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A new approach to overcoming resistance to immunotherapy: nanotechnology

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Immunotherapy for immune response has ushered in a new era of cancer treatment. In recent years, new immunotherapeutic agents have been introduced into clinical trials and even approved for marketing. However, the widespread use of immunotherapeutic agents faces an unavoidable challenge: immunotherapy does not work at all for some patients, or has good efficacy in the initial phase, but immunotherapy resistance develops within a short period of time, and immunotherapy can also cause serious adverse effects such as autoimmune inflammation and non-specific inflammation. How to enable patients to overcome drug resistance, reduce the toxic side effects of drugs, enhance patient compliance and improve patient survival has become a problem that clinicians have to face. The advent of nanotechnology provides an encouraging platform for immunotherapy. It can not only improve the bioavailability and stability of drugs and reduce toxic side effects, but also reduce resistance to immunotherapy. Here, we discuss these research advances and discuss potential challenges and future directions.

KEYWORDS

cancer, microenvironment, immunotherapy, drug resistance, nanotechnology

Introduction

In 2013, tumor immunotherapy was named the most important scientific breakthrough of the year by the journal *Science* for its outstanding efficacy and innovation (1). Immunotherapy has now become an important treatment for many malignant tumors, ushering in a new era of tumor treatment and bringing light to the fight against tumors. However, as the use of immunotherapy has become more popular, the problem of drug resistance to immunotherapy has gradually emerged. Due to its special mechanism of action, the mechanism of resistance to immunotherapy is different from that of resistance to conventional chemotherapy (2–6), so how to overcome resistance to immunotherapy is currently an urgent challenge to be solved.

Recent advances in nanomedicine have led to a plethora of new nanomedicines targeting immunotherapeutic targets (7–11). Furthermore, as research has progressed, it has been found that nanomedicines not only have the ability to target drug delivery, but

also have the ability to remodel the immune microenvironment, thereby enhancing the efficacy of anti-tumor immunotherapy (12). Therefore, we believe that nanomedicines provide a relevant reference for basic research and the development of improved clinical treatment regimens, and are expected to be an important weapon in overcoming drug resistance in immunotherapy. In this article, we review the mechanisms of immunotherapy resistance and summarize the recent research advances in nanomedicine with respect to the mechanisms of resistance, with the aim of providing clues for overcoming immunotherapy resistance.

Mechanisms of immune resistance

Tumors are inherently complex and heterogeneous, and resistance involves not only the tumor but also complex metabolic, inflammatory and neovascular mechanisms, many of which are still unknown. At present, the mechanisms of resistance to immunotherapy can be divided into intrinsic and extrinsic mechanisms. Intrinsic mechanisms of tumor immune resistance include alterations in anti-tumor immune response pathways and alterations in tumor cell signaling leading to a suppressive immunosuppressive microenvironment. External factors mainly include those associated with the local tumor microenvironment. The tumor immune microenvironment is a complex network of interactions involving tumor and various non-tumor cells, including fibroblasts, macrophages, B/T lymphocytes and antigen presenting cells (APCs), which in turn affect the whole body.

Aspects of tumor cell

APCs

The immune response pathway involves the processing of tumor-associated antigenic peptides by antigen-presenting cells (APCs), presentation to CD8⁺ T cells, stimulation of T cell proliferation and activation, and activation of T cells to kill tumor cells in the TME (13). Any alteration in the antitumor immune response pathway has the potential to lead to resistance to immunotherapy.

High tumor mutational burden (TMB) (non-synonymous mutations), microsatellite instability (MSI) and defective mismatch repair (dMMR) are intrinsic tumor features associated with anti-tumor immune responses and responses to immune checkpoint inhibitors (ICIs) (14, 15). These responses are closely associated with increased generation of tumor-associated antigens (TAA) and tumor-specific antigens (TSA), with neoantigens conferring greater immunogenicity and increased T-cell infiltration, as has been demonstrated in a variety of tumors (16–19). However, tumor cells tend to suppress T-cell activation by reducing or losing antigen expression (20) and regulate autoantigenicity by endocytosis of antigens or antigen shedding to mediate immune escape. In addition, the host can selectively eliminate TSA-expressing cells and, to some extent, promote the production of tumor antigen-losing variants (21). Tumor cells, like viruses, can also undergo ‘antigenic drift’, resulting in epitope

mutations that alter tumor antigenicity and thus evade T cell-mediated attack (22). Endoplasmic reticulum (ER) stress and autophagy determine the immunogenicity of tumor cell death (23, 24). The high presence of LC3b puncta in the cytoplasm of tumor cells represents an active autophagic mechanism within tumor cells and is associated with the infiltration of tumor-infiltrating lymphocytes (TILs) and a favorable clinical outcome, whereas tumor cells do not respond to ER stress or autophagy induction may lead to resistance to ICIS (25, 26).

