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Review

Targeted Nanophotoimmunotherapy Potentiates Cancer Treatment by Enhancing Tumor Immunogenicity and Improving the Immunosuppressive Tumor Microenvironment

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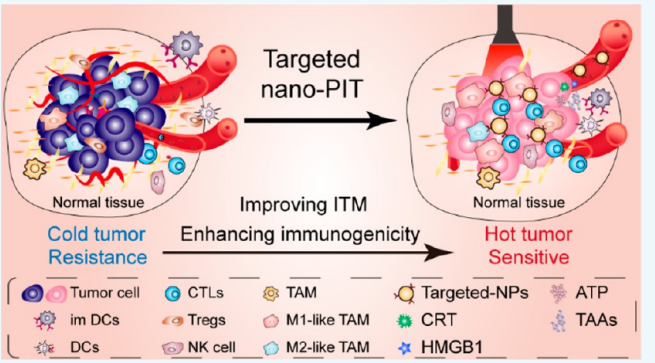
ABSTRACT: Cancer immunotherapy, such as immune checkpoint blockade, chimeric antigen receptor, and cytokine therapy, has emerged as a robust therapeutic strategy activating the host immune system to inhibit primary and metastatic lesions. However, low tumor immunogenicity (LTI) and immunosuppressive tumor microenvironment (ITM) severely compromise the killing effect of immune cells on tumor cells, which fail to evoke a strong and effective immune response. As an exogenous stimulation therapy, phototherapy can induce immunogenic cell death (ICD), enhancing the therapeutic effect of tumor immunotherapy. However, the lack of tumor targeting and the occurrence of immune escape significantly reduce its efficacy *in vivo*, thus limiting its clinical application. Nanophotoimmunotherapy (nano-PIT) is a precision-targeted tumor treatment that co-loaded phototherapeutic agents and various immunotherapeutic agents by specifically targeted nanoparticles (NPs) to improve the effectiveness of phototherapy, reduce its phototoxicity, enhance tumor immunogenicity, and reverse the ITM. This review will focus on the theme of nano-PIT, introduce the current research status of nano-PIT on converting "cold" tumors to "hot" tumors to improve immune efficacy according to the classification of immunotherapy targets, and discuss the challenges, opportunities, and prospects.



1. INTRODUCTION

Cancer has become one of the most challenging diseases globally because of its high incidence, high mortality, and high recurrence rate.[1] Traditional cancer treatments such as surgery, radiotherapy, and chemotherapy cannot effectively eradicate tumors, especially metastatic tumors. Moreover, there are serious side effects on the human body. Burnet and Thomas founded the immunosurveillance hypothesis, which suggests the immune system can play a surveillance role in identifying and destroying any "foreign" components or mutated cells that express new antigens to maintain the stability of the body's internal environment.[2] Tumors may occur when the immune surveillance function is low, and the "foreign" components or mutated cells are not effectively removed.[3] Cancer immunotherapy is the application of immunological principles and methods to improve the immunogenicity of tumor cells and the sensitivity of effector cells to enhance the antitumor immune response. Although immune checkpoint blockade (ICB), chimeric antigen receptor T (CAR-T) cell therapy, cytokine therapy, and vaccines have great success in clinical studies, cancer immunotherapy also has some problems. Immunotherapy is only effective in some patients. Responders present with "hot" (immune-inflamed) tumors characterized by infiltration of immune cells represented by T lymphocytes, while nonresponders may present with "cold" (immune-excluded/immune-desert) tumors characterized by the absence or exclusion of immune cells represented by T cells in the tumor parenchyma.[4,5] The low response rate is attributed to the LTI and ITM. The LTI cannot induce a strong and effective immune response. ITM severely affects the killing effect of immune cells on tumor cells. To address this scientific question, researchers have used immunotherapy with other treatments to enhance tumor immunogenicity or reverse the immunosuppressive microenvironment from "cold" to "hot" tumors to achieve powerful antitumor effects.

As an exogenous stimulation therapy, phototherapy can induce ICD to enhance immunotherapy's therapeutic effect.[6] Phototherapy, including photodynamic therapy (PDT) and photothermal therapy (PTT), is a kind of antitumor therapy

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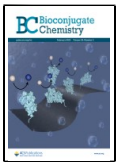
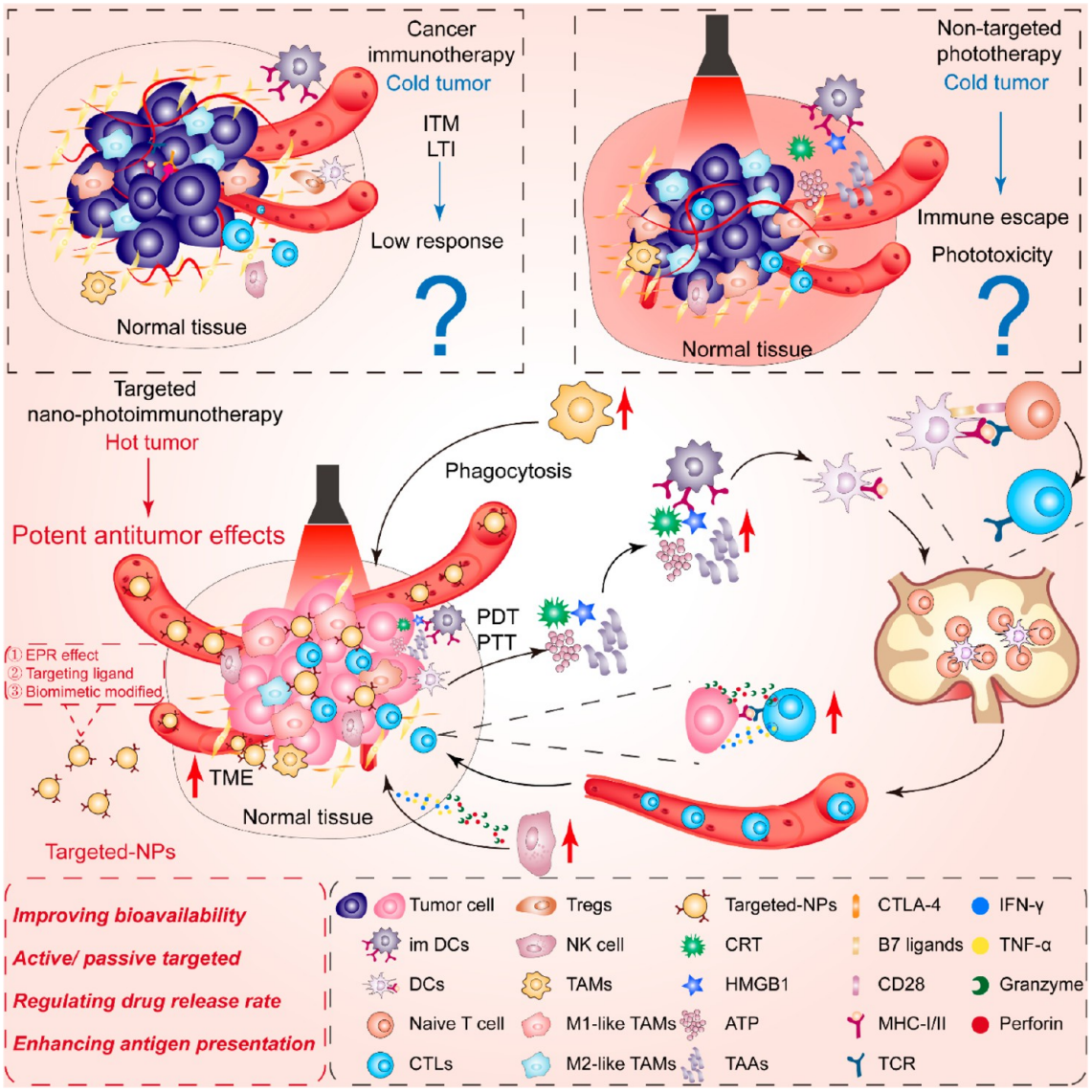


Scheme 1. Schematic Illustration of nano-PIT[a]



[a]LTI and ITM result in a low response rate to cancer immunotherapy. As an exogenous stimulation therapy, phototherapy, after laser irradiation, can produce cellular debris, generate TAAs, release DAMPs, induce ICDs, stimulate immune cells (DCs, macrophages, NK cells) to produce antitumor immune effects, and enhance the efficacy of tumor immunotherapy. However, phototherapy can also cause immune escape, and the phototoxicity of non-targeted phototherapy can damage normal tissue. Passive/active targeted NPs for targeted nano-PIT to co-deliver phototherapeutic agents and various immunotherapeutic agents to precise targeting of tumors through reducing phototoxicity, relieving immunosuppression, increasing tumor immunogenicity, and reversing ITM.

with minimally invasive, less toxic, and highly selective.[7] Phototherapy mainly depends on phototherapeutic agents to convert light into heat energy or produce reactive oxygen species (ROS). Then phototherapy can cause a series of damage to tumor cells and achieve an antitumor effect. Then, tumor cells release tumor-associated antigens (TAAs) and damage-related molecular patterns (DAMPs), stimulating immune cells to produce antitumor immune effects.[6] It has been demonstrated that phototherapy can lead to immune escape, limiting its antitumor effects, even though it can kill tumor cells and trigger specific immune responses. In addition, most phototherapeutic agents have poor therapeutic efficacy and severe phototoxicity due to their limited tumor-homing ability.[8]

Photoimmunotherapy (PIT), a precision-targeted tumor treatment that combines phototherapeutic agents' phototoxic effects with immunotherapy's target-seeking ability, is expected to solve the above problems.[9,10] Akalux, the first approved near-infrared (NIR)-PIT drug for head and neck cancer globally, is an antibody coupling drug.[11] A photosensitizer (IR700) was used to conjugate to monoclonal antibodies targeting epidermal growth factor receptors (EGFR), which was overexpressed on the surface of the head and neck cancer, esophageal cancer, lung cancer, colon cancer, pancreatic cancer, and other solid tumors.[12] Akalux is currently conducting phase III trials around the world (https://clinicaltrials.gov/ct2/show/NCT03769506). NIR-PIT based on antibody coupling drugs can precisely treat different tumors by coupling different tumor-targeting monoclonal antibodies.

