeminent capabilities of remodeling immunosuppressive TME, challenges also exist, which inevitably stave off the clinical translation of preclinically viable nanomedicines. Firstly, nanoparticles themselves have aroused wide concerns that potential or unexpected toxicity will be detrimental to normal organs and tissues[205]. Secondly, the lack of detailed understanding of TME and the immune landscape in a certain subset of patients may invalidate the precise delivery of nanomedicine. Moreover, cancer models adopted in preclinical tests cannot ideally simulate and represent the landscape of TME in clinical human cancer patients, thus posing the predicament that preclinically effective and safe nanomedicines received few benefits in the clinical inspection. For

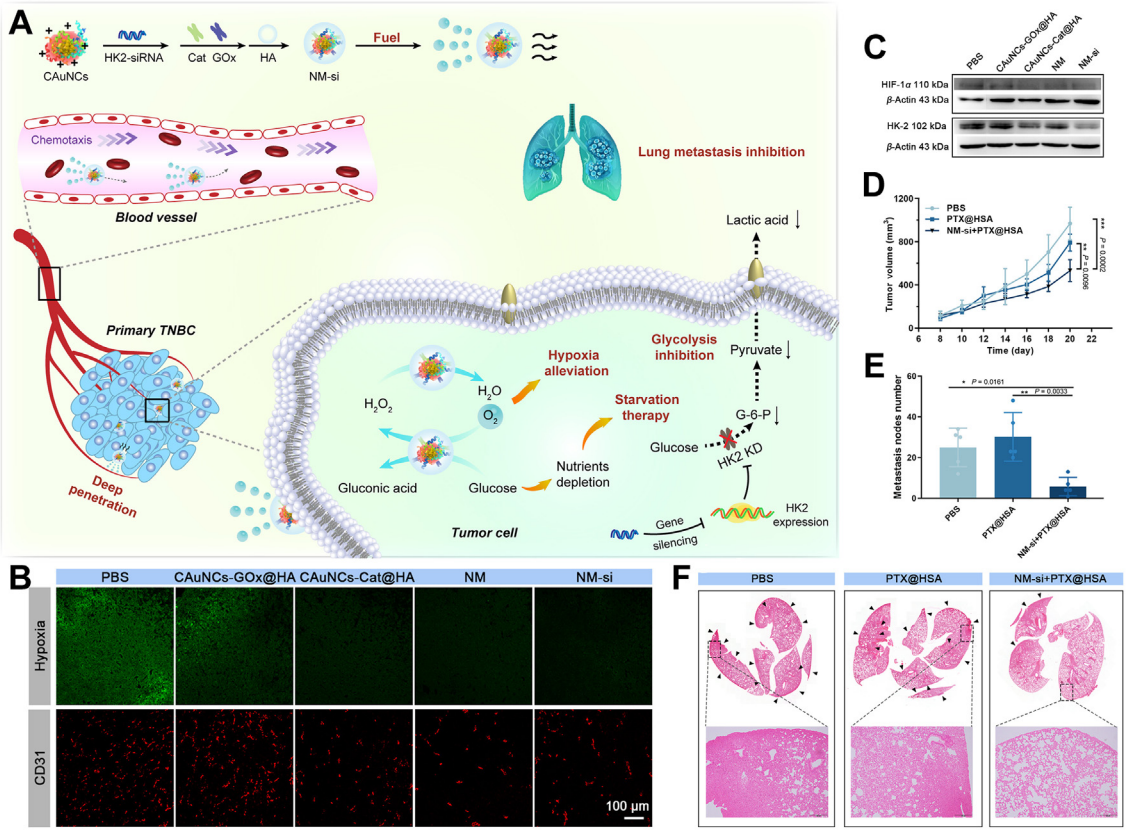


Figure 8 Nanomotors with siRNA to modulate TME *via* hypoxia alleviation and glycolysis suppression. (A) Schematic illustration of the cascade enzyme-driven NM-si for TME reconstruction. (B) Immunofluorescence images of tumor slices (scale bar = 100 μm). (C) Western blot analysis of HIF-1α and HK-2 expression in tumor following treatment with different drugs. (D) Growth curves after different treatments. (E) Number of metastasis nodules. (F) H&E staining of lung metastasis in 4T1 tumor-bearing mice. *P* values in (D) and (E) were calculated by one-way ANOVA with Tukey multiple comparisons post-test. Data are presented as mean ± SD ($n = 5$) $^*P < 0.05$ $^{**}P < 0.01$, and $^{***}P < 0.001$ *vs.* indicated. Reproduced with the permission from Ref. 200. Copyright © 2021, Chinese Pharmaceutical Association and Institute of Materia Medica. Chinese Academy of Medical Sciences.

instance, the EPR effect, as a major underlying mechanism for passive targeted nanomedicine-delivery systems, is universally acknowledged and has been extensively leveraged. But EPR effect-motivated accumulation of nanomedicines in transgenic spontaneous cancer models or humans are reckoned invalid or insufficient in comparison with subcutaneous and orthotopic cancer models, which are commonly utilized in most researches, thus provoking efficacy inconsistency between preclinical tests and clinical trials[206–208]. Additionally, the protein corona formed onto nanoparticles may greatly alter the *in vivo* distribution of targeted nanomedicines, leading to off-target distribution and high toxicity[209,210]. Therefore, the disposal of outdated nanomedicine design criteria and balancing clinical feasibility with innovation are crucial for future advancement. In general, for targeted nanomedicines-based immunotherapies, it is of great challenge to be successfully translated from the proof-of-concept stage to clinically available therapeutics. Faced with countless known and unknown obstacles, improving understanding of cancer heterogeneity, adopting more relevant animal models and testing protocols as well as pre-selecting patients that are likely to respond to corresponding therapies, are all effective approaches[211].

5. Conclusions and prospectives

It is well established that immunosuppressive TME plays a critical role in the resistance to antitumor immunotherapies. Reversing immunosuppression is undoubtedly conducive to the restoration of human immunity, which is a substantial foundation for immunotherapy. As previously mentioned, rehabilitating immune recognition, decreasing immunosuppressive-associated cytokines, modulating immunosuppressive cells, and impeding inhibitory co-stimulatory molecule-related pathways have manifested favorable efficacy for remodeling the immunosuppressive TME. At the same time, the fabrication elasticity of nanomedicines can be well harnessed during the design of specific delivery systems for immunotherapy. Of late, immunotherapies consisting of nano-engineering and immunosuppressive TME reprogramming have yielded considerable invaluable results, presenting multiple potential avenues for clinical practice.

Nevertheless, due to the intricacy and continuous evolvement of TME, massive researches are still required for further understanding of immuno-oncology. Moreover, according to the properties of specific patients and tumors, individualized

immunotherapy should be leveraged to realize the balance between efficacy and side effects. Also, attention should be concentrated on the latent long-term systematic toxicity. Despite the arduousness, we envisage that enhancing anticancer immunotherapy *via* remodeling immunosuppressive TME by well-designed targeted nanomedicines can address various bottlenecks of tumor therapy in a coordinated manner, thus achieving a new dimension for clinical cancer treatment.