Tumor cell-associated pathways

Deletion of the phosphatase and tensin homologue (PTEN) gene on chromosome 10 has been shown to be directly involved in the regulation of antitumor immunity. First, there is a significant correlation between loss of PTEN and reduced T-cell infiltration, ultimately leading to resistance to PD-1 monoclonal antibodies (27–29). In addition, dysfunctional PTEN also promotes the aggregation of suppressor immune cells, such as myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs) (30–33). More importantly, deletion of PTEN expression has been shown to down-regulate autophagy (34, 35), which can effectively support tumor progression.

In addition, alterations associated with the IFN- γ pathway can also affect immune resistance. In patients receiving immunotherapy, tumor cells can downregulate or alter the IFN- γ pathway, such as loss-of-function alleles in the gene encoding JAK1/2 and alterations in STAT1, to evade the effects of IFN- γ and thus develop resistance (36, 37). Zaretsky et al (38) showed that melanoma patients resistant to PD-1 treatment acquired loss-of-function mutations in JAK1/2. Although tumor cells were still recognized by T cells, their JAK1/2 mutation rendered them insensitive to the anti-proliferative effects of IFN- γ and they lacked IFN- γ -induced PD-L1 and MHC class I surface expression. Similarly, analysis of tumors from ipilimumab-refractory patients showed that mutations in the IFN- γ pathway genes IFNGR1/2, JAK1/2 and IRF1 inhibit the response of tumor cells to IFN- γ signaling (39). This facilitates tumor escape from T-cell immunity, thereby conferring resistance to anti-CTLA4 therapy.

Microenvironment

Immune checkpoint

Checkpoint blockade with specific mAbs helps to inhibit pathways that maintain the duration and strength of the immune system. Inhibition of these checkpoint molecules works by reinvigorating the adaptive immune system and selectively eliminating primary and metastatic tumors. Currently, cytotoxic T lymphocyte-associated antigen-4(CTLA4), programmed death receptor-1(PD-1) and its ligand(PD-L1) are the main targets of immunotherapy and are the most widely used in clinical practice (40). In one study, RNA sequencing analysis of patients with NSCLC resistant to PD-L1 inhibitors demonstrated the presence of PD-L1 variant fragments in patients and confirmed their inhibitory effect on T-cell activity (37). TIM-3 (T cell immunoglobulin domain and mucin domain-3) is a negatively

regulated immune checkpoint expressed on the surface of T cells, Treg cells and other innate immune cells and is capable of causing T cell depletion in cancer and chronic viral infections. It has been shown that T cells co-expressing TIM-3/PD-1 are more likely to fail, and that patients who fail to respond to anti-PD-1 therapy are often highly correlated with TIM-3 expression, while patients who are resistant to PD-1 therapy are also due to selective overexpression of TIM-3, resulting in tumor immune escape (41). Drugs and drug combinations targeting TIM-3 are therefore being developed to overcome immunotherapy resistance.

TAMs

Tumor-associated macrophages (TAMs) have also been implicated in patient response to immunotherapy (42, 43). TAMs are classified into M1 and M2 macrophages based on their different activation pathways and expression of surface molecules: M1 type macrophages promote anti-tumor immunity and M2 type macrophages promote tumor progression by supporting angiogenesis, tumor cell metastasis and suppression of effector CD8⁺ T cells and NK cells due to reduced efficiency of antigen presentation (44–46). Recruitment of TAMs to tumor sites is mediated by tumor-derived proteins (e.g. CSF-1, VEGF and chemokines). The recruitment of TAMs to tumor sites is mediated by tumor-derived effector proteins such as CSF-1, VEGF and chemokines (47), tumors (48–51). A higher density of TAMs is associated with a poor clinical prognosis in cancer patients (52, 53). Fritz et al (54) found that depletion of TAMs can reduce tumor growth in a mouse model of lung adenocarcinoma through downregulation of M2 macrophages. It has been suggested that inactivation of CCL2 and/or CCR2 signaling is responsible for this phenomenon. Similar findings have been reported in other cancer types (e.g. T-cell lymphoma (55), colorectal cancer (56), lung cancer and breast cancer (56–58), where suppression or elimination of these macrophages in the TME may improve patient prognosis.

