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REVIEW

# Utilizing Nanoparticles to Overcome Anti-PD-1/PD-L1 Immunotherapy Resistance in Non-Small Cell Lung cancer: A Potential Strategy

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**Abstract:** Lung cancer is the leading cause of cancer-related mortality globally, with non-small cell lung cancer (NSCLC) constituting 85% of cases. Immune checkpoint inhibitors (ICIs) represented by anti-programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) have emerged as a promising frontier in cancer treatment, effectively extending the survival of patients with NSCLC. However, the efficacy of ICIs exhibits significant variability across diverse patient populations, with a substantial proportion showing poor responsiveness and acquired resistance in those initially responsive to ICIs treatments. With the advancement of nanotechnology, nanoparticles offer unique advantages in tumor immunotherapy, including high permeability and prolonged retention(EPR) effects, enhanced drug delivery and stability, and modulation of the inflammatory tumor microenvironment-(TME). This review summarizes the mechanisms of resistance to ICIs in NSCLC, focusing on tumor antigens loss and defective antigen processing and presentation, failure T cell priming, impaired T cell migration and infiltration, immunosuppressive TME, and genetic mutations. Furthermore, we discuss how nanoparticles, through their intrinsic properties such as the EPR effect, active targeting effect, shielding effect, self-regulatory effect, and synergistic effect, can potentiate the efficacy of ICIs and reverse resistance. In conclusion, nanoparticles serve as a robust platform for ICIs-based NSCLC therapy, aiding in overcoming resistance challenges.

**Keywords:** PD-1/PD-L1, immunotherapy, resistance mechanisms, immunosuppression TME, nanoparticles, pro-inflammatory TME

## Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide, with NSCLC accounting for approximately 85% of cases.[1] Statistics indicate that two-thirds of global lung cancer cases are associated with smoking.[2] Without effective tobacco control policies and regulations, the incidence of lung cancer is poised to escalate further. ICIs represented by anti-PD-1/PD-L1 have emerged as a novel cancer immunotherapy approach aimed at reactivating the human immune system to target and destroy tumors. While ICIs have achieved some success in extending the survival of patients with advanced NSCLC, their efficacy varies significantly among patients. Some patients do not respond to treatment, and those who initially respond may develop acquired resistance over time.[3,4] Therefore, understanding the mechanisms of resistance to ICIs and exploring strategies to overcome resistance becomes increasingly urgent.

In recent years, the development of nanotechnology has led to increasing research combining nanoparticles with cancer immunotherapy.[5] Due to their unique structural properties, nanoparticles offer significant advantages in addressing the complex pathological environments and high heterogeneity of cancers. First, the size advantage of nanoparticles enables EPR effects. Surface functionalization allows for efficient targeting of tumor cells, increasing drug accumulation within tumor tissues, improving bioavailability, limiting drug exposure to normal tissues, and reducing systemic immunotoxicity. Nanoparticles can encapsulate drugs, preventing enzymatic degradation in the body and enhancing drug stability.[6–8] Additionally, nanoparticles are not only excellent drug delivery vehicles but also possess regulatory functions that can

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promote an inflammatory TME,[9,10] indirectly enhancing immunotherapeutic efficacy. Finally, the versatile design of nanoparticles enables combination therapies with multiple drugs and various treatment modalities,[11–13] further enhancing cancer treatment outcomes.[14–17]

This review summarizes the resistance mechanisms to ICIs in NSCLC and explores how nanoparticles can leverage their properties to enhance the effectiveness of ICIs in treating NSCLC, potentially reversing resistance. In conclusion, nanoparticles provide a powerful platform for ICIs therapy, helping to overcome resistance in NSCLC treatment.

## Stepwise Progression of Anti-Tumor Immunity

The efficacy of ICIs relies on the proper functioning of the body's anti-tumor immunity. The anti-tumor immune cycle is a series of immune-mediated functional events,[18] and any disruption in this cycle can result in the failure of anti-tumor responses. The process of anti-tumor immunity can be summarized in seven steps, as illustrated in Figure 1.[19] (1) Release of tumor antigens. The variety of gene mutations within tumor cells leads to their inherent instability, allowing for the release of tumor antigens.[20] Due to inadequate blood supply or therapeutic interventions the tumor cells apoptosis and subsequent release of tumor antigens. (2) Antigens process and presentation, dendritic cells (DCs) is the most potent antigen-presenting cells (APCs) in the body which efficiently capture, process, and present antigens. Immature DCs in various tissues recognize tumor antigens and degrade them into peptides. These peptides are then transferred into the endoplasmic reticulum (ER) via the transporter associated with antigen processing (TAP).[21] The peptides then bind to newly assembled major histocompatibility complex(MHC) class I molecules and are transported to the cell membrane, where mature DCs present them to $CD8^+$ T cells.[21,22] (3) T cell priming and activation, naive T cells recognize antigens by binding their T cell

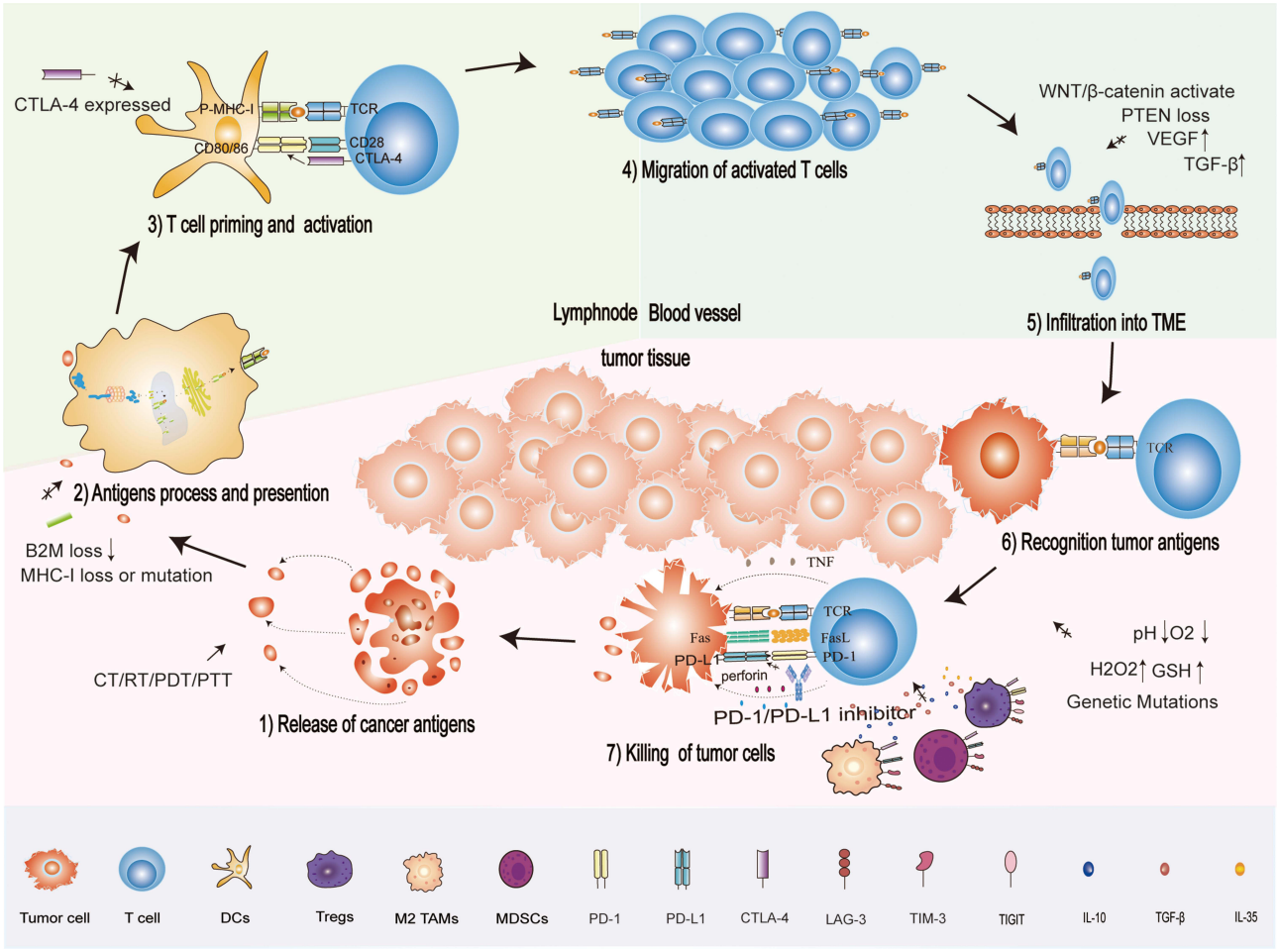


**Figure 1** The process of anti-tumor immunity, mechanisms of ICIs therapy and the resistance mechanisms of ICIs therapy.

receptors(TCRs) to the p-MHC-I complexes on APCs. This recognition is the first step in T cell activation, which requires both antigen stimulation and co-stimulatory signals. Various cytokines (eg, Interleukin-1 (IL-1), Interleukin-2 (IL-2), Interleukin-4 (IL-4) then promote T cell proliferation and differentiation. (4) Migration of activated T cells, $CD8^+$ T cells become activated, proliferate, and differentiate into effector Cytotoxic T lymphocytes (CTLs) in peripheral immune organs. They then migrate to the tumor site under the influence of chemokines. (5) Effector CTLs infiltrate the tumor tissue. (6) Recognition of tumor cells, effector CTLs recognize tumor cell by the tumor antigen presented by p-MHC-I complexes. (7) Killing of tumor cells, effector CTLs express high levels of adhesion molecules, bind to target cells and form an immunological synapse. This process enables CTLs to release effector molecules at high concentrations at the effector-target cell interface. Apoptosis is primarily induced through the perforin/granzyme pathway and the death receptor pathway. After inducing target cell apoptosis, CTLs disengage and seek new targets. Apoptotic tumor cells release antigens, perpetuating the cycle.

