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REVIEW

Design principles of nanomaterials for cancer immunotherapy: a mechanistic framework across the cancer immunity cycle

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ABSTRACT Cancer immunotherapy has revolutionized oncology by harnessing the immune system to eliminate malignant cells, yet its efficacy remains constrained by insufficient antigen presentation, limited T cell infiltration, and the immunosuppressive tumor microenvironment (TME). Nanotechnology provides strategies to address these barriers by enabling the precise delivery of antigens, adjuvants, cytokines, checkpoint inhibitors, and nucleic acids, while protecting labile cargos and allowing for controlled release. Beyond serving as carriers, nanoparticles can regulate antitumor immunity by enhancing antigen presentation, promoting T cell priming and infiltration, and remodeling the TME. This review outlines key physiological barriers to *in vivo* nanoparticle delivery and the corresponding engineering optimization strategies, and systematically summarizes representative advances in using nanomaterials to enhance antigen presentation, promote T cell priming and intratumoral infiltration, and remodel the tumor microenvironment. We further discuss major translational limitations, including heterogeneous tumor accumulation, intracellular trafficking bottlenecks, safety considerations, and manufacturing consistency, and finally highlight the realizable potential of nano-immunotherapy to improve both the efficacy and specificity of cancer immunotherapy.

KEYWORDS Cancer immunotherapy; nanoparticles; tumor microenvironment; T cell activation; immune modulation

Introduction

Cancer is a complex disease driven by dysregulated cellular processes such as uncontrolled proliferation, invasion, metabolic reprogramming, and aberrant signaling[1,2]. The immune system attempts to restrain tumor growth through the cancer-immunity cycle, a sequence of events initiated by the release of tumor-associated antigens (TAAs) after tumor cell death[3,4]. These antigens are captured by antigen-presenting cells (APCs), particularly dendritic cells, which prime T cells in lymph nodes. Activated cytotoxic T lymphocytes subsequently infiltrate tumors, recognize malignant cells, and induce cell death, thereby amplifying antigen release and sustaining immune activation[5]. However, the immunosuppressive tumor microenvironment (TME), encompassing tumor-associated macrophages (TAMs), regulatory T cells, fibroblasts, and other inhibitory components, often blunts antitumor immunity[6,7].

To address these barriers, multiple immunotherapeutic strategies have been developed, including cancer vaccines, immune checkpoint inhibitors (ICIs), adoptive cell transfer, and cytokine-based therapies[8-11]. Among these, ICIs have reshaped oncology, and antibodies targeting programmed death 1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte associated protein 4 (CTLA-4) have been approved by the U.S. Food and Drug Administration for malignancies such as melanoma, non-small cell lung cancer, and hepatocellular carcinoma[12]. Despite these advances, only 10%–30% of patients respond, because many tumors remain immunologically "cold", characterized by limited immune infiltration and poor antigen presentation[13]. Combination regimens, such as ICIs with tyrosine kinase inhibitors or chemotherapy, have increased efficacy in select contexts but remain constrained by immune-related toxicities, including autoimmune injury to the liver, kidney, and gastrointestinal tract, stemming from disrupted immune tolerance[14]. *Ex vivo* engineering of autologous immune cells, although

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clinically effective in some cases, is also hampered by high cost, labor intensity, and limited scalability[15]. These limitations underscore the need for strategies that broaden response rates, decrease systemic toxicity, and counteract tumor immunosuppression.

Nanotechnology offers promising solutions to these challenges. Nanoparticles (NPs), including liposomes (e.g., PEGylated liposomes, cationic liposomes, and immunoliposomes), polymeric NPs (e.g., PLGA-based NPs, PEG-PLA micelles, and chitosan NPs), inorganic carriers (e.g., gold NPs, mesoporous silica NPs, and iron oxide NPs), and hybrid nanostructures (e.g., lipid-polymer hybrid NPs, cell membrane-coated NPs, and MOF-based hybrid NPs), can be engineered as precise carriers for ICIs, vaccines, nucleic acids, or cytokines, thus enhancing therapeutic accumulation at tumor sites while minimizing off-target effects[16]. In addition, living materials such as cells, bacteria, and algae provide emerging routes for targeted delivery. Beyond serving as delivery vehicles, nanomaterials have physicochemical properties, including size, morphology, surface chemistry, and degradability, that can directly shape cellular stress responses and innate immune signaling, which enable active participation in immunoregulation. Under appropriate formulation and administration conditions, smaller NPs generally favor lymphatic drainage and uptake by dendritic cells (DCs), whereas larger or anisotropic architectures tend to enhance local tumor retention and phagocytic capture, thereby influencing antigen presentation efficiency and the strength of innate immune priming. Moreover, surface charge and chemical functionalities regulate protein corona formation and membrane interactions, and consequently affect cellular uptake pathways, endosomal escape, and cytosolic delivery efficiency. Ligand density and spatial presentation further modulate multivalent receptor engagement and cell-type selectivity, and bias delivery toward key cellular subsets. Material composition and degradability not only determine safety profiles and *in vivo* clearance but also can influence TAM polarization, cytokine networks, and the immunosuppressive state of the TME by tuning the intensity and duration of local inflammation, thereby promoting a shift from immunologically "cold" tumors to a more inflamed phenotype[17,18]. Overall, nanotechnology offers a transformative approach to overcoming the limitations of conventional cancer immunotherapy, with the potential to expand patient benefit and enable safer, more durable treatments.

Although several high-quality reviews have summarized the applications of nanomaterials in cancer immunotherapy, including those organized around the cancer immunity cycle, this review focuses on distilling generalizable design principles that link nanoengineering parameters to underlying immunological mechanisms and translational considerations. Specifically, we first introduce the physiological barriers that NPs must overcome before exerting immune-regulatory effects. We then summarize recent advances in NP-based cancer immunotherapy, focusing on strategies to enhance antigen presentation, boost T cell priming and infiltration, and modulate the TME. Finally, we discuss the current limitations of nanomaterials in immunotherapy and outline potential directions for future development (**Figure 1**).

Overcoming physiological barriers to NP delivery

Despite their promise, NP-based therapies face substantial obstacles to clinical translation. Most clinically approved NPs in oncology remain untargeted and rely on the enhanced permeability and retention (EPR) effect for passive tumor accumulation[19,20]. However, the clinical relevance of the EPR effect is increasingly questioned, because spontaneous human tumors typically exhibit weaker vascular abnormalities and denser stromal barriers than xenograft models[21,22]. Clinical imaging studies using radiolabeled or magnetic NPs have revealed heterogeneous uptake and retention, in which many particles are either trapped extracellularly or cleared by TAMs before releasing their cargo[23,24]. Although this extracellular distribution might be sufficient for small, diffusible drugs, macromolecules such as peptides and nucleic acids require efficient cellular internalization and cytoplasmic release to achieve therapeutic benefits. Importantly, several of these limitations are less restrictive, or even advantageous, for immunomodulatory nanomedicines. In contrast to using chemotherapeutic NPs, which must achieve widespread tumor cell penetration, delivery of cytokines or adjuvants to a small subset of APCs can initiate potent systemic immune responses[25]. Moreover, many immunotherapy targets, such as APCs and TAMs, reside within the TME near blood vessels and therefore are readily accessible to NPs[26,27]. In this setting, phagocytic clearance, traditionally viewed as a barrier, can be strategically exploited to enhance NP uptake by key immune subsets. Accordingly, next-generation nano-immunotherapies are being designed not only to circumvent but also to harness these biological processes (**Figure 2**).