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Bioconjugate Chem. 2023, 34, 283−301

NIR-PIT mainly uses the targeting effect of monoclonal antibodies to mitigate the phototoxicity of photosensitizers. This also seems to be achieved by NPs, which can passively target tumors by enhanced permeability and retention (EPR) effect, in addition to various modifications of the NPs to give them active targeting functions. Therefore, specifically targeted NPs have been designed to simultaneously load phototherapeutic agents and various immunotherapeutic agents to improve the antitumor effectiveness, reduce phototoxicity, enhance tumor immunogenicity, and reverse the ITM[13] (Scheme 1). NIR-PIT based on antibody coupling has been discussed in many reviews, and this review will focus on nano-PIT based on NPs. In this review, we describe the processes of targets in tumor immunity (which includes tumor cells and all elements of the tumor microenvironment (TME)), group them into categories based on the targets, and detail the current state of nano-PIT developed based on these targets. Finally, we will discuss several issues that need to be resolved and the potential of nano-PIT.

2. MECHANISM OF NANOPHOTOIMMUNOTHERAPY

2.1. Targeted Elements in Immunotherapy. Cancer immunotherapy activates the host's immune system in various ways to produce an immune response to tumors.[14] Innate immune cells, such as macrophages, dendritic cells (DCs), and natural killer (NK) cells, recognize conserved pathogen-associated molecular patterns (PAMPs) or DAMPs through pattern recognition receptors (PRRs), thus providing initial, first-line protection.[15] Adaptive immunity requires the activation of T and B lymphocytes. This activation involves T and B cell receptor recognition of specific antigens. It depends on antigen presentation by antigen-presenting cells (APCs), particularly DCs.[16] Immature DCs (im DCs) have efficient antigen uptake, processing, and migration ability, where abnormal signals in the peripheral tissue can be stimulated to differentiate and mature.[17,18] Then they migrate to the tumor-draining lymph nodes and present the information to T cells in time, thus activating a series of immune responses.[19] Mature DCs highly express major histocompatibility complex (MHC) class I and class II (MHC-I/II) molecules and receptors related to antigen uptake and transport. The captured antigens are processed into peptide fragments and combined with MHC to form complexes presented to T cells to activate an immune response.[20] DCs can promote effective antitumor immunity by recruiting and activating different immune cells.

T cells are the most crucial weapon of the immune system to kill tumor cells, and $CD8^+$ cytotoxic T cells are the most important. $CD8^+$ cytotoxic T cells can recognize endogenous antigenic peptides presented by MHC-I and directly kill tumor cells after activation with the assistance of $CD4^+$ helper T cells. At the same time, the optimal activation of naive T cells depends on the costimulatory signal provided by the interaction between CD28 receptors on T cells and b7 ligands (CD80 and CD86) on APCs.[21] $CD8^+$ cytotoxic T cells can indirectly secrete cytotoxic substances (such as perforin and granzymes) and cytokines (such as interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α)) to kill tumor cells.[22] There are many receptors on the surface of T cells, including stimulating receptors (such as glucocorticoid-induced tumor necrosis factor receptor family-related proteins (GITR)) and inhibitory receptors (such as programmed cell death protein 1 (PD-1)).[23]

NK cells, also a type of essential immune cell in innate immunity, are innate lymphocytes that can kill target cells directly without prior contact with any cells while not damaging healthy "self" cells.[24] The structural expression of a practical and fully functional lytic machinery, as well as the rapid release of IFN-γ and TNF-α upon cell activation, allow NK cells to intervene rapidly, leading to target cell killing and initiation of inflammatory responses.[25] According to the "missing self" recognition principle, NK cells can remove cells with insufficient MHC-I molecules.[26]

Macrophages clear pathogens and apoptotic cells by phagocytosis. The phagocytosis of macrophages is inhibited by specific signals, such as the "don't eat me" signal. These signals interact with most cell surface proteins on macrophages, such as CD47 and its receptors, to inhibit the phagocytosis of macrophages.[27] The abundant macrophages in TME are called tumor-associated macrophages (TAMs). Based on the concept of classical activation and alternating activation, TAMs are polarized into two types, called M1 and M2. M2-like TAMs usually promote tumor growth by activating neovascularization, secreting cytokines supporting tumor resistance to apoptosis, and stimulating proliferation and invasion of tumor cells.[28] M1-like TAMs are stimulated by helper T cell type 1 cytokines, such as IFN-γ and lipopolysaccharide (LPS), which activate Toll-like receptors (TLRs) to promote inflammation and inhibit tumor growth.[27]

After long-term evolution, tumor cells express some ligands that bind to inhibitory receptors on effect cells, such as programmed cell death ligand 1 (PD-L1), or produce molecules that inhibit tumor immune response, such as indoleamine 2,3-dioxygenase (IDO), interleukin-10 (IL-10), and transforming growth factor-β (TGF-β) to evade immune surveillance.[21] Targeting the immunological targets, ICB, CAR-T cell therapy, cytokine therapy, and vaccines have succeeded in clinical studies. However, LTI and ITM severely compromise the killing effect of immune cells on tumor cells, which fail to evoke a strong and effective immune response.

2.2. Mechanism of Phototherapy. PDT and PTT belong to phototherapy, but their mechanisms and characteristics differ. PDT causes a series of cytotoxic reactions through the production of ROS by photosensitizers in the presence of oxygen. ROS can interact with various biomolecules to damage cell structure or affect cell function. $^1O_2$ is a highly reactive and oxidizing energetic body with electrophilic properties, which can effectively oxidize biomolecules, such as unsaturated fatty acids, proteins, nucleic acids, and mitochondrial membranes, and induce tumor cells death.[29−31] It is found that the subcellular structure localization of photosensitizer greatly affected the type of cell death (necrosis or apoptosis). Photosensitizers located in mitochondria or endoplasmic reticulum (ER) generally induce cell apoptosis; location in the cell membrane or lysosome can easily cause cell necrosis after laser irradiation.[32,33] PTT mainly depends on photothermal conversion agents with specific absorption wavelengths to absorb light and convert light into heat energy. PTT leads to the increase of local temperature of the tumor site to induce tumor cells death and achieve the therapeutic effect of inhibiting tumor growth or even eliminating the tumor.[34]

As an exogenous stimulation therapy, phototherapy can also induce ICD, enhancing the therapeutic effect of cancer immunotherapy. The characteristics of ICD are that the DAMPs activate the corresponding molecular biological effects and improve the release of immunogenic signal molecules such

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Bioconjugate Chem. 2023, 34, 283−301

Table 1. Targeted nano-PIT Research in the Recent Years

Target	Targeting unit		Delivery platform	Active/passive targeted	Phototherapeutic agents	Note	Results	Refs
Tumor cells	Cell membrane proteins	PD-L1	aPD-L1 NVs-ICG/AAI-R837	Active (anti-PD-L1)	Indocyanine green (ICG)	Nanovesicles (NVs) displaying anti-PD-L1 antibodies	Reprogramming of TME; Inhibition of initial and distant tumors	44
			BMS/HC	Active (hyaluronic acid)	Chlorin e6 (Ce6)	Small-molecule inhibitor	Blocking the PD-1/PD-L1 pathway; Regression in distant tumors and lung metastasis	45
			PPC	Passive	Purpurin 18	PD-L1 antagonist peptide	Infiltration of cytotoxic T lymphocytes (CTLs) and maturation of DCs; Sensitization ICB for 4T1 tumor cells; Inhibition of initial and distant tumors and lung metastasis	46
			siRNA/PPA-NG	Passive	Pheophorbide a	Small interfering RNA (siRNA)	Significant ICD effect; Inhibition of PD-L1 expression in tumor cells; Strong inhibition of primary and distal tumors	47
	Intracellular proteins	Cell cycle protein-dependent kinase 4 (Cdk4)	msiPCN	Active (CT26 cell membranes)	Porphyrinic metal−organic framework based on Zr6 clusters	siRNA	Inhibition of the cell cycle and upregulation of PD-L1; Maturation of DCs and activation of CTLs	48
		Bromodomain-containing protein 4	HCJSP	Active (hyaluronic acid)	Pyropheophorbide a	Small-molecule inhibitor	Provoking T cells activation and overcoming adaptive immune resistance	49
			PCM	Active (T7 peptide)	MRP	Small-molecule inhibitor prodrug	Eliciting antitumor immunogenicity; Inhibition of the growth of glioblastoma *in vivo*	50
DCs	TAAs		IERL-Ps	Passive	Ce6	Liposomes capable of collecting TAAs	Effective tumor growth suppression and robust abscopal effect *in vivo*; Reduction of lung metastases	51
			HPDA@[OMV-CC]	Active (hybrid membrane)	Hollow polydopamine	A bacterial outer membrane vesicle and B16−F10 cancer cell membrane	Melanoma eradication without notable adverse effects	52
			hEX@BP	Active (serum exosomes)	Black phosphorus quantum dots	Serum exosomes	Better long-term PTT performance, more significant elevation of tumor temperature, and tumor targeting efficacy *in vivo*	53
			RuO_2@OVA NAs	Passive	"phototherapy-enzymatic" RuO_2	Ovalbumin (OVA)	Reversing the ITM, enhancing antitumor immune responses and phototherapeutic activity; Inhibition of primary and abscopal tumor growth	54
	Adjuvants	TLR-5	HIF	Active (hyaluronic acid)	IR-780	*Vibrio vulnificus* flagellin B (FlaB)	Regulation of TME by suppressing Tregs and increasing migratory DCs; Eliciting potent antitumor immunity	55
		TLR-7	MIRD	Active (magnetic targeting)	ICG	R837	Inhibiting tumor growth, metastasis, and recurrence	56
		TLR-7/8	AM@DLMSN@CuS/R848	Active (homogeneous cancer cell membrane)	Copper sulfide	R848	Synergistically tumor vaccination and T lymphocyte activation; Immune remodeling; Prevent TNBC recurrence and metastasis	57
		TLR-9	PC@GCpD(Gd)	Passive	Ce6	CpG ODN	Releasing endogenous cancer cell antigens; Modulating the TME; Enhancement of immune stimulation	58
	Vaccine-like drug delivery platform		DOX/ICG/CpG-P-ss-M/CD	Passive	ICG	CpG	Abundant tumor-specific antigen storage in situ; Effective antigen presentation	59
T cells	Inhibitory receptors	PD-1	AA@PN	Passive	Hollow gold nanoshells	Anti PD-1 peptide	Efficiently eradicating the primary tumors and inhibiting metastatic tumors	60
		CTLA-4	αPD-L1-αCTLA-4 Chloringlobulin	Passive	Ce6	Anti-PD-L1 and anti-CTLA-4	Eliciting potent systemic antitumor immunity and a long-lasting immune memory against tumor rechallenge	61
	CAR-T	GPC3	CIM	Active (CAR-T cell membranes)	IR-780	CAR-T cell membranes	Excellent capacities of tumor targeting and antitumor *in vitro* and *in vivo*	62