## Mechanisms of ICIs Therapy

The mechanism of anti-PD-1/PD-L1 ICIs in cancer therapy is well understood.[23] The PD-1 receptor is expressed on the surface of activated T cells, while its ligands PD-L1 and PD-L2 are expressed on DCs or macrophages.[24] PD-1 and PD-L1/PD-L2 are part of the immune checkpoint protein family acting as co-inhibitory factors that suppress or limit T cell responses.[24] The PD-1/PD-L1 interaction ensures that the immune system is activated only at appropriate times, minimizing the risk of chronic autoimmune inflammation.[24–26] Prolonged TCR stimulation leads to upregulation of PD-1 on T cells, while tumor cells modulate immune responses by expressing high levels of PD-L1 on their surface during interactions with immune cells.[27] The binding of PD-L1 to PD-1 on T cells inhibits their proliferation and cytokine production (eg, IL-2, Interferon-γ (IFN-γ)) and induces regulatory T cells (Tregs) formation.[28] PD-1/PD-L1 inhibitors block this pathway, restoring the immune-killing function of T cells and thereby targeting and destroying tumor cells (Figure 1).[28–30]

## The Resistance Mechanisms of ICIs Therapy

The efficacy of ICIs is contingent upon the infiltration of effector CTLs and the expression levels of PD-L1. Tumors with impaired anti-tumor immunity often lack effector CTLs infiltration, predisposing them to resistance against ICIs (Figure 1). The functional execution of effector CTLs requires a series of consecutive steps, including successful antigen presentation and recognition, activation and proliferation, trafficking, and execution of cytotoxic functions.

## Tumor Antigens Loss and Defective Antigen Processing and Presentation

The therapeutic success of anti-PD-1/PD-L1 ICIs hinges on the recognition of tumor cells by specific T cells within TME. Tumor cells release neo-antigens, but failure in antigen recognition or issues in antigen processing and presentation can disrupt the anti-tumor response, leading to ICIs therapy failure. MHC class I molecules are crucial for immune responses as they mediate antigen processing and presentation, activating T cells.[31,32] The loss or mutation of MHC class I can induce immune resistance in NSCLC.[33–35] β2-microglobulin (B2M) is a component of MHC class I molecules, essential for the proper folding and transport of these molecules to the cell surface. Loss or downregulation of B2M results in the absence of MHC class I molecules, preventing the formation and presentation of p-MHC-I complexes, which impairs T cell stimulation, leading to $CD8^+$ T cell dysfunction and reduced $CD8^+$ T cell presence in TME.[36] Deficiencies in the expression of MHC class II molecules in tumor cells and infiltrating lymphocytes hinder the activation of T helper cells(Th).[37] IFN-γ induces MHC expression and enhances T cell recognition. Abnormalities in the IFN-γ signaling pathway (eg, mutations in the IFN-γ receptor, Janus kinase (JAK) 1, and JAK2) are associated with defects in antigen presentation and resistance to ICIs.[38]

## Failure T Cell Priming

As we know, CD28 expressed on T cells, interacts with co-stimulatory molecules on APCs to provide the second activation signal for T cell activation.[39] The intracellular region of CD28 contains the immunoreceptor tyrosine-based activation motif (ITAM) that activates T cells. CD28's ligands are CD80/CD86 on APCs, and its co-stimulatory signals

play a pivotal role in T cell activation. These signals induce T cells to express anti-apoptotic proteins (Bcl-XL, etc)., preventing apoptosis, and stimulate the synthesis of cytokines like IL-2, promoting T cell proliferation and differentiation.[40] In contrast, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) is expressed on activated T cells and also binds to CD80/CD86. The affinity of CTLA-4 for its ligands is significantly higher than that of CD28. CTLA-4 contains the immunoreceptor tyrosine-based inhibitory motif (ITIM) in its intracellular region, leading to inhibitory signaling.[41,42] When CTLA-4 is expressed, its inhibitory signals replace the activating signals mediated by CD28, downregulating or terminating T cell activation.[43]

## Impaired T Cell Migration and Infiltration

A crucial factor in resistance to immunotherapy is the lack of specific T cell infiltration. Disruption at any stage of T cell activation, trafficking, and infiltration into tumor cells can result in resistance. Activated T cells migrate from lymph node to the tumor site under the influence of chemokines such as C-X-C Motif Chemokine Ligand(CXCL) 9, CXCL10, CXCL11, and C-C Motif Chemokine Ligand (CCL) 5.[44] Oncogenic pathways, including WNT/β-catenin, phosphatase and tensin homolog (PTEN), Liver kinase B1 (LKB1), and epidermal growth factor receptor(EGFR), can induce resistance by inhibiting chemokine production.[45–47] Abnormal IFN-γ signaling also affects T cell migration to the TME.[38]

Accumulation of genetic mutations in tumor cells increases $CD8^+$ T cell infiltration into the TME, slowing tumor growth. However, further mutations activating the WNT/β-catenin pathway downregulate CCL4, exclude conventional dendritic cells (cDCs), ultimately reducing $CD8^+$ T cell infiltration into the TME and promoting immune evasion.[48,49] PTEN is a potent tumor suppressor gene that negatively regulates the PI3K/mTOR/Akt oncogenic pathway.[50] Loss of PTEN reduces T cell infiltration into tumors by expressing immunosuppressive factors like VEGF, reducing effector CTLs, and promoting immune resistance. PTEN-deficient tumors exhibit high metastatic potential and fibrosis, secreting TGF-β/CXCL10 to induce $CD4^+$ T cell conversion to Tregs, increasing Tregs and immunosuppressive cell populations in the TME, and resisting PD-1 therapy.[51–54] Vascular Endothelial Growth Factor (VEGF) is a critical driver of angiogenesis, inhibiting APC maturation and thus T cell activation. VEGF also impedes T cell adhesion to endothelial cells, preventing T cell migration and infiltration, and suppresses the production of chemokines like CXCL10 and CXCL11.[55] Transforming Growth Factor-β (TGF-β) induces cancer-associated fibroblasts (CAFs) and interferes with the expression of CXCR3 on T cells, inhibiting T cell infiltration and disrupting chemokine-induced migration.[56,57]

## Immunosuppressive TME

TME is a highly heterogeneous milieu composed of tumor cells, immune cells, and cytokines. TME is characterized by elevated hydrogen peroxide ($H_2O_2$) and glutathione (GSH) levels, low pH, and hypoxia. These factors collectively suppress the antitumor functions of T cells. Various molecular signals modulate the antitumor response by altering the balance between inhibitory and cytotoxic reactions within the tumor vicinity.[58] Despite the infiltration of effector CTLs into the TME, tumors enhance immunosuppression through multiple mechanisms, creating a TME conducive to tumor progression and leading to resistance against ICIs therapy.[59]

The TME contains a substantial number of immunosuppressive cells, including Tregs, tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), and CAFs.[60] These cells secrete immunomodulatory agents such as IL-10, IL-35, and TGF-β, and express immune checkpoint proteins like PD-L1 and CTLA-4, inducing immune tolerance and interfering with the immune response at the tumor site. Tregs suppress the activity of T cells and APCs through several mechanisms. For instance, Tregs secrete IL-10 and TGF-β, which inhibit the activation and proliferation of $CD4^+$ and $CD8^+$ T cells.[61,62] Additionally, Tregs compete with effector T cells for IL-2, a cytokine crucial for T cell proliferation and the enhancement of natural killer (NK) cell cytotoxicity.[63] Tregs express high levels of immune checkpoint proteins such as PD-1 and CTLA-4 on their surface, inducing immune tolerance and thereby interfering with the immune response at the tumor site.[64] MDSCs directly suppress T effector cells through the secretion of TGF-β and IL-10,[65,66] promote the generation of FOXP3+ Tregs,[67,68] and inhibit lymphocyte homing and adenosine metabolism regulation enzymes.[69] TAMs can exhibit two different phenotypes: M1 and M2. M1 macrophages are associated with inflammation, pathogen clearance, and anti-tumor immunity, while M2 macrophages possess pro-tumor characteristics.[70,71] M2 macrophages secrete immunomodulatory

factors like prostaglandin E2 (PGE2), IL-10, and TGF-β, suppressing the cytotoxic activity of T lymphocytes and NK cells,[72] contributing to the conversion of Th cells into Tregs,[73] further inhibiting immune responses. TAMs recruit Tregs to the TME by secreting CCL5, CCL20, and CCL22. They also express checkpoint inhibitors such as T cell immunoglobulin and mucin domain 3 (TIM-3), T cell immunoglobulin and mucin domain 4 (TIM-4), PD-1, and PD-L1, which suppress macrophage phagocytosis, inflammasome activation, and effector cytokine production.[74,75]

In addition to PD-1, PD-L1, and CTLA-4, other immune checkpoint molecules such as Lymphocyte activation gene 3 (LAG-3), TIM-3 and T cell immunoreceptor with Ig and ITIM domains (TIGIT) are present in the TME. Chronic antigen stimulation by TCR results in T cell exhaustion. LAG-3 is expressed on activated $CD4^+$, $CD8^+$ T cells, NK cells, and Tregs. By binding to its ligand FGL1, LAG-3 inhibits T cell function. Elevated LAG-3 expression in Tregs within the TME dampens tumor-specific immune responses.[76–78] TIGIT is mainly expressed on activated T cells, Tregs, and NK cells, interacting with CD155 to increase IL-10 secretion, reduce IL-12 secretion, and inhibit T cell responses. TIGIT enhances Tregs immunosuppressive functions by upregulating markers such as Foxp3, Helios, neuropilin-1, CTLA-4, PD-1, and LAG-3.[79] TIM-3 is expressed on Th1/Th17 cells, Tregs, $CD8^+$ T cells, DCs, and NK cells. It primarily inhibits T cell activation and proliferation while reducing the production of pro-inflammatory cytokines, functioning as a negative regulator in antitumor immunity.[80]

Certain cytokine such as indoleamine 2.3-dioxygenase (IDO) and IFN-β can suppress immune responses when overexpressed. Tumor cells also release TGF-β, VEGF, IL-10, and chemokines like CCL2, CCL7, CCL8, and CCL13, which recruit immunoregulatory cells, interfere with immune recognition, and inhibit the proliferation and function of effector cells.