Building on this conceptual shift from avoiding to leveraging biological barriers, researchers have developed a range of advanced delivery strategies aimed at increasing the specificity and efficiency of NP–cell interactions. One major approach, cell-type-specific targeting, is achieved by functionalizing NP surfaces with ligands, antibodies, or polysaccharides that recognize receptors overexpressed on tumor or immune cell subsets. Representative tumor-associated receptors include human epidermal growth factor receptor-2 (HER2), folate receptor (FR), estrogen receptor (ER), and androgen receptor (AR), whereas CD11c, mannose receptor (CD206), and CD16 (FcγRIIIa) are valuable for selectively targeting immune subpopulations. These receptor-targeting strategies illustrate how surface engineering can bias NP biodistribution toward

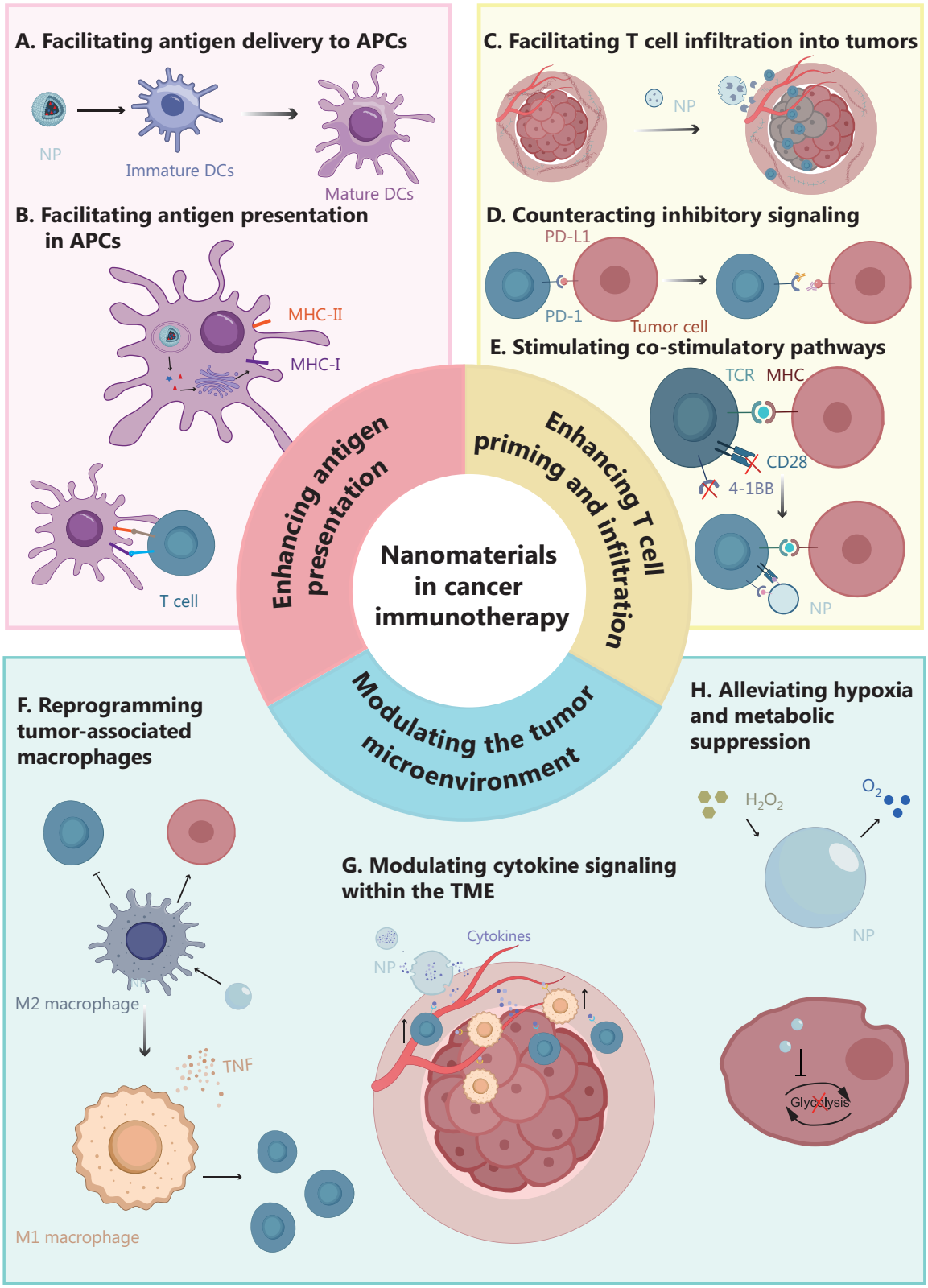


Figure 1 Schematic illustration of nanomaterial-mediated modulation of the cancer immunity cycle. This schematic illustrates the core strategies of nanomaterials in systematically enhancing cancer immunotherapy efficacy by promoting antigen presentation, boosting T cell priming and infiltration, and modulating the immunosuppressive tumor microenvironment. (A) Facilitating antigen delivery to APCs: NPs

co-deliver antigens and adjuvants that trigger dendritic cell (DC) maturation. (B) Facilitating antigen presentation in APCs: Engineered NPs facilitate endo-lysosomal escape, thereby enhancing major histocompatibility complex (MHC) class I and class II-mediated antigen cross-presentation. (C) Facilitating T cell infiltration into tumors: NPs remodel the tumor stroma and extracellular matrix (ECM), and promote deep T cell infiltration. (D) Counteracting inhibitory signaling: Targeted NPs block immune checkpoints and restore T cell cytotoxic activity. (E) Stimulating co-stimulatory pathways: Nanomodulators provide essential secondary signals that robustly activate T cells. (F) Reprogramming tumor-associated macrophages: NPs repolarize M2-type macrophages into a pro-inflammatory M1 phenotype, thereby amplifying the immune response. (G) Modulating cytokine signaling within the TME: NPs enable localized delivery of cytokines or nucleic acids, thus enhancing local immunity while significantly decreasing systemic toxicity. (H) Alleviating hypoxia and metabolic suppression: NPs alleviate the hypoxic microenvironment, inhibit tumor glycolysis, and ultimately restore T cell fitness. APCs, antigen-presenting cells; DC, dendritic cell; ECM, extracellular matrix; MHC, major histocompatibility complex; NPs, nanoparticles; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TCR, T cell receptor; TME, tumor microenvironment; TNF, tumor necrosis factor. Created in Adobe Illustrator.

desired cellular populations within the TME. For example, Liu et al. have developed immunoglobulin G-decorated immunomodulating NPs, which effectively target natural killer (NK) cells *via* immunoglobulin G/CD16 recognition[28]. Similarly, Shi et al. have reported arginine-glycine-aspartic acid-integrated mixed-shell polymeric micelles, which achieve precise tumor targeting through arginine-glycine-aspartic acid/integrin αvβ3 recognition[29]. Beyond these well-established targets, receptor expression can be dynamically regulated by external interventions, thus creating additional opportunities for targeted delivery. For example, radiotherapy upregulates P-selectin not only in irradiated tumors but also in distant unirradiated lesions, thereby enhancing the efficacy of P-selectin-targeted NPs and contributing to abscopal-like responses[30,31]. Likewise, certain chemotherapeutic agents and cytokine treatments can reshape receptor landscapes on both tumor and stromal cells. For example, doxorubicin (DOX) treatment significantly upregulates the expression of PD-L1 on tumor cells, and offers new opportunities for temporal coordination between conventional therapies and nanomedicine-based delivery[32,33].

Although targeting strategies can markedly increase NP enrichment on target cells and the likelihood of cellular uptake, whether delivery translates into therapeutic efficacy ultimately depends on the extent to which the cargo can evade intracellular degradation and reach the intended site of action. After receptor-mediated endocytosis, many NPs become sequestered in late endosomes, where cargos are readily degraded in the acidic environment, thereby significantly decreasing therapeutic efficacy[34]. To address this challenge, researchers have developed a variety of strategies to facilitate efficient cytosolic delivery. One widely explored approach is imparting positive charges to nanomaterials, thereby exploiting the "proton sponge" effect by destabilizing endosomal membranes and facilitating escape. For example, Liu et al. have reported a polyethyleneimine-based gene delivery system that rapidly escapes endosomes after being internalized by cells and achieves efficient gene transfection[35]. Similarly, Meng et al. have developed lipid NPs (LNPs) incorporating imidazole lipids that enable robust cytosolic delivery of ferroptosis-associated siRNA[36]. Another strategy involves bypassing the lysosomal pathway altogether to enable cargos to enter cells *via* membrane fusion or pore formation. For example, Liu et al. have designed an arginine-rich polymer (PTn-R2-C6) that undergoes direct membrane translocation and consequently avoids endosomal entrapment[37]. Likewise, Cai et al. have created fusogenic liposomes (Plofsomes) that fuse with cell membranes and circumvent the endo-lysosomal route, thereby preventing lysosomal degradation[38]. Collectively, these innovations highlight how rational NP design can overcome key intracellular barriers and broaden the therapeutic potential of nano-immunotherapy (**Table 1**).

