Advancement and Applications of Nanotherapy for Cancer Immune Microenvironment*

Jun-ju HE[1†], Qing-qing LI[1†], Chen ZHAO[1], Jin ZHOU[1], Jie WU[1], Hui-bo ZHANG[1], Ya-qi ZHAO[1], Hao-han ZHANG[1], Tian-yu LEI[1], Xin-yi ZHAO[1], Zuo YOU[2], Qi-bin SONG[1], Bin XU[1#]

[1]*Cancer Center, Renmin Hospital of Wuhan University, Wuhan 430060, China*
[2]*Department of Traditional Chinese Medicine, Xianfeng County People's Hospital, Enshi 445000, China*

© The Author(s) 2023

[Abstract] Cancer treatment has evolved rapidly due to major advances in tumor immunity research. However, due to the complexity, heterogeneity, and immunosuppressive microenvironment of tumors, the overall efficacy of immunotherapy is only 20%. In recent years, nanoparticles have attracted more attention in the field of cancer immunotherapy because of their remarkable advantages in biocompatibility, precise targeting, and controlled drug delivery. However, the clinical application of nanomedicine also faces many problems concerning biological safety, and the synergistic mechanism of nano-drugs with immunity remains to be elucidated. Our study summarizes the functional characteristics and regulatory mechanisms of nanoparticles in the cancer immune microenvironment and how nanoparticles activate and long-term stimulate innate immunity and adaptive immunity. Finally, the current problems and future development trends regarding the application of nanoparticles are fully discussed and prospected to promote the transformation and application of nanomedicine used in cancer treatment.
Key words: nanotherapy; tumor microenvironment; immunotherapy

Cancer poses a major threat to human health worldwide, accounting for nearly 10 million deaths in 2021, bringing a heavy burden on individuals, families, and society[1, 2]. How to "cure" tumors, prolong survival, and provide the highest possible quality of life after treatment are major goals of clinicians. The conventional cancer treatment strategies are chemotherapy, surgery, and radiotherapy. However, traditional chemotherapy lacks specificity and causes damage to both tumor and healthy tissues, making it difficult for patients to receive long-time chemotherapy maintenance[3]. Moreover, surgery and radiotherapy usually display a low rate of control over advanced or metastatic stage cancer[4]. Over the past decade, several breakthrough technologies have emerged in the field of tumor immunotherapy, including chimeric antigen receptor T cells (CAR-T), immune checkpoint blockade, cancer vaccines, and adoptive cell therapies[5–7]. With such technologies, an increasing number of patients receiving immunotherapy could achieve durable complete responses and enjoy prolonged long-term survival. Recent clinical trials show that CAR-T therapy has a significant benefit for patients with leukemia or lymphoma[8]. Immune checkpoint inhibitors bind to receptors on the surface of immune cells and prevent the immune system from shutting down before the cancer is completely eradicated. The first antibody targeting cytotoxic T-lymphocyte antigen 4 (CTLA-4) significantly improved overall survival in patients with advanced melanoma and was quickly approved by the U.S. Food and Drug Administration (FDA) in 2011[9]. Programmed cell death-1 (PD-1) and its ligand (PD-L1), found on many cancer cells, are the most widely used immune checkpoints. Immune checkpoint inhibitors promote persistent activation of immune cells (mainly T lymphocytes) by preventing tumors from transmitting inhibitory signals. However, the overactive immune system can cause multisystem non-specific damage that manifests clinically as rash, myocarditis, diarrhea, thyroid dysfunction, and hepatitis[10]. In addition, in recent years, the papillomavirus (HPV) vaccine protects against human HPV and has become one of the most powerful weapons in the prevention of cervical cancer[11]. In conclusion, novel types of immunotherapies are still in the development stage and have a bright future in terms of application.

Jun-ju HE, E-mail: junjuhe@whu.edu.cn; Qing-qing LI, E-mail: QQLi1130@whu.edu.cn
†These authors contributed equally to this work.
#Corresponding author, E-mail: xubin_oncology@whu.edu.cn

Many different types of tumors can be effectively controlled by immunotherapy. However, its apparent complexity and uncertainty hinder the clinical application of immunotherapy. Immunotherapy resistance and adverse immunotoxicity often result in reduced efficacy of treatment. For example, combination immunotherapies, especially agents targeting different immune checkpoints, such as co-treatment with CTLA-4 and PD1/PD-L1, have shown moderate improvement in efficacy, while causing a striking increase in toxicity. In clinical trials, grade ≥3 immune-related adverse events (irAEs) were reported to exceed 50% in the immune checkpoint inhibitors (ICIs) combination group[12–14]. To date, CAR-T have been shown to be an effective therapy for hematologic malignancies, while less so in the vast majority of solid tumors[15]. There are two major challenges facing current immunotherapy technologies. First, efficacy cannot be improved by further increasing the dose, and second, off-target toxicity can be difficult to reduce. To further enhance the advantages of immunotherapy, and with the rapid development of materials in the field of science and engineering, nanomaterials with unique physical, biological, and chemical properties can be utilized.

Nanotechnology has played a significant role in the detection, diagnosis, and treatment of cancer over the past 10 years. Due to their minimal size and high surface area to volume ratio, nanomaterials whose biological, physical, and chemical properties are constantly being altered by surface modifications and editing, exhibit some unique physicochemical properties as agent carriers in comparison to traditional drugs[16, 17]. Their physical characteristics (shape or morphology), aggregation, hydrophilic or hydrophobic nature, and the presence of biological moieties on the surface (peripheral coatings or functional groups) also make them distinct from traditional medicine. Nanomedicine has been shown to have several advantages over conventional drugs: Nanoparticles tend to penetrate and remain in tumor sites, referred to as enhanced permeability and retention (EPR) effects[18, 19]; thus nanoparticles could passively target tumor tissue through EPR effects and significantly increased local drug concentrations. In addition, nanoparticles as carriers can not only enhance drug solubility and bioavailability, strengthen biocompatibility, and prolong body circulation but also improve drug distribution in tumor tissues, thereby realizing the goal of safe and accurate drug administration. Moreover, synthetically modified nanoparticles could be sensitively targeted to a tumor microenvironment characterized by high potassium, high acidity, and hypoxia. Meanwhile, nanoparticles that efficiently release agents, antibodies, tumor antigens, and immunomodulators in tumor lesions could selectively kill tumor cells and improve immune

response[20, 21]. Up to now, many types of nanomaterials have been used in cancer treatment, mainly including inorganic, organic, and biomimetic nanomaterials[22].

Tumor cells can transform the microenvironment of normal tissues into one suitable for tumor growth by regulating immune cells and secreting immunosuppressive factors[23]. The tumor immune microenvironment consists of lymph node aggregates, immune cells, and cytokines. The immune system plays a crucial role in cancer immunotherapy, including CD8+ T cells, tumor-associated macrophages, myeloid suppressor cells, regulatory T (Treg) cells, and others. In the study, the authors review the advanced progress made in regulating nanoparticles in the cancer immune microenvironment.

1 NANOPARTICLES AND TUMOR IMMU-NOGENICITY/IMMUNOMODULATOR

Our study summarizes the functional characteristics and regulatory mechanisms of nanoparticles in the cancer immune microenvironment. The ability of tumor cell proteins to induce an immune response is known as tumor immunogenicity. Chemotherapy, targeted medicine, and radiotherapy are examples of exogenous stimuli that can induce tumor cell death that is either immunogenic or non-immunogenic. A type of apoptotic cell death known as immunogenic cell death (ICD) involves changes in cell surface composition as well as the release of numerous antigens and immunostimulatory factors. Endoplasmic reticulum (ER) stress with increased production of reactive oxygen species (ROS) is widely recognized as a causative agent of ICD. Immunogenic death can powerfully activate the antitumor immune response by enhancing the antigen-presenting function of dendritic cells (DCs) and subsequently activating the specific T-cell response[24, 25]. Immunomodulators are a group of drugs that can mediate the immune system to solve multiple diseases[26, 27].

1.1 Drug Delivery System

Nanotechnology could help overcome the limitations of conventional drug delivery by specifically targeting the primary or metastatic tumor site and subclinical focus. In addition, advances in nanotechnology are improving the stability and solubility of encapsulated cargoes, enhancing drug penetration and prolonging release potential to increase safety and efficacy[28]. In mouse tumor models, Kuai et al showed how high-density lipoprotein-like nanodiscs loaded with the common chemotherapy drug doxorubicin (DOX) can strengthen immune checkpoint blockade. The release of DOX led to tumor ICD and exerted anti-tumor efficacy while eliciting a robust T-cell response[29]. The ICD effect induced by chemotherapeutic agents could have promoted

intratumoral infiltration of cytotoxic T lymphocytes (CTLs).

However, the detrimental immune regulation mechanisms significantly reduce the therapeutic effect induced by ICD. To support the activation of various immune checkpoints, CTLs could have released some types of interferon (IFN). Therefore, immune agonists combined with chemotherapy may have compensated for the deficiency of monotherapy. Recent research has shown that a unique nanoparticle has been specifically designed to co-deliver chemotherapeutics and an indoleamine 2, 3-dioxygenase (IDO) inhibitor (NLG919). The nanoparticles release the chemotherapeutic drug into the tumor microenvironment and promote the intratumoral accumulation of CTLs by stimulating the ICD response. Meanwhile, NLG919 inhibits Treg cells and downregulates IDO-1-driven immunosuppression. In mouse models of breast and colon cancer, nanomedicine is significantly more effective in regressing tumor growth and preventing metastasis than other controls[30, 31]. Mu et al created a multifunctional nanoparticle with an iron oxide core that can simultaneously and selectively deliver the Toll-like receptor 3 (TLR3) agonist (polyinosinic polycytidylic acid) and DOX to DCs and cancer cells. In an aggressive and drug-resistant metastatic mouse model of triple-negative breast cancer, the nanoparticles significantly prolonged life and reduced tumor growth and metastasis[32].

