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REVIEW

Stimuli-Responsive Drug Delivery Systems for Enhanced Melanoma Immunotherapy

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Abstract: Melanoma results in the formation of malignant tumors and is the deadliest form of skin cancer with high mortality rate. Immunotherapy for melanoma has made great breakthroughs in recent decades. However, low patient response rates and side effects due to the immunosuppressive tumor microenvironment (iTME) and tumor heterogeneity limit the clinical application of melanoma immunotherapy. The tumor microenvironment (TME) exhibits characteristics such as weak acidity, hypoxia, and aberrantly expressed proteases. By exploiting these features, researchers have developed stimuli-responsive drug delivery systems (DDSs) to enhance antitumor immune responses in melanoma patients. This review aims to clarify how stimuli-responsive DDSs enhance melanoma immunotherapy and guide their use as therapeutic agents. We summarize the categorization and design of these DDSs, analyze their immune-enhancing pathways, and discuss current challenges and future prospects in the field.

Keywords: malignant melanoma, stimuli-responsive, nanoparticles, immunotherapy

Introduction

Malignant melanoma (MM) results in the formation of malignant tumors of melanocyte origin and is one of the most malignant, aggressive and treatment-resistant types of skin cancer.[1,2] According to the World Health Organization, melanoma accounts for approximately 17.7% of global skin cancer cases but causes over 80% of skin cancer-related deaths, with 331,722 new cases and 58,667 fatalities reported in 2022. This disparity underscores its disproportionate lethality compared to non-melanoma skin cancers.[3,4] Traditional treatments, such as surgery, chemotherapy, radiotherapy, and targeted therapy, are less effective against melanoma.[5] Many studies have shown that MM has a high mutation load and results in the production of many tumor-specific and associated antigens,[6] thus, immunotherapy has become one of the most promising treatment modalities for MM. Cancer immunotherapy can dynamically regulate the immune system to enable immune cells to attack and eliminate cancer cells,[7] effectively preventing tumor recurrence and metastasis in a highly targeted and specific manner.[8] At present, CTLA-4 antibodies, anti-PD-1/PD-L1 antibodies, cytokines, interferons and other biological products are commonly used for clinical melanoma immunotherapy.[9]

Although these agents have shown great progress in MM treatment, many problems remain in the clinical application of immunotherapy. On the one hand, the nonspecific accumulation of immunotherapeutic agents reduces immunotherapeutic efficacy and causes adverse reactions. On the other hand, the characteristics of the iTME, such as hypoxia, acidity, and the overexpression of specific enzymes, hinders immune cell infiltration and the immune response, resulting in poor antimelanoma efficacy.[10] Therefore, stimuli-responsive DDSs have been developed to solve these problems. Stimuli-responsive DDSs with tunable sizes, shapes and structures can cross biological barriers, respond to specific stimuli and release drugs into the TME or tumor site to reduce adverse reactions and amplify the immune-mediated killing of melanoma cells. Stimuli-responsive DDSs-loaded TME modulators or immunotherapeutics combat melanoma via metabolic reprogramming, macrophage polarization,

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TME remodeling, and immunogenic cell death (ICD) induction, synergistically reversing immunosuppression and boosting antitumor immunity. Stimuli-responsive DDSs can enhance the immune response through the above strategies, are safe and biodegradable, and have become one of the most commonly reported immunotherapy methods for melanoma.

Herein, we summarize the relevant studies and compile the related work into one review to provide an update on the methods by which stimuli-responsive DDSs enhance melanoma immunotherapy. We first introduce the categorization and design of stimuli-responsive DDSs for melanoma immunotherapy, including endogenous stimuli-responsive DDSs (such as pH, hypoxia, reactive oxygen species (ROS), enzyme and multistimuli) and exogenous stimuli-responsive DDSs (light, ultrasound, magnetic and multistimuli) (Table 1). The synergistic mechanisms of stimuli-responsive DDSs and

Table 1 The List of Different Stimuli-Responsive Drug Delivery Systems of Melanoma Immunotherapy