Using nanoparticles to enhance cancer immunotherapy

Enhancing antigen presentation

A critical early step in the induction of tumor-specific adaptive immunity is the recognition and uptake of tumor-derived neoantigens by professional APCs, particularly DCs[39]. After activation, DCs must process and present these antigens in the context of major histocompatibility complex (MHC) molecules together with co-stimulatory signals to prime effector T cells[63]. However, this process is often insufficient, hindered primarily by the low immunogenicity of tumors. In this section, we briefly introduce recent advances in nanomaterials to address these limitations and incerase the efficacy of cancer immunotherapies.

Facilitating antigen delivery to APCs

The initiation of effective antitumor immunity strongly relies on antigen presentation by professional APCs. However, tumor cells often evade immune recognition by downregulating antigen expression or interfering with APC activation. A promising strategy to overcome this challenge is the simultaneous delivery of tumor-derived antigens and immune

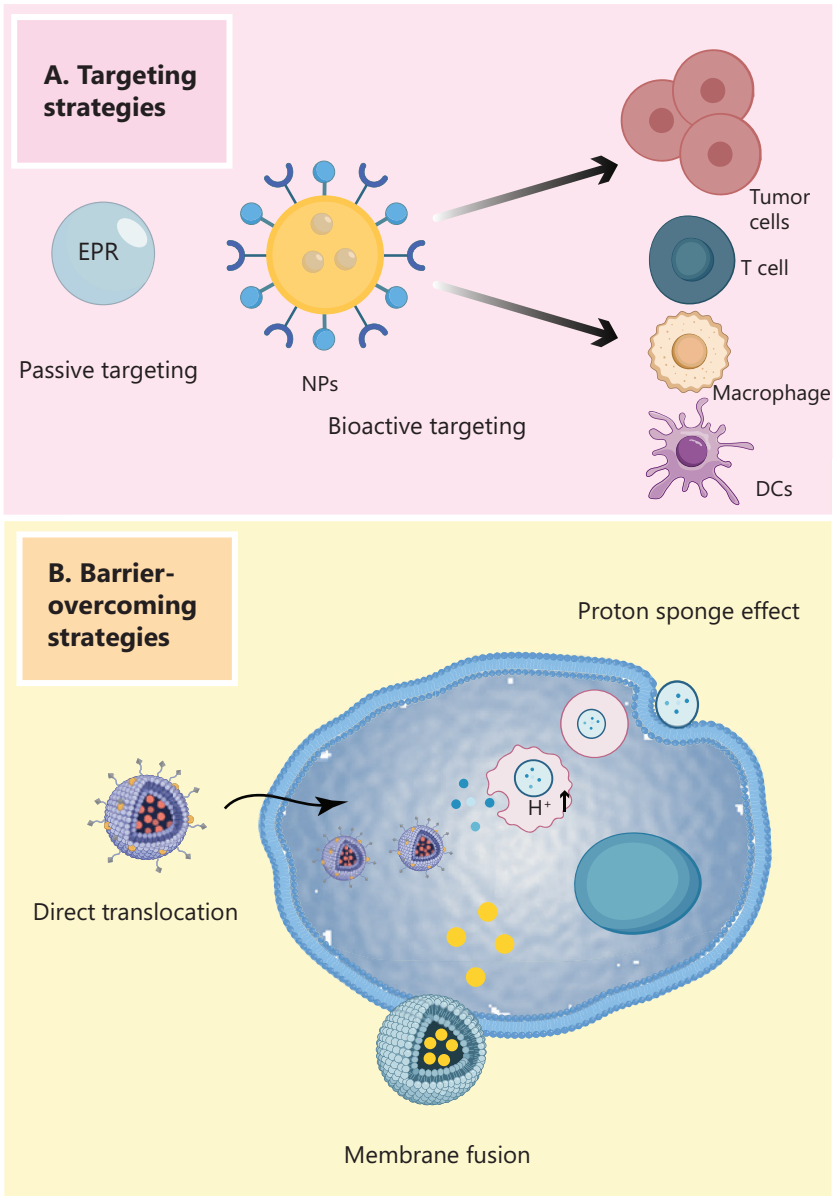


Figure 2 Nanomaterial delivery strategies for overcoming physiological and intracellular barriers. This schematic demonstrates how engineered nanocarriers bypass key delivery hurdles to reach their cellular and intracellular targets. (A) Targeting strategies: Nanoparticles accumulate at target sites *via* passive targeting (EPR effect) or receptor-mediated bioactive targeting. (B) Barrier-overcoming strategies: Engineered nanocarriers achieve efficient cytosolic delivery and evade lysosomal degradation through direct translocation, membrane fusion, or the proton sponge effect. DCs, dendritic cells; EPR, enhanced permeability and retention; NPs, nanoparticles. Created in Adobe Illustrator.

adjuvants with NP-based systems. For example, Wang et al. have reported antigen self-presenting dendritic cell vesicles, ODs/NP(cG, OVA), which have been found to significantly enhance antigen presentation in a B16-OVA melanoma mouse model. After subcutaneous injection at the tail base, ODs/NP(cG, OVA) effectively accumulated in the lymph nodes and achieved precise co-delivery of ovalbumin (OVA) and the STING agonist cyclic-di-GMP (cdGMP) to DCs *via* homology targeting. Consequently, ODs/NP(cG, OVA) elicited robust T cell-mediated antitumor immunity and significantly suppressed tumor growth[42]. Similarly, Shi et al. have reported a mannose-decorated heat shock protein (HSP)-inspired nanochaperone (nChap) for DC-targeted co-delivery of OVA and the Toll-like receptor (TLR) 7/8 agonist resiquimod (R848),

Table 1 Advanced NPs in cancer treatment

Nanomaterial	Carrier	Immune-related mechanism	Target cells	References
Tumor acidity-activated nanoimmunomodulator (TA-NIM)	pH-responsive PEG–PBAE polymer nanoparticle loaded with IL-2 plasmid and anti-PD-L1 peptide	Acid-triggered release of IL-2 and anti-PD-L1; promotes T-cell activation and checkpoint blockade	DCs, T cells	[39]
Antigen-capturing stapled liposome (ACSL/ACSL-A)	Folate-modified liposome with cross-linked polymer shell and maleimide groups	Captures TAAs after radiotherapy; enhances lysosomal escape, DC activation, and $CD8^+$ T-cell priming	DCs, T cells	[40]
HSP-mimicking nanochaperone (nChap)	Poly(ε-caprolactone) (PCL) hydrophobic core with mixed shell of poly(β-amino ester) (PAE) and mannose-modified PEG; contains TLR7/8 agonist (R848)	Mannose ligand promotes DC uptake *via* mannose receptor; PAE "proton sponge" effect enables lysosomal escape and cross-presentation; R848 induces DC maturation and T-cell activation	DCs, T cells	[41]
Dendrosome-swallowed nanovaccine [OD/NP(cG, OVA)]	Cationic Arg–Phe–PEA polyesteramide nanoparticle co-loaded with ovalbumin (OVA) and STING agonist (c-di-GMP), coated with dendritic cell-derived exosomal membrane (dendrosome) presenting OVA peptides	Co-delivery of antigen and STING agonist activates the STING–TBK1–IRF3 pathway; enhances DC maturation, type-I IFN secretion, and antigen cross-presentation, thereby eliciting strong CTL responses	DCs, T cells	[42]
PL1–OX40 mRNA nanovaccine	Phospholipid-derived lipid nanoparticle (PL1) formulated with DOPE, cholesterol, and DMG-PEG2000, delivering OX40 mRNA	Delivers OX40 mRNA to T cells and DCs, thereby enhancing OX40–OX40L co-stimulatory signaling, and increasing T-cell activation, secretion of cytokines (IFN-γ and TNF-α), and anti-tumor immunity	DCs, T cells	[43]
E3 ligase ligand-modified antigen nanovaccine (TAgD-TVac)	Lipid nanoparticle (LNP) composed of ionizable lipid 113-O12B, DOPE, cholesterol, and DMG-PEG2000, encapsulating AHPC-conjugated antigen (pVHL ligand-modified antigen)	AHPC ligand mediates E3 ubiquitin–proteasome degradation of antigen, thus enhancing MHC-I cross-presentation in DCs and priming of $CD8^+$ T cells; synergizes with PD-1 blockade for tumor immunity	DCs, T cells	[44]
H_2S-donor intelligent lipid nanoparticle (1-JK-PS-FA)	Tumor-targeting, TME-responsive LNP enabling an acid-triggered H_2S burst and activatable photodynamic (PDT) function	H_2S release normalizes the vasculature and oxygenation; enhances PDT-induced ICD and M1 polarization	Endothelial cells, TAMs, T cells	[45]
Vandetanib-loaded low-density lipoprotein nanoparticle (V@LDL NP)	Low-density lipoprotein (LDL) nanocarrier encapsulating the anti-angiogenic drug vandetanib	Sustained release of the anti-VEGFR2 inhibitor vandetanib maintains low-dose exposure, induces tumor vascular normalization, improves oxygenation, decreases fibrosis, and reprograms the TME, thereby favoring T-cell infiltration and anti-tumor immunity	Endothelial cells, macrophages, T cells	[46]
Thermo-sponge nanoparticle co-delivering PTX and IL-12 (PTX/IL-12@TSNPpH)	Acid-responsive core of mPEG-Dlinkm-PDLLA/PDLLA, with Pluronic F127 hydrophilic thermo-sponge shell; PTX loaded by nanoprecipitation, IL-12 loaded *via* low-temperature expansion of F127 shell	Acidic TME cleaves Dlinkm and triggers PTX + IL-12 release; PTX induces ICD and kills tumor cells; IL-12 activates local T cells, promotes M1 polarization of TAMs, increases IFN-γ, and decreases Tregs; overall enhances antitumor immunity and T-cell infiltration	DCs, TAMs, NK cells	[47]