Tumor autophagy plays a critical role in the anti-tumor immune response induced by chemoimmunotherapy. Chemotherapy causes tumor cells to die, subsequently initiating the autophagy program. Processing of endogenous antigens for presentation on MHC Ⅱ molecules, as well as the release of adenosine triphosphate (ATP) from dying cancer cells, which serves as a "find me" signal for DC precursors, is enabled by the activated autophagy, which also promotes the infiltration of CTLs into the tumor[33]. Wang et al[34] created an on-demand autophagy cascade amplification nanoparticle (ASN). The ASN is prepared by self-assembling autophagy-responsive C-TFG (cell penetrating peptide based amphiphilic peptide) micelles, to which oxaliplatin (OXA) prodrug hyaluronic acid-OXA (HA-OXA) is electrostatically bound. After entering the bloodstream, the nanoparticles selectively accumulate in the tumor microenvironment. Upon entry into the tumor, the ASN initially responds to the reduced microenvironment by releasing OXA to initiate ICD and subtly activate tumor autophagy. As a result, the exposed C-TFG micelle can respond sensitively to the OXA-induced autophagy and release STF-62247, a potent autophagy inducer, after which the cancer cells precisely switch to the overactivated autophagy stage, resulting in tumor cell death and subsequent enhanced tumor antigen exposure.

1.2 Nanoparticles Inducing Photodynamic Therapy or Photothermal Therapy

Photodynamic therapy (PDT) is a treatment that involves the use of light-sensitive medicine and a light source to destroy abnormal cells. Photothermal therapy (PTT) utilizes the conversion of light energy, usually in the near-infrared (NIR) region, into heat energy to promote subsequent tumor cell necrosis or apoptosis. Li et al[35] designed a double ER-targeting nanoparticle to perform PDT and PTT immunotherapy. This nanosystem consists of ER-targeting pardaxin (PAR, also known as FAL) peptides modified indocyanine green (ICG) conjugated-hollow gold nanospheres (FAL-ICG-HAuNS), together with an oxygen-delivering hemoglobin (Hb) liposome (FAL-Hb lipo). ER-targeting FAL-ICG-HAuNs induced intense ER stress due to the synchronous photothermal and photodynamic effect triggered by NIR light. In addition, increased ER stress leads to ER membrane rupture and calreticulin (CRT) translocation to the surface of the tumor cell. CRT, an important ICD marker, transmits an "eat me" signal to DC, strengthening the capacity of presenting antigens. As a result, a number of innate and adaptive immunity effects are activated, such as CD8+ T-cell proliferation and the secretion of cytotoxic cytokines. According to another piece of research, chlorin e6 (Ce6) photosensitizer placed on the surface of polymer hybrid nanoparticles enables sufficient photoabsorption for the accumulation of ROS in response to NIR irradiation. The in vivo experiments proved synergistic phototherapy can spur potent humoral and systemic anticancer immune responses and can hinder tumor recurrence and metastasis when used with immune checkpoint blockades[36]. A remarkable organic photosensitizer (called TPE-DPA-TCyp) is also reported to efficiently produce ICD by causing significant mitochondrial oxidative stress in cancer cells. It has a twisted molecular structure, strong aggregation-induced emission activity, and specific ability. TPE-DPA-TCyp is a better ICD inducer than commonly prescribed agents such as pheophorbide A, OXA, and Ce6[37]. However, there are still relatively few inducers available, and ICD cannot be induced sufficiently by photosensitizer-based inducers to elicit a strong and long-lasting antitumor immune response.

Hybrid nanoparticles including dual components might be a better strategy for improving immunotherapy. According to one study, OXA and the photosensitizer pyropheophorbide-lipid conjugate can be carried by core-shell nanoparticles made of the nanoscale coordination polymer (NCP). The release of tumor-associated antigens (TAAs) is caused by the interaction of chemotherapy and PDT, resulting in ICD and inflammation at the core tumor site. TAAs are provided and delivered by antigen-

presenting cells (APCs) to promote the proliferation of effector T lymphocytes[38]. To date, most light-responsive nanoparticles have been applied for the NIR light window (NIR-I, 650–950 nm) or NIR-II light window (1000–1500 nm), serving as photothermal or photodynamic transducers. Under deep-penetrating NIR photoirradiation, nanoparticles not only generate heat to ablate primary tumors and induce ICD but also release specific activated immunotherapeutic agents, such as resiquimod (R848), NLG919 (IDO-1 inhibitor), CpG oligodeoxynucleotides, and vipadenant, leading to maturation of DCs and enhancement of antitumor immune response[39].

In addition, a previous study demonstrated the development of cancer cell membrane-coated mesoporous organosilica nanoparticles (MONs) characterized by X-ray and ROS-responsive diselenide linkages, which enable controlled delivery of DOX to the tumor site. The incorporation of a PD-L1 checkpoint inhibitor could improve the suppression of tumor growth and metastasis while causing the least amount of systemic damage[40].

1.3 Acidity-activatable Nanoparticles

Nanocarriers are an optimal choice for de-livering chemoimmunotherapy because they can be easily constructed to encapsulate different types of therapeutics and achieve programmed drug delivery with temporal and spatial precision. However, designing nanocarriers that respond to signals in the tumor microenvironment is a challenging task. A typical feature of the tumor microenvironment is its acidity, allowing pH-based delivery nanoplatforms to represent a potential specific approach to target tumors. Song et al have created dynamic nanoparticles that are intracellularly acidity-activatable to induce immunogenicity by enhancing ferroptosis in tumor cells[41]. The nanoparticles are designed to deliver the glutathione peroxidase 4 inhibitor RSL-3, a ferroptosis inducer, to tumors by combining an ionizable block copolymer and acid-labile phenylboronate ester (PBE) dynamic covalent bonds. At neutral pH (pH 7.4), the RSL-3 could stably interact with PBE in the nanocarriers, while the covalent bond between the drug and PBE was cleaved by acidity triggering, resulting in the release of the payload. Moreover, the acid-activatable nanoparticles have the ability to execute the PDT effect by protonating the ionizable core, significantly attract T lymphocytes for IFN release, and further sensitize cancer cells to ferroptosis induced by RSL-3. The growth of melanoma tumors and lung metastasis of breast cancer are effectively inhibited by the nanoparticle in combination with a PD-L1 antibody. Moreover, other researchers[42] have provided a new pH and matrix metalloproteinase (MMP) dual-sensitive micellar nanocarrier that can co-deliver PD-1 and the chemotherapeutic agent paclitaxel for synergistic cancer chemoimmunotherapy. The weak acidity (pH 6.5) of the tumor microenvironment and abundant MMP-2, which can also convert the negatively charged micelle into a positively charged one, magnetic multicore particles (McP), for easy uptake into cancer cells, respectively, caused the PD-1 antibody to detach from the micellar nanocarrier.

Finally, the pH-sensitive core was expected to rapidly release paclitaxel inside the cancer cell via the induction of lysosomal acidity (pH 5.0), and tumor growth was significantly inhibited in the sAMcP group compared with the control group in vitro and in vivo. In addition, a copper chelating coil-comb block copolymer RGD-PEG-b-PGA-g-(TETA-DTC-PHis) (RPTDH) was synthesized by Zhou et al[43], and it could realize efficient loading, targeted delivery, and controlled release of Resiquimod R848 (TLR8 agonist). RPTDH can self-assemble into spherical nanoparticles with high pH sensitivity and possesses potent copper-chelating properties. R848 has been successfully encapsulated in nanoparticles and immediately released in a mildly acidic environment. Phosphohistidine (PHis) could gradually destabilize and disintegrate materials when exposed to the microacidic environment, and the PGA-g-(TETA-TDC-PHis) generated by PHis could chelate copper ions, accounting for the lack of copper around the tumor, thereby inhibiting angiogenesis. At the same time, the controlled release of the agonist R848 induced the activation of DCs and enhanced the immune response, effectively preventing the spread and inhibiting the growth of mouse breast cancer and prolonging the life of tumor-bearing mice.

1.4 Biomimetic Nanoparticles

Over the past few years, biomimetic nanoparticles have received renewed interest. In 2011, Hu's team surprisingly proposed to extract the erythrocyte cell membrane and apply it to camouflaged nanoparticles[44]. Camouflaged nanoparticles coated by the membranes and generally isolated from cancer cells, blood cells, immune cells, stem cells, bacteria, and exosomes were sought by researchers. The lipids, proteins, and sugars forming the biological membranes could play an important role in biological communication[45]. Nanoparticles modified by cell membranes can not only represent the physicochemical properties of the nanomaterial but also be endowed with the natural properties of the cell membrane. The erythrocyte membrane was the first to be used to modify nanocarriers, and the erythrocyte membrane-camouflaged nano-particles showed excellent bio-compatibility, effec-tively evading immune recognition and improved circulation half-life[44]. Furthermore, platelet-coated nanoparticles might be a promising tumor-targeted drug delivery vector. The plasma membrane from human platelets offers nanoparticles unique platelet-mimicking capabilities, such as selective adhesion to vascular

endothelial cells and cancer cells in tumor tissues. According to research by Bahmani et al[46], platelet-coated nanoparticles efficiently deliver Resiquimod (R848), a small molecule immunostimulatory adjuvant that is a member of the TLR7/8 agonist family, to the tumor site where it activates APCs and polarizes T-cell responses by binding to TLR7/8. Multiple immunomodulatory cytokines such as interleukin (IL)-6, IL-12, and IFN are then secreted. Applying the principles of biomimetic nanotechnology, Kroll et al[47] used the membrane derived from mouse melanoma cells to coat nanoparticles with CpG (CpG-NP). In vivo, the CpG-NP remarkably inhibited melanoma growth with an inhibition rate of up to 86%. There are a large number of immune cells in the tumor microenvironment that play some crucial roles in monitoring, recognizing, and killing tumors, thus nanoparticles packaged by immune cell membranes might have the ability of tumor-specific targeting. Three independent research groups prepared nanoparticles modified by NK, macrophage, or hybrid cell (cancer and DC) membranes, respectively[48–50]. In vivo experiments showed that these nanoparticles can effectively target primary and metastatic tumor sites, resulting in the induction of intense immunogenic death, activation of APCs, and enhancement of antitumor immune response. Some studies indicate that when stimulated by external stimuli, bacteria secrete bacterial vesicles with diameters of 20–250 nm, which are called bacterial outer membrane vesicles (OMVs)[51]. OMVs possess most of the immunogenic membrane-associated and surface-associated components of their bacterial parents, as well as the immunostimulatory ability to modify and activate the host immune response for cancer immunotherapy. OMVs show a tendency to concentrate in tumor tissue, almost like their bacterial parents, and are therefore considered to be excellent drug transporters. In addition, a recent study showed that OMVs administered intravenously can stimulate IFN production in tumor tissues to mediate a sustained anti-tumor immune response[52]. As an innovative bioengineering strategy, Qi et al proposed to coat OMVs on drug-loaded polymeric micelles to create a novel nanomedicine for cancer immunotherapy and metastasis prevention[51].