Type		Sensitive Molecules/Bond	The Released Immunomodulators	References
Endogenous stimuli-responsive DDSs	pH	Borate ester	Purpurin 18, epacadostat	[11]
		Hydrazone bond	All-trans retinal, ovalbumin (OVA)	[12]
			Low molecular weight heparin (LMWH), gambogic acid (GA), maraviroc (MAR)	[13]
		Imine bonds	Oxaliplatin (Oxa), sialidase (Sia)	[14]
		Schiff base	1-MT, OVA	[15]
		Acetal groups	Cinnamaldehyde (CA), (pheophorbide (PA)	[16]
		Protonation	CRISPR/Cas9-Cdk5 plasmid (Cas9-Cdk5), paclitaxel (PTX)	[17]
			Melanoma-associated antigen peptide Trp-2, TLR4 agonist MPLA	[18]
			DOX, plasmid ovalbumin (pOVA)	[19]
			HPPH, IND	[20]
	Hypoxia	Azobenzene linkers	siRNA	[21]
			Poly(I:C)	[22]
		Nitroimidazole groups	IL-12	[23]
	ROS	Sulfoether group	aPD-L1, dextro-1-methyl tryptophan	[24]
		Phenylboronic acid groups	SN38, aPDL1	[25]
		mPEG-b-PMet	Dox, R848, aPD-1	[26]
		Reversible cross-linking agent NHS-TK-NHS, HA hydrogels	aOX40, aPD-1	[27]
	GSH	Disulfide bonds	Bcl2 siRNA	[28]
			dsDNA	[29]
			2-bromopalmitate (2-BP), camptothecin (CPT)	[30]
			ICG, PD-1 inhibitory polypeptide AUNP12	[31]
	Enzymes	MMP-2 responsive peptide, photosensitizer	Ce6, MMP-2 antagonist SB-3CT	[32]
		Hyaluronic acid	BMS, Ce6	[33]
		GNP had the potential of MMP-responsive controlled drug release	CAT, CD73siRNA	[34]
	pH+ROS	$CaCO_3$	Zeb, aPD1	[35]
	pH+enzymes	Tertiary amines, Gly-Phe-Leu-Gly (GFLG)	Imidazoquinoline (IMDQ)	[36]
		4-arm-polyethylene glycolmaleic anhydride, MMP-2 sensitive peptide CC-14	Nano-hydroxyapatite, lactate dehydrogenase A inhibitor (R)-GNE-140	[37]
		Protonation, disulfide bond	PD-L1 siRNA, Resveratrol	[38]
		β-amino ester, disulfide bonds	STAT3 siRNA, OVA	[39]
	Enzyme+GSH	MOS nanoparticle, HA	ICG, Dox	[40]
	ROS+GSH	Phenylboronic esters, disulfide bond	Curcumin, miR155	[41]

(*Continued*)

Table 1 (Continued).

Type		Sensitive Molecules/Bond	The Released Immunomodulators	References
Exogenous stimuli-responsive DDSs	Light	PEGylated bilirubin	Ce6, DOX	[42]
		Gold nanocage (AuNC)	Vemurafenib	[43]
		DPPC, photosensitizer	Hematoporphyrin monomethyl ether, R848	[44]
	Ultrasound	Ultrasmall barium titanate (BTO)	αPD-L1	[45]
		Iron oxide nanoparticles	Immunostimulatory adjuvant CpG-1826	[46]
		MNPs	PolyIC, R837	[47]
	pH+light	Acid-labile bonds, iron oxide nanoparticles	R848	[48]
	pH+ultrasound	Lipo-Ce6/TPZ@MH	Ce6, TPZ	[49]
	pH+magnetic	MnO@mSiO2-iRGD NPs	Mn^{2+}	[50]

immunomodulation, such as remodeling the TME, inducing immunogenic death, and multipathway combination therapy, is particularly emphasized. Finally, the application challenges and future development trends of stimuli-responsive DDSs for immunotherapy are presented. We anticipate that this review will offer valuable insights and facilitate the advancement and implementation of stimuli-responsive DDSs for immunotherapy, establishing a new paradigm for the next generation of melanoma immunotherapy (Figure 1).

Categorization and Design of Stimuli-Responsive DDSs for Melanoma Immunotherapy

Endogenous Stimuli-Responsive DDSs

pH-Responsive DDSs

Under hypoxic and nutrient-deficient conditions, melanoma cells rely substantially on oxygen-independent glycolysis to generate energy, leading to the accumulation of a large quantity of lactate.[51] To mitigate the intracellular toxicity caused by lactate buildup, melanoma cells actively exocytose lactate and protons through various pathways, resulting in an acidic extracellular pH within the TME that typically ranges from 6.5 to 6.8.[52] This acidic microenvironment, in contrast to the normal cellular pH range of 7.2 to 7.4, presents a unique opportunity for targeting melanoma. As a result, researchers have utilized acid-sensitive carriers to develop pH-responsive DDSs to facilitate the targeted delivery and controlled release of drugs melanoma immunotherapy.[53]