Acknowledgments

This study was supported by National Natural Science Foundation of China (82173762), 111 Project (B18035, China), the Key Research and Development Program of Science and Technology Department of Sichuan Province (2022JDJQ0050, 2022YFS0334).

Author contributions

Yanyan Xu and Jingyuan Xiong conceived the review. Yanyan Xu wrote the manuscript and designed the figures. Yanyan Xu, Jingyuan Xiong, Xiyang Sun, and Huile Gao edited the manuscript. All of the authors have read and approved the final manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Riley RS, June CH, Langer R, Mitchell MJ. Delivery technologies for cancer immunotherapy. *Nat Rev Drug Discov* 2019;**18**:175−96.
2. Kiaie SH, Sanaei MJ, Heshmati M, Asadzadeh Z, Azimi I, Hadidi S, et al. Immune checkpoints in targeted-immunotherapy of pancreatic cancer: new hope for clinical development. *Acta Pharm Sin B* 2021;**11**:1083−97.
3. Suda K. Recent advances in cancer immunotherapy. *Biomolecules* 2021;**11**:335.
4. Dana H, Chalbatani GM, Jalali SA, Mirzaei HR, Grupp SA, Suarez ER, et al. CAR-T cells: early successes in blood cancer and challenges in solid tumors. *Acta Pharm Sin B* 2021;**11**:1129−47.
5. Al-Salama ZT. Durvalumab: a review in extensive-stage SCLC. *Target Oncol* 2021;**16**:857−64.
6. Ali S, Kjeken R, Niederlaender C, Markey G, Saunders TS, Opsata M, et al. The European medicines agency review of Kymriah (Tisagenlecleucel) for the treatment of acute lymphoblastic leukemia and diffuse large B-cell lymphoma. *Oncologist* 2020;**25**:e321−7.
7. Papadouli I, Mueller-Berghaus J, Beuneu C, Ali S, Hofner B, Petavy F, et al. EMA review of axicabtagene ciloleucel (yescarta) for the treatment of diffuse large B-cell lymphoma. *Oncologist* 2020;**25**:894−902.
8. Finn OJ. Immuno-oncology: understanding the function and dysfunction of the immune system in cancer. viii6-9 *Ann Oncol* 2012;**23**(Suppl 8).
9. Teng MW, Galon J, Fridman WH, Smyth MJ. From mice to humans: developments in cancer immunoediting. *J Clin Invest* 2015;**125**:3338−46.
10. Dunn GP, Bruce AT, Ikeda H, Old LJ, Schreiber RD. Cancer immunoediting: from immunosurveillance to tumor escape. *Nat Immunol* 2002;**3**:991−8.
11. Velcheti V, Schalper K. Basic overview of current immunotherapy approaches in cancer. *Am Soc Clin Oncol Educ Book* 2016;**35**:298−308.
12. Croci D, Salatino M. Tumor immune escape mechanisms that operate during metastasis. *CPB* 2011;**12**:1923−36.
13. Valkenburg KC, de Groot AE, Pienta KJ. Targeting the tumour stroma to improve cancer therapy. *Nat Rev Clin Oncol* 2018;**15**:366−81.
14. Huang J, Yang B, Peng Y, Huang J, Wong SHD, Bian L, et al. Nanomedicine-boosting tumor immunogenicity for enhanced immunotherapy. *Adv Funct Mater* 2021;**31**:2011171.
15. Li L, Yu R, Cai T, Chen Z, Lan M, Zou T, et al. Effects of immune cells and cytokines on inflammation and immunosuppression in the tumor microenvironment. *Int Immunopharmacol* 2020;**88**:106939.
16. Munn DH, Mellor AL. IDO in the Tumor microenvironment: inflammation, counter-regulation, and tolerance. *Trends Immunol* 2016;**37**:193−207.
17. Melincovici CS, Boşca AB, Şuşman S, Mărginean M, Mihu C, Istrate M, et al. Vascular endothelial growth factor (VEGF)−key factor in normal and pathological angiogenesis. *Rom J Morphol Embryol* 2018;**59**:455−67.
18. Monteran L, Erez N. The dark side of fibroblasts: cancer-associated fibroblasts as mediators of immunosuppression in the tumor microenvironment. *Front Immunol* 2019;**10**:1835.
19. DeNardo DG, Ruffell B. Macrophages as regulators of tumour immunity and immunotherapy. *Nat Rev Immunol* 2019;**19**:369−82.
20. Zhu Y, Yu X, Thamphiwatana SD, Zheng Y, Pang Z. Nanomedicines modulating tumor immunosuppressive cells to enhance cancer immunotherapy. *Acta Pharm Sin B* 2020;**10**:2054−74.
21. Zhang Y, Zhang Z. The history and advances in cancer immunotherapy: understanding the characteristics of tumor-infiltrating immune cells and their therapeutic implications. *Cell Mol Immunol* 2020;**17**:807−21.
22. O'Neill RE, Cao X. Co-stimulatory and co-inhibitory pathways in cancer immunotherapy. *Adv Cancer Res* 2019;**143**:145−94.
23. Hu J, Yuan X, Wang F, Gao H, Liu X, Zhang W. The progress and perspective of strategies to improve tumor penetration of nanomedicines. *Chin Chem Lett* 2021;**32**:1341−7.
24. Zhang W, Wang F, Hu C, Zhou Y, Gao H, Hu J. The progress and perspective of nanoparticle-enabled tumor metastasis treatment. *Acta Pharm Sin B* 2020;**10**:2037−53.
25. Peng S, Xiao F, Chen M, Gao H. Tumor-microenvironment-responsive nanomedicine for enhanced cancer immunotherapy. *Adv Sci (Weinh)* 2022;**9**:e2103836.
26. Muluh TA, Chen Z, Li Y, Xiong K, Jin J, Fu S, et al. Enhancing cancer immunotherapy treatment goals by using nanoparticle delivery system. *Int J Nanomedicine* 2021;**16**:2389−404.
27. Pérez-Herrero E, Fernández-Medarde A. Advanced targeted therapies in cancer: drug nanocarriers, the future of chemotherapy. *Eur J Pharm Biopharm* 2015;**93**:52−79.
28. Xie A, Hanif S, Ouyang J, Tang Z, Kong N, Kim NY, et al. Stimuli-responsive prodrug-based cancer nanomedicine. *EBioMedicine* 2020;**56**:102821.
29. Pérez-Herrero E, Fernández-Medarde A. The reversed intra- and extracellular pH in tumors as a unified strategy to chemotherapeutic delivery using targeted nanocarriers. *Acta Pharm Sin B* 2021;**11**:2243−64.
30. Jia W, Wang Y, Liu R, Yu X, Gao H. Shape Transformable strategies for drug delivery. *Adv Funct Mater* 2021;**31**:2009765.
31. Lin C, Tong F, Liu R, Xie R, Lei T, Chen Y, et al. GSH-responsive SN38 dimer-loaded shape-transformable nanoparticles with iRGD for enhancing chemo-photodynamic therapy. *Acta Pharm Sin B* 2020;**10**:2348−61.
32. Batrakova EV, Gendelman HE, Kabanov AV. Cell-mediated drug delivery. *Expert Opin Drug Deliv* 2011;**8**:415−33.
33. Mao Y, Zou C, Jiang Y, Fu D. Erythrocyte-derived drug delivery systems in cancer therapy. *Chin Chem Lett* 2021;**32**:990−8.
34. Nguyen VH, Lee BJ. Protein corona: a new approach for nanomedicine design. *Int J Nanomedicine* 2017;**12**:3137−51.
35. Song Y, Guo X, Fu J, He B, Wang X, Dai W, et al. Dual-targeting nanovesicles enhance specificity to dynamic tumor cells *in vitro* and