## Genetic Mutations

Genomic and epigenetic alterations in tumor cells can mediate immune evasion. Several driver genes have been identified in lung cancer, including EGFR, anaplastic lymphoma kinase (ALK), and Kirsten rat sarcoma virus oncogene homolog (KRAS).

Lung cancer patients with EGFR mutations and ALK rearrangements often have poor responses to PD-1/PD-L1 inhibitors.[81–84] ALK fusions can reduce neoantigen production and increase the number of immunosuppressive cells through the phosphoinositide 3-kinase (PI3K)-AKT and MEK-ERK pathways, leading to poor efficacy of checkpoint inhibitor monotherapy. EGFR mutations are associated with a reduced number of $CD8^+$ T cells and altered PD-L1 expression.[85] EGFR upregulates IL-6 expression, activating the IL-6/JAK/STAT3 signaling pathway to mediate PD-L1 expression.[86] Some studies suggest that activated EGFR induces PD-L1 expression via the p-ERK1/2/p-c-Jun signaling pathway.[87] Currently, many clinical trials exclude patients with EGFR mutations, and trials including these patients are limited, resulting in a lack of definitive evidence. EGFR mutations are not an absolute contraindication for immunotherapy, as some patients may still benefit. Therefore, identifying suitable patient populations and optimizing treatment strategies is of significant clinical importance.

KRAS is a key driver gene in the development of NSCLC, with major mutation subtypes including KRAS G12C, KRAS G12D, KRAS G12V, and KRAS G12A.[88,89] Compared to wild-type KRAS, NSCLC with KRAS mutations is considered more likely to benefit from ICIs treatment.[90] Numerous studies have shown a correlation between KRAS mutations and high PD-L1 expression. Research has also found that tumors with KRAS mutations exhibit a higher inflammatory phenotype, greater infiltration by $CD8^+$ tumor-infiltrating lymphocytes(TILs), and a higher tumor mutational burden. KRAS G12C mutation patients, in particular, show a good response to ICIs. The KEYNOTE-042 study reported that patients with KRAS G12C mutations had higher objective response rates and longer PFS and overall survival (OS) when treated with pembrolizumab monotherapy.[91–95] However, not all KRAS mutation patients benefit from ICIs. KRAS G12D mutations have been shown to inhibit $CD8^+$ T cell infiltration via the HMGA2-CXCL10 /CXCL11 axis and suppress PD-L1 expression through the P70S6K/PI3K/AKT axis, resulting in immune suppression and initial resistance to ICIs.[96] Moreover, KRAS mutations frequently co-occur with other gene mutations, with TP53 being the most common co-mutation.[97] Compared to KRAS mutation alone, tumors with KRAS and TP53 co-mutations exhibit higher levels of PD-L1 expression and greater lymphocyte infiltration, showing a better response to PD-1 blockade.[98,99] STK11 is the second most common co-mutated gene, typically secondary to KRAS mutations.[45] STK11

mutations reduce the density of infiltrating $CD8^+$ CTLs in tumors, leading to a desert or cold TME.[100,101] Studies have shown that STK11/LKB1 inactivation is a major driver of immune evasion and intrinsic resistance to PD-1 blockade in KRAS-mutant lung adenocarcinoma.[102]

Kelch-like ECH-associated protein 1 (KEAP1) is the third most common mutated gene in lung adenocarcinoma. KEAP1 is a tumor suppressor in lung cancer progression, independent of TP53 mutation status.[103–105] KEAP1 mutations activate the Nrf2 antioxidant program and cooperate with KRAS mutations to drive lung adenocarcinoma progression, supporting the need for tumor cells to overcome oxidative stress barriers during tumorigenesis.[105–109] KEAP1 often co-mutations with STK11, and despite high TME activity, co-mutations increase the difficulty of immunotherapy.[110–112] Research suggests that KEAP1 regulates the ubiquitination-mediated degradation of EMSY. Loss of KEAP1 leads to the accumulation of EMSY, inhibiting type I interferon response and disrupting innate immune signaling, thus promoting cancer immune evasion. KEAP1 loss induces EMSY stabilization, resulting in a homologous recombination repair (HRR)-deficient BRCAness phenotype, making tumors sensitive to PARP inhibitors.[113] HRR deficiency contributes to increased tumor mutational burden (TMB) and genomic instability, possibly explaining the high TMB observed in KEAP1-mutant tumors.

LKB1 mutations are a major driver of resistance to PD-1 therapy, irrespective of KRAS co-mutation. LKB1 positively regulates the expression of intercellular adhesion molecule-1 (ICAM1) in NSCLC. ICAM1, through its interaction with T cell Lymphocyte Function-Associated Antigen 1(LFA-1), mediates T cell adhesion and interaction with tumor cells. LKB1 mutations lead to the downregulation of ICAM1 expression, enabling tumor cells to evade T-cell adhesion and leading to resistance to PD-1 immunotherapy.[113,114] Another study reports that LKB1 positively regulates the expression of Stimulator of Interferon Genes (STING) in KRAS-mutant tumors.[115] Loss of LKB1 inhibits the STING pathway, inhibiting lung adenocarcinoma metastasis.[116]

Hepatocyte growth factor receptor (MET) is also an oncogenic driver that can be activated by MET exon 14 skipping mutations, gene amplification, or overexpression.[117] MET signaling reduces STING mRNA stability by phosphorylating UPF1 at the Y818 site, which enhances UPF1 binding to STING1 mRNA and promotes its degradation. This process inhibits the STING signaling pathway. MET gene amplification leads to a weakened STING-mediated IFN response, decreased infiltration of $CD8^+$ T cells, $CD4^+$ T cells, and NK cells, reducing tumor immunogenicity and resulting in resistance to immune checkpoint blockade (ICB) therapy.[118]

Homozygous deletion of 9p21.3 (9p21 loss) is one of the most common genetic deletions in human tumors, occurring in approximately 13% of cases. The loss of 9p21 leads to a "cold" tumor immune phenotype with reduced TILs, especially T, B, and NK cells. It also alters the spatial distribution of TILs, reduces immune cell migration and activation, decreases PD-L1 positivity, and activates immunosuppressive signals. Patients with 9p21 loss have significantly lower response rates to ICIs and poorer prognosis.[119]

## Utilizing Nanoparticles to Overcome the ICIs Therapy Resistance

Currently, there are no established strategies to address resistance that develops during ICIs immunotherapy. In this context, combining immunotherapy with other treatment modalities, such as targeted therapy, chemotherapy, and radiotherapy, is considered a promising and effective approach to modulate immune responses at different stages and overcome resistance. The goal is to convert immunologically "cold" tumors which have low immune activity into "hot" tumors which are more responsive to treatment, thereby enhancing therapeutic efficacy. Nanoparticles due to their unique structural properties (Figure 2) demonstrate great potential to overcome the ICIs immunotherapy resistance, as a summary in Table 1. By increasing the solubility of drugs, nanoparticles can enhance drug absorption and improve bioavailability. As advanced carriers for drug delivery, nanomedicines can employ various design strategies to enhance targeting, stability and controlled release at tumor sites. Furthermore, nanoparticles possess multifunctionality, enabling utilize in multimodal tumor diagnosis and treatment, such as photodynamic therapy (PDT), photothermal therapy (PTT), chemotherapy (CT), radiotherapy (RT), Chemodynamic therapy (CDT)and immunotherapy.[14,120]