An acid-sensitive group inserted into the DDS carrier can be cleaved or destabilized in the TME. The acid-sensitive groups used in pH-responsive DDSs for melanoma immunotherapy can be divided into two types: those that have chemical bonds that are cleaved and those that are protonated or deprotonated in the TME. The acid-sensitive groups that have been reported in the melanoma immunotherapy literature to be cleaved in the TME include borate ester,[11] hydrazones,[12,13] imine bonds,[14] Schiff base,[15] acetal groups[16] and so on. Carboxyl and tertiary amino groups have been reported to be protonated or deprotonated in the TME, changing the charge or amphiphilicity of the carrier and resulting in destabilization and acid responsiveness.[17–19] For example, Li et al[20] designed pH-responsive smart nanovesicles (pRNVs/HPPH/IND) to deliver HPPH, a photosensitizer (PS), and the indoleamine 2, 3-dioxygenase (IDO) inhibitor indoximod (IND) (Figure 2A). In an acidic environment, pRNVs/HPPH/IND escape from the endosome, releasing HPPH and IND due to the positive charge of the protonated tertiary amine in the block copolymer polyethylene glycol-b-cationic polypeptide (PEG-b-cPPT) (Figure 2B). The experiments showed that the cumulative release of HPPH and IND in acetate buffer at pH 5.0 was 60%, which was much greater than that in buffer at pH 7.4 (Figure 2C). IND restores the mTOR pathway via P-S6K phosphorylation, stimulates $CD8^+$ T cells to regulate the TME, directly kills cancer cells and activates the immune system by inducing ICD through photodynamic therapy (PDT) mediated by the PS HPPH (Figure 2D).

Through acid-sensitive bond disruption or protonation/deprotonation, the pH-sensitive DDSs enhance melanoma immunotherapy by dynamically altering their morphology to modulate the release of immune adjuvants and amplify

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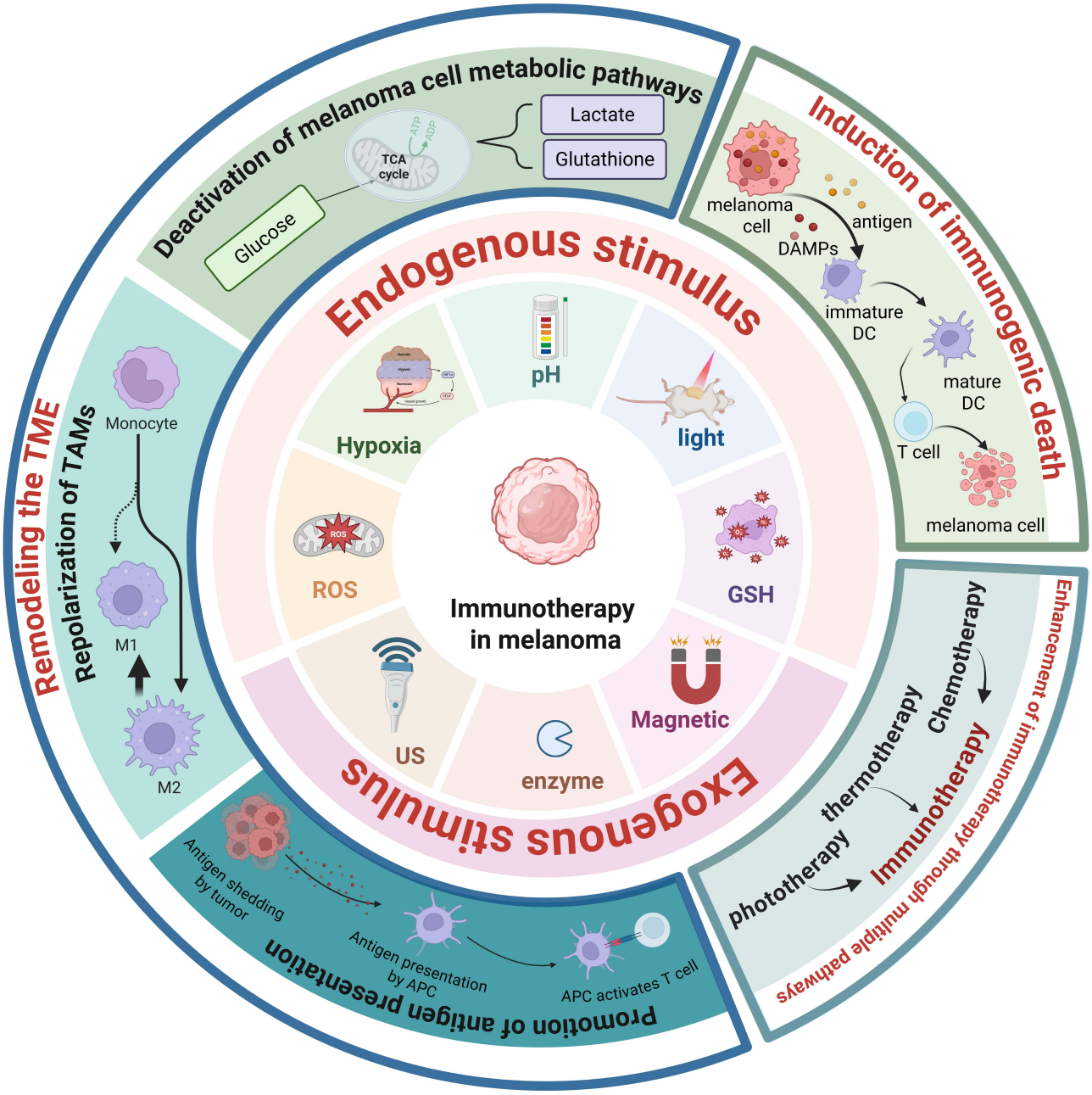