1.5 Antigen-capturing Nanoparticles

Efficient delivery of tumor antigens to APCs can lead to immune activation. Malignant neoplasms often strive to develop immunosuppressive networks and evade immune surveillance as a result of the evolution of malignant cells. This results in an immune desert within the tumor tissue and low levels of immune cells such as APCs and CTLs. It may be an effective therapeutic strategy to alter the surface modification of nanoparticles so that they can effectively bind tumor antigens and transfer the antigens to APCs. Min et al developed an antigen-capture nanoparticles (AC-NP)

coated with poly(lactic-co-glycolic acid). Using the melanoma mouse model, they demonstrated that AC-NPs can deliver tumor-specific proteins to APCs and dramatically increase the efficacy of anti-PD-1 therapy, resulting in a cure rate of up to 20% compared to 0% in the control group. Mechanistic studies showed that AC-NPs increased CD4+ T/Treg and CD8+ T/Treg ratios and caused the expansion of CD8+ cytotoxic T cells[53]. Other research groups designed Fe_3O_4-nanoparticles, a core-shell formulation (denoted as $Ce6/Fe_3O_4$-L), as the endogenous tumor antigens carrier. During local ultrasound therapy, a large amount of ROS was generated by Ce6, causing the core-shell structure to collapse and release Fe_3O_4 nanoparticles into the tumor tissue. At the same time, sonodynamic therapy damaged the tumor cells, which was followed by an increase in tumor ICD. Finally, endogenous tumor antigens generated after sonodynamic-induced cancer cell death could be captured by nano-Fe_3O_4 and transported to lymph nodes (LNs) via lymphatic flow to promote cancer immunity[54].

2 NANOPARTICLES AND T-CELL IMMUNO-THERAPY

The primary goal of tumor immunity is to prevent tumor growth by activating T cells to respond to MHC antigen complexes and pathogenic signals. Activated T cells subsequently develop into CD8+ CTLs and migrate to the tumor site to carry out their antitumor role. T cells are an essential component of adaptive immunity, and T-cell-based immunotherapies have the potential to treat a variety of cancers[55]. Although T-cell immunotherapy represents a significant advance in tumor immunotherapy, its therapeutic efficacy for solid tumors is still inadequate. However, emerging nanomaterials and could remarkably improve the efficacy of immunotherapies while reducing toxic side effects[56].

2.1 Advanced Nanoparticle Promotes Infiltration of T Cells

A biodegradable nanoparticle platform with innate immune stimulants was developed by Yin et al. The nanoparticles efficiently activated and/or expanded antigen-specific CD8+ tumor-infiltrating T cells and decreased regulatory CD4+ T cells and this had a dramatic inhibitory or eliminatory effect on tumor growth and led to the development of immune memory in surviving mice[57] (fig. 1A). A polymer multicellular nanoengager (SPNE) for synergistic NIR-II photothermal immunotherapy has been disclosed by Xu et al. The nanoengager is concealed by fused membranes made from immunologically modified tumor cells and DCs, which are based on an NIR-II absorbing polymer. SPNE induces immunogenic cell death, activates T cells, destroys the tumor, and initiates
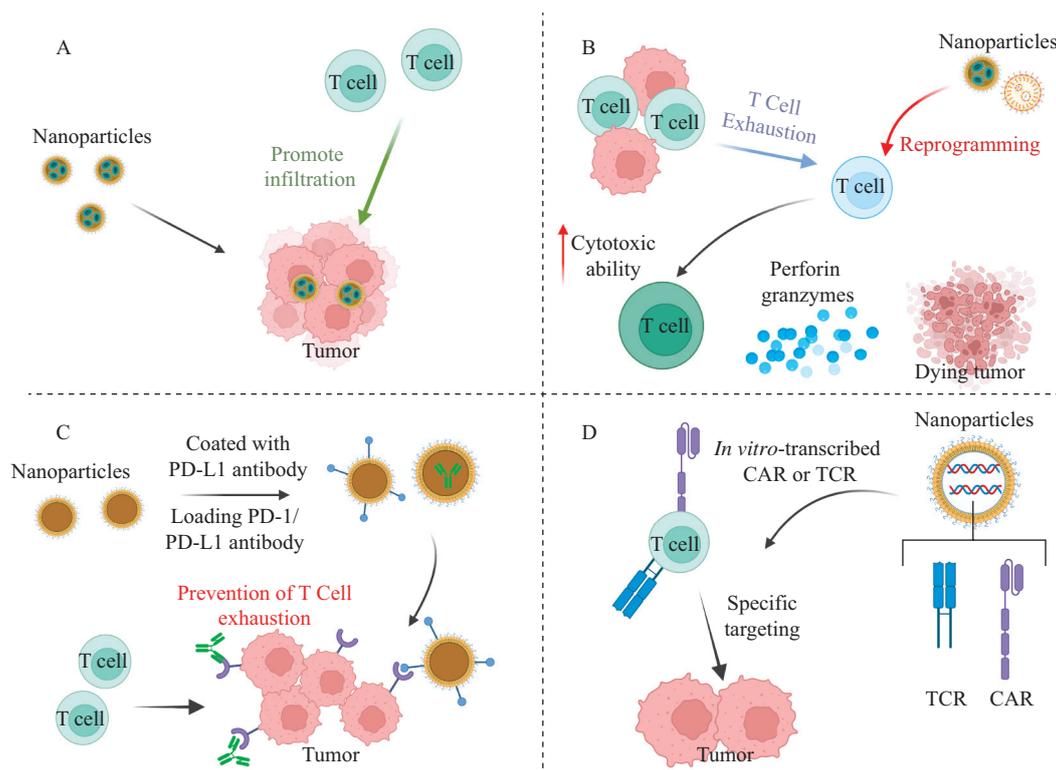
Fig. 1 Schematic of engineered nanoparticles (NPs) for activating T cells
A: NPs promote infiltration of T cells; B: NPs reprogram T cells and enhance their cytotoxic ability; C: NPs coated with PD-1/L1 antibody prevent exhaustion of T cells; D: T cells transcribed CAR or TCR by NPs *in vitro*. CAR:chimeric antigen receptor; TCR: T cell receptor

anti-tumor immunity[58].

2.2 Nanoparticle-enhanced Cytotoxic Ability of T Cells

T-cell immunotherapy has faced significant obstacles in the treatment of solid tumors due to poor tumor-specific targeting and low activation, resulting in reduced production and release of cytotoxic proteins[59]. To enhance the antitumor efficacy of T lymphocytes, researchers created a lysosome-targeting nanoparticle (LYS-NP) using mineralized metal-organic frameworks (MOFs) made of Zn^{2+}. The fundamental problems with solid tumor approaches are addressed by LYS-NPs, which reprogram the lysosomes of CD8+ T cells to create "super-deadly T lymphocytes" that target tumors and release cytotoxic proteins[60] (fig. 1B). In another study, a B-cell maturation antigen (BCMA)-specific peptide-encapsulated liposome or poly (lactic-co-glycolic acid) (PLGA) nanoparticle was created to stimulate CD8+ CTLs specific for BCMA. Inducing BCMA-specific CTLs with better antitumor capabilities in multiple myeloma, PLGA-based nanoparticles showed a progressive increase in peptide uptake by APCs[61]. Jiang *et al* created a biomimetic platform for nanoparticles expressing a co-stimulatory marker and consisting of a modified cancer cell membrane coating. This platform can be used to directly activate T cells without the need for APCs. It has been shown that the platform has the necessary signals to stimulate

T cells and that the CD80/ovalbumin double knock-in nanoparticle formulation can stop tumor development in mice. Current cell-based and engineered nanoparticle-based cancer immunotherapies are at odds with each other; however, the biomimetic approach to antigen presentation bridges this gap[62].

2.3 Nanomaterial-modified PD-1/PD-L1 Therapy

Immunotherapies targeting the PD-1/PD-L1 axis have shown exceptional efficacy in a wide variety of human malignancies. One of the major co-inhibitory receptors on T cells is PD-1. Upon interaction with its ligands, primarily PD-L1, PD-1 is activated. This leads to dephosphorylation and attenuation of molecular components in the T cell receptor (TCR) and CD28 pathways, which inhibits T-cell proliferation, activation, cytokine production, glycolysis or amino acid metabolism, and CTL functions. Activated T cells eventually die as a result of these effects[63]. Some drawbacks of ICI therapy include the heterogeneity of PD-L1 expression in tumors, active redistribution of the ligand after treatment, and limited targeting efficacy or binding strength of conventional antibody drugs[64]. An intrinsic the apeutic nanomedicine is expected to address the drawback of ICIs therapy by combining anti-PD-Ll and a T-cell activator. A number of studies have used modified nanoparticles to increase the binding avidity of ICIs and improve the antagonistic effect.

The NIR-IIb erbium-based rare-earth nanoparticles (ErNPs) were attached to anti-PD-L1 antibodies through cross-linked hydrophilic polymer layers. CTLs were found in the tumor microenvironment as a result of immunotherapy and immune activation altered CD8 signaling in the tumor and spleen. In mice, the cross-linked functionalized layer enabled 90% elimination of ErNP within two weeks without toxicity[65] (fig. 1C). Furthermore, according to Wang *et al*, the combination of tumor microenvironment-activatable αPD-L1 nanoparticle treatment and NIR laser irradiation-triggered activation of the photosensitizer ICG can inhibit tumor growth and metastasis. This effect was mediated by the generation of ROS, and it was also shown that this combination stimulated intratumoral infiltration of CTLs[66].

An enzyme/pH dual-sensitive nanoparticle with a micelle-liposome bilayer structure is combined with paclitaxel, the anti-cancer stem cell (CSC) drug thioridazine, and the PD-1/PD-L1 inhibitor. This nanodevice prolonged the survival of mice by increasing intratumoral drug concentrations in the animals and showed strong anticancer activity, while reducing the proportion of CSCs and increasing T-cell infiltration in tumor tissues[67] (fig. 1C). In addition, a fucoidan-based magnetic nanomedicine conjugated with a checkpoint inhibitor (anti-PD-L1) and T-cell activators (anti-CD3 and anti-CD28) can revive tumor-infiltrating lymphocytes while delivering the nanomedicine to the tumor via magnetic navigation to minimize off-target effects, reducing the incidence of adverse events and increasing median survival from 32 to 63 days[68].

PD-L1 and transforming growth factor-beta (TGF-β) mediate the immunosuppressive mechanisms of solid tumors and lead to T-cell exhaustion. Serial extrusion of CTLs through membranes containing micro-/nanosized holes and surface PD-1 and TGF receptors resulted in the production of T-cell-derived nanovesicles (TCNVs), which are small, transparent vesicles. TCNVs can prevent cytotoxic T cell exhaustion by blocking PD-L1 on cancer cells and scavenging TGF-β in the immunosuppressive tumor microenvironment (TME). Therefore, in syngeneic solid tumor-bearing mice, TCNVs successfully slow tumor development and provide a unique approach to circumvent cancer immunosuppressive pathways[69].