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Bioconjugate Chem. 2023, 34, 283−301

Table 1. continued

Target	Targeting unit		Delivery platform	Active/passive targeted	Phototherapeutic agents	Note	Results	Refs
	Tregs	GITR	PDA-ICG@CAT-DTA-1	Passive	ICG	anti-GITR antibody	Reduction of 4.3 fold for intratumoral Tregs; Inhibition rate of 95.1% for primary cancer and 68.7% for distant cancer	63
		Foxp 3	LBL hNPs	Active (anti-GITR)	IR-780	Imatinib	Tumor eradication; Reduction of tumor recurrence; Improvement of *in vivo* survival rate	64
NK cells	Activation of NK cells		CD@ MSNs	Passive	Carbon nanodots	Biodegraded debris	Proliferation and activation of NK cells and macrophages; Inhibition of the immune-mediated tumor metastasis	65
	activating receptor	NKG2D	PGIL	Passive	Ce6	Galectin-3-inhibitor	Excellent antitumor effect; Increasing the recognition of tumor cells by NK cells	66
	NK cell membrane	RANKL or DNAM-1	NK-NPs	Active (NK cell membranes)	4,4′,4″,4‴-(porphine-5,10,15,20-tetrayl) tetrakis (benzoic acid)	NK cell membranes	Elimination of primary tumor growth and inhibition of distant tumors	67
	Fc domain−mediated antibody-dependent cellular cytotoxicity (ADCC)	GPC3-His	hGC33-Vas	Active (antibodies)	ICG	NVs displaying full-length mAbs	Regulation of TME; Activation of NK cells; Tumor necrosis	68
TAMs	Reprogramming		HA-BP	Active (hyaluronic acid)	Black phosphorus	Low molecular weight hyaluronic acid (M W < 5 kDa)	The expression of CD206 was downregulated by 42.3%, and the percentage of CD86 was upregulated by 59.6%	69
	CD47-SIRPα signaling axis		GPPT@IC	Active (glucose)	IR-780	CUDC101, a multitarget inhibitor in clinical trials	CUDC101-triggered CD47 inhibition; M1 phenotype polarization; Transition from "cold" immunosuppressive to "hot" immunoresponsive TME	70
	CD24/Siglec-10		DOPC-*Pc* SUVs	Active (sialic acid (SA))	Phthalocyanines	SA	The potential for targeting siglec-expressing cells	71
Other Targets of TME	Tumor vascular normalization		GNR-T/CM-L	Passive	gold nanorods	Sodium tanshinone IIA sulfonate	Tumor blood vessel normalization and M1 TAM polarization	72
			RBCm/PAAV-SNO/1-MT+IR1061 NPs	Passive (red blood cell membrane)	IR1061	Thermal sensitive nitric NO donor	Normalizing the tumor vessels and comprehensively reprogramming ITM; Excellent therapeutic efficacy for primary breast cancer and metastases	73
	ECM	Hyaluronic acid	HAase/NM-Ce6	Passive	Ce6	Hyaluronidase (HAase)	Improvement of hypoxic TME; Enhanced EPR effect	74
		Collagen	PCB1-Bro	Passive	Semiconducting polymer nanoenzymes	Bromelain	Digesting collagen in the ECM; Enhanced nanoparticle accumulation in tumors	75
	CAFs	FAP	scFv-Z@FRT	Active (scFv)	Apoferritin	FAP-specific single chain variable fragment (scFv)	Elimination of CAFs; efficient tumor suppression	76
	Other targets	MDSCs	CuS/NorSun	Passive	Copper sulfide	receptor tyrosine kinase inhibitor and arginase inhibitor	Upregulation of tumor-infiltrating lymphocytes expression	77
		IDO	EAPV	Active	Ppa	NLG919	Enhanced antitumor efficacy in both CT26 colorectal and 4T1 breast xenograft tumor models	78
		TGF-β	rGO/MTX/SB	Passive	reduced graphene oxide	TGF-β inhibitor	Effect against tumors by in situ vaccination and inhibition of immunosuppressive microenvironment	79

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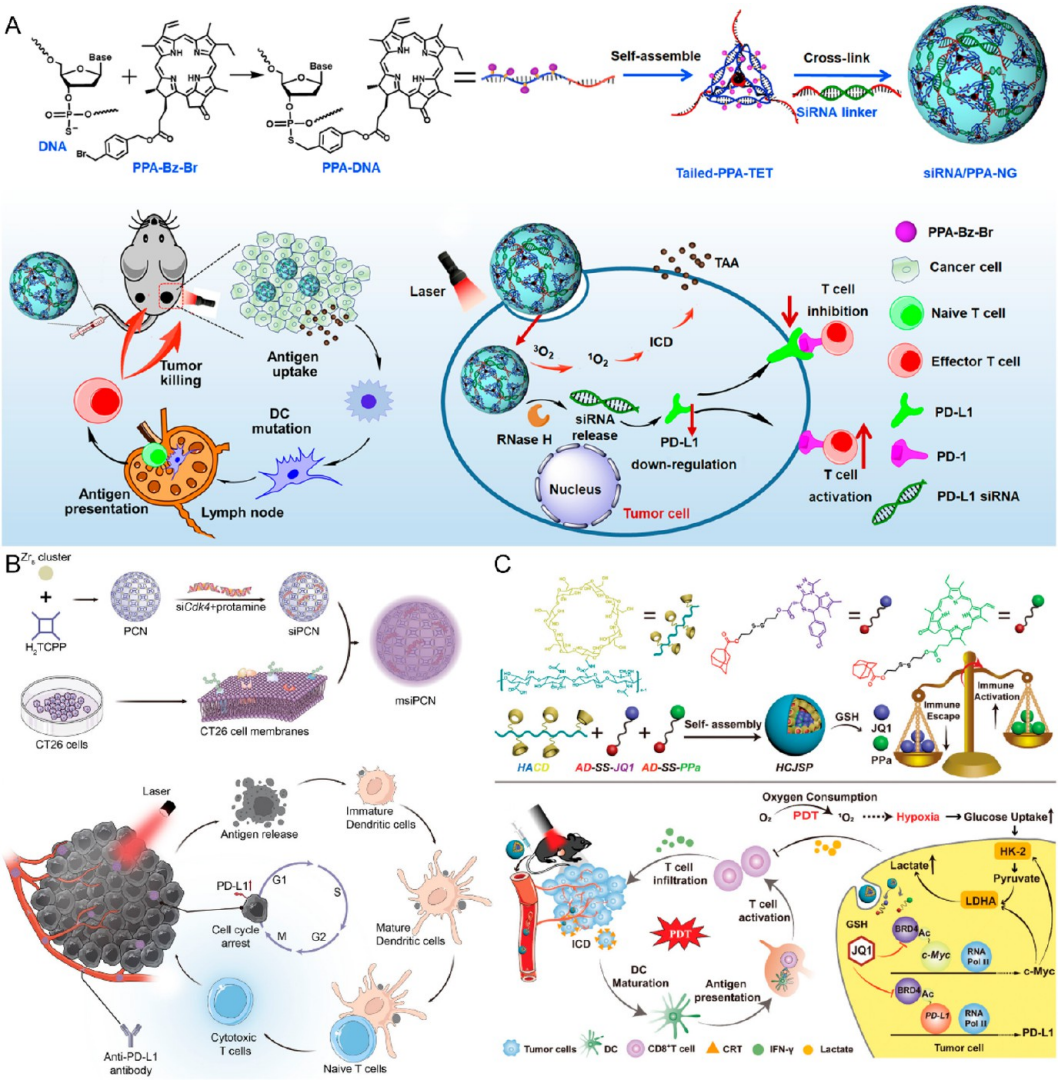

Figure 1. Nano-PIT by targeting tumor cells. (A) Syntheses of the siRNA/PPA-NG and the process of synergistic nano-PIT mediated by siRNA/PPA-NG *in vivo*.[47] Reproduced with permission from ref 47. Copyright [2022]. (B) Schematic illustration of the synergistic nano-PIT strategy mediated by the msiPCN.[48] Reproduced from ref 48. Copyright [2022]. (C) Mechanism of HCJSP-based nano-PIT in treating pancreatic tumor by inducing immunogenicity and overcoming adaptive immune resistance.[49] Reproduced with permission from 49. Copyright [2021].

as calreticulin (CRT), high mobility group box 1 (HMGB1), and adenosine triphosphate (ATP).[6] These DAMPs stimulate the maturation of DCs. TAAs and specific antigens can be released from dead tumor cells after phototherapy. APCs, especially DCs, can capture these antigens and present them to adaptive immune cells to increase the number of activated effector cells ($CD8^+$ T cells, $CD4^+$ T cells, NK cells) in activating tumor-specific $CD8^+$ T cells to attack the tumors. Effector cells release IL-2, IL-4, and IFN-γ, to inhibit distant and metastatic tumors.[35,36] Combining phototherapy and immunotherapy can enhance tumor immunogenicity and improve the ITM. However, the poor therapeutic efficacy and severe phototoxicity limited phototherapy due to photo-therapeutic agents' non-targeted.

2.3. Target-Specific PIT. Already in the 1980s, traditional PIT reduced the phototoxicity by conjugated coupling of conventional photosensitizers with monoclonal antibodies to targeted PDT.[37] Therapeutic effects were restricted to cells *in vitro* or tumors with intratumoral or intraspatial delivery *in vivo* because of the adverse chemical design that coupled antibodies with hydrophobic photosensitizers.[38] To solve this problem, Kobayashi et al. coupled a NIR water-soluble silicon-phthalocyanine derivative photosensitizer IRDye700DX (IR700) and monoclonal antibodies.[39] In Japan, the first NIR-PIT drug (Akalux) was approved for clinical use in September 2020.[38] NIR-PIT based on antibody-photosensitizer (IR700) conjugate has been widely studied, and monoclonal antibodies with different targets were used to target various tumor or non-tumor cells.