Figure 1 Schematic illustration of a stimuli-responsive DDS to enhance melanoma immunotherapy by remodeling the TME, inducing immunogenic death, and multi-pathway combination therapy. Created in BioRender. Zhang, G. (2025) https://BioRender.com/gb7alnr.

immune responses, and currently the acid-sensitive DDSs are the most commonly used stimuli-responsive DDSs for melanoma immunotherapy.[54,55] However, normal organs and lysosomes also have acidic environments, and thus, the accuracy of drug release from pH-sensitive DDSs needs to be further studied. To this, incorporation of molecular targeting moieties (eg, αvβ3 integrin ligands or CSPG4 antibodies) enables selective recognition of melanoma-specific surface markers, thereby improving tumor accumulation and reducing nonspecific payload release in normal tissues.[56] Secondly, the use of polymers with high pKa value to design DDS or destroy the lysosomal membrane through the "proton sponge effect". The resultant early endosomal escape mechanism effectively circumvents premature drug activation in lysosomal compartments while preserving therapeutic payload integrity until tumor-specific pH triggering occurs.[57]

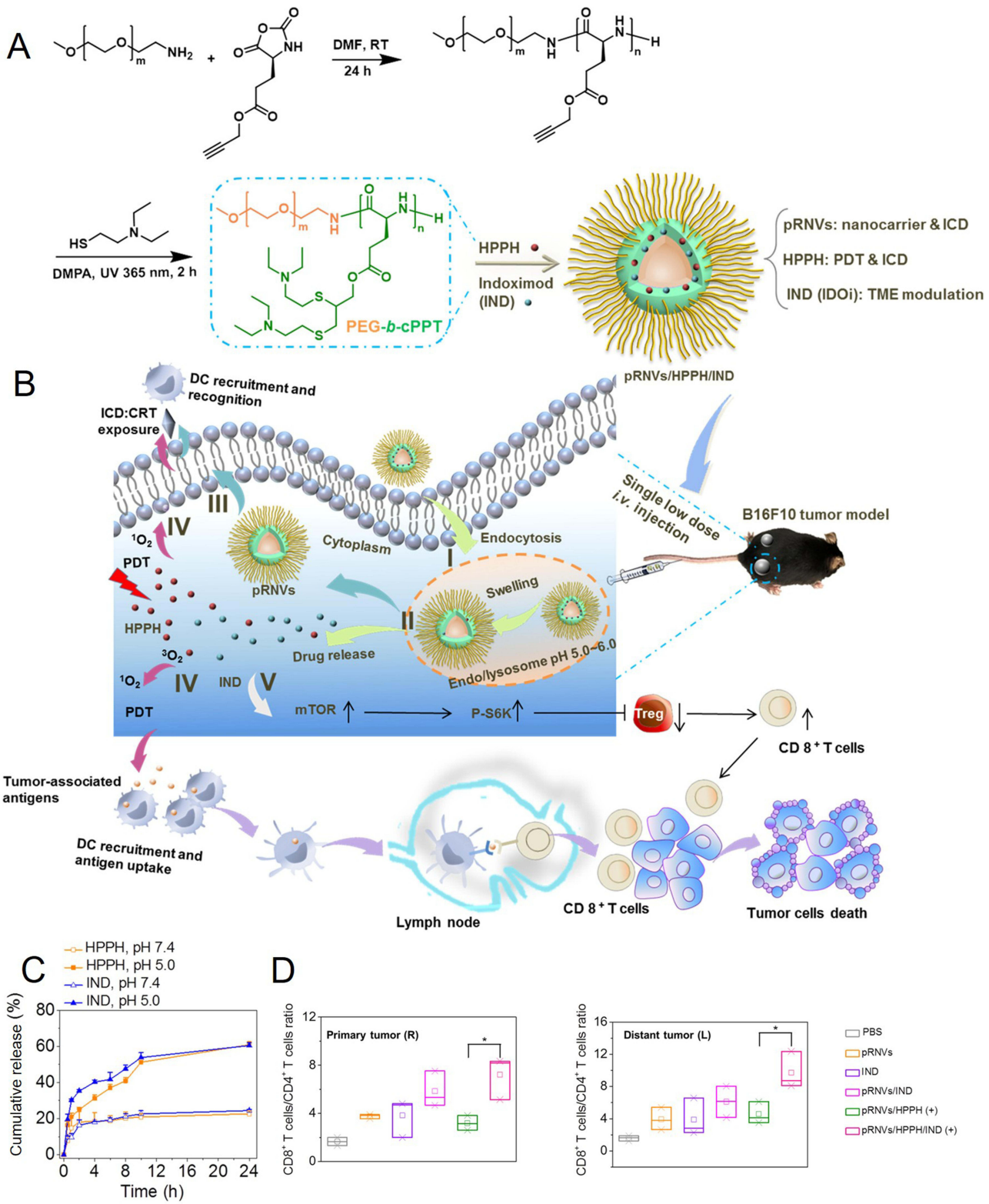

Figure 2 pH-responsive DDS. (**A**) Construction of pH-Responsive Nanovesicles (pRNVs/HPPH/IND). (**B**) Schematic illustration of pRNVs/HPPH/IND to promote host immunity and induce tumor cell death. (**C**) Transmission electron images of SNV incubated at pH 7.4 or 6.5 for 2 h. (**D**) Ratio of CD8 and CD4 T cells in both primary and distant tumors for mice after different formulation treatment. *P < 0.05. Image reproduced with permission from Yang W, Zhang F, Deng H et al. Smart Nanovesicle-Mediated Immunogenic Cell Death through Tumor Microenvironment Modulation for Effective Photodynamic Immunotherapy. *ACS Nano*. 2020;14(1):620–631. Copyright 2020 American Chemical Society.[20]

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Hypoxia-Responsive DDSs

The rapid proliferation of melanoma cells leads to increased oxygen consumption, and abnormal tumor angiogenesis leads to an insufficient oxygen supply. These two factors result in a melanoma cells existing in a hypoxic microenvironment.[58] Hypoxia-responsive functional groups, such as quinones, azobenzene derivatives[21,22] and nitroimidazole groups,[23] have been broadly integrated into carriers to construct hypoxia-responsive DDSs for melanoma immunotherapy.[59] Kang et al synthesized an anoxic cleavable block copolymer (PEG-azo-PLL) via azo splicing to deliver the double-stranded RNA analog polyinosine [poly(I:C)].[22] PEG-azo-PLL/poly(I:C) enhanced the polarization of M2-like tumor-associated macrophages (TAMs) that accumulate in the anoxic melanoma cells (Figure 3A and B). Under hypoxic conditions, the azobenzene linker was cleaved, removing the polyethylene glycol (PEG) shell from PEG-azo-PLL/poly(I:C), exposing positively charged PLL/poly(I:C) (Figure 3C and D). Poly(I:C) was then internalized by M2 macrophages, which reduced the number of M2-like TAMs in the TME, promoted the infiltration of $CD8^+$ T cells in vivo, reversed the immunosuppressive microenvironment and thus enhanced the effects of melanoma immunotherapy.