in vivo via manipulation of $\alpha v\beta 3$-ligand binding. *Acta Pharm Sin B* 2020;**10**:2183−97.
36. Tsvetkov P, Coy S, Petrova B, Dreishpoon M, Verma A, Abdusamad M, et al. Copper induces cell death by targeting lipoylated TCA cycle proteins. *Science* 2022;**375**:1254−61.
37. Fan W, Yung B, Huang P, Chen X. Nanotechnology for multimodal synergistic cancer therapy. *Chem Rev* 2017;**117**:13566−638.
38. He M, Yang T, Wang Y, Wang M, Chen X, Ding D, et al. Immune checkpoint inhibitor-based strategies for synergistic cancer therapy. *Adv Healthc Mater* 2021;**10**:e2002104.
39. Schreiber RD, Old LJ, Smyth MJ. Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. *Science* 2011;**331**:1565−70.
40. Ruan S, Huang Y, He M, Gao H. Advanced biomaterials for cell-specific modulation and restore of cancer immunotherapy. *Adv Sci (Weinh)* 2022;**9**:e2200027.
41. Gubin MM, Vesely MD. Cancer immunoediting in the era of immuno-oncology. *Clin Cancer Res* 2022;**28**:3917−28.
42. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011;**144**:646−74.
43. Aguirre-Ghiso JA. Models, mechanisms and clinical evidence for cancer dormancy. *Nat Rev Cancer* 2007;**7**:834−46.
44. Koebel CM, Vermi W, Swann JB, Zerafa N, Rodig SJ, Old LJ, et al. Adaptive immunity maintains occult cancer in an equilibrium state. *Nature* 2007;**450**:903−7.
45. Friedman LA, Bullock TN, Sloan EA, Ring KL, Mills AM. MHC class I loss in endometrial carcinoma: a potential resistance mechanism to immune checkpoint inhibition. *Mod Pathol* 2021;**34**:627−36.
46. Lee HJ, Song IH, Park IA, Heo SH, Kim YA, Ahn JH, et al. Differential expression of major histocompatibility complex class I in subtypes of breast cancer is associated with estrogen receptor and interferon signaling. *Oncotarget* 2016;**7**:30119−32.
47. Dhatchinamoorthy K, Colbert JD, Rock KL. Cancer immune evasion through loss of MHC class I antigen presentation. *Front Immunol* 2021;**12**:636568.
48. Zajonc DM. Unconventional peptide presentation by classical MHC class I and implications for T and NK cell activation. *Int J Mol Sci* 2020;**21**:7561.
49. Aptsiauri N, Ruiz-Cabello F, Garrido F. The transition from HLA-I positive to HLA-I negative primary tumors: the road to escape from T-cell responses. *Curr Opin Immunol* 2018;**51**:123−32.
50. Dusenbery AC, Maniaci JL, Hillerson ND, Dill EA, Bullock TN, Mills AM. MHC class I loss in triple-negative breast cancer: a potential barrier to PD-1/PD-L1 checkpoint inhibitors. *Am J Surg Pathol* 2021;**45**:701−7.
51. Dibbern ME, Bullock TN, Jenkins TM, Duska LR, Stoler MH, Mills AM. Loss of MHC class I expression in hpv-associated cervical and vulvar neoplasia: a potential mechanism of resistance to checkpoint inhibition. *Am J Surg Pathol* 2020;**44**:1184−91.
52. Vesely MD, Schreiber RD. Cancer immunoediting: antigens, mechanisms, and implications to cancer immunotherapy: tumor antigens and cancer immunoediting. *Ann NY Acad Sci* 2013;**1284**:1−5.
53. Wculek SK, Cueto FJ, Mujal AM, Melero I, Krummel MF, Sancho D. Dendritic cells in cancer immunology and immunotherapy. *Nat Rev Immunol* 2020;**20**:7−24.
54. Jhunjhunwala S, Hammer C, Delamarre L. Antigen presentation in cancer: insights into tumour immunogenicity and immune evasion. *Nat Rev Cancer* 2021;**21**:298−312.
55. Veglia F, Gabrilovich DI. Dendritic cells in cancer: the role revisited. *Curr Opin Immunol* 2017;**45**:43−51.
56. Dranoff G. Cytokines in cancer pathogenesis and cancer therapy. *Nat Rev Cancer* 2004;**4**:11−22.
57. Lippitz BE. Cytokine patterns in patients with cancer: a systematic review. *Lancet Oncol* 2013;**14**:e218−28.
58. Ramjiawan RR, Griffioen AW, Duda DG. Anti-angiogenesis for cancer revisited: is there a role for combinations with immunotherapy?. *Angiogenesis* 2017;**20**:185−204.
59. Carmeliet P. VEGF as a key mediator of angiogenesis in cancer. *Oncology* 2005;**69**(Suppl 3):4−10.
60. Fukumura D, Kloepper J, Amoozgar Z, Duda DG, Jain RK. Enhancing cancer immunotherapy using antiangiogenics: opportunities and challenges. *Nat Rev Clin Oncol* 2018;**15**:325−40.
61. Zhao Y, Yu X, Li J. Manipulation of immune−vascular crosstalk: new strategies towards cancer treatment. *Acta Pharm Sin B* 2020;**10**:2018−36.
62. Apte RS, Chen DS, Ferrara N. VEGF in signaling and disease: beyond discovery and development. *Cell* 2019;**176**:1248−64.
63. Gabrilovich DI, Chen HL, Girgis KR, Cunningham HT, Meny GM, Nadaf S, et al. Production of vascular endothelial growth factor by human tumors inhibits the functional maturation of dendritic cells. *Nat Med* 1996;**2**:1096−103.
64. Gavalas NG, Tsiatas M, Tsitsilonis O, Politi E, Ioannou K, Ziogas AC, et al. VEGF directly suppresses activation of T cells from ascites secondary to ovarian cancer *via* VEGF receptor type 2. *Br J Cancer* 2012;**107**:1869−75.
65. Sakai Y, Goodison S, Cao W, Urquidi V, Namiki K, Porvasnik S, et al. VEGF induces expression of BCL-2 and multiple signaling factors in microvascular endothelial cells in a prostate cancer model. *World J Urol* 2009;**27**:659−66.
66. Nör JE, Christensen J, Liu J, Peters M, Mooney DJ, Strieter RM, et al. Up-regulation of BCL-2 in microvascular endothelial cells enhances intratumoral angiogenesis and accelerates tumor growth. *Cancer Res* 2001;**61**:2183−8.
67. Munn DH, Mellor AL. Indoleamine 2,3-dioxygenase and tumor-induced tolerance. *J Clin Invest* 2007;**117**:1147−54.
68. Munn DH. Blocking IDO activity to enhance anti-tumor immunity. *Front Biosci (Elite Ed)* 2012;**4**:734−45.
69. Yang L, Pang Y, Moses HL. TGF-*b* and immune cells: an important regulatory axis in the tumor microenvironment and progression. *Trends Immunol* 2010;**31**:220−7.
70. Syed V. TGF-β signaling in cancer. *J Cell Biochem* 2016;**117**:1279−87.
71. Zou S, Tong Q, Liu B, Huang W, Tian Y, Fu X. Targeting STAT3 in cancer immunotherapy. *Mol Cancer* 2020;**19**:145.
72. Draghiciu O, Nijman HW, Daemen T. From tumor immunosuppression to eradication: targeting homing and activity of immune effector cells to tumors. *Clin Dev Immunol* 2011;**2011**:439053.
73. Whiteside TL. What are regulatory T cells (Treg) regulating in cancer and why?. *Semin Cancer Biol* 2012;**22**:327−34.
74. Tanaka A, Sakaguchi S. Regulatory T cells in cancer immunotherapy. *Cell Res* 2017;**27**:109−18.
75. Yang Q, Guo N, Zhou Y, Chen J, Wei Q, Han M. The role of tumor-associated macrophages (TAMs) in tumor progression and relevant advance in targeted therapy. *Acta Pharm Sin B* 2020;**10**:2156−70.
76. Chanmee T, Ontong P, Konno K, Itano N. Tumor-associated macrophages as major players in the tumor microenvironment. *Cancers (Basel)* 2014;**6**:1670−90.
77. Munir MT, Kay MK, Kang MH, Rahman MM, Al-Harrasi A, Choudhury M, et al. Tumor-associated macrophages as multifaceted regulators of breast tumor growth. *Int J Mol Sci* 2021;**22**:6526.
78. Zhu L, Fu X, Chen X, Han X, Dong P. M2 macrophages induce EMT through the TGF-β/Smad2 signaling pathway. *Cell Biol Int* 2017;**41**:960−8.
79. Chen Z, Wu J, Wang L, Zhao H, He J. Tumor-associated macrophages of the M1/M2 phenotype are involved in the regulation of malignant biological behavior of breast cancer cells through the EMT pathway. *Med Oncol* 2022;**39**:83.
80. Hwang I, Kim JW, Ylaya K, Chung EJ, Kitano H, Perry C, et al. Tumor-associated macrophage, angiogenesis and lymphangiogenesis markers predict prognosis of non-small cell lung cancer patients. *J Transl Med* 2020;**18**:443.
81. Hegde S, Leader AM, Merad M. MDSC: markers, development, states, and unaddressed complexity. *Immunity* 2021;**54**:875−84.