MDSCs

MDSCs contain a panel of neutrophils and monocytes with potent immunosuppressive properties that mediate immune responses induced by T cells, B cells and NK cells (59). Higher levels of neutrophils within the tumor are negatively associated with clinical outcome in cancer patients (60). Indeed, using multidimensional imaging, Si et al (61) provided direct evidence that MDSCs inhibit the expression of T_H1-secreted granzyme B and Ki67 (markers of T_H1 cytotoxicity and proliferation, respectively). The presence of MDSCs in TME is strongly correlated with the efficacy of immunotherapy, as blockade of these cells leads to improved preclinical (62) and clinical outcomes (63). Due to the important role of MDSCs in promoting angiogenesis, tumor invasion and metastasis, these cells have become therapeutic targets for cancer (59, 64–68).

CAFs

Cancer-associated fibroblasts (CAFs) are diverse stromal cell populations with multiple functions, including stromal deposition and remodeling, crosstalk with infiltrating leukocytes, and

interaction with cancer cells (69). The presence and role of activated CAFs in the microenvironment has been associated with poor prognosis in several cancers (70). CAFs suppress the immune system by promoting physical and chemical barriers. CAFs induce a TH2 phenotype in neighboring cells, and cytokines produced by TH2 cells induce myeloid differentiation into MDSCs (71). CAFs also induce monocytes to differentiate into M2-type TAMs (72, 73), produce fibronectin and secrete TGF- β and IDO (74), further indicating the expansion of Treg cells. In addition, CAFs inhibit the activity of CD8⁺ T cells by expressing PD-L1 (75, 76).

NK cells

NK cells can facilitate the recruitment of DC to solid tumors by releasing CC-chemokine ligand 5 (CCL5), XC-chemokine ligand 1 (XCL1) and XCL2. In addition, NK cells enter lymph nodes and influence the T cell response; and through the regulation of antigen-presenting cells, thereby regulating T cells. Activated NK cells can kill immature DCs while retaining mature DCs, thus ensuring successful T cell priming. Thus, the manipulation of NK cells in cancer aims to initiate a multilayered immune response, ultimately leading to protective and long-lasting immunity against the tumor (77).

In recent years, NK cell-associated immunotherapy has emerged as an alternative to ICB-based or vaccine-based immunotherapy (78–81). However, its therapeutic effects are largely limited by the downregulation of recognition ligands, and its immune effects can be further blocked by the secretion of tumor microenvironment such as transforming growth factor- β (TGF- β) (82–84). Researchers have demonstrated the benefits of combining immunotherapy with chemotherapy in cancer treatment (85–87). Therefore, there is great interest in developing combined strategies to enhance NK cell immunity.

Immune-related cytokines

Interferon gamma is a cytokine produced and secreted by effector T cells (TEFFs) and APCs. It acts through the JAK-STAT pathway (36) and has a dual role in anti-tumor immunity. Interferon γ can induce the production of the chemokines CXCL9 and CXCL10 and promote the recruitment of CXCR3⁺ lymphocytes and other immune cells around tumor cells, thereby exerting an anti-tumor immune effect (88); it can also exert direct anti-tumor cell proliferation and pro-apoptotic effects by binding to cell surface receptors and triggering a series of events that inhibit tumor cell growth and promote tumor cell death (89); In addition, IFN- γ can play a role in immune escape by increasing the expression of PD-L1 on the surface of tumor cells (89), and therefore altered IFN- γ secretion is thought to be closely associated with immune drug resistance.

Tregs

Tregs are an important subset of T cells that help prevent excessive immune responses and autoimmunity, and can infiltrate human tumors and promote tumor growth (90). These FoxP3-expressing cells inhibit the T_H1 response either directly through physical contact or indirectly by suppressing the secretion of

inhibitory cytokines including IL-10, IL-35 and TGF- β (91–94). After anti-CTLA-4 mAb treatment, the ratio of Tefs to Tregs was positively correlated with treatment response depending on the presence of macrophages expressing the Fc γ receptor (95), and the use of anti-CTLA4 antibodies with an enhanced Fc γ R binding profile is recommended to achieve robust anti-tumour responses and improved survival (96). In a clinical trial using ipilimumab to treat patients with advanced melanoma, increased TIL was found to be associated with better outcomes (97). A clinical follow-up study showed that although anti-CTLA-4 immunotherapy promoted intra-tumoral Teff infiltration, it did not lead to FoxP3 T-cell depletion in human cancers (98). These seminal studies on the balance between Tefs and Tregs suggest that increased numbers of tumour-infiltrating Tefs, rather than depletion of Tregs, can be used to predict sensitivity to anti-CTLA-4 immunotherapy. If the ratio of these two T cell subpopulations responding to immunotherapy in TME is unfavorable to Tefs, resistance may emerge throughout the course of treatment.