However, the TME is complex, and multiple factors often cause immunosuppressed "cold" tumors. Single NIR-PIT may be difficult to eradicate tumors. NPs promote synergistic cancer treatment and avoid some drug resistance mechanisms by co-delivering multiple active drug components. In addition, NPs have become attractive as potent antigen or adjuvant carriers for synthetic vaccine development, with the EPR effect, preferential uptake by APCs, sustained release of antigen or adjuvant, and NP-mediated phagosomes escape of antigen for cross-presentation.[40−43] Several therapeutic NP platforms, such as liposomes, albumin NPs, polymeric micelles, and some inorganic nanomaterials, have been approved for cancer treatment. NPs can regulate drug release rate, improve biofilm

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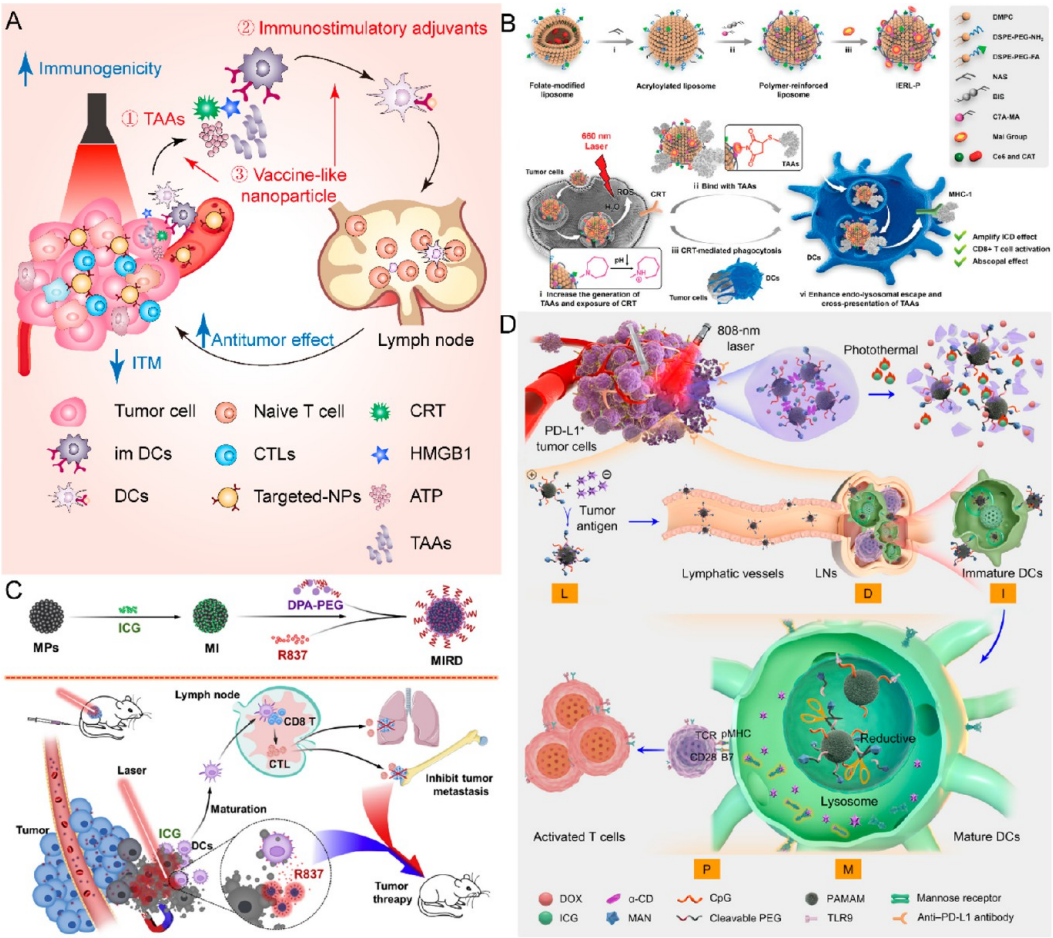

Figure 2. Nano-PIT by targeting DCs. (A) Schematic of the strategy of nano-PIT targeting DCs. (B) IERL-Ps enhance ICD by improving cross-priming to elicit T cell-dependent antitumor responses.[51] Reproduced with permission from ref 51. Copyright [2022]. (C) Schematic illustration of MIRDs for nano-PIT against tumor.[56] Reproduced with permission from ref 56. Copyright [2020]. (D) CpG-P-ss-M-mediated DC maturation for nano-PIT against tumor recurrence and metastasis.[59] Reproduced with permission from ref 59. Copyright [2020].

permeability, enhance drug targeting, improve drug utilization, and enhance antigen presentation efficiency.[13] NPs co-deliver phototherapeutic agents and various immunotherapeutic agents that can play a role in the precise treatment of tumors and have a powerful synergistic therapeutic effect to deal with the complex TME. Many nano-PIT strategies have been developed in recent years (Table 1).

3. NANO-PIT BY TARGETING TUMOR CELLS

3.1. Targeting Cell Membrane Proteins. Tumor cells express many specific proteins on their surface, and monoclonal antibodies can target them. Monoclonal antibodies bind specifically to receptors or antigens to produce antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity to kill tumor cells by blocking cell proliferation signals and inducing a tumor immune response. NIR-PIT mainly relies on monoclonal antibodies to target tumors and requires highly expressed targeting antigens on cells. Therefore, a new NIR-PIT coupling compound enhanced the antitumor immune effect by targeting PD-L1, an immune checkpoint molecule expressed on almost all tumor cells.[80] Monoclonal antibody blocks the interaction between PD-1 and PD-L1 by binding to ligands or receptors, showing significant clinical efficacy in various cancer patients, including melanoma, colorectal cancer, non-small cell lung cancer, and Hodgkin's lymphoma.[81] Bone marrow mesenchymal stem cell-derived nanovesicles (NVs) were used for the targeted delivery of anti-PD-L1 antibodies and photosensitizers. Anti-PD-L1 binding NVs delivered photosensitizers selectively to tumor tissue due to the high affinity and specificity.[44]

However, the efficacy of antibodies is affected by their high price, instability, and risk of autoimmune diseases. Small molecular inhibitors may be attractive substitutes for antibodies. BMS-202 is a small molecule inhibitor of PD-1/PD-L1 interaction. Some research experimentally revealed the possibility of replacing antibodies used for cancer immunotherapy with BMS-202 NPs.[45,82] Hyaluronic acid was conjugated with Ce6 to form a conjugate. Encapsulation of conjugate with the small molecule inhibitor BMS-202 formed micelles to construct a nanoplatform.[45] Peptide inhibitors can also be a good option.[46] In addition, PD-L1 small interfering RNA and photosensitizer bound and self-assembled to form a nanogel (Figure 1A).[47] The tumor-specific nanoplatform efficiently delivered small-molecule or peptide inhibitors to precise targets and significantly improved PD-1/PD-L1 pathway blockade.

3.2. Targeting Intracellular Proteins. Many intracellular proteins are associated with regulating tumor cell growth, including signal transduction molecules, cell cycle proteins,

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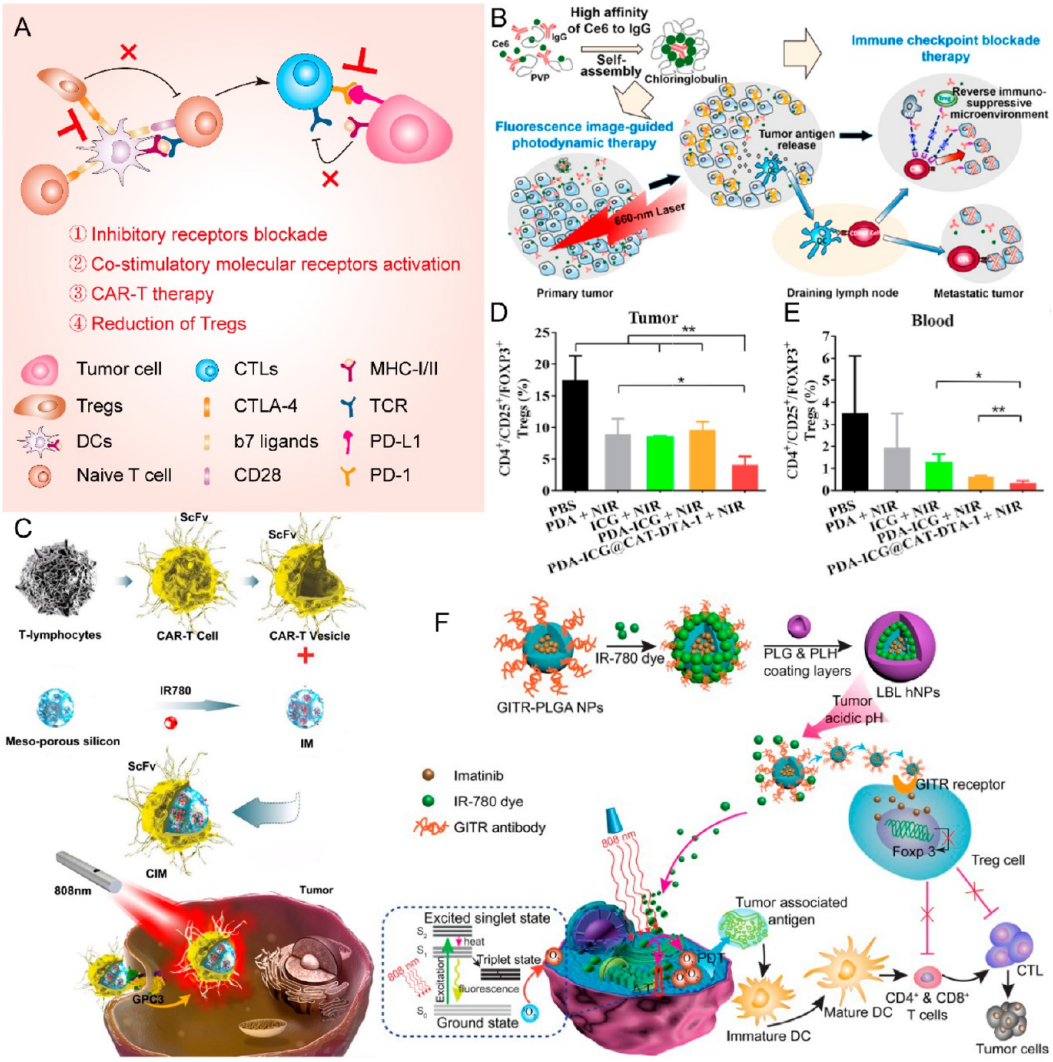

Figure 3. Nano-PIT by targeting T cells. (A) Schematic of the strategy of nano-PIT targeting T cells. (B) The chloringlobulin-based nano-PIT elicited systemic antitumor immunity and a durable immunological memory against tumor recurrence.[61] Reproduced from ref 61. Copyright [2019]. (C) Schematic illustration of CAR-T cell membrane-coated biomimetic NPs for highly specific tumor nano-PIT.[62] Reproduced with permission from ref 62. Copyright [2020]. Average proportions of $FOXP3^+/CD4^+/CD25^+$ Tregs in tumor (D) and blood (E) respectively.[63] Reproduced with permission from ref 63. Copyright [2020]. (F) Scheme of regulatory T cell modulation-based nano-PIT using layer-by-layer hybrid NPs.[64] Reproduced with permission from ref 64. Copyright [2018].

apoptosis regulators, and cellular epigenetic regulatory molecules.