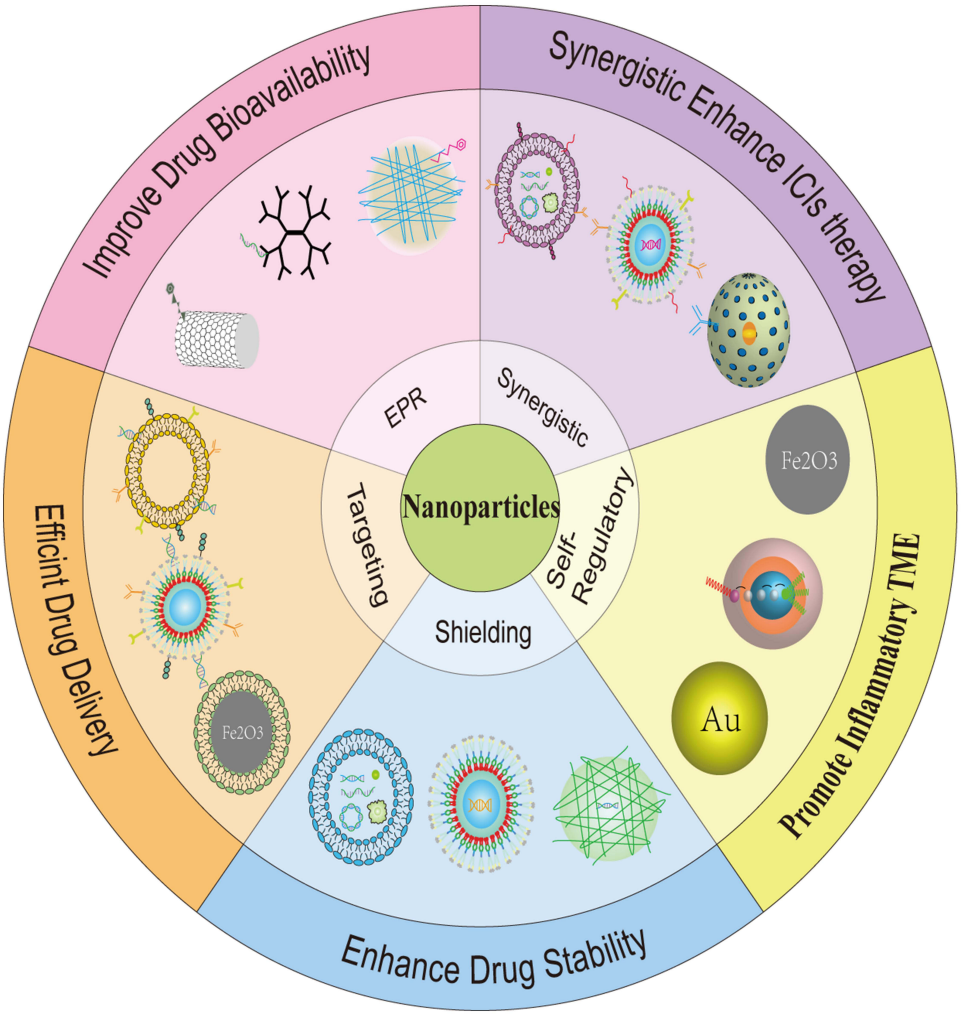


**Figure 2** The properties of nanoparticles.

## The EPR Effect of Nanoparticles: Passive Tumor Targeting, Enhanced Bioavailability and Reduced Toxicity

Tumor cells exhibit significantly higher growth rates than normal cells, and the endothelial cells of tumor vasculature are poorly aligned, creating permeable gaps. Additionally, tumors have inefficient lymphatic drainage and slower blood flow, allowing nanoparticles to easily accumulate in tumor tissues due to their small size. Leveraging the EPR effect, drugs can be passively targeted to tumor cells, thereby limiting systemic toxicity and significantly enhancing patient tolerance.[121]

The STING pathway can activate antigen-presenting cells and inflammatory cytokines, promoting the activation and recruitment of T cells, which play a crucial role in initiating antitumor immunity and converting "cold" tumors into "hot" tumors.[122] Particularly when combined with ICIs, this pathway significantly enhances the control of tumor growth.[123] However, STING agonists based on cyclic dinucleotide (CDN) face challenges such as poor metabolic stability, limited cell permeability, and suboptimal drug-likeness, necessitating intratumoral injection while still struggling with short half-life issues and cytosolic entry, leading to suboptimal clinical antitumor efficacy.[123,124] To address these challenges, researchers have utilized lipid- or polymer-based Nanoparticles to deliver STING agonists, enhancing both local and systemic therapeutic effects.This study designed a nebulized liposomal nanoparticle loaded with CDN (AeroNP-CDN). Inhalation of AeroNP-CDN effectively delivers CDN to deep lung tumors. Activation of CDN promotes the expression of IFN genes in macrophages and DCs, creating a pro-inflammatory TME. When combined with anti-PD-L1 antibody


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**Table 1** Overview of Nanoparticles Through Their Intrinsic Properties to Overcome ICIs Immunotherapy Resistance

| Nanoparticles 'Properties | | Functions | ICIs Immunotherapy | Ref |
|---|---|---|---|---|
| EPR Effect | | Passive tumor targeting, enhancing bioavailability and reduced toxicity; Delivery of STING agonists, CpG, etc. | Activating the immune system; promoting inflammatory TME | [125–127], [129] |
| Active targeting Effect | Environment-Responsive | Target TME and controlled drug release in response to TME changes. | Targeting and modulating TME | [139,140] |
| | Cell Membrane Coating | Coated with tumor, NK cell membrane,etc; target tumor and provide antigen source. | Increase tumor antigen; Increases T-cell infiltration; Remodeling TME | [142–146] |
| Shielding effect | | Avoiding recognition and clearance;, Delivery of PTEN mRNA, KRAS siRNA, P53 DNA, M1 macrophages, IL-12, etc. | Gene mutation repair; promoting inflammatory TME | [153, 154, 157, 160, 162] |
| Self-Regulatory Effect | Catalytic Effect | Modulating OXD and POD activities to generate ROS; simulating CAT activity to convert H2O2 to O2; utilizing Fenton reactions to enhance CDT therapy. | Remodeling TME | [166, 167], [170–172] |
| | Regulatory Effect | Polarizing macrophages from M2 to M1; enhancing the presentation of tumor antigens, boosting the differentiation and activation of $CD8^+$T cells and NK cells. | Activate the host immune system; promoting inflammatory TME | [175, 177, 180, 182, 184] |
| | Photothermal Effect | Absorbing near-infrared light to generate heat, killing tumor cells directly; enhancing ROS generation. | Activating the host immune response | [189] |
| Synergistic Effect | Synergistic Drug Combination | Co-delivering synergistic drugs; Co-delivery of PLK1 siRNA, PD-1/PD-L1 inhibitors, TLR7 agonists, etc. | Activating T cells; Promoting inflammatory TME | [192–195] |
| | Synergistic Treatment Combination | Combining various therapeutic modalities; Combining PTT, PDT, RT, CT, CDT, immunotherapy, etc. | Increase tumor antigen; Activating T cells; Promoting inflammatory TME | [197, 199, 200], [202–204] |

immunotherapy, it counteracts the overexpression of PD-L1 in tumor tissues induced by the IFN-γ signaling pathway, thereby eliciting a sustained systemic antitumor immune response.[125]

Furthermore, the researchers developed a nanoparticle based on poly(β-amino ester), covalently conjugated with the STING agonist CDN. This delivery method allows for the release of the STING agonist upon reaching target immune cells, eradicating tumors in mice and training their immune systems to recognize and eliminate future tumors, thereby achieving immune memory formation and preventing cancer recurrence.[126] In addition, the study developed a self-assembled coordination nanomedicine based on Mn2+ and CDN-STING agonists (CDN-Mn2+ particle, CMP). CMP effectively delivers STING agonists to immune cells. Through intratumoral or systemic intravenous injection, CMP induced a strong antitumor immune response, achieving significant therapeutic efficacy with minimal doses of STING agonists in various murine tumor models. CMP represents a major technological advancement in enhancing the potency of STING agonists, enabling drug dose reduction and minimizing side effects.[127]

CpG as a TLR9 agonist can activate immune responses upon intratumoral injection, stimulating both local and systemic antitumor responses.[128] Researchers found that compared to soluble CpG, the Particle Replication In Non-wetting Templates (PRINT) nanoparticle-conjugated PRINT-CpG formulation exhibited lower toxicity and higher antitumor efficacy in a syngeneic metastatic lung cancer mouse model. This nanomedicine effectively shifted macrophage polarization from the M2 to the M1 phenotype, generating an antitumor immune environment while reducing local and systemic toxicity.[129]

The EPR effect is widely recognized as a primary mechanism for nanoparticle accumulation in tumors. However, recent research has cast doubt on the EPR effect due to vascular heterogeneity across different species and tumor types, as well as the variability of the TME. There is substantial evidence suggesting that transcytosis may be the primary mechanism for nanoparticle accumulation in tumors. Currently, the clinical efficacy of the US Food and Drug Administration(FDA)-approved nanomedicines has not met expectations. Overestimation of the EPR effect may have

created a bottleneck in the development of nanomedicines. These findings have inspired researchers to develop technologies that enhance delivery efficiency through active transcytosis mechanisms.

## Active Targeting Effect of Nanoparticles: Efficient Drug Delivery to Tumor Cells

Active targeting of Nanoparticles enhances drug delivery and therapeutic efficacy by modifying the nanomaterial surfaces with specific molecules that recognize and bind to target cells or tissues. Ligand-receptor mediated targeting is one of the most common active targeting mechanisms. By modifying the surface of Nanoparticles with specific ligand molecules, these Nanoparticles can bind to receptors that are overexpressed on target cells, achieving specific targeting. Ligand molecules can include small molecules, peptides, proteins, or antibodies. Aptamers are single-stranded oligonucleotides selected from random DNA or RNA libraries through Systematic Evolution of Ligands by Exponential Enrichment (SELEX) technology, with high specificity and affinity for target recognition.[130,131] Aptamers can fold into unique tertiary structures, enabling specific target recognition.[132] By modifying Nanoparticles with specific aptamers, drugs can be targeted to lung cancer cells. S15-APT, an 85-base long single-stranded DNA, specifically binds to NSCLC.[133] With advances in nanotechnology and TME research, stimulus-responsive intelligent nanodrug carriers designed based on the TME have gained significant attention in antitumor drug delivery systems. Intelligent nanodrug carriers can stably transport drugs in vivo and respond to TME stimuli to control drug transport location and release rate, thereby significantly increasing drug concentration at the target site, enhancing antitumor activity, and reducing side effects. Cell membrane-coated nanoparticles (CNPs) are an emerging class of nanocarriers that encapsulate synthetic nanoparticle cores within natural cell membranes.[134] This configuration exhibits a variety of surface markers, allowing CNPs to mimic natural cell interactions. These properties enable CNPs to navigate complex biological environments effectively, evade immune clearance, and specifically accumulate at disease sites.[135]