Treatment

Tumor cell aspects

Targeting APCs

Over the past few decades, tremendous progress has been made in the clinical application of peripatetic immunotherapy in the fight against tumors. However, given the cost and complexity of generating tumor-specific T cells, there are many limitations to the practical clinical application of secondary immunotherapy. Nanomedicine can provide additional technical support to overcome these limitations (Figure 1). Using artificial antigen-presenting cells (aAPCs), scientists have loaded specific MHC peptides and co-stimulatory molecules onto nanoparticles to activate and promote the expansion of antigen-specific CD8⁺ T

cells (99). In some aAPCs, cytokines can also be used to promote activation and expansion of T cells in lymph nodes (100, 101). Iron-dextran nanoparticles and anti-biotin protein-coated quantum dot crystals have been synthesized using surface-coated MHC-I peptide complexes and biotin-CD28. These nanoparticles (NPs) are magnetic and can promote T-cell enrichment and activation using magnetic fields to promote TCR aggregation (102). IL-2 can activate T cells and with this in mind, Steenblock et al (100) constructed carbon nanotube polymers as aAPCs in which IL-2 was encapsulated and modified with MHC-I and α CD28. These aAPCs can induce activation and expansion of CD8⁺T cells with very low concentrations of IL-2 compared to conventional methods. In addition, Kelly et al (103) synthesized PLGA/PBAE aAPCs from poly(lactic acid-glycolic acid) (PLGA) and cationic polybasic amino esters (PBAE), nanoparticles that can expand antigen-specific cytotoxic CD8⁺ T cells *in vivo*.

As current T cell expansion rates are not ideal, research should also focus on biomaterials to improve *in vitro* T cell expansion (101, 102, 104). Cheung et al (105) designed an APC mimetic scaffold (APC-ms) that mimics natural APCs and compared this APC-ms to commercial expansion beads. This APC-ms promoted polyclonal expansion of mouse and human T cell generations by 2–10 times compared to commercial expansion beads (Dynabeads). The APC-ms consist of a liquid lipid bilayer supported by mesoporous silica microrods. After a single stimulation, the APC-ms resulted in antigen-specific expansion of a subpopulation of cytotoxic T cells in much larger numbers than autologous monocyte-derived dendritic cells. aAPCs may become the next focus of research in cancer nanomedicine, so more attention needs to be invested in optimizing the physicochemical properties of aAPCs, for example.

Targeting tumor cell-associated signaling pathway

Given the important role of PTEN in immunotherapy resistance, the design of PTEN-targeted nanomaterials has been

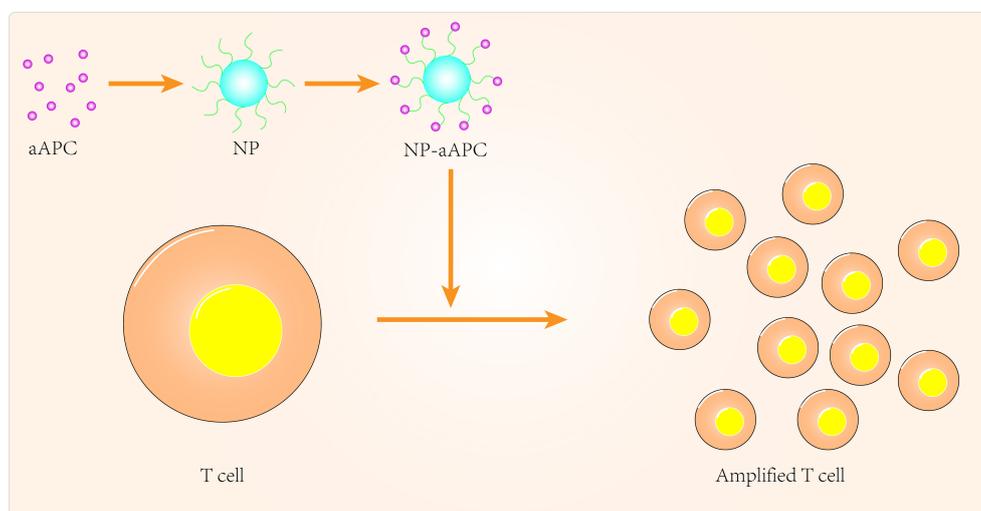


FIGURE 1
Targeted APCs to improve cancer immunotherapy.