Targeted delivery of photosensitizers and small interfering RNA with a tumor cell membrane-encapsulated metal−organic framework was used to knock down cell cycle protein-dependent kinase 4 (Cdk4). Cdk4 blockade inhibited the cell cycle of tumor cells, promoted antigens exposure, and increased the expression level of PD-L1. Under laser irradiation, PDT induced ICD, promoting the antitumor activity combined with anti-PD-L1 antibodies (Figure 1B).[48] The epigenetic inhibitor JQ1 and photosensitizer were coloaded into NPs modified by hyaluronic acid for precision targeting. Hyaluronic acid enabled tumor-targeting activity by recognizing CD44 highly expressed on the surface of pancreatic tumors. PDT enhanced the immunogenicity of tumor cells and promoted intratumoral infiltration of CTLs. Meanwhile, JQ1 regulated the expression of c-Myc and PD-L1, key regulators that inhibited tumor glycolysis and immune evasion, against PDT-mediated immune evasion through epigenetic modifications (Figure 1C).[49] In another research, NIR-II fluorescent probe, JPC (a prodrug of JQ1), and T7 peptide (a ligand that crosses the blood-brain barrier) modified PEG-DSPE self-assembled to form a dual-targeted nano-diagnostic therapeutic agent for precision PIT of glioblastoma.[50]

Targeting tumor cells is merely the first part of a complete immune response, which also involves the cooperation of DCs, T cells, NK cells, macrophages, and other elements of the TME.

4. NANO-PIT BY TARGETING DCS

The adaptive immune response is spearheaded by DCs, and nano-PIT can effectively stimulate DCs to increase their antitumor activity. Several nano-PIT strategies can reverse DCs immunosuppression in TME (Figure 2A): (1) targeted co-delivery of antigens and phototherapeutic agents; (2) targeted co-delivery of adjuvants and phototherapeutic agents; (3) building a vaccine-like drug delivery platform. The clinical

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Bioconjugate Chem. 2023, 34, 283−301

translation of conventional DC vaccines is not easy. Recently, some drug delivery platforms were designed with vaccine-like effects that could produce significant antitumor effects.

4.1. Based on the Co-delivery of TAAs. The immunogenicity of cell death relies on a combination of antigenicity (provided by neo-epitopes) and adjuvanticity (conferred by specific PAMPs or DAMPs).[6] For APCs, represented by DCs, to start the specific T-cell immune response, they must first recognize TAAs. The successful delivery of TAAs to DCs to trigger T-cell immune responses can be achieved by the co-delivery of phototherapeutic drugs and antigens.

Phototherapy induced ICD and produced TAAs, but large amounts of TAAs were trapped in the endolysosomes of tumor-infiltrating DCs. Some nano-PIT methods were designed to collect TAAs, promote the escape of TAAs from DCs, and enhance the cross-presentation of TAAs, leading to the amplification of ICD-related antitumor immune responses (Figure 2B).[51] Some cell membranes (including tumor cells, DCs), exosomes, and vesicles were used to wrap NPs to construct nano-PIT with self-contained TAAs to enhance antigen presentation.[52,53,83] In addition, the model antigen ovalbumin (OVA) was delivered together with photo-therapeutic agents by NPs to provide more TAAs to enhance nano-PIT against tumors.[54]

4.2. Based on the Co-delivery of Immunostimulatory Adjuvants. TAAs are taken up by DCs to start specific T-cell immune responses. There will nonetheless be some DCs that are not activated throughout this process. Immunostimulatory adjuvants can further activate DCs. Co-delivery of immunostimulatory adjuvants and phototherapeutic agents via NPs can produce more TAAs and further excite DCs via immunostimulatory adjuvants.

TLRs agonist is a commonly used adjuvant for immune stimulation. Most TLRs agonists currently used for cancer immunotherapy target TLR-5,[55] TLR-7/8,[57] and TLR-9.[58,84] Magnetic nanoparticle-based nano-PIT loaded with R837 resulted in magnetic resonance imaging guidance, magnetic targeting, and powerful therapeutic effects against tumors with low adverse effects (Figure 2C).[56] A unique TME-regulated nanostimulator consisted of TLR-5 adjuvant *Vibrio vulnificus* flagellin B (FlaB) bound to the surface of hyaluronic acid-stearyl-amine micelles loaded with IR780. In nano-PIT with TLR-5 adjuvant showed enhanced vaccine-like properties, modulating TME by suppressing regulatory T cells (Tregs) and increasing the proportion of $CD103^+$ migratory DCs.[55]

4.3. Based on Building a Vaccine-Like Drug Delivery Platform. A tumor vaccination can be produced by simultaneously delivering immunostimulatory adjuvants and TAAs. The application of tumor vaccines is limited because they are systemically immunotoxic and cannot satisfy all steps to activate T cells. One tumor vaccine method entailed administering local PTT to a few chosen tumors in order to release whole-cell TAAs. Then, a semisynthetic functionalized glucosamine polymer used as an immunological adjuvant was locally administered, activating APCs and promoting tumor antigen absorption.[85,86]

In recent years, some innovative NPs for nano-PIT platforms have been developed to deliver in one step rather than two injections. A cyclodextrin-based gel system combined the chemotherapeutic drug doxorubicin, the photothermal agent indocyanine green (ICG), and the immunomodulator CpG as vaccine-like NPs (Figure 2D). The therapy effectively inhibited primary tumor growth and induced a tumor-specific immune response against tumor recurrence and metastasis.[59] In another research, ICG and R837 were co-encapsulated by poly(lactic-*co*-glycolic) acid (PLGA). Three clinically approved components of the NPs could be used for NIR laser-triggered PTT ablation of primary tumors, generating TAAs in the presence of R837 as the adjuvant, showing vaccine-like functions.[87] Targeting nano-PIT, which enhanced DCs maturation and antigen presentation, could effectively enhance the antitumor effect.

5. NANO-PIT BY TARGETING T CELLS

T cells are the most important class of cells in the adaptive immune response. Although activating T cells by directing nano-PIT to DCs improves this process, activating inhibitory receptors on the surface of T cells also facilitates immunological evasion. In the TME, Tregs may also have a suppressive effect on T cells. So, to stop the immunological escape induced by T cells, nano-PIT can target T cells and block the inhibitory receptors, activate the activating receptors, and suppress the Tregs (Figure 3A).

5.1. Targeting Inhibitory Receptors of T Cells. Tumor cells can activate immune checkpoints to quietly escape from the pursuit of T cells. The immune function of T cells is limited and cannot play its due role in killing tumor cells. ICB can restore the function of T cells to recognize and kill tumor cells in the body. The constant response rate of ICB in most tumor cells is still meager. Therefore, nano-PIT co-delivered immune checkpoint inhibitors and phototherapeutic agents may improve the antitumor response rate and broaden the application of immunotherapy in metastatic tumors.

PD-1 is a T cell surface inhibitory receptor that functions as a T cell checkpoint and plays a central role in regulating T cell exhaustion.[88] When PD-1 is bound by its ligand, T-cell activation is inhibited. Some PD-1 antibodies have already been used in clinical. Unlike monoclonal PD-1 antibodies, PD-1 peptide inhibitors are low-cost and immunotoxic but are cleared rapidly *in vivo* and require frequent dosing. Hollow gold nanoshells (a photothermal agent) and AUNP12 (anti-PD-1 peptide) co-wrapped into PLGA NPs could sustain peptide release for 40 days. Moreover, a single intratumoral injection could replace frequently administered free AUNP12.[60]

Cytotoxic T lymphocyte antigen-4 (CTLA-4) is a widely recognized immune checkpoint protein. CTLA-4 competes with CD28 for CD80/CD86 ligands, blocking the CD28 costimulatory signal necessary for robust T cell activation and effector function.[89] It suppresses tumor immune response and down-regulates T cell activation.[90] Blocking the interaction between CTLA-4 and its ligand CD80/86 using anti-CTLA-4 monoclonal antibodies reduces Tregs and increases effector T cells, thus enhancing antitumor immunity.[91] The photosensitizer Ce6 was self-assembled with anti-PD-L1 and anti-CTLA-4 to form chloriglobulin for dual ICB-mediated nano-PIT, invoking strong systemic antitumor immunity and a durable immunological memory to prevent tumor recurrence (Figure 3B).[61]

T cell immunoglobulin mucin 3 (Tim-3) and lymphocyte activation gene 3 protein are two additional inhibitory receptors on the surface of T cells for which antibodies have been produced and are being studied in preclinical or clinical research.

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Bioconjugate Chem. 2023, 34, 283−301

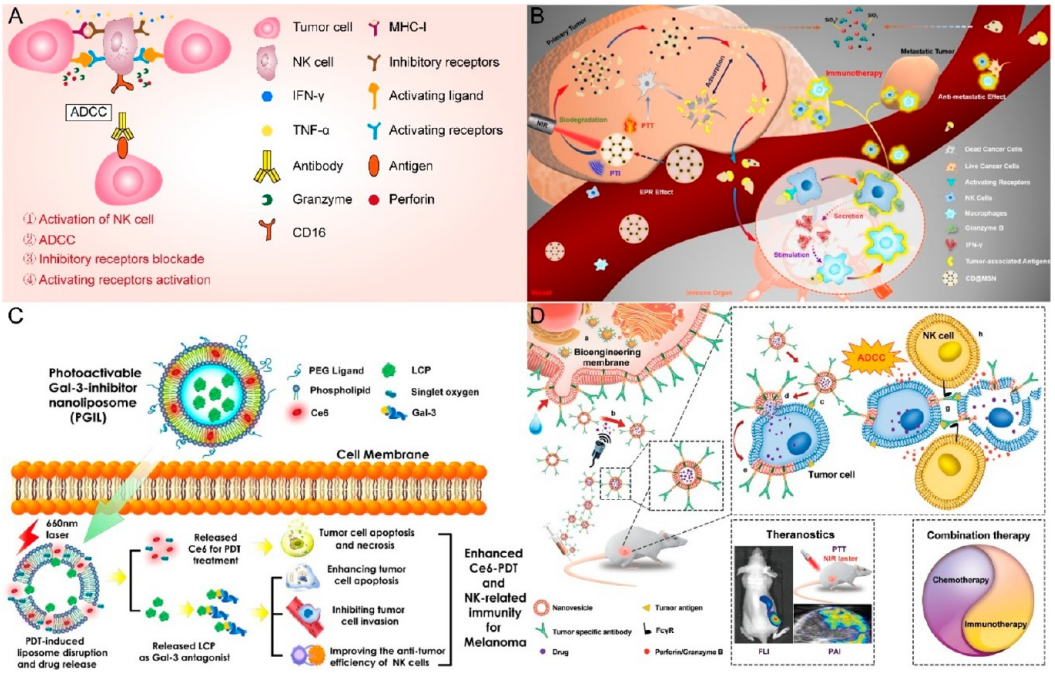

Figure 4. Nano-PIT by targeting NK cells. (A) Schematic of the strategy of nano-PIT targeting NK cells. (B) Schematic illustration of *in vivo* delivery process of framework swelling-triggered biodegradable CD@MSN and its application for photothermal imaging-guided tumor-targeted nano-PIT against tumor metastasis.[65] Reproduced from ref 65. Copyright [2019]. (C) The photoactivable Galectin-3 inhibitor nanoliposome (PGIL) scheme for enhancing PDT of melanoma and immune activation associated with NK cells.[66] Reproduced from ref 66. Copyright [2019]. (D) Mechanisms of VAs for dual-modal imaging and antitumor targeted combination therapy.[68] Reproduced with permission from ref 68. Copyright [2019].