Table 1 Continued

Nanomaterial	Carrier	Immune-related mechanism	Target cells	References
pH/H_2O_2 dual-responsive CRISPR/Cas13a nanoparticle (DLNP)	$PEI_{1.8}$k-HPBA/pDNA core with mPEG-b-PLys(SGD/CA) dual pH/H_2O_2-responsive polymer shell	Releases the CRISPR/Cas13a system, which silences PD-L1; reverses T-cell exhaustion and remodels the TME	Tumor cells, DCs, T cells, macrophages	[48]
pH/MMP-2 dual-sensitive micelle co-delivering anti-PD-1 and paclitaxel (sAMcP)	Micelle with MMP-2-cleavable anti-PD-1 conjugation and pH-responsive linkers, coated by a sheddable mPEG20k shield; PTX payload	PTX induces ICD; anti-PD-1 blocks PD-1/PD-L1 immune escape (particularly PD-L1 upregulation caused by PTX), thus achieving site-specific sequential release and synergistic chemo-immunotherapy; PEG shedding improves tumor accumulation	T cells, tumor cells	[49]
Antigen release agent and checkpoint inhibitor (ARAC)	Mesoporous silica nanoparticle (MSNP) core loaded with the PLK1 inhibitor volasertib, coated with polyethylenimine (PEI) and PEG, and conjugated with anti-PD-L1	PLK1 inhibition triggers PD-L1 upregulation *via* the MAPK–ERK pathway, thus causing cancer cell death and immune sensitization; anti-PD-L1 binding mediates checkpoint blockade and $CD8^+$ T-cell-dependent antitumor immunity; nanoparticle enables feed-forward targeting of PD-$L1^+$ cells	T cells, tumor cells	[50]
PL1 mRNA nanoparticle encoding OX40/CD137	PL1 phospholipid-derived LNP (authors designed and prepared phospholipid/glycolipid derivatives for mRNA delivery; PL1 used to deliver OX40/CD137 mRNA)	Delivers mRNA encoding co-stimulatory receptors OX40 or CD137, which enhances T-cell activation, proliferation, and cytokine production, and promotes dendritic cell maturation and antigen presentation	DCs, T cells	[51]
GO-APP3/28 artificial antigen-presenting particle (graphene-oxide based)	Graphene oxide (GO) micro-flakes functionalized to present anti-CD3/anti-CD28 for T-cell activation/expansion	Provides T-cell receptor and co-stimulatory signaling that increases IL-2 and CD25 expression and activates T cells	T cells	[52]
Multifunctional nanomodulator	Mesoporous silica nanoparticle (MSN) core; pH-responsive polymer shell (PMPC-based); surface anti-PD-L1 and anti-4-1BB; CTX payload	CTX decreases intratumoral Tregs; anti-PD-L1 blocks PD-1/PD-L1-mediated suppression; anti-4-1BB provides T-cell co-stimulation; increases IFN-γ/TNF-α/granzyme B; decreases TGF-β, MDSCs, and TAMs; elevates IL-12 and T cells	TAMs, T cells, tumor cells	[53]
Graphdiyne oxide (GDYO) nanosheet	Bare 2D GDYO nanosheet	Forms an intracellular protein corona that sequesters STAT3 and inhibits its activation/nuclear entry; drives TAM repolarization; boosts anti-PD-L1 therapy; increases T cells, raises IFN-γ/TNF-α/IL-12, and lowers IL-10/MDSCs	TAMs, T cells	[54]
Anti-CD47-loaded calcium carbonate nanoparticle (anti-CD47@$CaCO_3$ NP)	Calcium carbonate ($CaCO_3$) nanoparticle synthesized in PEG-b-P(Glu) solution and embedded in an in-situ-formed fibrin hydrogel after surgical tumor resection	Neutralizes acidic TME and releases anti-CD47, thus blocking CD47–SIRPα interaction; promotes macrophage phagocytosis and M1 polarization; activates dendritic cells; enhances T-cell-mediated antitumor immunity	DCs, TAMs, T cells	[55]

Table 1 Continued

Nanomaterial	Carrier	Immune-related mechanism	Target cells	References
IMD@CD/Ada–GMNP (TAM-targeted CuS nanoplatform)	Hollow CuS nanoparticle loaded with imiquimod (IMD), dual-surface modified with β-cyclodextrin (CD) and adamantane (Ada), coated with M2pep–gelatin (GM) shell	Selectively internalized by M2-like macrophages; intracellular CD–Ada host–guest interaction and sustained IMD release induce M1 polarization and enhance antitumor immune activation	DCs, TAMs, T cells	[56]
Biomimetic exosome-mimicking nanoparticle (MExo@Ce6/CAT)	Lipid–polymer hybrid nanoparticle composed of Ce6 photosensitizer, catalase (CAT), and membrane coating from M1 macrophage-derived exosomes	Generates oxygen and reactive oxygen species (ROS) under light, thus relieving hypoxia and inducing immunogenic cell death (ICD); enhances dendritic cell maturation; activates cytotoxic T cells	DCs, T cells, tumor cells	[57]
Catalytic hybrid lipid nanoparticle (Mn-LNP@RNA$^{IL\text{-}12}$)	Lipid nanoparticle embedded with Mn_3O_4 nanozyme catalytic core carrying IL-12 mRNA	Catalyzes O_2 generation; enhances IL-12 mRNA translation and CTL activation	T cells, tumor cells	[58]
PTX/IL-12@TSNP$_{pH}$	pH- and thermo-sensitive polymeric nanoparticle composed of mPEG-Dlinkm-PDLLA and Pluronic F127 for co-delivery of paclitaxel (PTX) and interleukin-12 (IL-12)	Induces immunogenic cell death; enhances T-cell activation through IL-12-mediated immune stimulation	DCs, T cells, NK cells	[59]
NP/OXA-ASP$_2$ [poly(amino acid) nanoplatform]	Poly(amino acid) nanoparticle [mPEG-P(Phe-co-Cys$_2$)] encapsulating oxaliplatin (IV)–aspirin prodrug	Inhibits tumor glycolysis; promotes immunogenic cell death, thus enhancing cytotoxic T-cell immunity	Tumor cells, T cells	[60]
NanoICD	Polyacrylamide-based nanoparticle encapsulating albumin or catalase with ER-targeting modification	Induces ER stress-mediated immunogenic cell death and DAMP release; catalase relieves hypoxia and enhances T-cell immunity	DCs, tumor cells, T cells	[61]
V(Hb)@DOX	Hemoglobin–poly(ε-caprolactone) conjugate self-assembled vesicle loaded with doxorubicin (DOX)	Targets M2 macrophages and releases O_2, thus alleviating hypoxia; reprograms the tumor microenvironment and enhances the cytotoxic T-cell response	T cells, TAMs	[62]

which has been found to markedly increase antigen presentation and tumor suppression in a B16F10-OVA melanoma mouse model (**Figure 3**)[41]. Although promising, these strategies of extracting TAAs *in vitro* and delivering them *in vivo* are often limited by insufficient antigen representativeness and instability. A highly attractive alternative approach uses NPs to capture TAAs *in situ*. For example, Liu et al. have developed maleimide/folate (FA) dual-decorated antigen-capturing stapled liposomes (ACSLs) to facilitate cross-presentation of TAAs. Under irradiation, ACSL efficiently captures the neoantigen through a click reaction between the sulfhydryl group on the antigen and the maleimide residue on the ACSL. Subsequently, ACSL directs the captured TAAs to DCs *via* FA/FR recognition, and significantly enhances antigen presentation and immune activation[40]. Similarly, Ding et al. have designed a TME-responsive covalent antigen-capturing nanoplatform (TDR848@FPB), which captures TAAs *in situ* by forming covalent bonds with nucleophilic amino acid residues in surrounding TAAs, and significantly enhances DC maturation and T cell activation[39].