ROS-Responsive DDSs

ROS, such as free oxygen radicals and nonradical oxidants, are intermediate products of the redox reactions in which oxygen (O_2) is converted into H_2O.[60] Due to stimulation by various oncogenes, inflammation, or mitochondrial damage, increased ROS production and accumulation have been observed in cancer cells compared with that in normal cells.[61] In addition, many factors, such as ultraviolet radiation, melanin synthesis and the presence of enzymes in the NADPH oxidase (NOX) family, also lead to excessive ROS production in melanoma cells.[62] As a result, melanoma cells contain extremely high levels of ROS, and these excess ROS can induce oxidative stress and accelerate melanoma growth and metastasis compared with other solid tumors.[63] Many studies on melanoma immunotherapy DDSs have utilized different cleavable bonds, such as sulfoether group[24] and phenylboronic acid groups,[25] and some ROS response materials to achieve the release of ROS-responsive drugs.[26] Yu et al[27] constructed a dual physical and chemical ROS-responsive nanogel platform (aPD-1NCs&aOX40)@gel with gelatin for the sequential release of aPD-1 and aOX40 (Figure 4A). First, aPD-1 formed the aPD-1NCs nanocomplex in the presence of a reversible, ROS-responsive crosslinker (NHS-TK-NHS) and was subsequently coated with ROS-responsive hyaluronic acid (HA) hydrogels and aOX40. Upon ROS stimulation, owing to the strong sensitivity of the polymeric HA hydrogel to ROS, the release rate of aOX40 was faster than the chemical hydrolysis of aPD-1, which ensured the sequential release of the two therapeutic agents (Figure 4C). The initial release of aOX40 augmented T-cell activation and synergized with the sustained release of aPD-1 to bolster T-cell-mediated immunity, weaken immunosuppressive cells and effectively inhibit both primary and metastatic melanoma (Figure 4B).

GSH-Responsive DDSs

In solid tumor cells such as melanoma cells, glutathione (GSH) is one of the most abundant reducing metabolites that plays an important role in maintaining the redox balance. Because tumor cells need to produce large amounts of substances such as GSH to reduce the extensive damage caused by ROS, the concentration of GSH in tumor cells (2–10 mM) is much higher than that extracellularly (2–20 μM).[64] This difference can be exploited to design GSH-responsive DDSs. Some GSH-cleavable bonds, such as disulfide bonds,[28–30] have been effectively applied to prepare GSH-responsive DDSs for melanoma immunotherapy.[65] Ying et al used a metal–organic framework (MOF) to construct a GSH-responsive DDS (ICG-MOF-SS-AUNP12).[31] The PD-1 inhibitor polypeptide AUNP12 was modified on the surface of the MOF by disulfide bonds, and the photothermal agent indocyanine green (ICG) was embedded in the core (Figure 5A). In response to the high concentration of GSH in tumor tissue, AUNP12 is released at the tumor site, effectively promoting the maturation of dendritic cells (DCs) and activating the immune response. Moreover, the in vivo experimental results revealed that the ICG-MOF-SS-AUNP12 and laser groups had greater abilities to induce DC maturation (the maturation rate reached 37.53%), indicating that the photothermal effect of ICG significantly enhanced the effect of immunotherapy (Figure 5B).