5.2. Targeting Co-stimulatory Molecular Receptors of T Cells. Some co-stimulatory receptors of T cells are undergoing preclinical or clinical studies. The co-stimulatory molecule CD27 is expressed on most effector T cells, memory B cells, and a small subset of NK cells.[92] Anti-CD27 stimulated $CD8^+$ T and NK cells to release cytokines to cause myeloid infiltration and macrophage activation.[93]

5.3. Based on CAR-T Cell Therapy. Chimeric antigen receptor provides apparent antigen specificity for T cell populations that target tumors independent of natural T cell receptors. CAR-T cells recognize TAAs and eliminate tumor cells via the single-chain variable region. Due to specific barriers, the remarkable therapeutic effect of CAR-T cells immunotherapy is observed in hematological malignancies but not solid tumors. The connective tissue structure of tumors and the ITM are often responsible for the reduced efficacy of CAR-T cell therapy in solid tumors.[94] Nano-PIT facilitated CAR-T cell accumulation and effector function within solid tumors, and CAR-T cell membrane-encapsulated NPs' superior targeting ability and antitumor capacity were confirmed both *in vitro* and *in vivo* (Figure 3C).[62]

5.4. Targeting Regulating T Cells. $CD4^+CD25^+Foxp3^+$ Tregs are recognized as immunosuppressive cells that play a crucial role in tumor immune escape and have become the target cells for systemic immunotherapy. Tregs inhibit the activation of $CD8^+$ T cells and NK cells to provide a permissible environment for tumor growth. An antibody photosensitizer conjugate coupled with anti-CD25 and IR700 was used to eliminate Tregs under NIR light irradiation selectively. It activated $CD8^+$ T cells and NK cells to initiate antitumor immune responses and released cytokines and chemokines, producing antitumor effects on distant tumors.[95]

In addition, the GITR antibody could target Tregs. Catalase was loaded with anti-GITR antibodies onto the photothermal/photosensitizer polydopamine to construct NPs. The NPs exhibited an intrinsic local thermal effect that promoted intratumor ROS production and eliminated tumor immunosuppression. The NPs reduced 4.3-fold $Foxp3^+$ Tregs in the tumor (Figure 3D) and 7.6-fold in the blood (Figure 3E) and promoted the production of DAMPs, thereby reviving the ICD effect compared with the control.[63] In another research, the hydrophobic drug imatinib was loaded into a GITR antibody-modified PLGA core. Imatinib reduced the activation of transcription factors STAT3 and STAT5 in Tregs, inhibited Foxp3 expression, and impaired Tregs' immunosuppressive functions *in vitro* and *in vivo*. The lipophilic cationic NIR dye IR-780 iodine was doped into the exterior of the GITR-PLGA core via electrostatic interactions. Polycationic and polyanionic coatings protected the photosensitizer and GITR-PLGA core from degradation and provided pH responsiveness (Figure 3F).[64] With nano-PIT, the layer-by-layer hybrid NPs have successfully eradicated tumor growth, reduced tumor recurrence, and improved *in vivo* survival rates.

A portion of the tumor cells will not be detected and killed by T cells because they lack MHC-I, despite the nano-PIT targeting T cells considerably enhancing their infiltration into the tumor tissue. Therefore, the involvement of innate immune cells such as NK cells and macrophages is also necessary to eradicate tumors.

6. NANO-PIT BY TARGETING NK CELLS

NK cells have extensive antitumor properties. When tumor cells do not express MHC-I, they are able to evade T cells, but because they lack MHC-I, they instead become the target of NK cells for destruction.[26] The inhibitory receptors on NK

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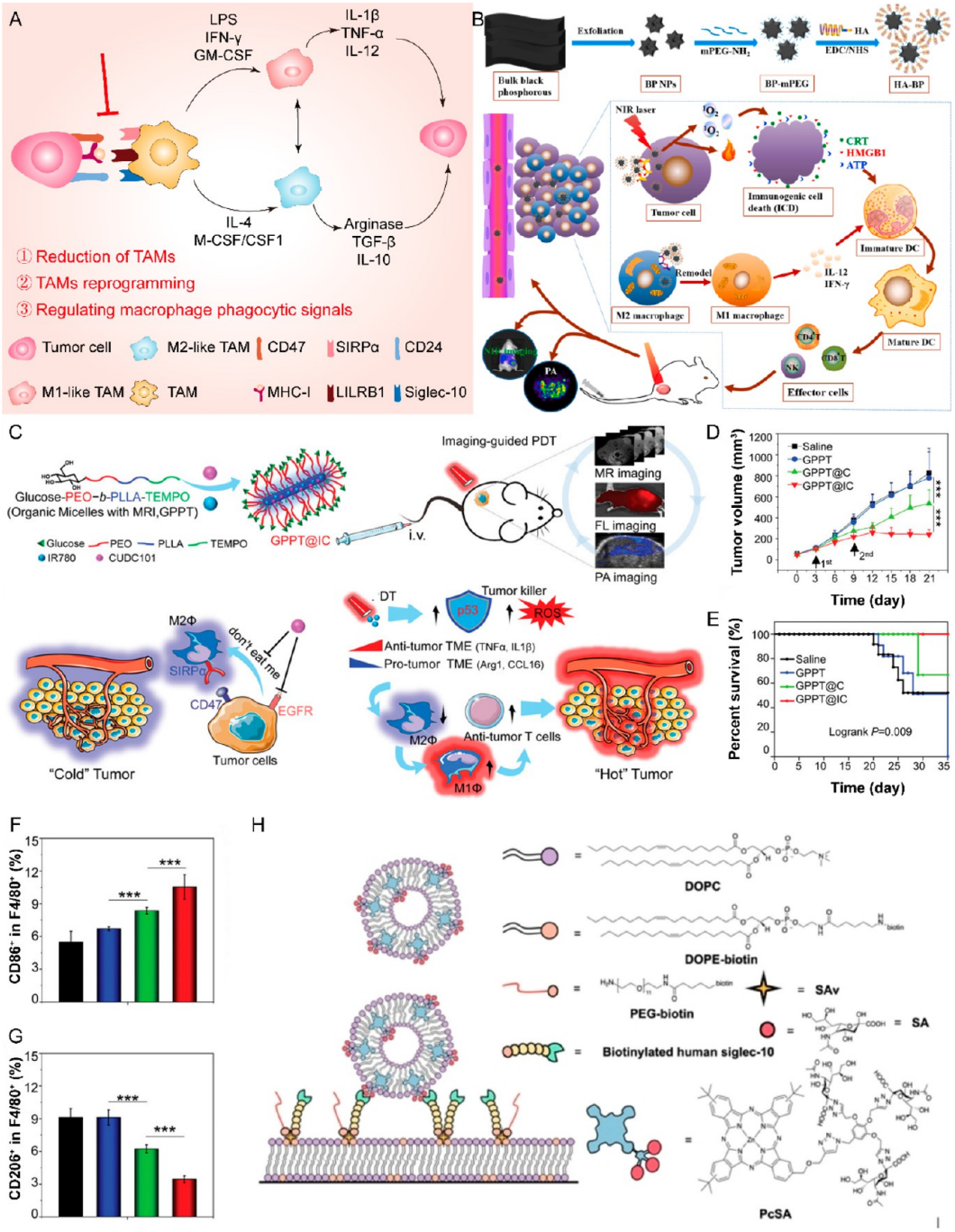

Figure 5. Nano-PIT by targeting TAMs. (A) Schematic of the strategy of nano-PIT targeting TAMs. (B) The synthetic scheme of HA-BP NPs and the function of HA-BP NPs *in vivo*.[69] Reproduced with permission from ref 69. Copyright [2020]. (C) Dual TME remodeling by glucose-contained radical micelles for nano-PIT.[70] Tumor growth curve (D) and percent survival analysis (E) between saline, GPPT polymers only, GPPT@C, and GPPT@IC groups.[70] M1-like macrophages (F) and M2-like macrophages (G) in spleen of Hep1−6 tumor-bearing C57BL/6 mice after indicated treatments.[70] Reproduced with permission from ref 70. Copyright [2021]. (H) Schematic representation of the potential for targeting Siglec-10-expressing cells with photosensitizing nanocarriers.[71] Reproduced with permission from ref 71. Copyright [2022].

cells' surface identify MHC-I expressed by healthy cells. Additionally, NK cells are also capable of eliminating tumor cells expressing MHC-I when activating receptors on their surface are increased. As a type of powerful effector cell, NK cells have received much attention in cancer immunotherapy research. Some strategies have been explored to enhance the immune effect of NK cells (Figure 4A), including (1) activation of NK cells; (2) Fc domain−mediated antibody-dependent cellular cytotoxicity (ADCC); (3) inhibitory receptors blockade; (4) activating receptors activation.