Facilitating antigen presentation in APCs

After antigen delivery to APCs, a critical step in eliciting T cell activation is antigen processing and cross-presentation on MHC class I (MHC-I) molecules[64,65]. However, the inherently low efficiency of antigen presentation poses a major barrier to the development of effective tumor vaccines[66]. One promising strategy to address this challenge uses NPs to promote endo/lysosomal escape of tumor antigens, thereby increasing their cytosolic availability and enhancing MHC-I-dependent cross-presentation. For example, Xu et al. have designed lipid-based nanomachines by co-assembling photoisomerizable amphiphilic Azo-based lipidoids and helper lipids. After internalization by DCs, the lipid-based nanomachines adhere to the endo/lysosomal membrane, where UV/visible light irradiation triggers continuous trans–cis–trans isomerization of azobenzene lipids and mechanically disrupts the compartment. This process enables efficient cytosolic release of the encapsulated OVA, which subsequently forms complexes with MHC-I molecules in DCs, thereby achieving robust cross-presentation and potent T cell activation[43]. Importantly, after endo/lysosome escape and before loading onto MHC-I binding grooves, exogenous antigens must be degraded into short peptides of 8–13 amino acids *via* the ubiquitin-proteasome pathway. Therefore, promoting proteasomal degradation of TAAs further enhances antigen presentation and antitumor immunity. Moreover, Xu et al. have developed a tumor vaccine (TAgD-YVac) designed to promote targeted antigen degradation and increase cross-presentation. In this system, the model antigen OVA is first conjugated with an adaptor ligand (OVA-AHCP) that recruits E3 ubiquitin ligase, and is then encapsulated in lymph node-targeting LNPs. After uptake by APCs, OVA-AHCP is released from the LNPs, engages E3 ubiquitin ligase under the guidance of AHCP, undergoes targeted proteasomal degradation, and is ultimately cross-presented as OVA-derived peptides on MHC-I molecules with high efficiency, thereby eliciting robust T cell responses[44]. Collectively, these results demonstrate that nanomaterials play critical roles in enhancing cancer vaccine efficacy by promoting antigen uptake, endo/lysosomal escape, targeted degradation, and MHC-I-mediated cross-presentation by APCs.

Enhancing T cell priming and infiltration

Nanomaterials, through their ability to enhance antigen uptake and cross-presentation by APCs, facilitate the progression of antitumor immune responses into an effector phase dominated by T cells. Activated $CD8^+$ T cells are the primary effectors of tumor-specific adaptive immunity. Once primed by APCs, these cells must infiltrate the tumor stroma and maintain sustained activity within the TME to achieve effective antitumor responses[67]. However, tumors often form a hostile TME or secrete immunosuppressive cytokines that hinder T cell infiltration. In addition, tumor cells may upregulate inhibitory ligands (e.g., PD-L1) or downregulate co-stimulatory signals (e.g., CD28), thereby impairing APC function and restraining the activation of infiltrating $CD8^+$ T cells[68]. In this section, we summarize recent advances in nanomaterials designed to overcome these barriers, with a focus on strategies to promote T cell priming, infiltration, and functional persistence within the TME.

Facilitating T cell infiltration into tumors

Even when robustly primed, effector T cells must successfully infiltrate tumor tissue to exert cytotoxic functions. However, the physical and biochemical barriers of the TME, including abnormal vasculature, dense extracellular matrix (ECM), and immunosuppressive stromal components, substantially hinder lymphocyte entry. Consequently, many tumors exhibit an "immune-excluded" phenotype, in which activated T cells accumulate at the tumor margin but do not penetrate the parenchyma, thus resulting in ineffective immune surveillance and poor therapeutic outcomes[45]. Therefore, strategies that promote T cell infiltration are indispensable for effective cancer immunotherapy. One promising approach is enzymatic degradation of the ECM. For example, Zhu et al. have developed a calcium phosphate (CaP) nanocarrier for tumor-targeted co-delivery of hyaluronidase (HAase), IL-12, and anti-PD-L1. After reaching the acidic TME, the CaP matrix dissociates and releases all 3 cargo molecules. HAase degrades the ECM, thereby decreasing physical barriers, anti-PD-L1 blocks the PD-1/PD-L1 axis and relieves immune suppression, and IL-12 boosts local immune activation, thus collectively facilitating deeper T cell infiltration and augmenting antitumor immunity[47]. Another complementary strategy is normalizing the tumor vasculature or transiently increasing vascular permeability. For example, Yuan et al. have engineered a nano-system (V@LDL NPs) for