the focus of many scientists. Kinoh et al (106) used pH-sensitive epirubicin-loaded micellar nanodrugs to synergize the efficacy of anti-PD-1 antibody (aPD-1) against PTEN-positive and PTEN-negative glioblastoma *in situ* (GBM). The combination of epirubicin-loaded micelles (Epi/m) with aPD-1 overcame the resistance of GBM to ICIs and reduced PD-L1 expression on tumor cells by inducing immunogenic cell death (ICD), eliminating MDSC and transforming the otherwise immune insensitive GBM into a hot tumor with high infiltration of anti-tumor immune cells. Catania et al (107) designed a combined local treatment based on Adriamycin (DOX) as an inducer of ICD and CpG (toll-like receptor-9 agonist, TLR-9 agonist) to synergistically eliminate GBM and found that a single intratumoral administration of HA-DOX + HA-CpG was effective in prolonging the survival of GBM animals. Teo et al (108) combined siRNA with folic acid-modified PEI, resulting in significant PD-1 silencing and enhanced T-cell activation. Yang et al (109) combined anti-PD-L1 (aPD-L1) with multiple polyethylene glycol (PEG) chains to improve the efficacy and safety of checkpoint blockade treatment in GBM. In mice with GBM *in situ*, single doses of glycosylated and polyethylene glycol-linked antibodies reactivated anti-tumor immune responses and induced immune memory to protect the animals from recurrent tumor cell attack and to suppress autoimmune responses in healthy tissues of the animals.

In addition to GBM, PTEN-targeted nanomaterials have been investigated for other tumor applications. Lin et al (110) delivered mRNA *via* polymeric nanoparticles to effectively induce PTEN expression in melanoma and prostate cancer cells, which in turn induced autophagy and triggered cell death-related immune activation by releasing damage-related molecular patterns. *In vivo*

experiments showed that PTEN mRNA nanoparticles reversed the immunosuppressive TME by promoting CD8⁺ T cell infiltration into tumor tissue, increasing pro-inflammatory cytokine expression and reducing Treg cells and MDSCs. The combination of PTEN mRNA nanoparticles with immune checkpoint inhibitors, aPD-1 antibodies, in a subcutaneous model of PTEN-mutant melanoma and PTEN-negative prostate cancer *in situ* models, produced potent anti-tumor effects (Figure 2).

Microenvironment

Targeting immune checkpoint

When anti-CTLA4 antibodies are loaded into functionalized mesoporous silica (FMS) and administered intratumorally, they prolong local release under physiological conditions compared to free antibodies. FMS can be non-covalently linked to antibodies to promote sustained prolonged release (111, 112). Blockade of PD-1 with siRNA loaded into cationic lipids and polymeric NPs has been investigated (112). Wang et al (113) combined the synergistic delivery of anti-PD-1 antibodies and CpG oligodeoxynucleotides to prevent cancer recurrence. Ye et al (114) demonstrated dual targeting of IDO and PD-1 by a microneedle-based transdermal delivery approach. Xiao et al (115) designed aPD-L1 functionalized mimetic polydopamine-modified gold nanostellar nanoparticles (PDA/GNS@aPD-L1 NPs) which, in addition to disrupting PD-1/PD-L1 immunosuppressive signaling, aPD-L1 scFv on the membranes of PDA/GNS@aPD-L1 NPs contributed to the accumulation of PDA-GNS at tumor sites. Importantly, PDA-GNS-induced photothermal ablation of tumors reverses the

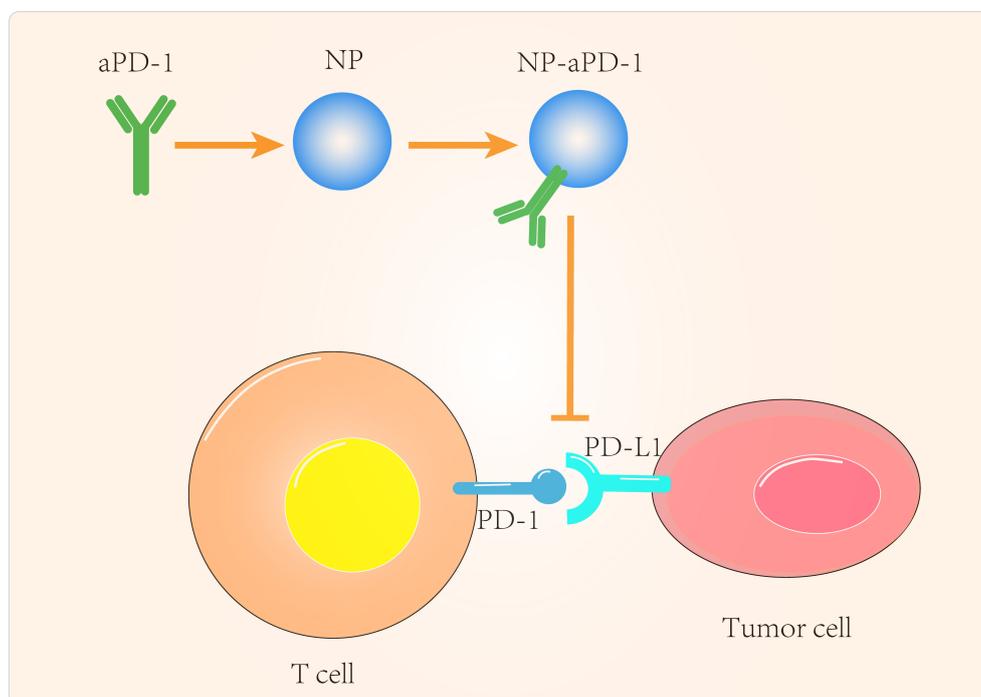


FIGURE 2
Targeted tumor cell-Associated signaling pathway to improve cancer immunotherapy.

immunosuppressive tumor microenvironment, further enhancing the efficacy of PD-1/PD-L1 blockade therapy.