2.4 Nanomaterial-modified CAR-T Therapy

Nanoparticle-based bispecific T-cell engagers (nanoBiTEs) and nanoparticles conjugating multiple monoclonal antibodies (mAbs) against multiple cancer antigens for T-cell engagement (nanoMuTEs) targeting multiple cancer antigens have been developed to address the major limitations of T-cell-based immunotherapy, including CAR-T and bispecific T-cell engagers (BiTEs), which had poor pharmacokinetics and the ability to target only one antigen. Alhallak *et al* created nanoparticles conjugating multiple mAbs against different tumor antigens and liposomes coated with anti-CD3 mAbs (targeting T cells), called "nanoBiTEs" (nanoMuTEs). Because nanoBiTEs and nanoMuTEs have a long half-life of about 60 hours, once-weekly treatment rather than continuous infusion is possible while maintaining *in vitro* and *in vivo* efficacy[70].

It has been found that an injectable nanocarrier can carry *in vitro* transcribed (IVT) chimeric antigen receptor (CAR) or TCR mRNA to temporarily rewire circulating T cells. In mouse models of leukemia, prostate cancer, and liver cancer, repeated infusions of these polymeric nanocarriers resulted in a large number of host T cells expressing tumor-specific CARs or virus-specific TCRs, leading to disease regression[71].

Nanogels (NGs) of cell surface-conjugated proteins respond to an increase in T-cell surface-reducing potential upon antigen identification and prevent drug transport into the tumor microenvironment. The NG system selectively increased T cells in tumors by 16-fold and allowed for more than 8-fold higher doses of cytokines to be administered without toxicity compared to systemic administration of naked cytokines. Using NG delivery, human and murine CAR-T therapies were able to significantly improve tumor clearance *in vivo*[72] (fig. 1D).

3 NANOPARTICLES AND APC IMMUNOTHE-RAPY

A diverse collection of immune cells called APCs can process and display protein antigens for T cells to recognize and initiate an immune response at the cellular level[73]. Classical APCs include DCs, macrophages, Langerhans cells, and B cells. APCs naturally play a critical role in the fight against cancer by delivering tumor-related antigens to B lymphcytes and CTLs, which then produce antibodies against the antigen and destroy cancer cells[73–75].

3.1 Nanoparticles and DCs

DCs are a type of APC that play an important role in the adaptive immune system. A superparamagnetic Fe_3O_4 core encased in a photonic ZnO shell was created by Cho *et al*[76] to operate as both an imaging tool and a vehicle for the delivery of a carcinoembryonic antigen (CEA) into DCs. The *ex vivo* antigen loading of DCs, *in vivo* monitoring, and production of potent CEA-specific immune responses were all dramatically enhanced with the use of nanoparticles in a straightforward and consistent manner. Furthermore, the nanoparticles capsuled RNA, encoding of any polypeptide-based antigen, for delivery to DCs and macrophages is an efficient immune-activating method (fig. 2A). Kranz *et al* demonstrated that intravenously delivered RNA-lipoplexes (RNA-LPX) may target DCs precisely and
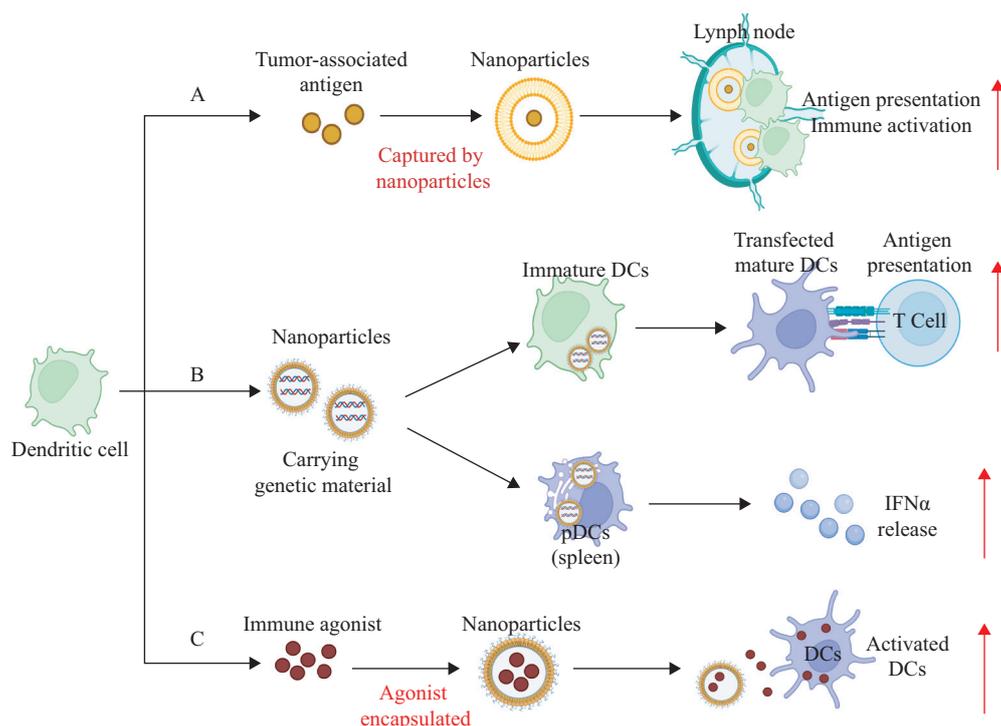
Fig. 2 Schematic of engineered nanoparticles (NPs) for regulating dendritic cells (DCs)

A: NPs capture tumor-associated antigen and deliver antigen to lymph node; B: NPs carrying genetic material promote maturation and interferon α (IFNα) release of DCs; C: Immune agonist encapsulated into NPs can activate DCs.

successfully *in vivo*. The LPX promote the effective absorption and production of the encoded antigen by DC populations and macrophages in diverse lymphoid compartments while shielding RNA from external ribonucleases[77]. The RNA-LPX encoding of viral or mutant neo-antigens or endogenous self-antigens enhances DCs maturation *in situ* and generates significant effector and memory T-cell responses, which in turn mediate potent IFN-dependent rejection of advanced malignancies. RNA-LPX treatment of the first 3 melanoma patients resulted in significant IFN and robust antigen-specific T-cell responses, according to the conclusions of a phase Ⅰ dose-escalation experiment (fig. 2B). In addition, immune agonists could be encapsulated in nanoparticles and delivered to tumor sites to induce potent anti-tumor immune responses. The commonly used nanoparticle-packaged immune agonists, such as stimulator of interferon genes (STING) agonists and TLR agonists, allowed for rapid tumor distribution and subsequent uptake by APCs[78–80] (fig. 2C).

3.2 Nanoparticles and Tumor-associated Macrophages

Tumor-associated macrophages (TAMs), a type of immune cells, are highly prevalent in the tumor microenvironment. TAMs can selectively differentiate into one of two functionally distinct subtypes: classically activated M1 macrophages or activated M2 macrophages, in response to a variety of external conditions[81]. Immune-activating M1 macrophages elicit an anticancer immune response by modifying cytotoxicity and antibody-dependent cell-mediated cytotoxicity (ADCC) to eliminate cancer cells. In the oxygen-starved microenvironment, macrophages tend to differentiate into the M2 type, which overexpresses anti-inflammatory cytokines such as TGF and IL-10, inhibits T cell-mediated antitumor immune response, recruits more myeloid-derived suppressor cells (MDSCs), and enhances immunosuppression of Treg cells[82–84]. Thus, M2 macrophages promote the development of an immunosuppressive micr-oenvironment that allows tumor cells to evade surveillance and clearance by the immune system[85, 86]. In most cancers, a low M1/M2 macrophage ratio often indicates a poor prognosis in patients with malignant tumors[87]. In addition, TAMs are thought to play an essential role in treatment resistance to radiotherapy, chemotherapy, and immunotherapy[88–90].

Due to changes in the tumor microenvironment or therapeutic treatments, M1 and M2 macrophages are highly flexible and can be transformed into each other. Recently, researchers reported that some nanoparticles, such as iron-chelated melanin-like nanoparticles and ferumoxytol, can be phagocytosed by macrophages and promote the repolarization of macrophages from M2 to M1[91, 92]. To reprogram TAMs to the M1 phenotype, which induces antitumor immunity and promotes neoplasm regression without systemic toxicity, Zhang *et al* created a targeted nanocarrier that could carry mRNA, IFN regulatory factor 5, in conjunction with