82. Rashid MH, Borin TF, Ara R, Piranlioglu R, Achyut BR, Korkaya H, et al. Critical immunosuppressive effect of MDSC-derived exosomes in the tumor microenvironment. *Oncol Rep* 2021;**45**:1171−81.
83. Davidson S, Coles M, Thomas T, Kollias G, Ludewig B, Turley S, et al. Fibroblasts as immune regulators in infection, inflammation and cancer. *Nat Rev Immunol* 2021;**21**:704−17.
84. Zhang Y, Zheng J. Functions of immune checkpoint molecules beyond immune evasion. *Adv Exp Med Biol* 2020;**1248**:201−26.
85. Kraehenbuehl L, Weng CH, Eghbali S, Wolchok JD, Merghoub T. Enhancing immunotherapy in cancer by targeting emerging immunomodulatory pathways. *Nat Rev Clin Oncol* 2022;**19**:37−50.
86. Zhao Y, Yang W, Huang Y, Cui R, Li X, Li B. Evolving roles for targeting CTLA-4 in cancer immunotherapy. *Cell Physiol Biochem* 2018;**47**:721−34.
87. Liu Y, Zheng P. Preserving the CTLA-4 checkpoint for safer and more effective cancer immunotherapy. *Trends Pharmacol Sci* 2020;**41**:4−12.
88. Jin HT, Ahmed R, Okazaki T. Role of PD-1 in regulating T-cell immunity. *Curr Top Microbiol Immunol* 2011;**350**:17−37.
89. Yokosuka T, Takamatsu M, Kobayashi-Imanishi W, Hashimoto-Tane A, Azuma M, Saito T. Programmed cell death 1 forms negative costimulatory microclusters that directly inhibit T cell receptor signaling by recruiting phosphatase SHP2. *J Exp Med* 2012;**209**:1201−17.
90. Cai J, Qi Q, Qian X, Han J, Zhu X, Zhang Q, et al. The role of PD-1/PD-L1 axis and macrophage in the progression and treatment of cancer. *J Cancer Res Clin Oncol* 2019;**145**:1377−85.
91. Wolf Y, Anderson AC, Kuchroo VK. TIM3 comes of age as an inhibitory receptor. *Nat Rev Immunol* 2020;**20**:173−85.
92. Workman CJ, Vignali DA. The CD4-related molecule, LAG-3 (CD223), regulates the expansion of activated T cells. *Eur J Immunol* 2003;**33**:970−9.
93. Woo SR, Turnis ME, Goldberg MV, Bankoti J, Selby M, Nirschl CJ, et al. Immune inhibitory molecules LAG-3 and PD-1 synergistically regulate T-cell function to promote tumoral immune escape. *Cancer Res* 2012;**72**:917−27.
94. Yang M, Du W, Yi L, Wu S, He C, Zhai W, et al. Checkpoint molecules coordinately restrain hyperactivated effector T cells in the tumor microenvironment. *Oncoimmunology* 2020;**9**:1708064.
95. Saleh R, Toor SM, Khalaf S, Elkord E. Breast cancer cells and PD-1/PD-L1 blockade upregulate the expression of PD-1, CTLA-4, TIM-3 and LAG-3 immune checkpoints in $CD4^+$ T cells. *Vaccines (Basel)* 2019;**7**:E149.
96. Galluzzi L, Humeau J, Buqué A, Zitvogel L, Kroemer G. Immunostimulation with chemotherapy in the era of immune checkpoint inhibitors. *Nat Rev Clin Oncol* 2020;**17**:725−41.
97. Song Y, Fu Y, Xie Q, Zhu B, Wang J, Zhang B. Anti-angiogenic agents in combination with immune checkpoint inhibitors: a promising strategy for cancer treatment. *Front Immunol* 2020;**11**:1956.
98. Li M, Song L, Qin X. Glycan changes: cancer metastasis and anticancer vaccines. *J Biosci* 2010;**35**:665−73.
99. Häuselmann I, Borsig L. Altered tumor-cell glycosylation promotes metastasis. *Front Oncol* 2014;**4**:28.
100. van Houtum EJH, Büll C, Cornelissen LAM, Adema GJ. Siglec signaling in the tumor microenvironment. *Front Immunol* 2021;**12**:790317.
101. van de Wall S, Santegoets KCM, van Houtum EJH, Büll C, Adema GJ. Sialoglycans and siglecs can shape the tumor immune microenvironment. *Trends Immunol* 2020;**41**:274−85.
102. Bärenwaldt A, Läubli H. The sialoglycan-Siglec glyco-immune checkpoint−a target for improving innate and adaptive anti-cancer immunity. *Expert Opin Ther Targets* 2019;**23**:839−53.
103. Singh N, Lee YG, Shestova O, Ravikumar P, Hayer KE, Hong SJ, et al. Impaired death receptor signaling in leukemia causes antigen-independent resistance by inducing CAR T-cell dysfunction. *Cancer Discov* 2020;**10**:552−67.
104. Bagchi S, Yuan R, Engleman EG. Immune checkpoint inhibitors for the treatment of cancer: clinical impact and mechanisms of response and resistance. *Annu Rev Pathol* 2021;**16**:223−49.
105. Zhang M, Gao S, Yang D, Fang Y, Lin X, Jin X, et al. Influencing factors and strategies of enhancing nanoparticles into tumors *in vivo*. *Acta Pharm Sin B* 2021;**11**:2265−85.
106. Rahoui N, Jiang B, Taloub N, Huang YD. Spatio-temporal control strategy of drug delivery systems based nano structures. *J Control Release* 2017;**255**:176−201.
107. Soppimath KS, Aminabhavi TM, Kulkarni AR, Rudzinski WE. Biodegradable polymeric nanoparticles as drug delivery devices. *J Control Release* 2001;**70**:1−20.
108. Markman JL, Rekechenetskiy A, Holler E, Ljubimova JY. Nanomedicine therapeutic approaches to overcome cancer drug resistance. *Adv Drug Deliv Rev* 2013;**65**:1866−79.
109. Wang Y, Wang J, Zhu D, Wang Y, Qing G, Zhang Y, et al. Effect of physicochemical properties on *in vivo* fate of nanoparticle-based cancer immunotherapies. *Acta Pharm Sin B* 2021;**11**:886−902.
110. Musetti S, Huang L. Nanoparticle-mediated remodeling of the tumor microenvironment to enhance immunotherapy. *ACS Nano* 2018;**12**:11740−55.
111. Li J, Burgess DJ. Nanomedicine-based drug delivery towards tumor biological and immunological microenvironment. *Acta Pharm Sin B* 2020;**10**:2110−24.
112. 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.
113. Ahmed A, Tait SWG. Targeting immunogenic cell death in cancer. *Mol Oncol* 2020;**14**:2994−3006.
114. Qin L, Cao J, Shao K, Tong F, Yang Z, 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.
115. Yu W, He X, Yang Z, Yang X, Xiao W, Liu R, et al. Sequentially responsive biomimetic nanoparticles with optimal size in combination with checkpoint blockade for cascade synergetic treatment of breast cancer and lung metastasis. *Biomaterials* 2019;**217**:119309.
116. Yang X, Hu C, Tong F, Liu R, Zhou Y, Qin L, et al. Tumor microenvironment-responsive dual drug dimer-loaded pegylated bilirubin nanoparticles for improved drug delivery and enhanced immune-chemotherapy of breast cancer. *Adv Funct Mater* 2019;**29**:1901896.
117. Ren H, Yong J, Yang Q, Yang Z, Liu Z, Xu Y, et al. Self-assembled FeS-based cascade bioreactor with enhanced tumor penetration and synergistic treatments to trigger robust cancer immunotherapy. *Acta Pharm Sin B* 2021;**11**:3244−61.
118. Hu Q, Huang Z, Duan Y, Fu Z, Liu Bin. Reprogramming tumor microenvironment with photothermal therapy. *Bioconjug Chem* 2020;**31**:1268−78.
119. Chen X, Zou J, Zhang K, Zhu J, Zhang Y, Zhu Z, et al. Photothermal/matrix metalloproteinase-2 dual-responsive gelatin nanoparticles for breast cancer treatment. *Acta Pharm Sin B* 2021;**11**:271−82.
120. Jiao X, Sun L, Zhang W, Ren J, Zhang L, Cao Y, et al. Engineering oxygen-deficient ZrO_{2-x} nanoplatform as therapy-activated "immunogenic cell death (ICD)" inducer to synergize photothermal-augmented sonodynamic tumor elimination in NIR-II biological window. *Biomaterials* 2021;**272**:120787.
121. Zhang L, Li M, Zhou Q, Dang M, Tang Y, Wang S, et al. Computed tomography and photoacoustic imaging guided photodynamic therapy against breast cancer based on mesoporous platinum with insitu oxygen generation ability. *Acta Pharm Sin B* 2020;**10**:1719−29.
122. Ma S, Song W, Xu Y, Si X, Lv S, Zhang Y, et al. Rationally designed polymer conjugate for tumor-specific amplification of oxidative stress and boosting antitumor immunity. *Nano Lett* 2020;**20**:2514−21.
123. Gong N, Ma X, Ye X, Zhou Q, Chen X, Tan X, et al. Carbon-dot-supported atomically dispersed gold as a mitochondrial oxidative stress amplifier for cancer treatment. *Nat Nanotechnol* 2019;**14**:379−87.