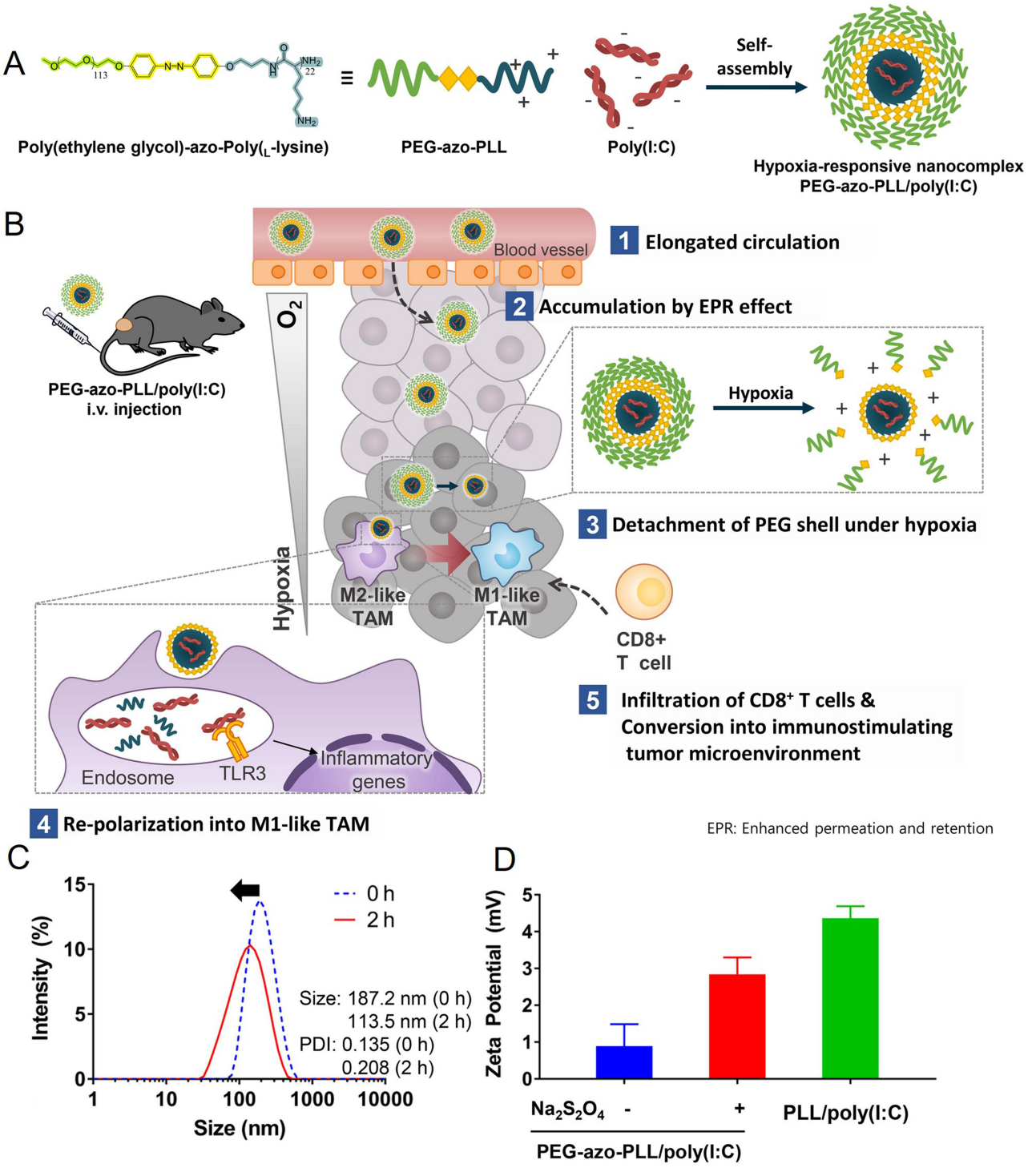

Figure 3 Hypoxia-responsive DDS. (**A**) Overall scheme illustrating re-polarization into M1-like TAMs by hypoxia-responsive PEG-azo-PLL/poly(I:C). (**B**) Preparation of PEG-azo-PLL/poly(I:C). (**C**) Overall scheme illustrating re-polarization into M1-like TAMs by hypoxia-responsive PEG-azo-PLL/poly(I:C) Hydrodynamic size profile of nanocomplex before and after the cleavage of the azobenzene linker. (**D**) Zeta