Combination immunotherapy with PD-L1 antibodies and CXCL12 inhibitors has better anti-tumor efficacy than single immunotherapy (116, 117). However, combination therapy has some drawbacks, including unpredictable PK/PD and overlapping toxicity. Therefore, targeting PD-L1 while reducing the duration of drug administration *in vivo* may help to reduce the cytotoxicity caused by free aPD-L1. Based on this concept, Miao et al (118) designed a chimeric PD-L1 trap protein. When a plasmid encoding the PD-L1 trap protein was encapsulated in lipid-fisetin DNA NPs and delivered to CT26 colon tumors and KPC pancreatic tumors, the highest expression was observed from day 2 to day 4 and finally declined by day 6. This transient expression and high affinity for PD-L1 molecules could serve as a promising therapeutic approach with reduced side effects.

Targeting TAMs

NP can also regulate TAMs by inhibiting macrophage recruitment, by inhibiting TAMs survival through the use of chemicals, by enhancing the activity of M1-type TAMs and by blocking the activity of M2-type TAMs (Figure 3) (119). Qian et al (120) used a novel bi-peptide in which scavenger receptor B type 1 (SRB1) was linked to a specific TAMs binding peptide which specifically blocked the M2-TAMs survival signals. Alternatively, we could try to reprogramme M2-type TAMs back to M1-type (121–123). When IL-12 in poly(β -amino ester) NPs was administered intravenously in a B16F10 melanoma model, M2-type macrophages were reduced and M1-type macrophages were increased (121). Specific miRNA-125b increased expression of MHCII, CD40, CD80, CD86 and increased responsiveness to IFN- γ in macrophages (124). Parayath et al (125) intraperitoneal injection of miRNA 125-b complexed with hyaluronic acid-fixed poly(ethyleneimine) NPs into the TME of G12/P53 mice resulted in increased M1-type macrophages and decreased M2-type

macrophages. Zanganeh et al (126) repolarized M2-type TAMs back to M1-type *via* hydroxyl radicals for breast cancer treatment. Macrophages produce H₂O₂, which can be converted to cytotoxic hydroxyl radicals *via* iron oxide NPs. When co-cultures of macrophages and MMTV-PyMT cancer cells were treated with iron oxide NPs, there was an increase in the number of M1-type cells and a decrease in the number of M2-type cells. The effect of M1-type TAMs in the TME could be maximized by the use of immune checkpoint blockers or combination therapy with NPs carrying these modulators. Parayath et al (127) found that hyaluronic acid-based nanoparticles encapsulated with miR-125b (HA-PEI-miR-125b) could specifically target homozygous ID8-VEGF ovarian cancer mouse. The imbalance in the ratio of M1 to M2 TAMs populations and the uncontrolled increase of M1 TAMs stimulate the inflammatory response. In contrast, TAMs can sometimes express both M1- and M2-type markers (128), which limits the application of specific targeting of M2-type TAMs.

Targeting MDSCs

Strategies to regulate MDSCs primarily require specific blockade of MDSCs development, differentiation of MDSCs into mature cells, and depletion and inhibition of MDSC function by small molecule drugs (129–133). Gold NPs based on high-density lipoprotein (HDL) loaded with apoA-1 have been used to inhibit MDSCs, and in a study in B16F10 melanoma mice, MDSCs were depleted by lipid-encapsulated calcium phosphate NPs loaded with gemcitabine (134, 135). Plebanek et al (136) synthesized a HDL receptor with high affinity for HDL that inhibited MDSCs activity by specifically binding SCARB1. In another study, Kong et al (137) used mesoporous silica NPs loaded with all-trans retinoic acid and Dox, coated with IL-2 and subsequently modified with dipalmitoylphosphatidylcholine cholesterol and DSPE-PEG 2000. Intravenous administration of these NPs reduced the MDSCs population by 2.7-fold and increased the population of NK cells, mature DCs and cytotoxic T cells in the TME. Similarly, IL-2