its activating kinase IKKs [inhibitor of NF-κB (IκB) kinase][93]. Another research team created a membrane-coated nucleic acid nanogel (Vir-Gel) that mimics a virus and is embedded with miR155, which has the potential to switch macrophages and microglia from an anti-inflammatory M2 phenotype to a pro-inflammatory M1 phenotype. The therapeutic effects of Vir-Gel were next tested in a glioma mouse model, and the results clearly showed that Vir-Gel exhibited outstanding tumor inhibitory efficacy and active tumor targeting capability[94]. In addition, Rodell *et al* established a small-molecule drug screening system for repolarizing TAMs, and they found that the agonists of the pattern recognition receptors, TLR7 and TLR8 found in the morphometric-based screen, had the strongest polarizing effects. Based on these findings, the researchers developed CDNP-R848 (R848, an agonist of TLR7 and TLR8), which can effectively deliver drugs to TAMs and dramatically increase the therapeutic response *in vivo*[95] (fig. 3A).
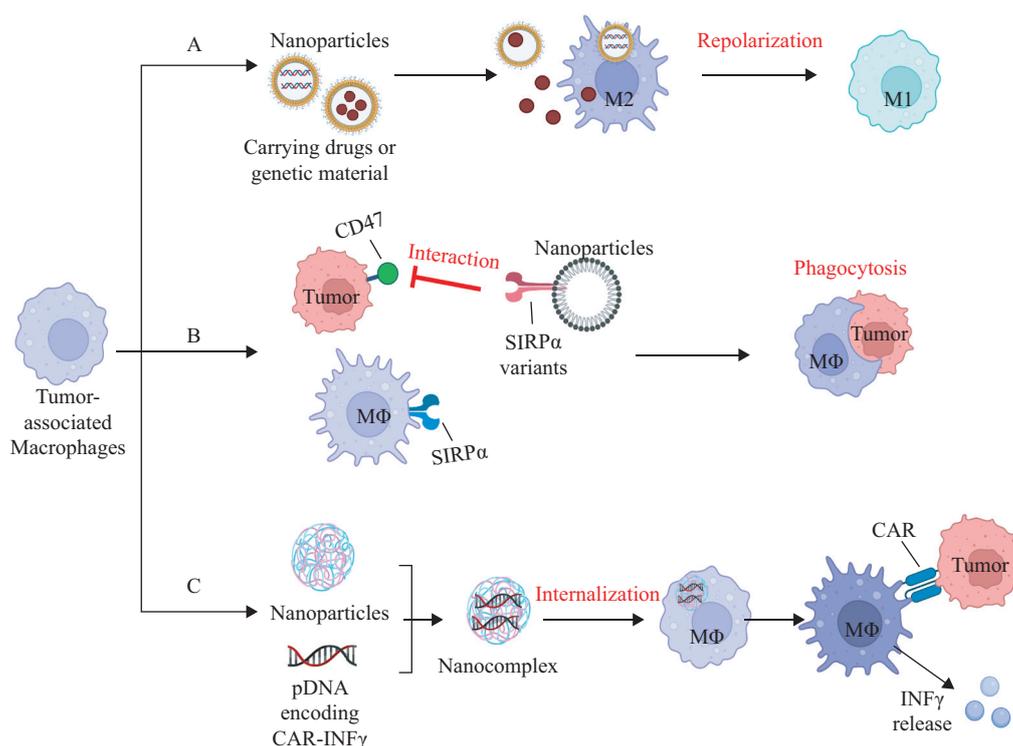
Fig. 3 Schematic of engineered nanoparticles (NPs) for regulating macrophage
A: NPs carrying genetic material or drugs promote repolarization of TAMs; B: NPs block the interaction between CD47-SIRPα and promote phagocytosis; C: Nanocomplex-mediated programming to CAR-M1 macrophages. CAR: chimeric antigen receptor; SIRPα: signal regulatory protein alpha

As the most important element of the innate immune system, macrophages play a key role in initiating the body's first line of defense against pathogen infection and cancer. Unfortunately, the ligand CD47, a "don't eat me" signal, is upregulated on the cell surface of cancer cells and protects them from phagocytosis by binding to the signal regulatory protein alpha (SIRPα) receptor on TAMs[96]. According to recent research, CD47 checkpoint inhibitors have the ability to generate potent T-cell immune responses in addition to stimulating TAMs to directly engulf cancer cells[97, 98]. In addition, clinical trials clearly showed that the use of CD47 checkpoint inhibitors caused some side effects, such as thrombocytopenia and anemia[99, 100]. The ability of nanoparticles entrapped in engineered cell membranes with overexpressed SIRP variants to disrupt the CD47-SIRP signaling axis that promotes M2-to-M1 transition has recently been reported by two different laboratories[101, 102] (fig. 3B).

CAR-T immunotherapy has shown promising clinical results in hematological malignancies. Nevertheless, its clinical application is limited due to the complex *in vitro* cell manufacturing process and poor therapeutic efficacy in solid tumors. Therapeutic failure is primarily caused by the limited infiltration of CAR-T cells into solid tumors and their deactivation in the immunosuppressive tumor microenvironment. Here, the investigators reprogramed macrophages by transfecting the CAR *in vivo*, allowing the transforming macrophage to intrinsically infiltrate solid tumors. CAR-M macrophages exhibit an extraordinary capacity for cancer-targeted phagocytosis and antitumor activity. Recent studies have shown that mannose receptors are overexpressed in macrophages[103, 104].

Mannose-conjugated polyethyleneimine (MPEI), one of the nanocarriers modified by the mannose moiety, has dramatically improved macrophage targeting efficacy both *in vitro* and *in vivo*[105]. The researchers programmed pro-tumoral M2 TAMs to an antitumoral M1 phenotype by delivering CAR IFN-encoding plasmid DNA using MEPI as a nanovesicle. This allowed CAR expression on the TAMs[105] (fig. 3C).

4 NANOPARTICLES AND NATURAL KILLER CELLS IMMUNOTHERAPY

Innate immune cells known as natural killer (NK) cells mediate responses against viruses and tumors. Because NK cells lack an antigen-specific cell surface receptor, they are able to respond immediately without prior to exposure to pathogen or the malignant cell. NK cells produce a variety of cytokines, including IL-10 and tumor necrosis factor (TNF). The function of the typical pro-inflammatory cytokines TNF and IL-10 in priming DCs, neutrophils, and macrophages is to influence the subsequent regulation of antigen-specific T- and B-cell responses. The Fc receptor (FcR), an activating biochemical receptor that binds the Fc component of IgG class antibodies, has also been reported to be highly expressed on the NK cell membrane. As a result, when humoral immunity is activated, NK cells can target and lyse cancer cells through antibody-dependent cytotoxicity (ADCC). Activated NK cells mainly release perforin and granzyme B to directly kill target cells, while releasing inflammatory cytokines and chemokines to produce indirect antitumor effects.

Recently, some studies have exploited the efficient potential of NK cells to kill cancer cells through the ADCC effect. The research found that nanoparticles can be specifically designed to target tumor surface proteins and carry Fc peptides. When nanoparticles bound to tumor cells, Fc peptides on the surface of nanoparticles were exposed and recognized by NK cells, which activated the NK cells and mediated the ADCC effect, effectively killing a variety of solid tumors[106, 107]. Additionally, the ability to reengineer immune cells using nanoparticle-delivered genetic material has been validated. According to research by Kim *et al*, for *in vivo* tracking of NK cells using non-invasive magnetic resonance (MR) and fluorescence, optical imaging was possible with multifunctional nanoparticles (MF-NPs). The EGFR-CAR plasmid can be transferred by the MF-NPs to tumor-infiltrating NKs, causing the expression of EGFR-CARs on the NK cell surface, which enhances the anticancer cytotoxic effect both *in vitro* and *in vivo*[108]. Another study group discovered that a non-viral lipid nanoparticle (LNP)-based delivery method for small interfering RNAs (siRNAs) could interfere with the expression of

critical intrinsic inhibitory genes in NK cells, including SHP-1, Cbl-b, and c-Cbl. To eliminate malignancies, the nanoparticles precisely targeted NK cells *in vivo*, silenced inhibitory checkpoint signaling molecules, and increased NK cell activity[109]. Finally, nanovesicles can deliver some types of drugs to tumor tissues, such as selenic acid, selenopeptide, and STING agonists, which play a remarkable role in immunomodulatory function by stimulating NK cell activation[110–112].

5 NANOPARTICLES AND MYELOID-DERIVED SUPPRESSOR CELLS IMMUNOTHERAPY

A diverse group of immune cells from the myeloid lineage are known as MDSCs. MDSCs exhibit potent immunosuppressive activities by secreting immunosuppressive factors (nitric oxide, arginase, ROS) and interacting with other immune cell types to regulate their functions[113, 114]. The multilayer polymer nanocapsules developed by Ledo *et al*[115] have the ability to co-deliver two different immunomodulatory drugs, a chemokine, and an RNAi sequence, which can reverse MDSC-induced immunosuppression. The chemokine ligand 2 (CCL2), also known as monocyte chemoattractant protein 1, has a strong ability to attract MDSCs to the site of inflammation. On the other hand, shC/EBP and miR 142-3p, two different RNAi sequences that control the CCAAT/enhancer-binding protein beta (C/EBP) pathway, were effectively linked to the polymer shell of the nanoparticles. The multilayer nanocapsules were composed of chemokine CCL2, immunomodulatory drugs polyarginine and hyaluronic acid, and RNA sequences shC/EBPβ and miR142-3p. In a fibrosarcoma mouse model, C/EBPβ mRNA levels were downregulated in MDSCs, and monocyte polarization in the tumor microenvironment was reduced. Ding *et al*[116] prepared a bifunctional nanoparticle using liposome to encapsulate a photosensitizer Ce6 and a PI3Kγ inhibitor IPI-549. Under laser irradiation, the nanoparticles absorbed by colorectal cancer cells generate ROS, which led to immunogenic tumor cell death. IPI-549 could inhibit the PI3K pathway, which in turn caused the downregulation of arginase 1 (Arg-1) and ROS to increase MDSC death and prevent immunosuppressive effects on CD8+ T cells. IPI-549 was delivered to MDSCs via nanoliposomes. While reducing tumor infiltration of immunosuppressive Treg cells, MDSCs and M2-TAMs, nanodrug-mediated immunogenic photodynamic therapy targeted MDSC cytotoxicity, remarkably inhibiting tumor growth by promoting DC maturation and CD8+ T cell infiltration.

Tumor-associated myeloid cells (TAMCs) are a critical subset of immunosuppressive cells in glioblastoma. TAMs and MDSCs make up the diverse population of myeloid cells known as TAMCs, which

are derived from hematopoietic progenitors. Several studies have shown that PD-L1 is highly expressed in glioma-associated TAMCs. For example, an anti-PD-L1 therapeutic antibody surface-coated LNP was successfully created by Zhang *et al*[117]. Dinaciclib, a cyclin-dependent kinase inhibitor, was incorporated into PD-L1-targeted LNPs, which resulted in a significant reduction of TAMCs and attenuation of their immunosuppressive effects. The penetration and drug delivery capabilities of nanomedicine are robustly enhanced by radiotherapy combined with nano-immunotherapy, and thus dramatically prolong the survival of glioma mice models.

6 NANOPARTICLES AND TREG CELLS IMMUNOTHERAPY

Treg cells, formerly known as suppressor T cells, play a critical role in maintaining immune self-tolerance. The biomarkers CD4, FOXP3, and CD25, which are highly expressed in Treg cells, are thought to be derived from the same lineage as naive CD4+ cells. Treg cells are a type of immunosuppressive cells and generally inhibit the downregulation induction and proliferation of effector T cells.

Ursolic acid (UA) is a potent triterpenoid found in plants and fruits. It can modulate important cell signaling pathways involving STATs, NF-κB, and TRAIL. UA-liposomes were prepared by Zhang *et al*[118] using HP-CD-assisted active loading. The UA-liposomes can successfully modify CD4+CD25+Foxp3+ T cells from 4T1 tumor-bearing mice by reducing STAT5 phosphorylation and IL-10 production but are generally not hazardous to 4T1 triple-negative breast cancer cells. *In vivo* treatment with UA liposomes at a dose of 10 mg/kg resulted in a decrease in the number of Treg cells and MDSCs remaining in tumor tissue. These adjustments represented the elimination of the tumor-induced immunosuppressive microenvironment. UA liposome therapy alone was able to inhibit tumor growth. According to Ou *et al*, the tLyp1 peptide-modified hybrid nanoparticles had high stability, were efficient in targeting Treg cells, and improved the ability of imatinib to reduce Treg cell suppression by inhibiting STAT3 and STAT5 phosphorylation. In addition, an *in vivo* study showed that the hybrid nanoparticle accumulated significantly in tumors. In particular, when paired with checkpoint blockade using anti-CTL antigen-4 antibody, prolonged survival, increased tumor inhibition, reduced intratumoral Treg cells, and increased intratumoral CD8+ T cells against the tumor were found[119].