Biodegradable nanofragments could obtain TAAs from photothermally lethal tumor cells and stimulate the proliferation and activation of NK cells and macrophages while up-regulating the secretion of the corresponding cytokines (IFN-γ and granzyme B), synergistically achieving immune-mediated tumor metastasis inhibition (Figure 4B).[65] In malignant tumors, the overexpressed β-galactoside-binding protein

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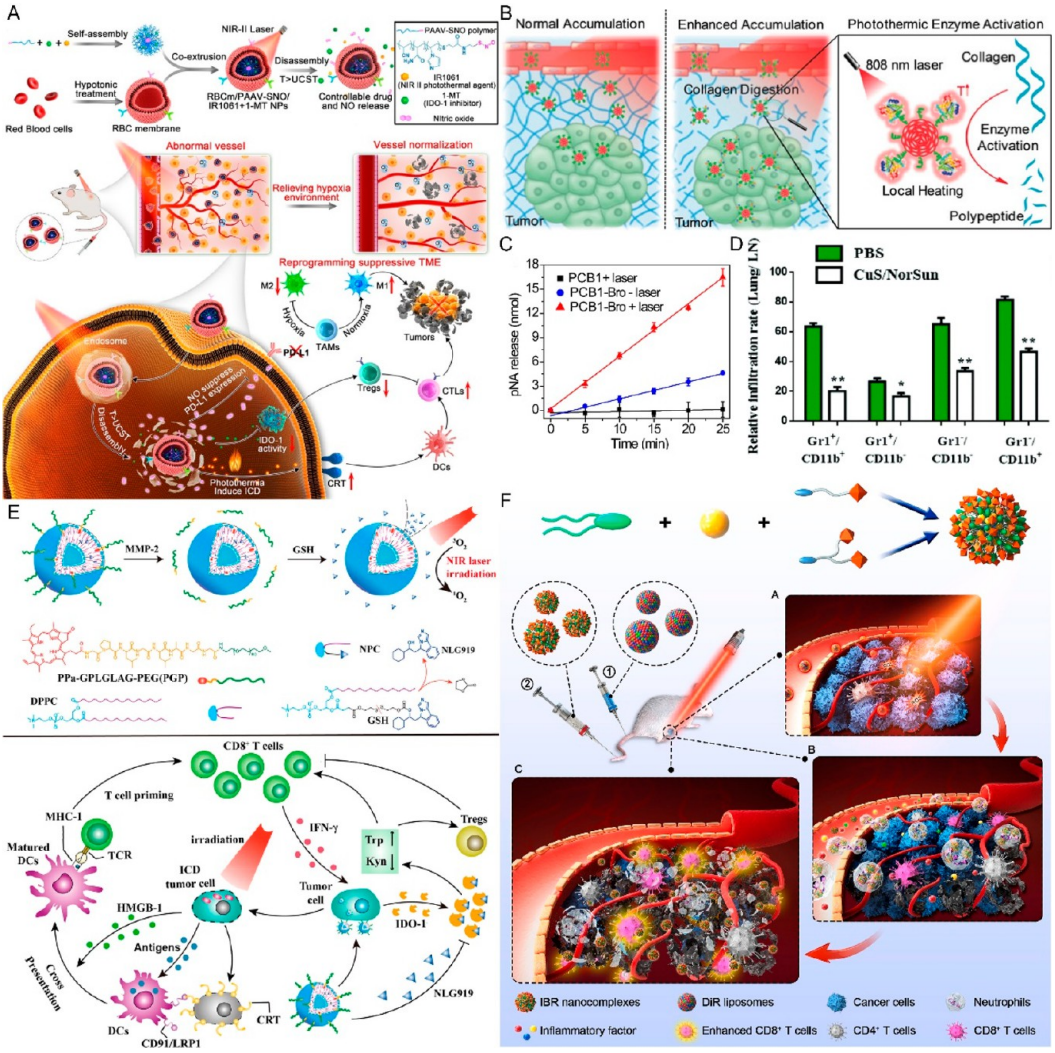

Figure 6. Nano-PIT by relieving the ITM. (A) The structure and therapeutics releasing process of erythrocyte membrane-camouflaged nanobullets and their capacities to reprogram the ITM and fight "cold" immune tumors.[73] Reproduced from ref 73. Copyright [2020]. (B) Mechanisms of photothermally triggered enzyme activation of semiconducting polymer nanoenzymes toward collagen digestion for enhanced accumulation of NPs in tumors.[75] (C) Enzymatic activity of PCB1-Bro with or without NIR laser irradiation using the peptide (Z-A-A-pNA) as substrate.[75] Reproduced with permission from ref 75. Copyright [2018]. (D) MDSC subset activation and expansion in C57BL/6 mice.[77] Reproduced with permission from ref 77. Copyright [2020]. (E) Schematic illustration of the MMP-2-sheddable and GSH-activatable prodrug vesicle for nano-PIT.[78] Reproduced from ref 78. Copyright [2020]. (F) Scheme of activating neutrophils tumor infiltration by PDT/PTT to deliver nanocomplexes for enhanced tumor immunotherapy.[104] Reproduced with permission from ref 104. Copyright [2021].

Galectin3 (Gal-3) inhibited tumor cell recognition by decreasing the affinity of NKG2D (an activating receptor) on NK cell membranes and MHC proteins on tumor cell membranes, significantly promoting immune escape of tumor cells.[96] Photoactivatable Gal-3 inhibitor-loaded nanoliposomes were used to enhance PDT and immune activation of NK cells (Figure 4C).[66] Tim-3 is one of the inhibitory receptors on NK cells, and phosphatidylserine binding to Tim-3 can inhibit NK cell activation. A photoconvertible ligand for Tim-3 was developed to produce active/inactive Tim-3 ligands under 365 or 455 nm light irradiation, thereby regulating NK cell function *in vitro* and *in vivo*.[97] This photoconvertible ligand may be used for nano-PIT.

NK cell membranes were used to encapsulate the photosensitizer to eliminate primary tumors and inhibit distant tumors.[67] Cell membrane-derived NVs could display full-length monoclonal antibodies capable of selectively delivering the cytotoxic agents to tumor cells and exerting potent inhibitory effects. They can mediate ADCC to eradicate tumor cells by recruiting and activating NK cells in the tumor (Figure 4D). The photosensitizer ICG could load into the vesicular antibodies for nano-PIT.[68]

7. NANO-PIT BY TARGETING TAMS

TAMs play an important role in tumor invasion and metastasis and are essential in tumor drug resistance. Therefore, nano-PIT targeting TAMs can develop potential new strategies to overcome macrophage-associated immune tolerance. At present, tumor immune methods targeting TAMs include (1) reduction of TAMs; (2) TAMs reprogramming; (3) regulating macrophage phagocytic signals (Figure 5A).

Most TAMs at tumor sites are of the M2 phenotype, and M2 macrophages specifically express CD206, also known as the macrophage mannose receptor. NIR-PIT, formed by coupling an anti-CD206 monoclonal antibody with a NIR

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Bioconjugate Chem. 2023, 34, 283−301

phthalocyanine dye, reduced the number of TAMs and inhibited the growth of sorafenib-resistant tumors.[98]

Many immunomodulatory agents have been used to regulate the phenotype of macrophages. Some nano-PIT strategies have also been shown to significantly polarize anti-inflammatory M2-like TAM to pro-inflammatory M1-like TAM.[99] Low molecular weight hyaluronic acid (M.W.<5 kDa) reprogrammed TAMs from M2 to M1 (Figure 5B).[69]

CD47 on tumor cells send a "don't eat me" signal that interacts with signal regulatory protein α (SIRPα) on macrophages to prevent phagocytosis. Anti-CD47 has a low response rate when used alone as a CD47/SIRP axis blocker. Nano-PIT has been used to enhance the therapeutic efficacy of anti-CD47. The combination of black phosphorus-based PTT and anti-CD47 antibody-based immunotherapy was previously reported to synergistically enhance tumor treatment.[100] A recent study found hybrid cell membrane NVs displaying SIRPα variants with significantly increased affinity to CD47 and containing M2-to-M1 repolarization signals.[101] A multitarget inhibitor, CUDC101, and photosensitizer co-delivery were shown to inhibit CD47 and polarize TAMs to the M1 phenotype (Figure 5C). More surprisingly, PDT-induced p53 was also found to reprogram TAMs. As a result, the dual TME remodeling changed the ITM for potent therapeutic efficacy in combating tumor cells (Figure 5D-G).[70] TAM-expressed inhibitory receptor sialic-acid-binding Ig-like lectin 10 (Siglec-10) interacts with tumor-expressed CD24 to promote immune escape.[102] A nano-PIT strategy that co-delivered photosensitizer and sialic acid (SA) could target TAMs with high Siglec-10 expression and eliminate immunosuppression (Figure 5H).[71]

8. NANO-PIT BY RELIEVING THE ITM

The immunosuppressed TME is one of the reasons why many therapeutic approaches fail to exert the desired antitumor effect. All non-cancerous host cells in tumors, such as fibroblasts, endothelial cells, and adaptive and innate immune cells, and other noncellular elements like the extracellular matrix (ECM) and soluble products like chemokines, cytokines, and growth factors, are included in the TME.[103] TME plays different roles in tumor maintenance proliferative signaling, cell death resistance, angiogenesis induction, invasion and metastasis activation, tumor-promoting inflammation induction, and immune destruction avoidance. By focusing on TME elements or their signaling pathways, therapeutic interventions are made possible by this dependence on TME. The immune cells in TME have already been discussed separately, and this section focuses on the other elements in TME.