## Environment-Responsive Targeting

Compared to traditional nanodrugs, stimulus-responsive nanoparticles modulate TME, converting “cold tumors” into “hot tumors”, enhancing patient immune responses. Common TME stimuli include pH, reducing agents, enzyme concentrations, ROS, and adenosine-5’-triphosphate.[136,137]

pH-responsive nanodrug delivery systems exploit the physiological pH differences between tumor tissues and normal tissues to target and release chemotherapeutic agents specifically at the tumor site.[138] In this study, we developed a pH-sensitive nanoparticle formulation using histidine-conjugated star-shaped PLGA (sPLGA-His). The surface of these NPs was decorated with D-α-tocopheryl polyethylene glycol succinate (TPGS) to prevent macrophage phagocytosis. The release of DTX and DSF from the pH-sensitive NPs was significantly higher at pH 6.8 compared to pH 7.4, and these NPs demonstrated enhanced penetration in three-dimensional tumor spheroids. Additionally, TPGS-modified NPs exhibited reduced plasma protein binding and decreased macrophage uptake. In vivo studies showed that TPGS-modified pH-sensitive NPs increased tumor delivery by approximately fourfold compared to non-pH-sensitive NPs, significantly enhancing the antitumor effect, indicating their strong targeting capability.[139]

Tumor tissues exhibit an abnormal metabolic profile, resulting in a highly reductive intracellular environment. In certain drug-resistant tumor cells, GSH levels can be up to ten times higher. This disparity in redox conditions between the intracellular and extracellular environments of tumor cells offers a novel approach for designing reduction-responsive nanodrug carriers to achieve intracellular drug release in tumor cells.In this context, we innovatively developed GSH-sensitive polyurethane nanoparticles (GPUs). These nanoparticles incorporate drug payloads linked via cleavable disulfide bonds within the polyurethane matrix. Upon introduction into the lung cancer cell environment, the elevated GSH levels in tumor cells induce a reduction reaction, leading to the cleavage of disulfide bonds and subsequent release of the encapsulated drug. Experimental results demonstrated that these GSH-sensitive nanoparticles, when loaded with cisplatin (referred to as CGPU), exhibited a GSH concentration-dependent release of cisplatin. This finding underscores the high sensitivity of these nanocarriers to GSH.[140]

## Cell Membrane-Coated Targeting

Cell membrane-coated nanoparticles (CNPs) which encapsulate synthetic nanoparticle cores within natural cell membranes. The use of different cell membrane sources imparts distinct characteristics to the nanoparticles. Notably, CNPs derived from cancer cell membranes exploit the homotypic binding properties of cancer cells, facilitating targeted delivery to tumor cells. Many cancer cells exhibit a tendency to adhere to each other, promoting tumor development and metastasis.[141] This homotypic binding property makes cancer cell membrane-coated nanoparticles effective as targeted drug delivery vehicles and as antigen sources for immunotherapy, providing immune stimulation signals for ICIs.

The research designed biomimetic nanoparticles (CMNP@Osi) composed of a polymeric nanoparticle core coated with membranes derived from tumor cells. This design integrates membrane-mediated homotypic and molecular targeting strategies to enhance the efficacy of osimertinib. Upon intravenous injection, CMNP@Osi accumulates at tumor sites and shows enhanced uptake by cancer cells through homotypic targeting. Subsequently, osimertinib is released into the cytoplasm, inhibiting upstream EGFR phosphorylation and downstream AKT signaling pathways, thereby suppressing the proliferation of NSCLC cells. This dual-targeting strategy using biomimetic nanoparticles significantly improves molecular targeted drug delivery and clinical efficacy.[142] The study developed doxorubicin-induced tumor membrane-coated iron (II)-cytosine-phosphate-guanine nanoparticles (DM@NPs). These nanoparticles effectively deliver tumor antigens and immune adjuvants to tumor cells. The surface of DM@NPs features membrane proteins associated with immunogenic cell death (ICD), enhancing the uptake by DCs, promoting their maturation, and releasing pro-inflammatory cytokines. The application of DM@NPs significantly increases T-cell infiltration, effectively remodeling the tumor immune microenvironment and inhibiting tumor progression in vivo.[143] Another study designed NK cell membrane-biomimetic nanoparticles (NK-NPs) for tumor immunotherapy, achieving the desired therapeutic outcomes in animal models. NK cell membranes induce macrophage polarization towards the pro-inflammatory M1 phenotype within tumors, mediated by the cell membrane. Additionally, the photosensitizer loaded in NK-NPs can trigger PDT-induced immunogenic cell death, activating APCs and damage-associated molecular patterns, thereby enhancing the nanoparticles' anti-tumor efficiency.[144]

Another approach involves hybrid membrane coatings, where membranes from different cell types are fused. The resulting CNP formulations exhibit characteristics from multiple cell sources. This study innovatively developed a Dox-loaded RAW-4T1 hybrid biomimetic membrane camouflaged-poly(lactic-co-glycolic acid) (PLGA) nanoparticle system (DPLGA@ [RAW-4T1] NPs). This system comprises Dox-loaded PLGA nanoparticles doubly coated with membranes from RAW264.7 macrophages (RAW) and 4T1 breast cancer cells (4T1). The RAW membrane significantly enhances the tumor-targeting specificity of the nanoparticles, while the 4T1 membrane enables precise targeting of homologous cancer cells. This allows the nanoparticles to actively migrate to tumor sites and release Dox within the tumor, achieving anti-tumor effects. In vitro results demonstrate that DPLGA@ [RAW-4T1] NPs exhibit significant anti-tumor activity, effectively inhibiting tumor metastasis, extending survival, and showing low systemic toxicity.[145] This research developed a magnetic iron oxide nanoparticle ($Fe_3O_4$ MNPs) platform and utilized CMBMNPs derived from various cancer cell lines to study homotypic targeting capabilities. The results indicated that cancer cell membrane-biomimetic $Fe_3O_4$ MNPs could highly specifically recognize their source cancer cell lines in vitro and show excellent targeting capabilities in homologous tumors. Even in the presence of heterotypic tumor competition, these nanoparticles selectively targeted homologous tumors.[146]

Despite the reported advancements in CNP manufacturing methods, further efforts are needed to scale up production to clinically relevant quantities while consistently meeting stringent quality requirements to ensure efficacy and safety. Given that various metal, inorganic, and polymer nanoparticles are already approved for human use or in late-stage clinical trials, much of the focus may shift to the derivation and coating processes of cell membranes. Fortunately, many existing industrial-scale technologies can be readily adapted for high-yield production.

## Shielding Effect of Nanocarriers: Avoid Recognition and Efflux by Transport Proteins, Enhance Drug Stability, and Increase Intracellular Drug Concentrations

Various nanomaterial-based drug delivery systems have been developed, including liposomes, polymer carriers, mesoporous silica, micelles, and other nanoparticles. Among these, lipid nanoparticles are particularly widely used in the research and application of nucleic acid drugs.[148] They function as a "cloak" for nucleic acid molecules, tightly encapsulating them. Upon entering the body, these lipid nanoparticles protect the drug molecules from digestion and absorption by endogenous enzymes. Additionally, because their components are similar to cell membranes, they have natural affinity and can fuse with cell membranes, releasing mRNA molecules into cells to exert their therapeutic effects.[149] Mesoporous silica nanoparticles have garnered attention as nanoscale drug carriers due to their large surface area, high stability, negligible toxicity, customizable pore size, and ease of encapsulating various biomolecules.[150] Compared to liposomes, polymer nanoparticles offer high stability and inherent sustained and controlled drug release characteristics. They can prolong drug release, delay metabolism and detoxification, extend circulation time, avoid systemic clearance, and enhance intracellular uptake. Additionally, exosome delivery systems are another major method of drug delivery.[151] Exosomes are membranous vesicles released into the extracellular matrix following the fusion of multivesicular bodies with the cell membrane.

Patients with NSCLC driven by genetic mutations often do not benefit from ICIs treatment, whereas nucleic acid drugs are recognized as potent tools against tumors. However, the delivery of nucleic acid drugs into the body faces three major challenges: (1) large molecular weight and negative charge of nucleic acids prevent free passage through biological membranes; (2) RNA is easily degraded by enzymes in plasma and tissues, rapidly cleared by the liver and kidneys, and recognized by the immune system; (3) once inside the cells, they can be trapped in endosomes, preventing them from functioning.[152] To overcome these obstacles, Nanoparticles can be used to deliver nucleic acid drugs, repairing mutated or inactivated proteins to make them responsive to ICI therapy.[153] This study developed a nanodrug called mPTEN@NPs, which encapsulates PTEN mRNA within a polymer NPs core. This nanodrug effectively protects mRNA from ribonuclease degradation, achieving efficient delivery of PTEN mRNA to tumor sites. By restoring the function of lost or mutated PTEN protein, mPTEN@NPs successfully reverses the tumor immunosuppressive microenvironment, inducing immunogenic cell death in tumor cells.[147] This study demonstrates the use of nanotechnology for mRNA delivery, enhancing stability and targeting while restoring tumor suppressor function without substantial toxicity, providing new insights for designing mRNA nanodrugs targeting mutation repair.

Furthermore, this study designed an innovative inhalable siRNA nanodrug named siKRAS@GCLPP NPs. This formulation encapsulates siKRAS in liposomes, effectively protecting siRNA from ribonuclease degradation. Using biodegradable PLGA-PEG as the matrix increases siRNA stability during nebulization and facilitates mucus penetration during inhalation. Additionally, [D-Lys6]-LHRH is conjugated to the PEG molecule's end, achieving targeted endocytosis in tumor cells. PEG-modified nanoparticles exhibit enhanced mucosal penetration. Experimental results show that siKRAS@GCLPP NPs can reach deep lung tumor cells, successfully escape endosomes or lysosomes, and silence mutant KRAS genes, resulting in strong tumor growth inhibition with minimal side effects.[154] Utilizing lipid nanocarriers for siRNA delivery demonstrates excellent antitumor efficacy and effective silencing of mutant genes, providing new ideas for designing siRNA nanodrugs targeting genetic mutations.