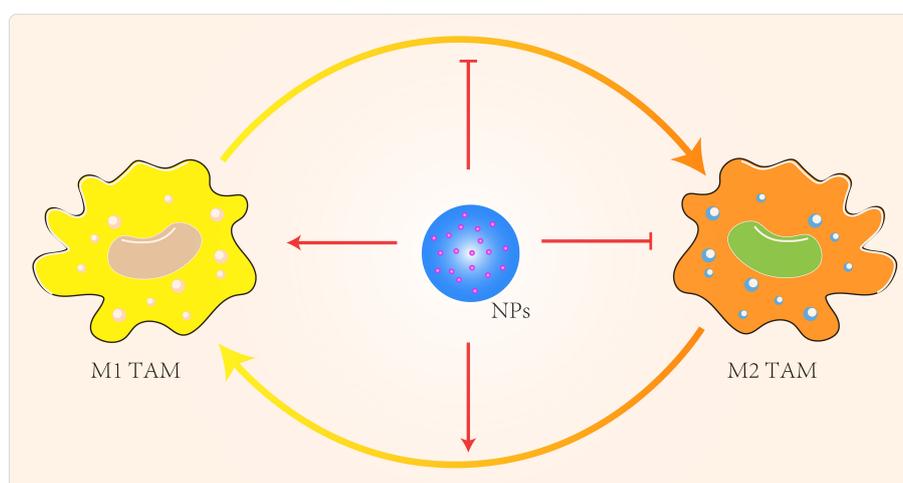


FIGURE 3
Targeted TAMs to improve cancer immunotherapy.

encapsulated NPs were designed to remodel the TME cell population, but were associated with poor secondary cytokine responses (138).

Targeting CAFs

Blocking the pathway activated by CAFs can reverse mesenchymal-mediated multidrug resistance. In one study, targeting CAFs with anti-FAP SCFV-modified ferritin nanomaterials containing the photosensitizer zinc hexadecafluorophthalocyanine led to CAF ablation and increased the number of CD8⁺ T cells in the TME when irradiated with 671nm light (139). Intraperitoneal injection of homogeneous gold nanoparticles in the ASPC1 human pancreatic cancer cell and CAF19 pancreatic stellate tumor mouse models led to a reduction in fibronectin, collagen and α -SMA (140). These NPs specifically target α -SMA-positive CAFs through the interaction of serum albumin encapsulated on NPs during circulation with cysteine-rich acidic protein (SPARC) secreted on the surface of CAFs (141).

Targeting NK cells

NK cells play a pivotal role in tumor immunotherapy, and more and more scholars have started to design nanomedicines for NK cell-related immune resistance. Liu et al (142) designed a nanoemulsion system (SSB-NMs) to load TGF- β inhibitors and selenocysteine (Se-C), and the experimental results showed that the nanoparticles significantly enhanced the efficacy of NK cell-mediated immunotherapy against triple-negative breast cancer. Lai et al. (143) used a selenium-containing ruthenium complex (Ru-Se) to synergistically enhance NK cell-mediated killing of prostate cancer cells. The complex was found to effectively enhance NK cell lysis of PC3 cells and was demonstrated in 10 clinical patients. NK cells are superior to T cells in their ability to fight tumors in the absence of specific antigens, making them a potential target for tumor immunotherapy.

Targeting immune-related cytokines

Zaretsky et al (38) melanoma patients resistant to PD-1 treatment acquired loss-of-function mutations in JAK1/2. Although tumor cells were still recognized by T cells, their JAK1/2 mutation rendered them insensitive to the anti-proliferative effects of IFN- γ and they lacked IFN- γ induced PD-L1 and MHC class I surface expression. Similarly, analysis of tumors from patients resistant to treatment with the anti-CTLA4 drug Ipilimumab showed that mutations in the IFN- γ pathway genes IFNGR1/2, JAK1/2 and IRF1 inhibit the response of tumor cells to IFN- γ signaling (39). This facilitates tumor escape from T-cell immunity, thereby conferring resistance to anti-CTLA4 therapy.

After treatment with Frax NEs, the T cofactor 1 (Th1) cytokine of IFN- γ was effective in inducing anti-tumor immunity (144). Transforming growth factor- β (TGF- β), chemokine (C-C motif) ligand 2 (CCL2) and interleukin 6 (IL6), which inhibit the development of anti-tumor immunity, were reduced. Although Frax NEs have shown an inhibitory effect on tumor growth, this monotherapy is only partially effective against tumors and does not

maintain the tumor growth effect long after administration has stopped.