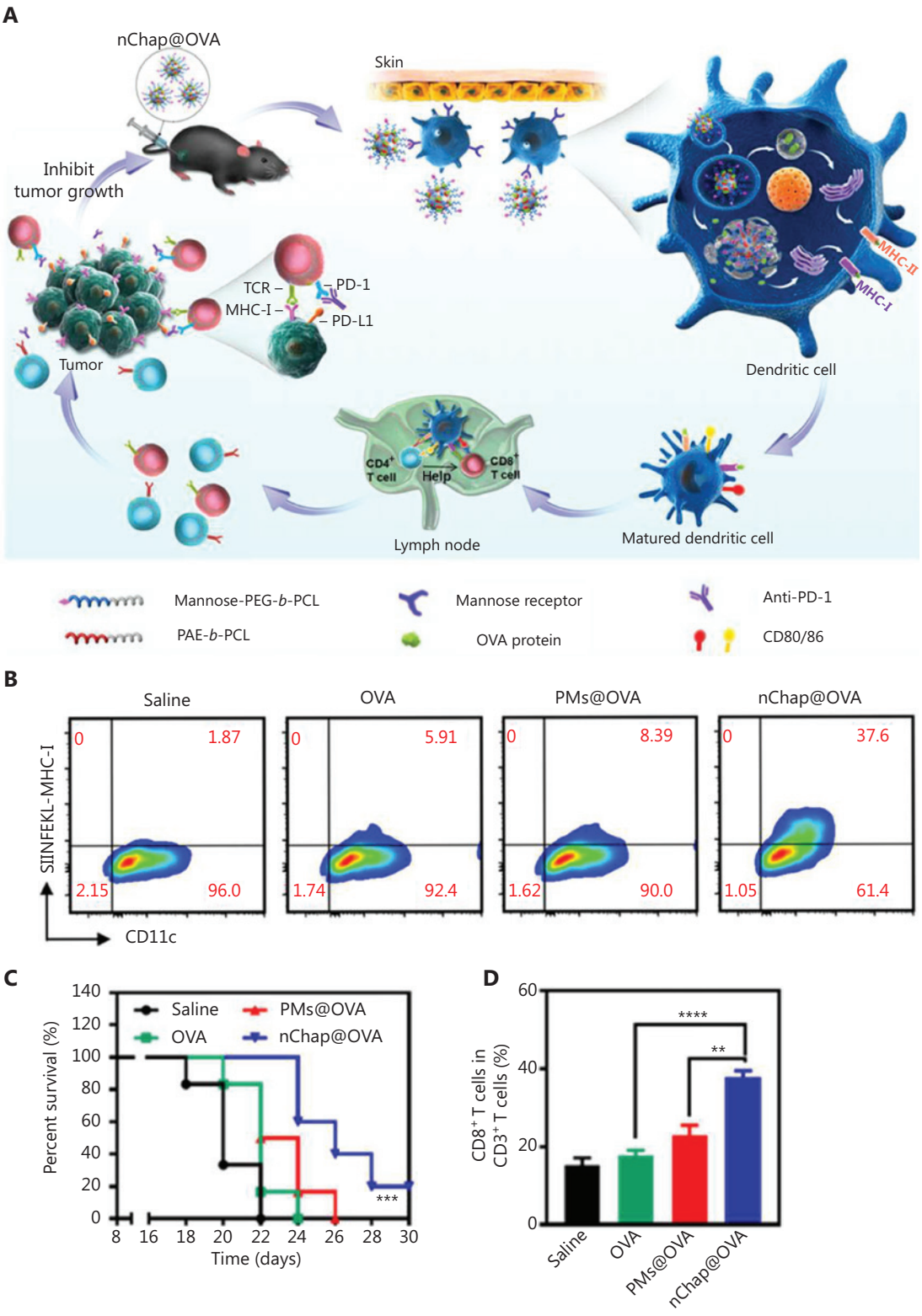


Figure 3 Mimetic heat shock protein nanochaperone (nChap) as a potent nanovaccine for enhanced cancer immunotherapy. This figure illustrates the design, mechanism, and therapeutic efficacy of a self-assembled nanochaperone (nChap) inspired by heat shock proteins (HSPs) to boost antitumor immune responses through efficient antigen delivery and cross-presentation. (A) Schematic illustration: The nanovaccine (nChap) captures antigens (OVA) *via* its hydrophobic surface. After injection, it targets dendritic cells (DCs) through mannose receptors.

Inside the cell, nChap triggers lysosomal escape; subsequently, antigens released into the cytoplasm activate T cells in the lymph nodes. This process, combined with anti-PD-1 therapy, leads to powerful tumor destruction. (B) Antigen presentation: Flow cytometry data indicate that nChap@OVA treatment results in much higher antigen presentation (37.6%) on the surface of DCs than other treatments. (C) Therapeutic efficacy: In a melanoma mouse model, the nChap@OVA group, compared with control groups, shows a significantly increased survival rate over 30 days. (D) T cell activation: nChap@OVA increases the percentage of tumor-killing $CD8^+$ T cells within tumor tissue compared to control groups. DCs, dendritic cells; MHC, major histocompatibility complex; nChap, nanochaperone; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PEG, polyethylene glycol; PMs, polymeric micelles; TCR, T cell receptor; OVA, ovalbumin[41]. Copyright, 2020 American Chemical Society.

sustained intratumoral release of the anti-VEGFR2 inhibitor vandetanib. After intratumoral injection, V@LDL NPs gradually release vandetanib within tumors, and consequently downregulate VEGFA and VEGFR2 while upregulating the vascular normalization factor VEGFR1. This remodeling of the vascular network induces vessel normalization and significantly enhances T cell infiltration into the tumor parenchyma[46]. Similarly, Ye et al. have developed an intelligent lipid NP (1-JK-PS-FA) that selectively responds to tumor-specific cues and releases H_2S. The released H_2S effectively reprograms the TME by promoting angiogenesis, increasing vascular permeability, and decreasing interstitial fluid pressure, thereby facilitating CTL infiltration[69].

Counteracting inhibitory signaling

The immunosuppressive TME, largely governed by immune checkpoints such as PD-1/PD-L1 and CTLA-4, severely restricts T cell activity. Although ICIs have demonstrated notable clinical success, their systemic administration often induces immune-related toxicities[70]. Nanotechnology offers a promising strategy to localize ICIs within tumors, thereby increasing their therapeutic index. For example, Shuai et al. developed pH- and matrix metalloproteinase (MMP-2)-responsive polymeric micelles (sAMcPs) that co-deliver anti-PD-1 and the chemotherapeutic paclitaxel (PTX). Within the TME, sAMcP releases anti-PD-1 in response to the overexpressed MMP-2. Its positively charged micelle core is subsequently internalized by tumor cells and releases PTX in response to lysosomal acidity. Consequently, sAMcP significantly enhances T cell-mediated antitumor immunity and markedly suppresses tumor growth[49]. Similarly, Yantasee et al. have developed silica NPs for co-delivery of a polo-like kinase 1 (PLK1) inhibitor, volasertib, and anti-PD-L1, thus significantly enhancing tumor suppression in a non-small cell lung cancer mouse model[50]. Beyond the delivery of ICIs, gene-editing tools offer an alternative strategy to silence or knock down inhibitory ligand expression on tumor cells. For example, Liu et al. have developed dual-locking NPs (DLNPs) for tumor-targeted delivery of clustered regularly interspaced short palindromic repeat (CRISPR)/CRISPR-associated (Cas) enzyme-PD-L1 systems (**Figure 4**). In the TME, the acidic pH and elevated H_2O_2 levels synergistically unlock DLNPs, thus enabling precise, tumor-specific gene editing and effective PD-L1 disruption. This intervention relieves immune suppression, restores T cell activity, and elicits potent antitumor immune responses[71]. Beyond gene editing, protein degradation technologies provide another means of decreasing inhibitory ligand expression. For example, Liu et al. have developed a lysosome-targeting chimera nanoplatform that selectively degrades PD-L1 on tumor surfaces by shuttling it from the plasma membrane into lysosomes, thereby markedly enhancing antitumor immunity in a B16F10 melanoma mouse model[72].

Stimulating co-stimulatory pathways

Blocking inhibitory signals can restore T cell activity, but full and durable activation additionally requires sufficient co-stimulatory input. In the TME, however, the frequent downregulation of co-stimulatory ligands predisposes T cells to functional exhaustion[73]. Strategies that reinforce co-stimulatory signaling are therefore essential to sustain T cell proliferation, survival, and effector function. Nanomaterials offer a promising platform for delivering agonistic antibodies or genetic modulators to boost these pathways while minimizing systemic toxicity. For example, Huang et al. have developed an antigen-presenting platform (GO-APP) by anchoring anti-CD3 and anti-CD28 onto graphene oxide. Through dual interactions with CD3 and CD28 on T cells, GO-APP effectively mimics the immune synapses formed between APCs and T cells, and leads to robust T cell proliferation while preserving multifunctionality and potent effector activity[52]. Similarly, Liu et al. have designed a multifunctional nano-modulator co-decorated with anti-PD-L1 and anti-4-1BB, which simultaneously blocks the PD-1/PD-L1 pathway and activates the 4-1BB co-stimulatory pathways, and ultimately significantly enhances antitumor immunity[53]. In addition, upregulating the expression of co-stimulatory receptors on T cells with gene-editing tools provides an alternative strategy to facilitate T cell activation. For example, Dong et al. have reported a phospholipid NP (PL-1) that efficiently delivers OX40 mRNA to tumor-infiltrating T cells and leads to a 47.4% increase in OX40 expression on T cell surfaces. This intervention markedly boosts T cell-mediated antitumor immunity and has achieved a 60% complete response rate in an A20 lymphoma model[51]. Collectively, these results demonstrate that nanomaterials can systematically modulate multiple steps in the antitumor immune cascade, thus increasing T cell priming, infiltration, and functional persistence, and ultimately enhancing both the magnitude and durability of antitumor immunity.