The tumor suppressor p53 is a transcription factor that regulates cell cycle arrest and apoptosis in response to genotoxic and oncogenic stress.[155,158,159] Given that over 50% of human cancers have p53 mutations and pathway alterations,[160] delivering tumor-suppressing p53 genes to tumor cells using tumor-targeted nanoparticles to restore p53 function can enhance ICIs therapy. This study developed a novel tumor-targeted nanodrug combining anti-PD1 antibodies with SGT-53.[155] SGT-53 is based on a nanocomplex encapsulating plasmid DNA encoding human wild-type p53 (wtp53) for gene therapy. SGT-53 treatment increases immunogenic cell death (ICD) in tumors and, combined with anti-PD1, enhances innate and adaptive immune responses while mitigating tumor-induced immunosuppression.[155] SGT-53 reduces the lethality of xenogeneic hypersensitivity reactions associated with anti-PD1 antibodies.[155] Data indicate that restoring p53 function with SGT-53 can enhance antitumor immunity, sensitize tumors previously unresponsive to anti-PD1 immunotherapy, and reduce immune-related adverse events.

Delivering cells using Nanoparticles is also a novel delivery method. Tumor cells evade immune response by modulating M1 and M2 macrophage polarization states. M1 macrophages, classically activated, produce nitric oxide, ROS, and inflammatory cytokines, directly or indirectly killing tumor cells and activating other immune cells such as T cells and NK cells, participating in antitumor immunity.[161] Therefore, M1 macrophages are considered tumor-suppressing allies. Delivering M1 cells directly to the TME using nanocarriers can enhance ICIs therapy. This study utilized nanocarriers containing celastrol (NP@M1) to deliver M1 macrophages to tumor cells, achieving antitumor effects. Celastrol nanoparticles maintain the polarization state of M1 macrophages, effectively enhancing antitumor efficacy through dual actions.[156] Utilizing the dual functionality of Nanoparticles and drug delivery, this approach directly targets TME, converting it into a pro-inflammatory state.

Additionally, Nanoparticles can be used to deliver cytokines.IL-12 is a heterodimeric cytokine that typically induces the conversion of tumor-supporting macrophages to tumor-suppressing macrophages, aiding subsequent antitumor responses.[162] Although cytokines can re-educate immune system cells, they are unstable and associated with systemic side effects. Intratumoral injection can avoid systemic side effects but limits the broad application of cytokines. This study synthesized IL-12 P1 nanoparticles, encapsulating hydrophilic IL-12 as a TAM modulator in an environment-responsive polymer (P1) using a double emulsion water-in-oil-in-water technique. IL-12 P1 nanoparticles accumulate at tumor sites and release IL-12 sustainably, reversing tumor-infiltrating macrophages from M2 to M1 to exert antitumor effects. These environment-responsive IL-12 P1 nanoparticles can be administered systemically, releasing IL-12 within tumors and minimizing systemic side effects.[157]

## Self-Regulatory Effect of Nanoparticles: Promoting Inflammatory TME

Nanoparticles serve not only as excellent drug delivery carriers but also play a significant role in tumor therapy through their intrinsic properties. This review discusses the catalytic, regulatory, and photothermal effects of nanoparticles in enhancing the efficacy of ICIs in tumor treatment.

## Catalytic Effect

Extensive research has demonstrated that Nanoparticles possess nanozyme characteristics, including carbon-based Nanoparticles (such as fullerenes, graphene, graphene oxide, and carbon nanotubes), metallic nanoparticles (such as gold, silver, platinum, palladium, copper, iron, and cobalt), metal oxide nanostructures (such as $Fe_3O_4$, $CeO_2$, $TiO_2$, and $V_2O_5$), and emerging materials like metal-organic frameworks (MOFs), covalent organic frameworks (COFs), metal chalcogenides, and nanohybrids.[163] Nanozymes are Nanoparticles that mimic the catalytic activity of natural enzymes. Since the discovery of $Fe_3O_4$ nanoparticles exhibiting peroxidase-like activity in 2007, hundreds of Nanoparticles have been found to mimic the activities of various enzymes, including peroxidase (POD), oxidase (OXD), catalase (CAT), glucose oxidase (GOx), glutathione peroxidase (GPx), and superoxide dismutase (SOD).[164] Many Nanoparticles have been reported to exhibit multiple enzyme activities simultaneously.

ROS can kill tumor cells by damaging DNA and proteins. Nanozymes such as iron oxide, gold nanoparticles, and manganese dioxide can mimic OXD and POD activities to generate ROS, inducing oxidative stress and killing tumor cells.[165] Studies have shown that nanozymes formed by combining gold nanoparticles with porous hollow carbon nanospheres (Au@HCNs) can generate ROS through OXD and POD activities under acidic conditions, significantly enhancing the photothermal effect of Au@HCNs for antitumor therapy.[166]

However, limitations such as insufficient nanozyme activity and low substrate (eg, $H_2O_2$) concentration hinder the efficacy of tumor therapy. Current strategies involve cascading amplification of ROS production and weakening antioxidant defenses to disrupt ROS homeostasis, considered effective for anticancer treatment. A novel Ir-N5 single-atom nanozyme (Ir-N5 SA) has been developed, showing superior catalytic performance compared to Ir-N4 SA due to the synergistic effect of the central Ir single atom and axial N coordination. At the tumor site, Ir-N5 SA generates large amounts of ROS through OXD and POD activities. Ir-N5 SA also produces $O_2$ and $H_2O_2$ via CAT and NADH oxidase (NOX) activities, achieving efficient nanozyme catalytic therapy. Additionally, Ir-N5 SA disrupts intracellular NADH/$NAD^+$ balance by mimicking NOX, synergizing with fatty acid synthase (Cer) to interfere with tumor cell energy metabolism homeostasis.[167] The designed Ir-N5 SA/Cer nanoagent effectively overcomes the drawbacks of current

nanozyme catalytic therapy, significantly enhancing antitumor efficacy by disrupting redox and metabolic homeostasis in the tumor region through cascaded enzymatic reactions.

CDT which generates highly cytotoxic ROS through intracellular chemical reactions, has gained widespread attention. Nanometal ions such as iron and manganese enhance CDT efficacy by decomposing $H_2O_2$ into hydroxyl radicals via Fenton or Fenton-like reactions, working synergistically with chemotherapy drugs.[168,169]

The hypoxic TME not only increases the likelihood of tumor metastasis but also limits the application of therapies such as PDT, sonodynamic therapy, and radiotherapy. Nanozymes like Pt, Au, and iron oxide simulate CAT activity to catalyze the conversion of $H_2O_2$ into $O_2$, alleviating tumor hypoxia, promoting tumor cell apoptosis, and providing oxygen for PDT and radiotherapy, thus synergizing in tumor treatment. Studies have shown that Pt@BP nanohybrids combine the photodynamic activity of BP nanosheets and the CAT activity of Pt nanoparticles. Under hypoxic tumor conditions, Pt nanoparticles catalyze the decomposition of $H_2O_2$ into $O_2$, significantly enhancing the PDT efficiency of BP nanosheets under NIR light. Additionally, alleviating tumor hypoxia downregulates HIF-1α expression, reducing tumor apoptosis resistance and further enhancing treatment efficacy.[170] A novel GDY-$CeO_2$ nanozyme, formed by stably anchoring $CeO_2$ nanoparticles on two-dimensional graphdiyne (GDY), has demonstrated superior POD activity, decomposing $H_2O_2$ into $O_2$, significantly alleviating tumor hypoxia, and inducing DNA damage for tumor therapy.[171] Hybrid nanozymes constructed with GOx exhibit dual enzyme activities. GOx-Mn nanoparticles catalyze the production of $O_2$ from $H_2O_2$ at the tumor site, facilitating glucose consumption by GOx in the nanoparticles and modulating glucose metabolism in the tumor region. The $H_2O_2$ produced also benefits the nanozyme's catalytic reactions. The fusion of nanozymes and GOx achieves cascading amplification of glucose consumption, inducing cell pyroptosis and triggering a robust antitumor immune response. Glucose consumption also leads to increased expression of PD-L1 on tumor cells, enhancing the effectiveness of PD-L1/PD-1 immune checkpoint blockade therapy.[172]

## Regulatory Effect

Nanoparticles exhibit broad potential in modulating macrophages. These Nanoparticles include metallic nanoparticles, glyconanoparticles, graphene and carbon nanotubes, quantum dots, nanofibers, and various other nanoparticles. The mechanisms for regulating macrophages are diverse, primarily involving the modulation of macrophage activity, cytokine secretion, and intracellular signaling pathways.

Among metallic and metal oxide nanoparticles, gold nanoparticles (AuNPs), iron oxide nanoparticles (IONPs), and manganese dioxide ($MnO_2$) nanoparticles have been extensively studied. IONPs not only induce pro-inflammatory macrophage polarization in tumor tissues but also specifically induce autophagy in macrophages by activating TLR4 and stimulating the expression of inflammatory cytokines.[173,174] Additionally, zero-valent iron nanoparticles (ZVI-NPs) have been reported to possess dual anticancer activity: inducing ferroptosis in cancer cells and modulating the TME to favor antitumor immune responses. ZVI-NPs activate the AMPK/mTOR signaling pathway, promoting NRF2 degradation via GSK3β/β-TrCP, thereby disrupting redox balance and inducing ferroptosis in lung cancer cells. In vitro and in vivo models have shown that ZVI-NPs significantly reprogram macrophages from the immunosuppressive M2 phenotype to the antitumor M1 phenotype, enhancing $CD8^+$ T cell cytotoxicity, reducing Treg proportion, and bolstering antitumor immunity. Moreover, ZVI-NPs preferentially accumulate in tumor and lung tissues, significantly inhibiting tumor growth and metastasis.[175] This dual-function nanomedicine offers an effective strategy to synergistically induce ferroptosis in lung cancer cells and reprogram the immunosuppressive microenvironment, thereby enhancing antitumor efficacy.