Targeting Tregs

Lin et al. (110) constructed PTEN mRNA nanoparticles (mPTEN @ NPs) delivered to tumour cells with PTEN deletion or mutation to restore the TME, stimulate immune response and enhance the efficacy of immune checkpoint blockade (ICB) therapy by inducing autophagy activation and damage-associated molecular patterns (DAMPs) release. In their study, mPTEN @ NPs restored tumour sensitivity to immunotherapy and triggered the release of DAMPs and autophagy, thereby promoting the formation of autophagosomes. *In vivo* studies showed that PTEN repair induced a strong CD8⁺ T cell response and restored TME by inhibiting the production of Tregs and monocyte MDSCs and promoting the production of pro-inflammatory cytokines. In addition, they evaluated the anti-tumour effects of mPTEN @ NPs in combination with anti-PD-1 immunotherapy in a PTEN-deficient or mutated tumour model, showing that this combination therapy strategy has significant therapeutic efficacy and immunological memory. These results suggest that nanomedicine mRNA repair of tumour suppressors can enhance the sensitivity of tumors to ICB therapy and provide an effective cooperative treatment strategy for a variety of malignancies.

Conclusion and perspective

Despite the remarkable achievements of immunotherapy in cancer treatment, all current treatment strategies have serious limitations and often encounter difficulties in clinical treatment. There are many reasons for treatment failure, including poor oral bioavailability of some drugs and serious drug-related side effects. The most challenging problem is that patients receiving immunotherapy almost always develop drug resistance. While much progress has been made in recent years in understanding the mechanisms of resistance to cancer immunotherapy, overcoming drug resistance remains an important unmet clinical need. Thus, immune resistance in tumors has become a major obstacle to cancer immunotherapy, and overcoming resistance is a goal actively pursued by current and future oncologists (145).

The emergence of nanotechnology offers a novel solution to immunotherapy resistance. Nanomedicines can improve the bioavailability of insoluble drugs, prolong drug circulation, cross the biological barrier, achieve tumor-targeted therapy through passive or active targeting, improve anti-tumor effects and reduce tumor resistance to immunotherapy. A number of nanomaterials have now completed Phase III clinical trials (Table 1). The convergence of these two disciplines will certainly provide a tremendous impetus to improve cancer treatment. The advantages of nanomedicines over current therapeutic strategies will continue to be exploited as more nanomedicines are developed and optimized. It is therefore believed that nanomedicines will be an attractive strategy for reversing or overcoming resistance to cancer immunotherapy.

Drug resistance in tumor immunotherapy involves multiple mechanisms working together, so here we have only reviewed the

TABLE 1 Summary of Phase 3 Clinical Trials for Cancer Nanomedicine Products.

Composition	Responsible Party	Indication	NCT number	Status
Liposomal paclitaxel	SynCore Biotechnology Co., Ltd.	Pancreatic adenocarcinoma	NCT03126435	Completed
Thermally sensitive liposomal doxorubicin	Imunon	Hepatocellular carcinoma	NCT00617981	Completed
Liposomal VCL-1005 plasmid	Vical	Melanoma	NCT00395070	Completed
Liposomal MUC1 antigen	EMD Serono	Non-small-cell lung cancer	NCT00409188	Completed
Hafnium-oxide nanoparticle	Nanobiotix	Sarcoma	NCT02379845	Completed
Hafnium-oxide nanoparticle	American Regent, Inc.	Non-small-cell lung cancer	NCT00243867	Completed
Irinotecan PEG conjugate	Nektar Therapeutics	Breast cancer	NCT02915744	Completed
			NCT01492101	Completed
Cisplatin micellar	Orient Europharma Co., Ltd.	Pancreatic cancer	NCT02043288	Completed
Paclitaxel micellar	Nippon Kayaku Co., Ltd.	Breast cancer	NCT01644890	Completed

more mature aspects of nanomaterial development, as for other aspects of drug resistance mechanisms such as hypoxic environment (146, 147), lactate metabolism (148), glycolytic metabolism (149), tryptophan metabolism (150), cholesterol metabolism (151–154), which also play an important role in drug resistance. These mechanisms of drug resistance may also provide additional clues for the application of nanomedicine.

Currently, a lot of researchers are concentrating on creating organically produced NPs, which are safer as well as more biocompatible and able to activate the body's own immune cells and use that immune response to help eradicate cancers (155). But in this case, there is a more subtle biological element and a well-defined treatment process. In conclusion, it is encouraging to see how NPs might increase the body's immunological resilience. It is thought that through in-depth research in this area and the design of more effective nanomaterials, it is possible to overcome immune resistance, reduce toxic side effects on patients, and achieve better therapeutic effects for the benefit of cancer patients, despite some limitations in its clinical application.

Author contributions

JS carried out the primary literature search, drafted and revised the manuscript. YJ helped modify the manuscript and participated in discussions. CJ conceived and approved the final manuscript.

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Conflict of interest

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