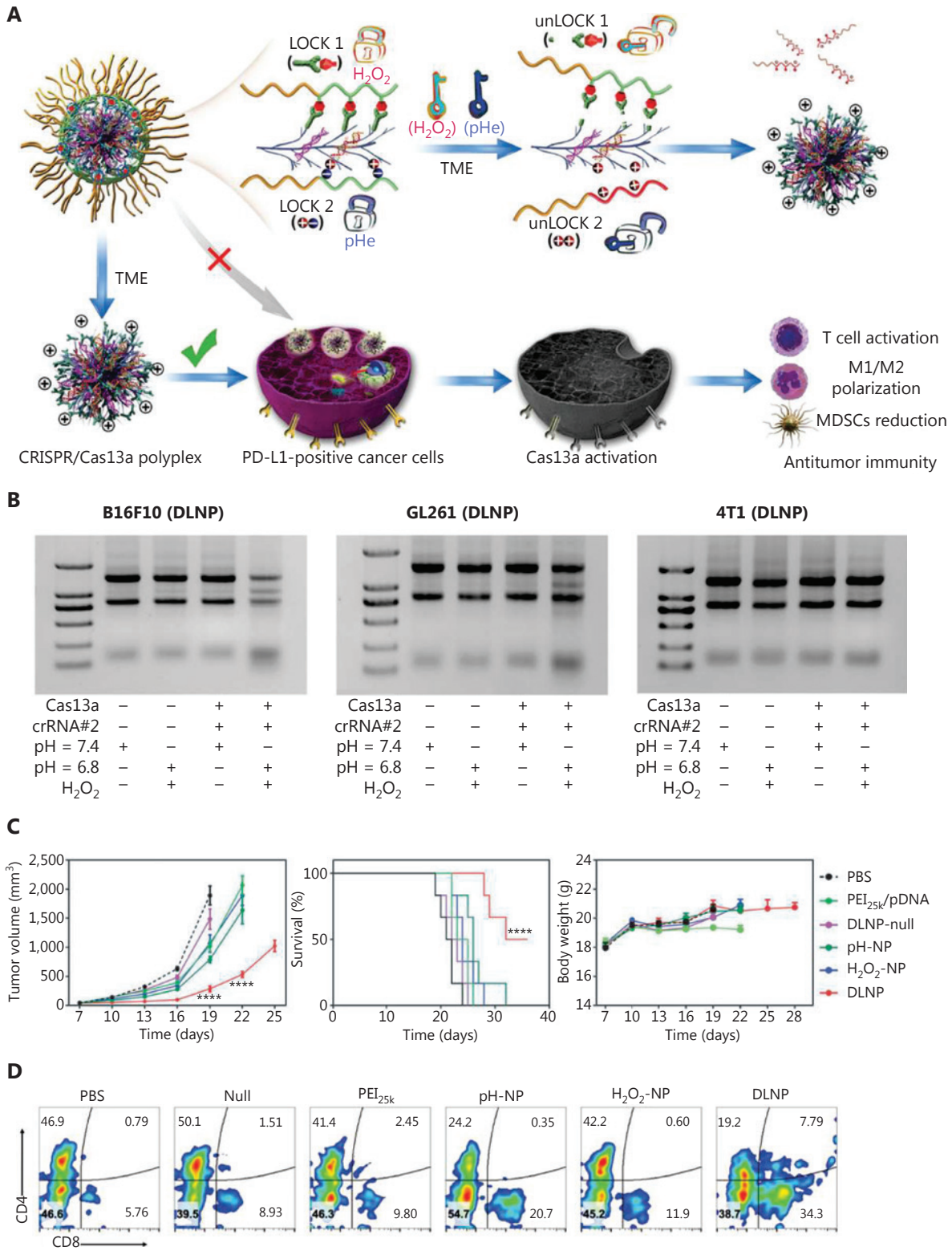


Figure 4 Dual-locking nanoparticles (DLNPs) restrict CRISPR/Cas13a activation for precise cancer immunotherapy. This figure demonstrates the design and efficacy of a dual-responsive nanoplatform that activates gene editing only in the tumor microenvironment (TME) and consequently disrupts the PD-1/PD-L1 pathway. (A) Schematic illustration: DLNP encapsulates the CRISPR/Cas13a system within a polymer shell that remains stable in normal tissues. Activation requires 2 specific TME "keys": low pH and high H_2O_2 levels. Once "unlocked", the system

is released into PD-L1-positive cancer cells, where it triggers cell death and activates antitumor immunity. (B) Gene disruption: RNA gels confirm that DLNP-induced RNA cleavage (Cas13a activity) is restricted to PD-L1$^+$ cells (B16F10, GL261) only under TME-mimicking conditions, whereas no effect is observed on PD-L1-negative cells (4T1). (C) Therapeutic efficacy: *In vivo* tumor volume, survival rate, and body weight evaluation. (D) T cell activation: Flow plots reveal that DLNP treatment leads to a notable sixfold increase in CD8$^+$ T cell infiltration (34.3%), thereby reversing tumor immune evasion. CRISPR, clustered regularly interspaced short palindromic repeats; MDSCs, myeloid-derived suppressor cells; PBS, phosphate-buffered saline; PD-L1, programmed death-ligand 1; pDNA, plasmid DNA; PEI, polyethylenimine; DLNPs, dual-locking nanoparticles; TME, tumor microenvironment.[71] Copyright 2019, Wiley.

Modulating the tumor microenvironment

Effective antitumor immunity depends not only on the activation and infiltration of effector cells but also on maintaining their functionality within the TME. However, the aberrant vasculature of tumors and the elevated aerobic glycolysis of cancer cells together generate a hypoxic and acidic milieu that severely restricts immune cell infiltration and cytotoxic activity. Concurrently, immunosuppressive cell populations, including regulatory T cells (Tregs), M2-polarized TAMs, and tumor-associated fibroblasts, further attenuate antitumor responses and promote tumor progression through diverse mechanisms[74]. In this section, we summarize recent advances in using nanomaterials to selectively target these immunosuppressive cell populations and remodel the TME, thereby enhancing the overall efficacy of cancer immunotherapy.

Reprogramming tumor-associated macrophages

M1-type TAMs not only secrete abundant pro-inflammatory cytokines, such as tumor necrosis factor (TNF), which promote CTL responses and suppress tumor growth, but also upregulate genes associated with antigen processing and presentation, thereby facilitating T cell activation and tumor eradication. However, within the TME, TAMs are polarized predominantly toward an immunosuppressive M2 phenotype that fosters tumor progression and inhibits antitumor immunity[75,76]. Reprogramming TAMs toward a pro-inflammatory (M1) state has therefore emerged as a promising strategy to remodel the TME and enhance immune responses. For example, Gu et al. have developed a sprayed fibrin gel composed of a thrombin solution and anti-CD47-loaded $CaCO_3$ NPs (aCD47@$CaCO_3$). When sprayed into the tumor resection cavity, the mixtures rapidly form a fibrin gel *in situ*, and $CaCO_3$ continuously neutralizes local acidity, thereby driving TAM repolarization toward the M1 phenotype[55]. Similarly, Chen et al. have engineered locally immunomodulatory graphene dioxide (GDYO) nanosheets that reprogram TAMs by inhibiting the intracellular activation of signal transducer and activator of transcription 3 (STAT3)[54]. In addition, several small-molecule adjuvants have been used to modulate TAM polarization. For example, Wang et al. have reported a multifunctional nanoplatform functionalized with an M2 macrophage-binding peptide to selectively deliver imiquimod (IMD) to TAMs. This system enables sustained intracellular release of IMD, and achieves durable M1 polarization and long-term alleviation of the immunosuppressive microenvironment[56]. Overall, targeted TAM reprogramming is expected to reinforce local pro-inflammatory signaling and enhance antigen presentation, thereby amplifying T cell-mediated immune responses. However, clinical translation will require careful consideration of off-target inflammatory risks associated with unintended immunostimulant leakage, as well as challenges associated with batch reproducibility and process controllability during the scale-up manufacturing of multicomponent nanoplatforms.

Modulating cytokine signaling within the TME

Cytokines, bioactive small proteins secreted by both immune and non-immune cells, mediate intracellular communication, and coordinate the initiation, amplification, and resolution of immune responses. However, the frequently downregulated cytokine expression in the TME limits immune activation and effector function[77]. Using nanomaterials to deliver cytokines directly to tumor tissues offers an effective strategy to overcome these challenges. For example, Zhang et al. have developed an acid-sensitive nanocarrier (TSNPs) for tumor-targeted co-delivery of PTX and the pro-inflammatory cytokine IL-12. This platform prolongs the systemic circulation of IL-12 and enables decreased dosing frequency, thereby promoting local T cell activation, inducing TAM repolarization, and enhancing antitumor immunity[59]. Similarly, Shi et al. have presented a nanochaperone (P-nChap) for tumor-targeted delivery of denatured IL-12. After reaching the TME, P-nChap facilitates refolding of denatured IL-12 into its native conformation and subsequent release, thereby mitigating systemic toxicity and eliciting robust T cell-mediated antitumor responses[57]. In addition, gene-editing approaches can provide a sustained local source of immunostimulatory proteins within tumors. For example, Yu et al. have designed hybrid lipid NPs (Mn-LNPs) for tumor-targeted delivery of circular RNA encoding IL-12. After internalization, Mn-LNPs effectively scavenge intracellular reactive oxygen species (ROS) and elevate ATP levels. Consequently, enhanced RNA translation efficiency and durable IL-12 production ultimately lead to remodeling of the immunosuppressive TME and boosting of cancer immunotherapy efficacy[58]. Likewise, Li et al. have constructed novel lipid NPs, U-101-LNPs, for tumor-targeted delivery of IL-2F mRNA, which markedly increase IL-2 expression within

the TME and significantly enhance antitumor immunity[78]. Despite the high efficiency of LNPs for intratumoral mRNA delivery, their *in vivo* fate is strongly influenced by protein corona formation and apolipoprotein E (ApoE)-mediated pathways; consequently, off-target hepatic accumulation and associated toxicity often result. To address this translational bottleneck, Guo et al. have developed morphologically engineered, flower like lipid NPs termed RLNPs. By partially replacing conventional cholesterol with R-cholesterol, RLNP effectively decreases ApoE-mediated liver uptake and enables efficient local transfection while markedly mitigating IL-12-associated hepatotoxicity. This strategy provides a feasible approach to expanding the therapeutic safety window for intratumoral cytokine mRNA delivery[79].