7 CONCLUSION AND FUTURE PERSPECTIVES

At present, immunotherapy is widely revolu-tionizing the field of cancer treatment with the combination of immunology and nanomaterials giving full play to the advantages of immunotherapy. Nanocarriers provide an unparalleled delivery model for immunotherapy, as they can effectively reduce its systemic cytotoxicity due to specific accumulation in solid tumors or lymph nodes. And through the continuous slow release of immunotherapeutic agents, immune cells are induced to generate a long-term memory immune response. Nanoparticles could deliver various types of immunomodulators, such as antigens, antibodies, nucleic acids, cytokines, ligands, etc., and protect the immunomodulator from rapid degradation during transport. In addition, nanomedicine can be combined with conventional therapies such as chemotherapy and radiotherapy to promote synergistic tumor treatment.

Although recent studies found that the application of nanomaterials in immunotherapy could achieve excellent therapeutic results, there are still many challenges and barriers in practical clinical application. First, the ability of nanodrugs to target tumors mainly depends on the EPR effect. Since the EPR phenomenon was reported, it has been recognized as an important driving force for the accumulation of nanoparticles at tumor sites. However, recent studies by the University of Toronto team proposed that endocytosis of tumor endothelial cells may be the main mechanism for nanoparticle enrichment. Regardless of how the EPR effect or tumor endocytosis effect works, the amount of nanodrugs retained in tumor tissue is still very small. Even though some early clinical trials have adopted intratumoral administration of nanomedicine, systemic risk and toxicity of nanomedicine are still inevitable. Second, the tumor immune microenvironment is a complex and highly heterogeneous environment, and most of the nanomedicines have only been validated in the subcutaneous tumor-forming environment with a single tumor cell line, lacking a more convincing experimental animal model. The third challenge is the reliable and efficient delivery of genetic material-encoding CARs, TCRs, or tumor antigens to immune cells *in vivo*. Currently, most transfections are reported to be targeted into cells *in vitro*, while *in vivo* transfection efficiency remains low and there is a high risk of off-target gene contamination.

Nanomedicine in cancer immunotherapy has shown good results in recent decades; nano-immunotherapy has successfully completed clinical trials, and several projects are currently in clinical trials (table 1). It can be predicted that in the future, tumor nano-immunotherapy could achieve the following goals: (1) By combining new omics tools such as second-generation sequencing, liquid biopsy, proteomics, and single-cell sequencing, the personalized design of nanomedicine could significantly improve the targeting

Table 1

No.	Pre-asphyxia	Types of clinical trials	Objective	Nanomedicine	Recruitment Status	ClinicalTrials.gov Identifier
1	Camille *et al* (2016)	Phase I	Radiosensitization of multiple brain metastases using AGuIX	AGuIX gadolinium based nanoparticle	Completed	NCT02820454
2	Niu *et al* (2015)	Phase I	Nano drug interventional therapy using digital subtraction angiography for pancreatic carcinoma	The nano drug is made by mixing Gemzar® with compound glycyrrhizin injection	Completed	NCT02449135
3	Niu *et al* (2015)	Phase I / II	Nano drug interventional therapy using digital subtraction angiography for liver carcinoma	The nano drug is made by mixing Gemzar® with compound glycyrrhizin injection	Completed	NCT02449109
4	Niu *et al* (2015)	Phase I / II	Nano drug interventional therapy using digital subtraction angiography for lung carcinoma	The nano drug is made by mixing Gemzar® with compound glycyrrhizin injection	Completed	NCT02449122
5	Baldassarre *et al* (2019)	Phase II	NanO2TM combined with radiation and temozolomide in patients with newly-diagnosed glioblastoma multiforme	NanO2TM particles	Recruiting	NCT03362430
6	Hana'a *et al* (2022)	Phase I / II	Therapeutic efficacy of quercetin *versus* its encapsulated nanoparticle on tongue squamous cell carcinoma cell line	Quercetin encapsulated by PLGA-PEG nanoparticls	Recruiting	NCT02995603
7	Juliette *et al* (2021)	Phase I / II	Phase I / II study of AGuIX nanoparticles with radiotherapy plus concomitant temozolomide in the treatment of newly diagnosed glioblastoma	Polysiloxane Gd-chelates based nanoparticles (AGuIX)	Recruiting	NCT04881032
8	Dan *et al* (2008)	Phase I	Targeted atomic Nano-Generators (Actinium-225-labeled humanized anti-CD33 monoclonal antibody HuM195) in patients with advanced myeloid malignancies	Actinium-225-labeled humanized anti-CD33 monoclonal antibody HuM195 (225Ac-HuM195)	Completed	NCT00672165
9	Jonathan *et al* (2021)	Phase I / II	Nanoparticles with MR guided SBRT in genrtally located lung tumors and pancreatic cancer	Polysiloxane Gd-chelates based nanoparticles (AGuIX)	Recruiting	NCT04789486
10	Timothy *et al* (2019)	Phase I	Evaluatation of early immunologic pharmacodynamic parameters for the PD-1 antibody pembrolizumab with autologous tumor lysate-pulsed dendritic cell vaccination in patients with surgically accessible recurrent/progressive glioblastoma	Poly ICLC	Recruiting	NCT04201873
11	Bonn *et al* (2019)	Phase I / II	Single-arm dose-escalation phase 1/2 study of olaptesed pegol (NOX-A12) in combination with irradiation in inoperable or partially resected first-line glioblastoma patients with unmethylated MGMT promoter	Olaptesed Pegol (NOX-A12)	Recruiting	NCT04121455
12	Tora *et al* (2022)	Phase I	Patients with recurrent grade 3 and grade 4 glioma will be recruited for treatment with 177Lu-PSMA.	68Ga/177Lu-PSMA	Not yet recruiting	NCT05644080
13	Joohang *et al* (2020)	Phase I	A phase I, open-label, dose-finding study to evaluate the safety, tolerability, and pharmacokinetics of intravenously infused SNB-101 (as SN-38) in patients with advanced solid tumors	SNB-101	Recruiting	NCT04640480
14	Joann *et al* (2016)	Phase I	Phase I study of C6 ceramide nanoliposome in patients with advanced solid tumors	C6 ceramide nanoliposome	Recruiting	NCT02834611
15	Daniel *et al* (2021)	Phase I	Phase I study of C6 ceramide nanoliposome in patients with relapsed/refractory acute myeloid leukemia	C6 ceramide nanoliposome	Recruiting	NCT04716452

specificity and accuracy and remarkably improve the therapeutic safety by strictly controlling drug delivery; (2) The addition of various probes on the surface of nanocarriers enables real-time tracking imaging and evaluation of therapeutic effects; (3) The process of transforming nanomedicines from laboratory to clinical application is shortened, and drugs are more accessible and widely applicable.

Open Access

Conflict of Interest Statement

The authors declare that there are no conflicts of interest relevant to this article.

REFERENCES

1   Xia C, Dong X, Li H, *et al*. Cancer statistics in China and United States, 2022: profiles, trends, and determinants. Chin Med J (Engl), 2022,135(5):584-590

2   Siegel RL, Miller KD, Fuchs HE, *et al*. Cancer statistics, 2022. CA Cancer J Clin, 2022,72(1):7-33

3   DeVita VT, Chu E. A history of cancer chemotherapy. Cancer Res, 2008,68(21):8643-8653

4   Chandra RA, Keane FK, Voncken FEM, *et al*. Contemporary radiotherapy: present and future. Lancet, 2021,398(10295):171-184

5   Waldman AD, Fritz JM, Lenardo MJ. A guide to cancer immunotherapy: from T cell basic science to clinical practice. Nat Rev Immunol, 2020,20(11):651-668

6   Wang Z, Cao YJ. Adoptive Cell Therapy Targeting Neoantigens: A Frontier for Cancer Research. Front Immunol, 2020,11:176

7   Saxena M, van der Burg SH, Melief CJM, *et al*. Therapeutic cancer vaccines. Nat Rev Cancer, 2021,21(6):360-378

8   Singh AK, McGuirk JP. CAR T cells: continuation in a revolution of immunotherapy. Lancet Oncol, 2020,21(3):e168-e178

9   Postow MA, Callahan MK, Wolchok JD. Immune Checkpoint Blockade in Cancer Therapy. J Clin Oncol, 2015,33(17):1974-1982

10 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, 2021,16:223-249

11 Petrosky E, Bocchini JA Jr, Hariri S, *et al*. Use of 9-valent human papillomavirus (HPV) vaccine: updated HPV vaccination recommendations of the advisory committee on immunization practices. MMWR Morb Mortal Wkly Rep, 2015,64(11):300-304

12 Paz-Ares L, Ciuleanu TE, Cobo M, *et al*. First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial. Lancet Oncol, 2021,22(2):198-211

13 Hellmann MD, Paz-Ares L, Bernabe Caro R, *et al*. Nivolumab plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer. N Engl J Med, 2019,381(21):2020-2031

14 Hodi FS, Chiarion-Sileni V, Gonzalez R, *et al*. Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial. Lancet Oncol, 2018,19(11):1480-1492

15 Hou AJ, Chen LC, Chen YY. Navigating CAR-T cells through the solid-tumour microenvironment. Nat Rev Drug Discov, 2021,20(7):531-550

16 Goldberg MS. Improving cancer immunotherapy through nanotechnology. Nat Rev Cancer, 2019,19(10):587-602

17 Irvine DJ, Dane EL. Enhancing cancer immunotherapy with nanomedicine. Nat Rev Immunol, 2020,20(5):321-334

18 Matsumura Y, Maeda H. A new concept for macromolecular therapeutics in cancer chemotherapy: mechanism of tumoritropic accumulation of proteins and the antitumor agent smancs. Cancer Res, 1986,46(12 Pt 1):6387-6392

19 Iyer AK, Khaled G, Fang J, *et al*. Exploiting the enhanced permeability and retention effect for tumor targeting. Drug Discov Today, 2006,11(17-18):812-818