AuNPs can interact with receptors on macrophage membranes, activating specific signaling pathways such as NF-κB and MAPK, promoting M1 polarization, and inducing the release of pro-inflammatory cytokines (eg, TNF-α, IL-6) and immune-stimulatory factors (eg, IFN-γ), thereby enhancing the formation and function of M1 macrophages.[176] Au@PG nanoparticles (NPs), comprising gold and polyaniline-glyco structures (PG), synthesized from o-nitrophenyl-β-D-galactopyranoside (ONPG), exhibit robust M1 macrophage polarization activity, promoting the shift of the TME from cold to hot, enhancing cytotoxic T cell responses and tumor inhibition. Combining Au@PG NPs with anti-PD-1 therapy improves both tumor inhibition and immune suppression, accompanied by the secretion of immunogenic cytokines.[177]

$MnO_2$ Nanoparticles not only induce the transformation of macrophages from M2 to M1 phenotype but also activate the host immune system through the cGAS-STING pathway.[178] $Mn^{2+}$ promotes the maturation of DCs and macrophages, enhancing the presentation of tumor-specific antigens, and boosting the differentiation and activation of $CD8^+$ T cells and NK cells, showing substantial potential in tumor immunotherapy.[179] Gao et al utilized PEG-modified manganese phosphate (MnP) nanoclusters to activate the cGAS-STING pathway, enhancing tumor immunotherapy. Upon endocytosis, $Mn^{2+}$ ions are released from MnP-PEG under the acidic conditions of lysosomes, leading to potent STING activation. In vivo experiments demonstrated that MnP-PEG nanoclusters significantly promoted tumor infiltration and maturation of DCs and macrophages, enhancing the activation and cytotoxicity of $CD8^+$ T cells and NK cells.[180] Combined with checkpoint inhibitors, this approach significantly suppressed tumor growth and metastasis. Similarly, PEGylated manganese-based metal-organic frameworks (MOFs) have demonstrated effective treatment against pancreatic tumors by increasing the number of DCs in the TME. Manganese-based Nanoparticles exhibit broad application prospects in tumor immunotherapy.

Glyconanoparticles (GNPs) are nanoparticles functionalized with sugar molecules on their surface, such as glucose, mannitol, or other monosaccharides and polysaccharides.[181] By interacting with glycoreceptors on the macrophage surface, GNPs can activate M1 polarization and have shown a promising ability to reverse M2 polarization.[182,183] For instance, GNPs can bind specifically to lectin receptors on TAMs, increasing the secretion of immunostimulatory IL-12 and reducing the secretion of immunosuppressive IL-10, arginase-1, and CCL22, thereby reversing TAMs to an antitumor phenotype. The combination of GNPs with anti-PD-L1 antibodies significantly improves the immunosuppressive TME, highlighting their substantial potential in cancer immunotherapy.[182]

Mesoporous silica nanoparticles (MSNs) play a significant role not only in drug delivery but also by directly interacting with TLR4 receptors on macrophages, activating downstream NF-κB signaling pathways. This activation promotes the secretion of chemokines CCL5, CXCL9, and CXCL10, enhancing $CD8^+$ T cell infiltration. When combined with anti-PD-1 antibodies, MSNs can rapidly establish a T cell-inflamed TME in the early stages of treatment, overcoming tumor resistance to PD-1 antibodies and effectively inhibiting tumor growth.[184]

## Photothermal Effect

Photothermal effect refer to the ability of nanoparticles to generate heat upon absorbing near-infrared laser light, thereby heating the tumor site. This process enhances the levels of hydrogen peroxide and ROS in the TME and directly induces thermal damage to tumor cells, achieving synergistic catalytic therapy. Common Nanoparticles with photothermal effects include gold nanoparticles, silver nanoparticles, carbon Nanoparticles (such as carbon nanotubes, graphene, and carbon quantum dots), and iron oxide nanoparticles.

Metal nanoparticles, such as gold and silver nanoparticles, exhibit localized surface plasmon resonance (LSPR) at specific wavelengths, absorbing and converting light energy into heat.[185,186] Carbon Nanoparticles like carbon nanotubes and graphene, and metal oxide nanoparticles such as titanium dioxide and iron oxide, possess excellent photothermal properties, generating localized heat under light irradiation for applications in photothermal therapy and as carriers for photosensitizers.[187] Organic-inorganic hybrid Nanoparticles, such as MOFs, combine organic molecules with inorganic Nanoparticles, providing stable carriers for photosensitizers and exhibiting superior photothermal properties.[188]

PTT can ablate tumors through thermal treatment while simultaneously activating the host immune response to prevent tumor recurrence and metastasis. To achieve this, researchers synthesized poly(tannic acid)-coated PLGA nanoparticles (PLGA-pTA NPs) for combined photothermal immunotherapy. pTA, a coordination complex of tannic acid and $Fe^{3+}$, can easily coat PLGA NPs within seconds, achieving a coating rate of 5.89%. As a photothermal agent, PLGA-pTA exhibits high photothermal conversion efficiency and excellent photostability under 808 nm laser irradiation, with strong photothermal cytotoxicity against 4T1 cells.[189] PTT based on PLGA-pTA induces the release of DAMPs, effectively triggering DC maturation. Animal experiments showed that PLGA-pTA, combined with laser irradiation, raised tumor temperatures to approximately 60°C, effectively inhibiting primary tumor growth. More importantly, PLGA-pTA-mediated PTT activated antitumor responses, significantly suppressing the progression of distant tumors and lung metastasis. When further combined with anti-PD-L1 antibodies, tumor growth and metastasis were almost

completely inhibited.[189] This study provides a versatile platform for achieving enhanced efficacy in photothermal immunotherapy.

## The Synergistic Effects of Nanocarriers: Enable the Combined Delivery of Drugs and Therapeutic Modalities, Thereby Enhancing the Effectiveness of ICIs Therapy

In cancer treatment, leveraging Nanoparticles to achieve synergistic effects from multiple drugs and therapeutic approaches represents a cutting-edge strategy. This method combines treatments with different mechanisms, improving therapeutic outcomes while reducing side effects.

## Combined Drug Therapies for Cancer Treatment

Functionalization of Nanoparticles enhances drug targeting and enables the simultaneous delivery of multiple drugs within a single nanocarrier, thereby augmenting the efficacy of ICIs in cancer treatment.

Polo-like kinase 1 (PLK1) is a critical mitotic kinase overexpressed in various cancers, contributing to oncogenic properties.[190] PLK1 expression creates an immunosuppressive TME by inhibiting immune cell infiltration and anti-tumor immune responses.[191] Inhibiting PLK1 can enhance antitumor immunity and synergize with immunotherapy.[191] This study introduces a nanoparticle-based immunotherapy called ARAC (Antigen Releasing Agent and Checkpoint Inhibitor), which uses polymer-modified MSNPs to co-deliver a PLK1 inhibitor (volasertib) and an anti-PD-L1 antibody. The PLK1 inhibitor is loaded into the MSNP core, followed by modifications with polyethyleneimine (PEI) and polyethylene glycol (PEG), and finally loaded with the PD-L1 antibody. Results show that the PLK1 inhibitor upregulates PD-L1 expression in cancer cells, reducing cytotoxic T cell function. Compared to single-agent therapies, ARAC significantly reduced tumor burden and extended survival in lung cancer-bearing mice. Additionally, nanoparticle delivery reduced the effective doses of both the PLK1 inhibitor and PD-L1 antibody to one-fifth of their original doses. ARAC treatment did not cause weight loss in mice, indicating good safety profiles.[192]

The study also developed a C-siPLK1-NP system, which uses the MSNP platform to couple an EGFR antibody with MSNP and deliver PLK1 siRNA. C-siPLK1-NPs bind to and internalize via EGFR receptors, leading to EGFR depletion and phosphorylation. Concurrently, siPLK1 loaded on the nanoparticles is released into the cytoplasm, integrating into the RNA-induced silencing complex (RISC) and mediating PLK1 mRNA cleavage, thereby reducing PLK1 protein expression. C-siPLK1-NP significantly inhibited tumor growth in an orthotopic lung tumor model without causing weight loss, demonstrating the safety of the nanoparticle platform.[193]

Additionally, the research developed a novel PD-L1/TLR7 dual-targeting nanodrug complex (NDC). The TLR7 agonist SZU-101 was first PEGylated, and then the carboxyl group of SZU-101 was conjugated with the amino group of the anti-PD-L1 nanobody n16 using a condensation reagent, forming the dual-targeting nanodrug complex. The PD-L1 nanodrug exhibits superior tumor targeting, delivering the TLR7 agonist to tumor tissues via endocytosis. The TLR7 agonist enhances tumor immunogenicity by activating innate immunity and promoting intratumoral antigen presentation, converting “cold” tumors to “hot” tumors. Furthermore, the TLR7 agonist induces high PD-L1 expression within tumors, allowing the PD-L1 nanodrug to exhibit better antitumor effects and responses in tumors with low PD-L1 levels.[194] Conjugating nanobodies with small molecule agonists addresses the challenge of traditional antibody-drug conjugates (ADCs) in penetrating solid tumors. This approach not only enhances tumor immunogenicity but also overcomes immune tolerance, providing a new direction for ADC development. The study also developed a nanodrug capable of co-delivering docetaxel and curcumin. The novel T7 peptide-modified nanoparticles (T7-CMCS-APE, CBT) based on carboxymethyl chitosan (CMCS) can target transferrin receptors (TfR) expressed on lung cancer cells and precisely regulate drug release in response to pH and ROS levels.[195]

## Combined Diverse Therapeutic Modalities for Cancer Treatment

Nanoparticles, leveraging their unique photothermal properties or by loading photosensitizers and photothermal agents, can facilitate the combined application of various therapeutic modalities such as PDT, PTT,RTand CDT, thereby enhancing the antitumor efficacy.