124. Ding F, Li F, Tang D, Wang B, Liu J, Mao X, et al. Restoration of the immunogenicity of tumor cells for enhanced cancer therapy *via* nanoparticle-mediated copper chaperone inhibition. *Angew Chem Int Ed Engl* 2022;**61**:e202203546.
125. Chen Y, He P, Jana D, Wang D, Wang M, Yu P, et al. Glutathione-depleting organic metal adjuvants for effective NIR−II photothermal immunotherapy. *Adv Mater* 2022;**34**:e2201706.
126. Green DR, Ferguson T, Zitvogel L, Kroemer G. Immunogenic and tolerogenic cell death. *Nat Rev Immunol* 2009;**9**:353−63.
127. Chen YL, Chang MC, Chiang YC, Lin HW, Sun NY, Chen CA, et al. Immuno-modulators enhance antigen-specific immunity and anti-tumor effects of mesothelin-specific chimeric DNA vaccine through promoting DC maturation. *Cancer Lett* 2018;**425**:152−63.
128. Lee K, Kim TS, Seo Y, Kim SY, Lee H. The combined hybrid structure of siRNA tailed IVT mRNA (ChriST mRNA) for enhancing DC maturation and subsequent anticancer T cell immunity. *J Control Release* 2020;**327**:225−34.
129. Liu X, Li J, Liu Y, Ding J, Tong Z, Liu Y, et al. Calreticulin acts as an adjuvant to promote dendritic cell maturation and enhances antigen-specific cytotoxic T lymphocyte responses against non-small cell lung cancer cells. *Cell Immunol* 2016;**300**:46−53.
130. Kaur A, Baldwin J, Brar D, Salunke DB, Petrovsky N. Toll-like receptor (TLR) agonists as a driving force behind next-generation vaccine adjuvants and cancer therapeutics. *Curr Opin Chem Biol* 2022;**70**:102172.
131. Liang J, Fu J, Kang H, Lin J, Yu Q, Yang Q. The stimulatory effect of TLRs ligands on maturation of chicken bone marrow-derived dendritic cells. *Vet Immunol Immunopathol* 2013;**155**:205−10.
132. Liu Y, Han Y, Dong H, Wei X, Shi D, Li Y. Ca^{2+}-mediated surface polydopamine engineering to program dendritic cell maturation. *ACS Appl Mater Interfaces* 2020;**12**:4163−73.
133. Xu X, Deng G, Sun Z, Luo Y, Liu J, Yu X, et al. A biomimetic aggregation-induced emission photosensitizer with antigen-presenting and hitchhiking function for lipid droplet targeted photodynamic immunotherapy. *Adv Mater* 2021;**33**:e2102322.
134. Song Y, Tang C, Yin C. Combination antitumor immunotherapy with VEGF and PIGF siRNA *via* systemic delivery of multi-functionalized nanoparticles to tumor-associated macrophages and breast cancer cells. *Biomaterials* 2018;**185**:117−32.
135. Gao F, Yang C. Anti-VEGF/VEGFR2 monoclonal antibodies and their combinations with PD-1/PD-L1 inhibitors in clinic. *Curr Cancer Drug Targets* 2020;**20**:3−18.
136. Modi SJ, Kulkarni VM. Discovery of VEGFR-2 inhibitors exerting significant anticancer activity against $CD44^+$ and $CD133^+$ cancer stem cells (CSCs): reversal of TGF-β induced epithelial-mesenchymal transition (EMT) in hepatocellular carcinoma. *Eur J Med Chem* 2020;**207**:112851.
137. Zhang Y, Jia H, Liu Z, Guo J, Li Y, Li R, et al. D-MT prompts the anti-tumor effect of oxaliplatin by inhibiting IDO expression in a mouse model of colon cancer. *Int Immunopharmacol* 2021;**101**:108203.
138. Li Q, Liu J, Fan H, Shi L, Deng Y, Zhao L, et al. IDO-inhibitor potentiated immunogenic chemotherapy abolishes primary tumor growth and eradicates metastatic lesions by targeting distinct compartments within tumor microenvironment. *Biomaterials* 2021;**269**:120388.
139. Liu M, Li Z, Yao W, Zeng X, Wang L, Cheng J, et al. IDO inhibitor synergized with radiotherapy to delay tumor growth by reversing T cell exhaustion. *Mol Med Rep* 2020;**21**:445−53.
140. Xing L, Gong JH, Wang Y, Zhu Y, Huang ZJ, Zhao J, et al. Hypoxia alleviation-triggered enhanced photodynamic therapy in combination with IDO inhibitor for preferable cancer therapy. *Biomaterials* 2019;**206**:170−82.
141. Liu Y, Lu Y, Zhu X, Li C, Yan M, Pan J, et al. Tumor microenvironment-responsive prodrug nanoplatform *via* co-self-assembly of photothermal agent and IDO inhibitor for enhanced tumor penetration and cancer immunotherapy. *Biomaterials* 2020;**242**:119933.