potential of PEG-azo-PLL/poly(I:C) or PLL/poly(I:C) complex after incubation. Image reproduced with permission from Kang Y, Lim J, Saravanakumar G et al. Immunostimulation of tumor microenvironment by targeting tumor-associated macrophages with hypoxia-responsive nanocomplex for enhanced anti-tumor therapy. *J Control Release*. 2022;343:78–88. [22]

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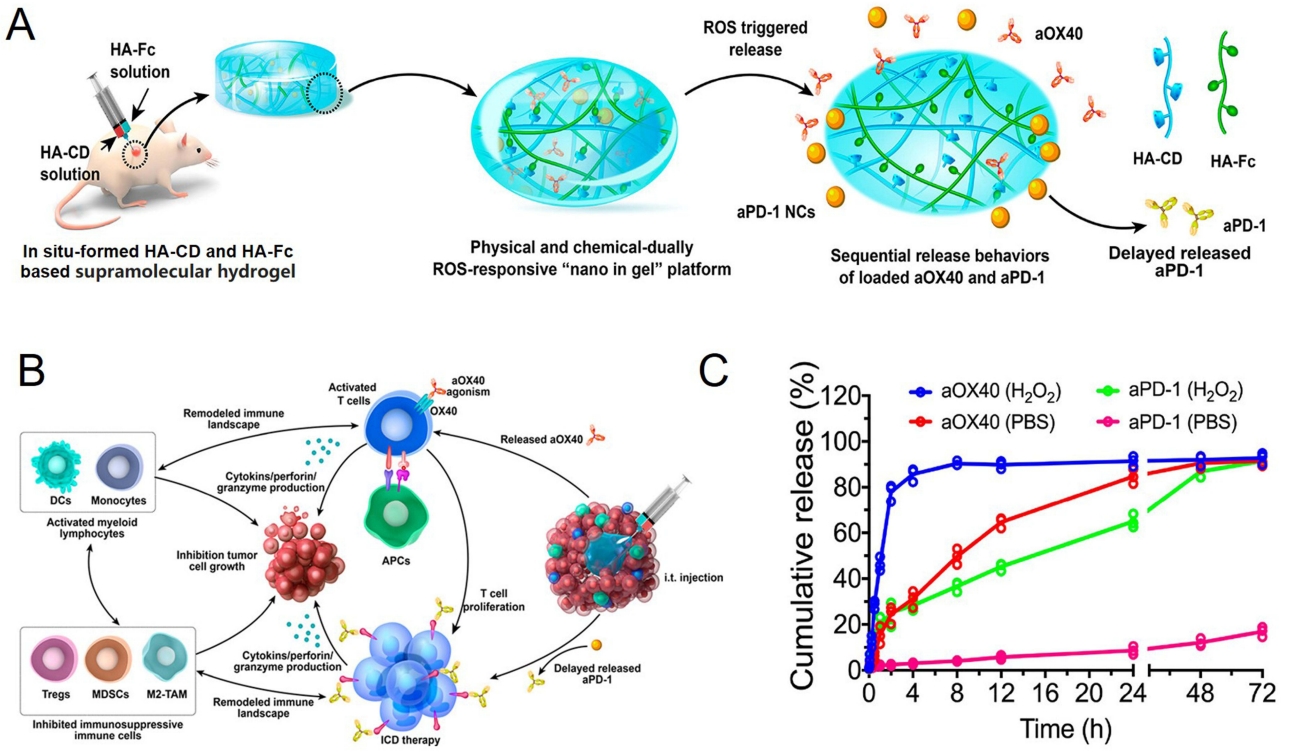