nMOFs (nanoscale metal-organic frameworks) possess crystalline structures, porosity, and tunable functionalities, making them suitable as delivery platforms for drugs and macromolecules, coupled with their photothermal properties, enabling their application in combined therapeutic approaches such as radiotherapy.[196] This study developed a surface modification strategy based on Hf-DBP nMOF for the simultaneous delivery of hydrophobic small molecule Toll-like receptor 7 agonist imiquimod (IMD) and hydrophilic macromolecular anti-CD47 antibody (αCD47), achieving modulation of tumor-associated macrophages and reversal of immune suppression. IMD polarizes immunosuppressive M2 macrophages into immunostimulatory M1 macrophages, while αCD47 promotes phagocytosis by blocking CD47 markers on tumor cells. nMOFs, acting as excellent radiosensitizers in radiotherapy-chemodynamic therapy (RT-RDT), in combination with X-ray irradiation, synergistically interact with IMD@Hf-DBP/αCD47 and anti-PD-L1 ICIs, effectively modulating the immunosuppressive TME, activating innate and adaptive immunity, and successfully eradicating primary and distant tumors in a bilateral colorectal tumor model.[197]

Nanovesicles, a class of nanoscale membranous vesicles secreted or released by cells, serve as vehicles for intercellular substance and information transfer, regulating cellular functions and signaling pathways.[199] In recent years, with the development of nanotechnology and molecular biology, nanovesicles, as an emerging biomedical tool, have been widely used in drug delivery and immunotherapy. Muhammad Younis et al developed nanovesicles named IGU-Rh-PD-1, loaded with Iguratimod (IGU) and rhodium (Rh) nanoparticles (NPs), for the synergistic treatment of lung cancer. These PD-1 nanovesicles (PD-1 NVs) recognize PD-L1 on the surface of tumor cells and reinvigorate $CD8^+$ T cells by blocking the PD-L1 signaling pathway, while IGU inhibits the mTOR signaling pathway and Rh-NPs induce cancer cell death through near-infrared (NIR) radiation. The study demonstrated that IGU-Rh-PD-1 nanovesicles effectively activate immune T cells and disrupt the PD-1/PD-L1 signaling axis, enabling more efficient recognition and elimination of cancer cells. Additionally, these nanovesicles, by targeting specific sites, inhibit the mTOR and EMT signaling pathways, thereby suppressing tumor growth.[198]

In the combined delivery of immunostimulatory proteins and photothermal agents, PTT induces tumor cell apoptosis, increases tumor antigens, and activates DCs through immunostimulatory proteins, mediating the generation of tumor-specific T cells and enhancing the immunotherapeutic effect against tumors. In this study, a novel heat-responsive nanoparticle (F-TRH) was developed, incorporating the immunostimulatory recombinant protein FimH and the near-infrared (NIR) absorber indocyanine green on its surface. Experimental results demonstrated that F-TRH induced apoptosis of CT-26 cells in vitro via photothermal effect. In mouse tumor models, after 21 days of laser treatment, tumors completely disappeared, validating the antitumor effect of F-TRH. Furthermore, increasing the temperature of near-infrared laser promoted the release of FimH from F-TRH, activating DCs, mediating the production of tumor-specific T cells, and thereby preventing the recurrence of CT-26 and 4T1 cells in the lungs of mice.[200] This novel nanoparticle formulation induces apoptosis of initially invasive tumor cells through PTT while enhancing immune responses, preventing secondary tumor invasion.

By combining ICD induced by PDT, peptide vaccines, and immune checkpoint blockade, synergistic therapy against tumors can be achieved.Upconversion nanoparticles(UPNPs) exhibit excellent chemical and optical stability as well as outstanding biocompatibility, enabling fusion with other functional materials to construct more robust functional nanosystems.[202] This study created a therapeutic strategy named UCMS@Pep-aPDL1-RB, consisting of upconversion nanoparticles core and mesoporous silica shell, loaded with photosensitizer Rose Bengal, and coated with FimH peptide. UCMS@Pep-aPDL1-RB induced ICD response upon near-infrared laser activation, enhancing the release of antitumor cytokines TNF-α and IL-12 and boosting the infiltration of specific T cells, reversing the immunosuppressive TME. The combination of peptide vaccine AL-9 and PDT exhibited synergistic effects, enhancing the antitumor efficacy of anti-PD-1 therapy.[201]

Stimuli-responsive Nanoparticles can target TME, precisely delivering small molecule drugs, nucleic acids, and photosensitizers to the TME, and achieving enhanced antitumor efficacy through targeted immunotherapy and PDT. This study reported a pH-responsive nanocarrier based on micelle complexes for tumor PDT and immunotherapy. The nanocarrier PCPP@MTPP@siPD-L1, composed of photosensitizer MTPP and siPD-L1 encapsulated in hybrid micelles of PEGCDM-PDEA and PEI-PDEA, demonstrated tumor-specific drug release and immunomodulation upon laser irradiation, leading to enhanced antitumor immune responses and PD-L1 gene silencing-mediated immunosuppression

reversal. PCPP@MTPP@siPD-L1, through the combined action of PDT-induced antitumor immune responses and RNA-mediated PD-L1 blockade, synergistically inhibited tumor growth.[203]

Moreover, by enhancing the targeting of nanodrugs through cell membrane modification and combining macrophage M1 polarization self-regulated by noble metal nanoparticles with enzyme catalysis characteristics and loading small molecule inhibitors, multiple improvements in the TME can be achieved, enhancing the therapeutic efficacy against tumors when combined with CDT. This study developed a mesoporous Au@Pt@Rh trimetallic nanoenzyme and further prepared a nanotherapeutic agent, LY-Au@Pt@Rh-CM nanocomplex, capable of immune-modulated nanocatalytic tumor therapy. LY-Au@Pt@Rh-CM nanocomplex improved the immunosuppressive TME, promoting macrophage polarization from M2 to M1, enhancing $H_2O_2$ production, and increasing catalytic activity. In vitro and in vivo experiments demonstrated that LY-Au@Pt@Rh-CM effectively reprogrammed the immunosuppressive TME, alleviated tumor hypoxia, generated highly toxic ·OH, thereby enhancing tumor therapy efficiency under laser irradiation.[204] This study provides a promising strategy for immunomodulation-enhanced tumor catalytic therapy based on multimetal nanoenzymes.

## Summary and Perspective

ICIs immunotherapy's effectiveness in combating resistance is primarily limited by the expression levels of PD-L1 on the surface of tumor cells and the infiltration of specific T cells within TME. Nanotechnology can address these limitations by not only exerting its intrinsic regulatory functions but also adsorbing and encapsulating drugs to precisely target the TME. This enhances the specificity for certain subpopulations and synchronously delivers co-stimulatory signals, promoting a more pro-inflammatory TME. Additionally, nanomedicines can improve the selectivity of drugs for tissues, organs, or cells, boasting high bioavailability, thereby enhancing therapeutic efficacy and reducing adverse effects, which improves treatment safety. The diverse design strategies of nanomedicines enable combination therapies to overcome immunotherapy resistance and enhance therapeutic outcomes. These advantages indicate that nanomedicines have significant potential in lung cancer treatment, overcoming the limitations of immunotherapy and providing an effective therapeutic avenue. The application of nanotechnology in personalized immunotherapy and precision medicine has emerged as a significant frontier in cancer treatment, with immense potential and promising prospects. Through nanotechnology, it is possible to tailor immune activation strategies based on the specific tumor characteristics of individual patients, thereby enhancing the efficacy of immunotherapy. For example, the design of nanovaccines based on individual tumor neoantigens can effectively stimulate patient-specific immune responses. Furthermore, nanotechnology can integrate genomic, proteomic, and metabolomic data to formulate personalized diagnostic and therapeutic strategies. Nanoparticles can also deliver the CRISPR/Cas9 system for precise gene editing, enabling the knockout of tumor-driving genes or the correction of mutated genes. Additionally, nanotechnology can be used to deliver siRNA or mRNA to inhibit the expression of tumor-associated genes or restore tumor-suppressor gene function.

However, some nanoparticles may exhibit toxicity or induce nonspecific immune responses, necessitating in-depth studies on their long-term biocompatibility and safety. The synthesis and modification processes of nanoparticles are complex, requiring high-precision manufacturing techniques, and present substantial challenges for commercial production. Quality control of nanoparticles is also problematic, with more complex synthesis processes demanding stricter quality control measures. Although regulatory bodies have issued guidelines for nanomedicine quality control, these guidelines may not suffice as nanomedicine design becomes increasingly complex. The in vivo distribution, metabolism, excretion, and mechanisms of action of nanoparticles are intricate and may be difficult to predict and control, necessitating comprehensive pharmacokinetic and pharmacodynamic studies. Finally, the clinical trial design for nanomedicines is complex, requiring consideration of numerous factors, potentially making the approval process more stringent and intricate.

In summary, while nanoparticles hold significant promise in overcoming resistance to ICIs and improving cancer treatment outcomes, they also present numerous challenges. Research in this field not only expands therapeutic options but also offers the potential for more effective and personalized treatment regimens for cancer patients. Future research in nanomedicine will focus on developing smarter, safer, and more precise nanomaterials to address tumor heterogeneity and treatment resistance. Interdisciplinary collaboration will play a crucial role in advancing nanomedicine from the

laboratory to clinical applications. By integrating the strengths of materials science, biomedical research, artificial intelligence, and clinical medicine, new multifunctional nanomaterials can be designed and developed to improve targeting efficiency and biodegradability. In-depth studies of the mechanisms of action of nanomaterials in cells and tumor microenvironments, along with the use of bioinformatics and AI to optimize nanomaterial design and personalized treatment plans, will drive the translational application of nanotechnology in clinical diagnostics and treatment. With continuous technological breakthroughs and interdisciplinary collaboration, nanomedicine is expected to play an increasingly prominent role in future cancer therapies, offering more precise and personalized treatment options for patients.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest in this work.

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