142. Hu C, Lei T, Wang Y, Cao J, Yang X, Qin L, et al. Phagocyte-membrane-coated and laser-responsive nanoparticles control primary and metastatic cancer by inducing anti-tumor immunity. *Biomaterials* 2020;**255**:120159.
143. Liu R, An Y, Jia W, Wang Y, Wu Y, Zhen Y, et al. Macrophage-mimic shape changeable nanomedicine retained in tumor for multimodal therapy of breast cancer. *J Control Release* 2020;**321**:589−601.
144. Liu R, Yu M, Yang X, Umeshappa CS, Hu C, Yu W, et al. Linear chimeric triblock molecules self-assembled micelles with controllably transformable property to enhance tumor retention for chemo-photodynamic therapy of breast cancer. *Adv Funct Mater* 2019;**29**:1808462.
145. Wang N, Zhang J, Li Q, Xu H, Chen G, Li Z, et al. Discovery of potent indoleamine 2,3-dioxygenase (IDO) inhibitor from alkaloids in Picrasma quassioides by virtual screening and *in vitro* evaluation. *Fitoterapia* 2019;**133**:137−45.
146. Xu J, Lamouille S, Derynck R. TGF-*b*-induced epithelial to mesenchymal transition. *Cell Res* 2009;**19**:156−72.
147. Guo R, Deng M, He X, Li M, Li J, He P, et al. Fucoidan-functionalized activated platelet-hitchhiking micelles simultaneously track tumor cells and remodel the immunosuppressive microenvironment for efficient metastatic cancer treatment. *Acta Pharm Sin B* 2022;**12**:467−82.
148. Park SJ, Choi YS, Lee S, Lee YJ, Hong S, Han S, et al. BIX02189 inhibits TGF-β1-induced lung cancer cell metastasis by directly targeting TGF-β type I receptor. *Cancer Lett* 2016;**381**:314−22.
149. Bayry J, Tartour E, Tough DF. Targeting CCR4 as an emerging strategy for cancer therapy and vaccines. *Trends Pharmacol Sci* 2014;**35**:163−5.
150. Buzzatti G, Dellepiane C, Del Mastro L. New emerging targets in cancer immunotherapy: the role of GITR. *ESMO Open* 2019;**4**:e000738.
151. Sun Q, Yang Z, Lin M, Peng Y, Wang R, Du Y, et al. Phototherapy and anti-GITR antibody-based therapy synergistically reinvigorate immunogenic cell death and reject established cancers. *Biomaterials* 2021;**269**:120648.
152. Motoyoshi Y, Kaminoda K, Saitoh O, Hamasaki K, Nakao K, Ishii N, et al. Different mechanisms for anti-tumor effects of low- and high-dose cyclophosphamide. *Oncol Rep* 2006;**16**:141−6.
153. Ghiringhelli F, Larmonier N, Schmitt E, Parcellier A, Cathelin D, Garrido C, et al. $CD4^+CD25^+$ regulatory T cells suppress tumor immunity but are sensitive to cyclophosphamide which allows immunotherapy of established tumors to be curative. *Eur J Immunol* 2004;**34**:336−44.
154. Ruan S, Xie R, Qin L, Yu M, Xiao W, Hu C, et al. Aggregable nanoparticles-enabled chemotherapy and autophagy inhibition combined with anti-PD-L1 antibody for improved glioma treatment. *Nano Lett* 2019;**19**:8318−32.
155. Xie R, Ruan S, Liu J, Qin L, Yang C, Tong F, et al. Furin-instructed aggregated gold nanoparticles for re-educating tumor associated macrophages and overcoming breast cancer chemoresistance. *Biomaterials* 2021;**275**:120891.
156. He Y, Fang Y, Zhang M, Zhao Y, Tu B, Shi M, et al. Remodeling "cold" tumor immune microenvironment *via* epigenetic-based therapy using targeted liposomes with in situ formed albumin corona. *Acta Pharm Sin B* 2022;**12**:2057−73.
157. Wanderley CW, Colón DF, Luiz JPM, Oliveira FF, Viacava PR, Leite CA, et al. Paclitaxel reduces tumor growth by reprogramming tumor-associated macrophages to an M1 profile in a TLR4-dependent manner. *Cancer Res* 2018;**78**:5891−900.
158. Cao M, Yan H, Han X, Weng L, Wei Q, Sun X, et al. Ginseng-derived nanoparticles alter macrophage polarization to inhibit melanoma growth. *J Immunother Cancer* 2019;**7**:326.
159. Wang YC, Wang X, Yu J, Ma F, Li Z, Zhou Y, et al. Targeting monoamine oxidase A-regulated tumor-associated macrophage polarization for cancer immunotherapy. *Nat Commun* 2021;**12**:3530.
160. Binnemars-Postma K, Storm G, Prakash J. Nanomedicine strategies to target tumor-associated macrophages. *Int J Mol Sci* 2017;**18**:E979.