20 Wang J, Zhang B, Sun J, *et al*. Nanomedicine-Enabled Modulation of Tumor Hypoxic Microenvironment for Enhanced Cancer Therapy. Adv Ther (Weinh), 2020,3(1):1900083

21 Jin MZ, Jin WL. The updated landscape of tumor microenvironment and drug repurposing. Signal Transduct Target Ther, 2020,5(1):166

22 Shields CWt 4th, Wang LL, Evans MA, *et al*. Materials for Immunotherapy. Adv Mater, 2020,32(13):e1901633

23 Thomas PD, Kahn M. Kat3 coactivators in somatic stem cells and cancer stem cells: biological roles, evolution, and pharmacologic manipulation. Cell Biol Toxicol, 2016,32(1):61-81

24 Zhou J, Wang G, Chen Y, *et al*. Immunogenic cell death in cancer therapy: Present and emerging inducers. J Cell Mol Med, 2019,23(8):4854-4865

25 Kroemer G, Galluzzi L, Kepp O, *et al*. Immunogenic cell death in cancer therapy. Annu Rev Immunol, 2013,31:51-72

26 Banstola A, Jeong JH, Yook S. Immunoadjuvants for cancer immunotherapy: A review of recent developments. Acta Biomater, 2020,114:16-30

27 Mohamed SIA, Jantan I, Haque MA. Naturally occurring immunomodulators with antitumor activity: An insight on their mechanisms of action. Int Immunopharmacol, 2017,50:291-304

28 Mitchell MJ, Billingsley MM, Haley RM, *et al*.

Engineering precision nanoparticles for drug delivery. Nat Rev Drug Discov, 2021,20(2):101-124

29 Kuai R, Yuan W, Son S, *et al*. Elimination of established tumors with nanodisc-based combination chemoimmunotherapy. Sci Adv, 2018,4(4):eaao1736

30 Ding Y, Sun Z, Gao Y, *et al*. Plasmon-Driven Catalytic Chemotherapy Augments Cancer Immunotherapy through Induction of Immunogenic Cell Death and Blockage of IDO Pathway. Adv Mater, 2021,33(34):e2102188

31 Feng B, Zhou F, Hou B, *et al*. Binary Cooperative Prodrug Nanoparticles Improve Immunotherapy by Synergistically Modulating Immune Tumor Microenvironment. Adv Mater, 2018,30(38):e1803001

32 Mu QG, Lin G, Jeon M, *et al*. Iron oxide nanoparticle targeted chemo-immunotherapy for triple negative breast cancer. Mater Today (Kidlington), 2021,50:149-169

33 de Souza ASC, Goncalves LB, Lepique AP, *et al*. The Role of Autophagy in Tumor Immunology-Complex Mechanisms That May Be Explored Therapeutically. Front Oncol, 2020,10:603661

34 Wang X, Li M, Ren K, *et al*. On-Demand Autophagy Cascade Amplification Nanoparticles Precisely Enhanced Oxaliplatin-Induced Cancer Immunotherapy. Adv Mater, 2020,32(32):e2002160

35 Li W, Yang J, Luo L, *et al*. Targeting photodynamic and photothermal therapy to the endoplasmic reticulum enhances immunogenic cancer cell death. Nat Commun, 2019,10(1):3349

36 Yan S, Zeng X, Tang Y, *et al*. Activating Antitumor Immunity and Antimetastatic Effect Through Polydopamine-Encapsulated Core-Shell Upconversion Nanoparticles. Adv Mater, 2019,31(46):e1905825

37 Chen C, Ni X, Jia S, *et al*. Massively Evoking Immunogenic Cell Death by Focused Mitochondrial Oxidative Stress using an AIE Luminogen with a Twisted Molecular Structure. Adv Mater, 2019,31(52):e1904914

38 He C, Duan X, Guo N, *et al*. Core-shell nanoscale coordination polymers combine chemotherapy and photodynamic therapy to potentiate checkpoint blockade cancer immunotherapy. Nat Commun, 2016,7:12499

39 Xu C, Jiang Y, Huang J, *et al*. Second Near-Infrared Light-Activatable Polymeric Nanoantagonist for Photothermal Immunometabolic Cancer Therapy. Adv Mater, 2021,33(36):e2101410

40 Shao D, Zhang F, Chen F, *et al*. Biomimetic Diselenide-Bridged Mesoporous Organosilica Nanoparticles as an X-ray-Responsive Biodegradable Carrier for Chemo-Immunotherapy. Adv Mater, 2020,32(50):e2004385

41 Song R, Li T, Ye J, *et al*. Acidity-Activatable Dynamic Nanoparticles Boosting Ferroptotic Cell Death for Immunotherapy of Cancer. Adv Mater, 2021,33(31):e2101155

42 Su Z, Xiao Z, Wang Y, *et al*. Codelivery of Anti-PD-1 Antibody and Paclitaxel with Matrix Metalloproteinase and pH Dual-Sensitive Micelles for Enhanced Tumor Chemoimmunotherapy. Small, 2020,16(7):e1906832

43 Zhou P, Qin J, Zhou C, *et al*. Multifunctional nanoparticles based on a polymeric copper chelator for combination treatment of metastatic breast cancer. Biomaterials, 2019,195:86-99

44 Hu CM, Zhang L, Aryal S, *et al*. Erythrocyte membrane-camouflaged polymeric nanoparticles as a biomimetic delivery platform. Proc Natl Acad Sci USA, 2011,108(27):10980-10985

45 Kroll AV, Fang RH, Zhang L. Biointerfacing and Applications of Cell Membrane-Coated Nanoparticles. Bioconjug Chem, 2017,28(1):23-32

46 Bahmani B, Gong H, Luk BT, *et al*. Intratumoral immunotherapy using platelet-cloaked nanoparticles enhances antitumor immunity in solid tumors. Nat Commun, 2021,12(1):1999

47 Kroll AV, Fang RH, Jiang Y, *et al*. Nanoparticulate Delivery of Cancer Cell Membrane Elicits Multiantigenic Antitumor Immunity. Adv Mater, 2017,29(47)

48 Liu WL, Zou MZ, Liu T, *et al*. Expandable Immunotherapeutic Nanoplatforms Engineered from Cytomembranes of Hybrid Cells Derived from Cancer and Dendritic Cells. Adv Mater, 2019,31(18):e1900499

49 Deng G, Sun Z, Li S, *et al*. Cell-Membrane Immunotherapy Based on Natural Killer Cell Membrane Coated Nanoparticles for the Effective Inhibition of Primary and Abscopal Tumor Growth. ACS Nano, 2018,12(12):12096-12108

50 Cao H, Dan Z, He X, *et al*. Liposomes Coated with Isolated Macrophage Membrane Can Target Lung Metastasis of Breast Cancer. ACS Nano, 2016,10(8):7738-7748

51 Chen Q, Bai H, Wu W, *et al*. Bioengineering Bacterial Vesicle-Coated Polymeric Nanomedicine for Enhanced Cancer Immunotherapy and Metastasis Prevention. Nano Lett, 2020,20(1):11-21

52 Kim OY, Park HT, Dinh NTH, *et al*. Bacterial outer membrane vesicles suppress tumor by interferon-gamma-mediated antitumor response. Nat Commun, 2017,8(1):626

53 Min Y, Roche KC, Tian S, *et al*. Antigen-capturing nanoparticles improve the abscopal effect and cancer immunotherapy. Nat Nanotechnol, 2017,12(9):877-882

54 Wang B, An J, Zhang H, *et al*. Personalized Cancer Immunotherapy via Transporting Endogenous Tumor Antigens to Lymph Nodes Mediated by Nano Fe_3O_4. Small, 2018,14(38):e1801372

55 Lei K, Kurum A, Tang L. Mechanical Immunoengineering of T cells for Therapeutic Applications. Acc Chem Res, 2020,53(12):2777-2790

56 Zhou Z, Zhang B, Zai W, *et al*. Perfluorocarbon nanoparticle-mediated platelet inhibition promotes intratumoral infiltration of T cells and boosts immunotherapy. Proc Natl Acad Sci USA, 2019,116(24):11972-11977

57 Yin Q, Yu W, Grzeskowiak CL, *et al*. Nanoparticle-enabled innate immune stimulation activates endogenous tumor-infiltrating T cells with broad antigen specificities. Proc Natl Acad Sci USA, 2021,118(21):e2016168118

58 Xu C, Jiang Y, Han Y, *et al*. A Polymer Multicellular Nanoengager for Synergistic NIR-Ⅱ Photothermal Immunotherapy. Adv Mater, 2021,33(14):e2008061

59 Voskoboinik I, Whisstock JC, Trapani JA. Perforin and granzymes: function, dysfunction and human pathology. Nat Rev Immunol, 2015,15(6):388-400

60 Zhao Q, Gong Z, Li Z, *et al*. Target Reprogramming Lysosomes of CD8+ T Cells by a Mineralized Metal-Organic Framework for Cancer Immunotherapy. Adv

Mater, 2021,33(17):e2100616

61 Bae J, Parayath N, Ma W, *et al*. BCMA peptide-engineered nanoparticles enhance induction and function of antigen-specific CD8(+) cytotoxic T lymphocytes against multiple myeloma: clinical applications. Leukemia, 2020,34(1):210-223

62 Jiang Y, Krishnan N, Zhou J, *et al*. Engineered Cell-Membrane-Coated Nanoparticles Directly Present Tumor Antigens to Promote Anticancer Immunity. Adv Mater, 2020,32(30):e2001808

63 Ai L, Xu A, Xu J. Roles of PD-1/PD-L1 Pathway: Signaling, Cancer, and Beyond. Adv Exp Med Biol, 2020,1248:33-59

64 Brahmer JR, Tykodi SS, Chow LQ, *et al*. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med, 2012,366(26):2455-2465

65 Zhong Y, Ma Z, Wang F, *et al*. *In vivo* molecular imaging for immunotherapy using ultra-bright near-infrared-IIb rare-earth nanoparticles. Nat Biotechnol, 2019,37(11):1322-1331

66 Wang D, Wang T, Yu H, *et al*. Engineering nanoparticles to locally activate T cells in the tumor microenvironment. Sci Immunol, 2019,4(37):eaau6584

67 Lang T, Liu Y, Zheng Z, *et al*. Cocktail Strategy Based on Spatio-Temporally Controlled Nano Device Improves Therapy of Breast Cancer. Adv Mater, 2019,31(5):e1806202

68 Chiang CS, Lin YJ, Lee R, *et al*. Combination of fucoidan-based magnetic nanoparticles and immunomodulators enhances tumour-localized immunotherapy. Nat Nanotechnol, 2018,13(8):746-754