8.1. Based on the Tumor Vessel. The tumors' vasculature is highly abnormal and dysfunctional. The possibility of eradicating tumor by selectively destroying tumor blood vessels may represent an attractive therapeutic avenue.[105] Blocking angiogenesis slows tumor growth but may paradoxically increase metastasis. This paradox can be resolved by vascular normalization, including increasing pericyte coverage, improving tumor vascular perfusion, and decreasing vascular permeability, thereby reducing hypoxia. Tumor vascular normalization (TVN) can repair damaged tumor vessels, promote immune cell infiltration, and reduce the signaling of tumor metastasis.[106] TVN improves ITM and reduces hypoxia at the tumor site, resulting in immune checkpoint down-regulation, cytokines and immunosuppressive cells decrease.[107−109] The combination of PTT with sodium tanshinone IIA sulfonate (for TVN) enabled TME reengineering.[72] Nitric oxide (NO) is an important signaling molecule that regulates human life activities and induces the expression of endogenous angiogenic factors such as vascular endothelial growth factor and fibroblast growth factor. Nano-PIT could normalize tumor vasculature, alleviate hypoxia, and reprogram the immunosuppressed TME by coencapsulating NO donors and photothermal agents (Figure 6A).[73]

8.2. Targeting the Stromal Barriers. Solid tumors are characterized by a dense fibrotic stroma composed of abundant cancer-associated fibroblasts (CAFs) and an excessive ECM. These stromal barriers seriously compromise drug delivery to tumor cells and impede the antitumor effect. The first one targets the ECM by blocking its biogenesis, inhibiting its stiffness, and promoting its degradation. The second is to target CAFs by eliminating them, reducing their activity, and inducing CAFs quiescence. The last targets pro-stromal signaling by removing pro-stromal cytokines, blocking receptor activation, and inhibiting downstream signaling pathways.[110]

Hyaluronic acid is a major component of ECM in tumors. HAase could break down hyaluronic acid to enhance the EPR effect and improve the efficacy of nanoparticle-based PDT for tumor treatment *in vivo*.[74] Collagen is the most abundant tumor ECM protein. A semiconductor polymer nanoenzyme with photothermal activity was synthesized to digest collagen (Figure 6B). Under NIR light irradiation, the activity of the nanoenzyme could be increased 3.5-fold to digest collagen in the tumor ECM (Figure 6C), thereby increasing the accumulation of NPs in the tumor and thus improving PTT.[75] In addition to eliminating the ECM, eliminating CAFs is also an excellent therapeutic option. A fibroblast activating protein-specific single-stranded variable fragment was conjugated to a photosensitizer carrier's surface to kill CAFs selectively.[76]

8.3. Targeting the Other Immunosuppressive Targets of TME. Myeloid-derived suppressor cells (MDSCs) are a type of immunosuppressive cells of myeloid origin, consisting of immature macrophages, granulocytes, and DCs.[111] MDSCs can inhibit T-cell function through inducible NO synthase and arginase-1.[112,113] In a mouse lung cancer model, arginase inhibitor and receptor tyrosine kinase inhibitor prodrug complexes loaded by copper sulfide NPs were directed at MDSCs (Figure 6D) to counteract their immunosuppressive effect and increase the antitumor immune response.[77] IDO, an enzyme involved in the breakdown of tryptophan, serves a crucial immunosuppressive purpose in TME.[114] IDO causes a severe ITM characterized by a rise in functionally active Tregs and MDSCs and a decrease in T lymphocytes and NK cells.[115,116] IDO is essential for controlling peripheral immune tolerance. IDO overexpression in TME can potentially cause immunosuppression and facilitate immune evasion. IDO inhibitors can turn "cold" TME into "hot" TME and reactivate a potent immunological response. Various NPs have been developed recently for nano-PIT that combine phototherapeutic agents and IDO inhibitors with improving the overall antitumor effect.[117−119] The antitumor effects of phototherapy and IDO inhibitors, which target precise treatment at tumor locations and minimize side effects, have also been improved by many intelligent, responsive nanoplatforms.[120] Li et al. showed that inhibiting IDO-1 might overcome the adaptive immunological resistance brought on by PDT (Figure 6E).[78] The TGF-β inhibitor SB-431542 and

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Bioconjugate Chem. 2023, 34, 283−301

the chemotherapy medication mitoxantrone were placed onto reduced graphene oxide to construct a nano-PIT for great antitumor effect.[79]

8.4. Targeting Synergistic Reversal of ITM. The components of TME are interrelated and act together as a system, and when one pathway is regulated, it frequently leads to changes in other pathways. It may not be possible for cancer patients to treat the disease by focusing only on one target; instead, combined multi-target therapy will be attempted. Nano-PIT reversed ITM in increasing tumor immunogenicity after phototherapy, enhancing antigen presentation by targeting DCs, improving the response rate of ICB due to phototherapy-mediated immune checkpoint upregulation and resolving immune escape.[57,120]

Other cells in the TME are also used to improve ITM. The most prevalent white blood cells in peripheral circulation, neutrophils, move to inflammatory tumors.[121] Neutrophils are typically the first leukocytes to be drawn to sites of inflammation because they can infiltrate tumor sites and traverse vascular barriers.[122] Ibrutinib, a medication that affected ITM, was encapsulated in SA-coated liposome to target peripheral blood neutrophils after PDT/PTT to increase tumor internalization (Figure 6F). Ibrutinib enhanced antitumor effects by downregulating anti-inflammatory cytokines and inducing T-cell polarization.[104]

9. DISCUSSION

In tumor treatment, a single treatment method is often prone to tolerance or immune escape at a later stage and cannot completely cure the tumor. Researchers are therefore working to develop promising combination therapies to eradicate tumors completely. Antibody coupling-based NIR-PIT specifically binds photosensitizer-antibody couples to target cells by the antibody's ability to kill the target cells after laser irradiation. Due to the complexity of the TME, a single NIR-PIT cannot eradicate tumors and must be combined with other therapies, such as anti-PD-L1 and anti-CTLA-4, to effectively treat tumors. Additionally, they are typically administered sequentially when using NIR-PIT in combination with other techniques. This sequential drug administration makes it difficult to avoid the disadvantages of each of the two ways. Due to the different pharmacokinetic characteristics of these two drug molecules, this sequential dosing approach also usually makes it difficult to achieve effective synergy between the two therapeutic modalities. Therefore, nano-PIT is a promising strategy for cancer therapy, where NPs can co-encapsulate drugs with different immunotherapeutic agents and can be modified to have a variety of targeting or response capabilities. However, among the nano-PIT research in recent years, no projects have entered clinical trials for the time being. The construction of a nano-PIT with biocompatibility and stable co-delivery of multiple drugs is still a challenge, and some precise, targeted, and environmentally responsive nano-PIT are difficult to move from laboratory trials to mass production because of the complicated preparation methods. Several currently FDA-approved liposomes are prepared as lyophilized agents, which still need to be examined for the stability of nano-PIT when lyophilized.

In addition, some of the current nano-PIT strategies are only effective in animal tumor models. However, there are specific differences between animal and human tumors, and what is effective in animals may not necessarily apply to patients. It is exciting that FDA-approved liposomes, polymers, and albumin NPs have confirmed the promise of NPs for clinical applications. This also indicates that the application of nano-PIT is promising. In addition, the synergistic therapeutic index needs to be examined for different immunotherapeutic agents and phototherapeutic agents, and sometimes more is not better.

10. CONCLUSION AND PROSPECTS

Nano-PIT co-delivers phototherapeutic and immunotherapeutic agents to the tumor site for targeted PIT by constructing a specifically targeted nanoplatform that can lead to powerful antitumor effects. In this process, nano-PIT can reduce phototoxicity to normal tissues due to the targeting of NPs. Phototherapeutic agents can induce the ICD via PTT/PDT, release DAMPs and enhance immunogenicity at the tumor site. Nano-PIT can significantly improve the antitumor effect by enhancing immunogenicity, activating immune cells, and reversing immunosuppression in TME, which may effectively address the two barriers of weak immunogenicity and the presence of immunosuppression at tumor sites. There are more and more targets for cancer immunotherapy and more options for nano-PIT. Various immunotherapeutic agents further enhance the antitumor effect by targeting different targets to reverse the ITM or enhance the tumor immunogenicity and the effector cells' viability. Researchers have recently identified new targets for cancer immunotherapy, which could be combined with phototherapeutic agents for nano-PIT. B7 family related protein V-set and Ig domain-containing 4 (VSIG4)[123] and B7−H3 (CD276)[124] are negative regulators of T cell activation. Some new targets are associated with tumor immune escape: DDR1 (discoidin domain receptor 1),[125] mono-ADP-ribosyltransferase 1 (ART1),[126] endosomal sorting complex required for transport (ESCRT) proteins,[127] and CD161.[128] Several newly discovered targets have been shown to affect macrophage function: P-selectin glycoprotein ligand-1 (PSGL-1),[129] E3 ubiquitin ligase Cop1,[130] and G protein-coupled receptor 65 (GPR65).[131] To address the clinical needs, more biocompatible and widely applicable NPs are expected to be developed for the co-delivery of immunotherapeutic and phototherapeutic agents. Although nano-PIT is not yet available in clinics, many NPs have done so, which is encouraging for the future of nano-PIT. In the future, we hope that more attention will be paid to nano-PIT to realize its potential in cancer treatment and benefit more patients.

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Bioconjugate Chem. 2023, 34, 283−301

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Author Contributions

D.L. conceived the projects and writing-review and editing draft. K.L. and D.Y. analyzed and discussed the data. K.L. wrote the original paper. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

ADCC, antibody-dependent cellular cytotoxicity; APCs, antigen-presenting cells; ATP, adenosine triphosphate; CAFs, cancer-associated fibroblasts; CAR-T, chimeric antigen receptor T; Cdk4, cell cycle protein-dependent kinase 4; Ce6, chlorin e6; CRT, calreticulin; CTLA-4, cytotoxic T lymphocyte antigen-4; CTLs, cytotoxic T lymphocytes; DAMPs, damage-related molecular patterns; DCs, dendritic cells; ECM, extracellular matrix; EGFR, epidermal growth factor receptors; EPR, enhanced permeability and retention; ER, endoplasmic reticulum; FlaB, flagellin B; Gal-3, galectin3; GITR, glucocorticoid-induced tumor necrosis factor receptor family-related proteins; HAase, hyaluronidase; HMGB1, high mobility group box 1; ICD, immunogenic cell death; ICB, immune checkpoint blockade; ICG, indocyanine green; IDO, indoleamine 2,3-dioxygenase; IFN-γ, interferon-γ; IL-10, interleukin-10; im DCs, immature DCs; ITM, immunosuppressive tumor microenvironment; LPS, lipopolysaccharide; LTI, low tumor immunogenicity; MDSCs, myeloid-derived suppressor cells; MHC-I/II, major histocompatibility complex (MHC) class I and class II; NIR, near-infrared; NK, natural killer; NPs, nanoparticles; NVs, nanovesicles; OVA, ovalbumin; PAMPs, pathogen-associated molecular patterns; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; PDT, photodynamic therapy; PIT, photoimmunotherapy; PLGA, poly(lactic-*co*-glycolic); PRRs, pattern recognition receptors; PTT, photothermal therapy; ROS, reactive oxygen species; SA, sialic acid; scFv, single chain variable fragment; Siglec-10, sialic-acid-binding Ig-like lectin 10; siRNA, small interfering RNA; SIRPα, signal regulatory protein α; TAAs, tumor-associated antigens; TAMs, tumor-associated macrophages; TGF-β, transforming growth factor-β; Tim-3, T cell immunoglobulin mucin 3; TLRs, Toll-like receptors; TME, tumor microenvironment; TNF-α, tumor necrosis factor-α; TVN, tumor vascular normalization

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Bioconjugate Chem. 2023, 34, 283−301