161. Yang T, Hu Y, Miao J, Chen J, Liu J, Cheng Y, et al. A BRD4 PROTAC nanodrug for glioma therapy *via* the intervention of tumor cells proliferation, apoptosis and M2 macrophages polarization. *Acta Pharm Sin B* 2022;**12**:2658−71.
162. Jiménez-García L, Higueras MÁ, Herranz S, Hernández-López M, Luque A, de las Heras B, et al. A hispanolone-derived diterpenoid inhibits M2-macrophage polarization *in vitro via* JAK/STAT and attenuates chitin induced inflammation *in vivo*. *Biochem Pharmacol* 2018;**154**:373−83.
163. Tang X, Sui D, Liu M, Zhang H, Liu M, Wang S, et al. Targeted delivery of zoledronic acid through the sialic acid−Siglec axis for killing and reversal of M2 phenotypic tumor-associated macrophages−a promising cancer immunotherapy. *Int J Pharm* 2020;**590**:119929.
164. Pramanik A, Bhattacharyya S. Myeloid derived suppressor cells and innate immune system interaction in tumor microenvironment. *Life Sci* 2022;**305**:120755.
165. Wang T, Wang J, Jiang H, Ni M, Zou Y, Chen Y, et al. Targeted regulation of tumor microenvironment through the inhibition of MDSCs by curcumin loaded self-assembled nano-filaments. *Mater Today Bio* 2022;**15**:100304.
166. Shanmugam MK, Rane G, Kanchi MM, Arfuso F, Chinnathambi A, Zayed ME, et al. The multifaceted role of curcumin in cancer prevention and treatment. *Molecules* 2015;**20**:2728−69.
167. Ye H, He X, Feng X. Developing neobavaisoflavone nanoemulsion suppresses lung cancer progression by regulating tumor microenvironment. *Biomed Pharmacother* 2020;**129**:110369.
168. Ledo AM, Sasso MS, Bronte V, Marigo I, Boyd BJ, Garcia-Fuentes M, et al. Co-delivery of RNAi and chemokine by poly-arginine nanocapsules enables the modulation of myeloid-derived suppressor cells. *J Control Release* 2019;**295**:60−73.
169. Long Y, Lu Z, Xu S, Li M, Wang X, Zhang Z, et al. Self-delivery micellar nanoparticles prevent premetastatic niche formation by interfering with the early recruitment and vascular destruction of granulocytic myeloid-derived suppressor cells. *Nano Lett* 2020;**20**:2219−29.
170. Wu C, Muroski ME, Miska J, Lee-Chang C, Shen Y, Rashidi A, et al. Repolarization of myeloid derived suppressor cells *via* magnetic nanoparticles to promote radiotherapy for glioma treatment. *Nanomedicine* 2019;**16**:126−37.
171. Chen X, Song E. Turning foes to friends: targeting cancer-associated fibroblasts. *Nat Rev Drug Discov* 2019;**18**:99−115.
172. Lang J, Zhao X, Qi Y, Zhang Y, Han X, Ding Y, et al. Reshaping prostate tumor microenvironment to suppress metastasis *via* cancer-associated fibroblast inactivation with peptide-assembly-based nanosystem. *ACS Nano* 2019;**13**:12357−71.
173. Li X, Yong T, Wei Z, Bie N, Zhang X, Zhan G, et al. Reversing insufficient photothermal therapy-induced tumor relapse and metastasis by regulating cancer-associated fibroblasts. *Nat Commun* 2022;**13**:2794.
174. Nicolás-Boluda A, Vaquero J, Laurent G, Renault G, Bazzi R, Donnadieu E, et al. Photothermal depletion of cancer-associated fibroblasts normalizes tumor stiffness in desmoplastic cholangiocarcinoma. *ACS Nano* 2020;**14**:5738−53.
175. Chen Y, Hu M, Wang S, Wang Q, Lu H, Wang F, et al. Nano-delivery of salvianolic acid B induces the quiescence of tumor-associated fibroblasts *via* interfering with TGF-β1/Smad signaling to facilitate chemo- and immunotherapy in desmoplastic tumor. *Int J Pharm* 2022;**623**:121953.
176. Zhou Q, Zhou Y, Liu X, Shen Y. GDC-0449 improves the antitumor activity of nano-doxorubicin in pancreatic cancer in a fibroblast-enriched microenvironment. *Sci Rep* 2017;**7**:13379.
177. Zhu Y, Yu F, Tan Y, Hong Y, Meng T, Liu Y, et al. Reversing activity of cancer associated fibroblast for staged glycolipid micelles against internal breast tumor cells. *Theranostics* 2019;**9**:6764−79.
178. Darvin P, Toor SM, Sasidharan Nair V, Elkord E. Immune checkpoint inhibitors: recent progress and potential biomarkers. *Exp Mol Med* 2018;**50**:1−11.
179. Yi M, Zheng X, Niu M, Zhu S, Ge H, Wu K. Combination strategies with PD-1/PD-L1 blockade: current advances and future directions. *Mol Cancer* 2022;**21**:28.
180. Jiang CT, Chen KG, Liu A, Huang H, Fan YN, Zhao DK, et al. Immunomodulating nano-adaptors potentiate antibody-based cancer immunotherapy. *Nat Commun* 2021;**12**:1359.
181. Naidoo J, Page DB, Li BT, Connell LC, Schindler K, Lacouture ME, et al. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. *Ann Oncol* 2015;**26**:2375−91.
182. Hahn AW, Gill DM, Agarwal N, Maughan BL. PD-1 checkpoint inhibition: toxicities and management. *Urol Oncol* 2017;**35**:701−7.
183. Shergold AL, Millar R, Nibbs RJB. Understanding and overcoming the resistance of cancer to PD-1/PD-L1 blockade. *Pharmacol Res* 2019;**145**:104258.
184. Hu C, He X, Chen Y, Yang X, Qin L, Lei T, et al. Metformin mediated PD-L1 downregulation in combination with photodynamic−immunotherapy for treatment of breast cancer. *Adv Funct Mater* 2021;**31**:2007149.
185. Chang HN, Liu BY, Qi YK, Zhou Y, Chen YP, Pan KM, et al. Blocking of the PD-1/PD-L1 interaction by a D-peptide antagonist for cancer immunotherapy. *Angew Chem Int Ed Engl* 2015;**54**:11760−4.
186. Wang H, Yao H, Li C, Shi H, Lan J, Li Z, et al. HIP1R targets PD-L1 to lysosomal degradation to alter T cell-mediated cytotoxicity. *Nat Chem Biol* 2019;**15**:42−50.
187. Liu X, Yin M, Dong J, Mao G, Min W, Kuang Z, et al. Tubeimoside-1 induces TFEB-dependent lysosomal degradation of PD-L1 and promotes antitumor immunity by targeting mTOR. *Acta Pharm Sin B* 2021;**11**:3134−49.
188. Jin W, Luo Q. When artificial intelligence meets PD-1/PD-L1 inhibitors: population screening, response prediction and efficacy evaluation. *Comput Biol Med* 2022;**145**:105499.
189. Deng H, Tan S, Gao X, Zou C, Xu C, Tu K, et al. Cdk5 knocking out mediated by CRISPR-Cas9 genome editing for PD-L1 attenuation and enhanced antitumor immunity. *Acta Pharm Sin B* 2020;**10**:358−73.
190. Guo Y, Zhang Q, Zhu Q, Gao J, Zhu X, Yu H, et al. Copackaging photosensitizer and PD-L1 siRNA in a nucleic acid nanogel for synergistic cancer photoimmunotherapy. *Sci Adv* 2022;**8**:eabn2941.
191. Kim S, Heo R, Song SH, Song KH, Shin JM, Oh SJ, et al. PD-L1 siRNA−hyaluronic acid conjugate for dual-targeted cancer immunotherapy. *J Control Release* 2022;**346**:226−39.
192. Abbaszadeh Z, Çeşmeli S, Biray Avcı Ç. Crucial players in glycolysis: cancer progress. *Gene* 2020;**726**:144158.
193. Park JH, Pyun WY, Park HW. Cancer metabolism: phenotype, signaling and therapeutic targets. *Cells* 2020;**9**:E2308.
194. Kumagai S, Koyama S, Itahashi K, Tanegashima T, Lin YT, Togashi Y, et al. Lactic acid promotes PD-1 expression in regulatory T cells in highly glycolytic tumor microenvironments. *Cancer Cell* 2022;**40**:201−218.e9.
195. Ma X, Yang S, Zhang T, Wang S, Yang Q, Xiao Y, et al. Bioresponsive immune-booster-based prodrug nanogel for cancer immunotherapy. *Acta Pharm Sin B* 2022;**12**:451−66.
196. Pavlova NN, Thompson CB. The emerging hallmarks of cancer metabolism. *Cell Metab* 2016;**23**:27−47.
197. Zang S, Huang K, Li J, Ren K, Li T, He X, et al. Metabolic reprogramming by dual-targeting biomimetic nanoparticles for enhanced tumor chemo-immunotherapy. *Acta Biomater* 2022;**148**:181−93.
198. Zhou Y, Tong F, Gu W, He S, Yang X, Li J, et al. Co-delivery of photosensitizer and diclofenac through sequentially responsive bilirubin nanocarriers for combating hypoxic tumors. *Acta Pharm Sin B* 2022;**12**:1416−31.
199. Gottfried E, Lang SA, Renner K, Bosserhoff A, Gronwald W, Rehli M, et al. New aspects of an old drug−diclofenac targets MYC and glucose metabolism in tumor cells. *PLoS One* 2013;**8**:e66987.
200. Yu W, Lin R, He X, Yang X, Zhang H, Hu C, et al. Self-propelled nanomotor reconstructs tumor microenvironment through synergistic