Alleviating hypoxia and metabolic suppression

The TME is characterized by severe hypoxia and metabolic dysregulation, primarily resulting from aberrant tumor vasculature and uncontrolled tumor cell proliferation[80-82]. These conditions strongly suppress antitumor immunity by impairing T cell metabolism; facilitate the accumulation of immunosuppressive metabolites such as lactate and adenosine; and drive macrophages and MDSCs toward immunosuppressive phenotypes. Moreover, oxygen deprivation restricts the production of ROS and the activity of cytotoxic molecules such as perforin and granzyme B in CTLs, thereby diminishing their killing capacity. Strategies that alleviate hypoxia or reprogram tumor metabolism are therefore critical to restoring immune cell functionality and enhancing immunotherapy efficacy[62]. For example, Liu et al. have developed immune-modulating NPs (nanoICD/CAT) by encapsulating catalase (CAT) within a rationally designed polymer shell. After reaching the tumor tissues, the polymer layers effectively induce immunogenic cell death (ICD) of tumors, while the encapsulated CAT decomposes intratumoral H_2O_2 into oxygen, thereby relieving hypoxia and synergistically amplifying T cell-mediated antitumor immunity[61]. Similarly, Gao and colleagues have designed a TME-responsive metal-phenolic nanozyme, termed RPP nanozyme. By catalyzing the conversion of H_2O_2 into ROS and oxygen, while simultaneously decreasing intracellular glutathione (GSH) and lactate levels, the RPP nanozyme effectively disrupts redox homeostasis in tumor cells and consequently increases immunotherapeutic efficacy. Notably, beyond enzyme-mediated oxygen generation, direct oxygen delivery provides an alternative strategy to rapidly relieve intratumoral hypoxia[83]. For example, Zhou et al. have designed a biomimetic nano red blood cell system [V(Hb)@DOX] for the co-delivery of DOX and oxygen. After accumulation in tumor tissues, V(Hb)@DOX rapidly responds to acidic conditions by releasing both DOX and oxygen, thus effectively alleviating hypoxia and potentiating cancer immunotherapy[62]. Moreover, nanocarriers designed to deliver metabolic inhibitors offer an alternative strategy to reshape TME by interfering with tumor glycolysis, decreasing nutrient competition, and rebalancing immune–tumor metabolic interactions. For example, Chen et al. have reported a glucose metabolism-targeted formulation (NP/OXA-ASP2) for co-delivery of oxaliplatin (IV) and an aspirin prodrug to suppress glycolysis and enhance chemo-immunotherapy. In colorectal cancer, NP/OXA-ASP2 treatment has been found to inhibit glycolysis more effectively than the combination of free drugs, by decreasing lactate efflux by 27.6% and increasing the proportion of $CD8^+$ T-cells by 153%, thereby markedly boosting antitumor immunity[60]. Collectively, through selective intervention targeting immunosuppressive cell populations, cytokine signaling, and hypoxia associated stress, nanomaterials provide an engineering toolkit to create a microenvironment conducive to sustained T cell function.

Summary and perspectives

Nanotechnology has emerged as a powerful platform for advancing cancer immunotherapy. NPs, by enabling precise delivery of antigens, adjuvants, cytokines, checkpoint inhibitors, and gene-editing tools, address many limitations of conventional treatments. Their small sizes, tunable surfaces, and multifunctionality allow them to cross physiological barriers, penetrate tumors, and provide sustained or controlled release of therapeutic cargos. Beyond delivery, NPs can modulate antitumor immunity by promoting antigen presentation, enhancing T cell priming and infiltration, reshaping the TME through reprogramming immunosuppressive cells, regulating cytokine signaling, and alleviating hypoxia and metabolic stress. Owing to these unique capabilities, NPs-based immunomodulatory strategies have demonstrated robust antitumor efficacy across diverse preclinical studies. For example, InnoPCV, a personalized tumor neoantigen mRNA vaccine, entered clinical trials in 2024. This platform integrates next-generation sequencing of patient tumor samples with computational prediction to identify candidate neoantigens, which are subsequently encoded into mRNA and delivered *via* LNPs. This approach elicits broader and more potent neoantigen-specific T-cell responses, thereby enhancing antitumor immunity. In agreement with this mechanism, InnoPCV has induced marked neoantigen-specific T-cell responses in patients with advanced non-small cell lung cancer (NCT06497010).

Despite these advantages, several barriers limit the clinical translation of NP-based immunotherapies. Tumor heterogeneity poses a fundamental biological barrier to effective cancer immunotherapy. Among diverse tumor phenotypes, immunologically “cold” tumors predominate in most solid malignancies and are a major contributor to immune tolerance. These tumors are characterized by limited immune cell infiltration, low antigenicity, and dense stromal architecture, which collectively impair immune priming and activation. Consequently, restricted immune access and physical stromal barriers further limit immune amplification and ultimately

constrain therapeutic efficacy. Despite the considerable promise of NP-based immunotherapies, multiple barriers continue to hinder their clinical translation. Tumor uptake of NPs is often highly heterogeneous, and many preclinical strategies still rely on passive delivery *via* the EPR effect. However, even in relatively permeable tumors, the vascular endothelium remains a substantial obstacle to efficient NP extravasation. After cellular internalization, therapeutic cargos are frequently trapped within endosomal compartments, thus decreasing cytosolic availability and therapeutic activity. Additional technical challenges include achieving precise cell-type targeting, coordinating NP-based interventions with conventional therapies, and exerting fine control over intracellular cargo release. Although multifunctional nanoplatforms offer synergistic and multimodal therapeutic benefits, increased system complexity places substantial demands on scalable manufacturing, process control, and batch-to-batch reproducibility. Finally, unresolved concerns regarding the long-term safety, biodegradation, and potential immunogenicity of nanomaterials remain major obstacles to their widespread clinical application.

In the future, several strategies may help overcome these limitations in NP-based cancer immunotherapy. i) Bioinspired nanomaterials, by emulating natural biological structures and processes, such as cell membranes, extracellular vesicles, or pathogen-associated patterns, are expected to play an increasingly important role in increasing immune recognition and delivery efficiency, and achieving more balanced immune activation with diminished off-target toxicity. Additionally, the development of nanomaterials for co-delivering complementary immunomodulators or harnessing endogenous immune pathways may elicit stronger and more durable antitumor responses. ii) The integration of personalized nanovaccines with artificial intelligence-driven analytics has substantial promise. Advances in neoantigen identification, NP design optimization, and predictive modeling of biodistribution and immune responses could enable patient-specific vaccination strategies tailored to the unique tumor and immune landscapes of individual patients. iii) Combining nanotechnology with established therapies, engineered cell therapies, or emerging modalities such as mRNA vaccines and CRISPR-based interventions may expand the therapeutic landscape. iv) Fostering sustained collaboration across nanotechnology, immunology, and oncology may realize the full potential of nano-immunotherapy, by achieving safe, durable, and broadly effective cancer treatments.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the analysis: Yang Liu, Zhanzhan Zhang.
Collected the data: Nana Feng.
Wrote the paper: Yating Bai, Zhihao Lan, Yang Lin, Zhanzhan Zhang.

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