69 Hong J, Kang M, Jung M, *et al*. T-Cell-Derived Nanovesicles for Cancer Immunotherapy. Adv Mater, 2021,33(33):e2101110

70 Alhallak K, Sun J, Wasden K, *et al*. Nanoparticle T-cell engagers as a modular platform for cancer immunotherapy. Leukemia, 2021,35(8):2346-2357

71 Parayath NN, Stephan SB, Koehne AL, *et al*. *In vitro*-transcribed antigen receptor mRNA nanocarriers for transient expression in circulating T cells *in vivo*. Nat Commun, 2020,11(1):6080

72 Tang L, Zheng Y, Melo MB, *et al*. Enhancing T cell therapy through TCR-signaling-responsive nanoparticle drug delivery. Nat Biotechnol, 2018,36(8):707-716

73 Gaudino SJ, Kumar P. Cross-Talk Between Antigen Presenting Cells and T Cells Impacts Intestinal Homeostasis, Bacterial Infections, and Tumorigenesis. Front Immunol, 2019,10:360

74 Schuijs MJ, Hammad H, Lambrecht BN. Professional and 'Amateur' Antigen-Presenting Cells In Type 2 Immunity. Trends Immunol, 2019,40(1):22-34

75 Lindenbergh MFS, Stoorvogel W. Antigen Presentation by Extracellular Vesicles from Professional Antigen-Presenting Cells. Annu Rev Immunol, 2018,36:435-459

76 Cho NH, Cheong TC, Min JH, *et al*. A multifunctional core-shell nanoparticle for dendritic cell-based cancer immunotherapy. Nat Nanotechnol, 2011,6(10):675-682

77 Kranz LM, Diken M, Haas H, *et al*. Systemic RNA delivery to dendritic cells exploits antiviral defence for cancer immunotherapy. Nature, 2016,534(7607):396-401

78 Nuhn L, De Koker S, Van Lint S, *et al*. Nanoparticle-Conjugate TLR7/8 Agonist Localized Immunotherapy Provokes Safe Antitumoral Responses. Adv Mater, 2018,30(45):e1803397

79 Liu Y, Crowe WN, Wang L, *et al*. An inhalable nanoparticulate STING agonist synergizes with radiotherapy to confer long-term control of lung metastases. Nat Commun, 2019,10(1):5108

80 Atukorale PU, Raghunathan SP, Raguveer V, *et al*. Nanoparticle Encapsulation of Synergistic Immune Agonists Enables Systemic Codelivery to Tumor Sites and IFNbeta-Driven Antitumor Immunity. Cancer Res, 2019,79(20):5394-5406

81 Pan Y, Yu Y, Wang X, *et al*. Tumor-Associated Macrophages in Tumor Immunity. Front Immunol, 2020,11:583084

82 Mehla K, Singh PK. Metabolic Regulation of Macrophage Polarization in Cancer. Trends Cancer, 2019,5(12):822-834

83 Locati M, Curtale G, Mantovani A. Diversity, Mechanisms, and Significance of Macrophage Plasticity. Annu Rev Pathol, 2020,15:123-147

84 Yunna C, Mengru H, Lei W, *et al*. Macrophage M1/M2 polarization. Eur J Pharmacol, 2020, 877:173090

85 Noy R, Pollard JW. Tumor-associated macrophages: from mechanisms to therapy. Immunity, 2014,41(1):49-61

86 Cassetta L, Pollard JW. Tumor-associated macrophages. Curr Biol, 2020, 30(6):R246-R248

87 Zhang M, He Y, Sun X, *et al*. A high M1/M2 ratio of tumor-associated macrophages is associated with extended survival in ovarian cancer patients. J Ovarian Res, 2014,7:19

88 Mantovani A, Allavena P. The interaction of anticancer therapies with tumor-associated macrophages. J Exp Med, 2015,212(4):435-445

89 Zhou J, Tang Z, Gao S, *et al*. Tumor-Associated Macrophages: Recent Insights and Therapies. Front Oncol, 2020,10:188

90 Li C, Xu X, Wei S, *et al*. Tumor-associated macrophages: potential therapeutic strategies and future prospects in cancer. J Immunother Cancer, 2021,9(1):e001341

91 Zanganeh S, Hutter G, Spitler R, *et al*. Iron oxide nanoparticles inhibit tumour growth by inducing pro-inflammatory macrophage polarization in tumour tissues. Nat Nanotechnol, 2016,11(11):986-994

92 Rong L, Zhang Y, Li WS, *et al*. Iron chelated melanin-like nanoparticles for tumor-associated macrophage repolarization and cancer therapy. Biomaterials, 2019,225:119515

93 Zhang F, Parayath NN, Ene CI, *et al*. Genetic programming of macrophages to perform anti-tumor functions using targeted mRNA nanocarriers. Nat Commun, 2019,10(1):3974

94 Gao X, Li S, Ding F, *et al*. A Virus-Mimicking Nucleic Acid Nanogel Reprograms Microglia and Macrophages for Glioblastoma Therapy. Adv Mater, 2021,33(9):e2006116

95 Rodell CB, Arlauckas SP, Cuccarese MF, *et al*. TLR7/8-agonist-loaded nanoparticles promote the polarization of tumour-associated macrophages to enhance cancer immunotherapy. Nat Biomed Eng, 2018,2(8):578-588

96 Majeti R, Chao MP, Alizadeh AA, *et al*. CD47 is an adverse prognostic factor and therapeutic antibody target on human acute myeloid leukemia stem cells. Cell, 2009,138(2):286-299

97 Chao MP, Alizadeh AA, Tang C, *et al*. Anti-CD47 antibody synergizes with rituximab to promote phagocytosis and eradicate non-Hodgkin lymphoma. Cell, 2010,142(5):699-713

98 Willingham SB, Volkmer JP, Gentles AJ, *et al*. The CD47-signal regulatory protein alpha (SIRPa) interaction is a therapeutic target for human solid tumors. Proc Natl Acad Sci U S A, 2012,109(17):6662-6667

99 Feng M, Jiang W, Kim BYS, *et al*. Phagocytosis checkpoints as new targets for cancer immunotherapy. Nat Rev Cancer, 2019,19(10):568-586

100 Advani R, Flinn I, Popplewell L, *et al*. CD47 Blockade by Hu5F9-G4 and Rituximab in Non-Hodgkin's Lymphoma. N Engl J Med, 2018,379(18):1711-1721

101 Rao L, Wu L, Liu Z, *et al*. Hybrid cellular membrane nanovesicles amplify macrophage immune responses against cancer recurrence and metastasis. Nat Commun, 2020,11(1):4909

102 Rao L, Zhao SK, Wen C, *et al*. Activating Macrophage-Mediated Cancer Immunotherapy by Genetically Edited Nanoparticles. Adv Mater, 2020,32(47):e2004853

103 Apostolopoulos V, McKenzie IF. Role of the mannose receptor in the immune response. Curr Mol Med, 2001,1(4):469-474

104 Azad AK, Rajaram MV, Schlesinger LS. Exploitation of the Macrophage Mannose Receptor (CD206) in Infectious Disease Diagnostics and Therapeutics. J Cytol Mol Biol, 2014,1(1):1000003

105 Kang M, Lee SH, Kwon M, *et al*. Nanocomplex-Mediated *In Vivo* Programming to Chimeric Antigen Receptor-M1 Macrophages for Cancer Therapy. Adv Mater, 2021,33(43):e2103258

106 Zheng C, Wang Q, Wang Y, *et al*. In Situ Modification of the Tumor Cell Surface with Immunomodulating Nanoparticles for Effective Suppression of Tumor Growth in Mice. Adv Mater, 2019,31(32):e1902542

107 Ji T, Lang J, Ning B, *et al*. Enhanced Natural Killer Cell Immunotherapy by Rationally Assembling Fc Fragments of Antibodies onto Tumor Membranes. Adv Mater, 2019,31(6):e1804395

108 Kim KS, Han JH, Park JH, *et al*. Multifunctional nanoparticles for genetic engineering and bioimaging of natural killer (NK) cell therapeutics. Biomaterials, 2019,221:119418

109 Biber G, Sabag B, Raiff A, *et al*. Modulation of intrinsic inhibitory checkpoints using nano-carriers to unleash NK cell activity. EMBO Mol Med, 2022,14(1):e14073

110 Gao S, Li T, Guo Y, *et al*. Selenium-Containing Nanoparticles Combine the NK Cells Mediated Immunotherapy with Radiotherapy and Chemotherapy. Adv Mater, 2020,32(12):e1907568

111 Wei Z, Yi Y, Luo Z, *et al*. Selenopeptide Nanomedicine Activates Natural Killer Cells for Enhanced Tumor Chemoimmunotherapy. Adv Mater, 2022:e2108167

112 Nakamura T, Sato T, Endo R, *et al*. STING agonist loaded lipid nanoparticles overcome anti-PD-1 resistance in melanoma lung metastasis via NK cell activation. J Immunother Cancer, 2021,9(7):e002852

113 Veglia F, Sanseviero E, Gabrilovich DI. Myeloid-derived suppressor cells in the era of increasing myeloid cell diversity. Nat Rev Immunol, 2021,21(8):485-498

114 Gabrilovich DI. Myeloid-Derived Suppressor Cells. Cancer Immunol Res, 2017,5(1):3-8

115 Ledo AM, Sasso MS, Bronte V, *et al*. Co-delivery of RNAi and chemokine by polyarginine nanocapsules enables the modulation of myeloid-derived suppressor cells. J Control Release, 2019,295:60-73

116 Ding D, Zhong H, Liang R, *et al*. Multifunctional Nanodrug Mediates Synergistic Photodynamic Therapy and MDSCs-Targeting Immunotherapy of Colon Cancer. Adv Sci (Weinh), 2021,8(14):e2100712

117 Zhang P, Miska J, Lee-Chang C, *et al*. Therapeutic targeting of tumor-associated myeloid cells synergizes with radiation therapy for glioblastoma. Proc Natl Acad Sci U S A, 2019,116(47):23714-23723

118 Zhang N, Liu S, Shi S, *et al*. Solubilization and delivery of Ursolic-acid for modulating tumor microenvironment and regulatory T cell activities in cancer immunotherapy. J Control Release, 2020,320:168-178

119 Ou W, Thapa RK, Jiang L, *et al*. Regulatory T cell-targeted hybrid nanoparticles combined with immuno-checkpoint blockage for cancer immunotherapy. J Control Release, 2018,281:84-96