hypoxia alleviation and glycolysis inhibition for promoted anti-metastasis. *Acta Pharm Sin B* 2021;**11**:2924−36.
201. Vijayan D, Young A, Teng MWL, Smyth MJ. Targeting immunosuppressive adenosine in cancer. *Nat Rev Cancer* 2017;**17**:709−24.
202. Yu M, Zeng W, Ouyang Y, Liang S, Yi Y, Hao H, et al. ATP-exhausted nanocomplexes for intratumoral metabolic intervention and photoimmunotherapy. *Biomaterials* 2022;**284**:121503.
203. Mao C, Yeh S, Fu J, Porosnicu M, Thomas A, Kucera GL, et al. Delivery of an ectonucleotidase inhibitor with ROS-responsive nanoparticles overcomes adenosine-mediated cancer immunosuppression. *Sci Transl Med* 2022;**14**:eabh1261.
204. Lei Q, Wang D, Sun K, Wang L, Zhang Y. Resistance mechanisms of anti-PD1/PDL1 therapy in solid tumors. *Front Cell Dev Biol* 2020;**8**:672.
205. De Jong WH, Borm PJA. Drug delivery and nanoparticles: applications and hazards. *Int J Nanomedicine* 2008;**3**:133−49.
206. Danhier F. To exploit the tumor microenvironment: since the EPR effect fails in the clinic, what is the future of nanomedicine?. *J Control Release* 2016;**244**:108−21.
207. Sun D, Zhou S, Gao W. What went wrong with anticancer nanomedicine design and how to make it right. *ACS Nano* 2020;**14**:12281−90.
208. Luan X, Yuan H, Song Y, Hu H, Wen B, He M, et al. Reappraisal of anticancer nanomedicine design criteria in three types of preclinical cancer models for better clinical translation. *Biomaterials* 2021;**275**:120910.
209. Xiao W, Gao H. The impact of protein corona on the behavior and targeting capability of nanoparticle-based delivery system. *Int J Pharm* 2018;**552**:328−39.
210. Farshbaf M, Valizadeh H, Panahi Y, Fatahi Y, Chen M, Zarebkohan A, et al. The impact of protein corona on the biological behavior of targeting nanomedicines. *Int J Pharm* 2022;**614**:121458.
211. Hare JI, Lammers T, Ashford MB, Puri S, Storm G, Barry ST. Challenges and strategies in anti-cancer nanomedicine development: an industry perspective. *Adv Drug Deliv Rev* 2017;**108**:25−38.