Figure 4 ROS-responsive DDS. (**A**) Schematic illustration of physical- and chemical-dually ROS-responsive nano-in-gel platform local delivery and sequential release of aOX40 and aPD-1. (**B**) Schematic illustration of (aPD-1NCsandaOX40)@Gels' antitumor mechanism. (**C**) In vitro release kinetics of aOX40 and aPD-1 from (aPD-1NCsandaOX40)@gels in PBS solutions with or without 0.5 mM H_2O_2. Image reproduced with permission from Fu Y, Huang Y, Li P et al. Physical- and Chemical-Dually ROS-Responsive Nano-in-Gel Platforms with Sequential Release of OX40 Agonist and PD-1 Inhibitor for Augmented Combination Immunotherapy. *Nano Lett.* 2023;23-(4):1424–1434. Copyright 2023 American Chemical Society.[27]

Enzyme-Responsive DDSs

The melanoma site contains numerous highly expressed enzymes, such as proteases (eg, matrix metalloproteinases and gelatinases), peptidases (eg, aminopeptidases), and lipases (eg, phospholipase A2), that play key roles in supporting and facilitating tumor growth, invasion and metastasis.[32] Melanoma cells express multiple matrix metalloproteinases (MMPs), and among them are gelatinases (MMP-2 and MMP-9), which drive tumor invasion and metastasis through two key mechanisms: facilitating epithelial-mesenchymal transition (EMT) to enhance cell motility, and degrading extracellular matrix (ECM) components to enable tissue penetration.[33,66] Various enzymes can specifically cleft polypeptide sequences, such as MMP-2/9 cleft GPLGVRGK and PLGLAG, aminopeptidase cleft unacylate amino acid, cytosolic phospholipaseA2 (cPLA2) cleavage acyl ester bond of membrane phospholipids at the *sn*-2 position.[67] Enzyme-responsive DDSs have been developed for use in melanoma immunotherapy by incorporating specific enzyme substrates into carriers.[68] Due to its high affinity for MMPs, the biocompatible material gelatin can be effectively cleaved by MMPs. Yuan et al[34] designed an MMP-responsive gelatin nanoparticle (CSG@B16F10) for the codelivery of oxygen-producing catalase (CAT) and CD73 siRNA (Figure 6A). Gelatin was effectively cleaved by the MMPs abundant in the melanoma TME to trigger the release of CAT and CD73 siRNA (Figure 6C and D). CAT transformed the excess hydrogen peroxide (H_2O_2) into O_2 to relieve hypoxia, and CD73 siRNA effectively inhibited CD73 protein expression (Figure 6B). After intravenous administration of CSG@B16F10 to melanoma-bearing mice, the levels of cytotoxic T cells and antitumor cytokine secretion increased and the levels of regulatory T cells (Tregs) decreased, and PD-L1 checkpoint blockade achieved optimal tumor suppression (~ 83%) (Figure 6E).

Multistimuli-Responsive DDSs

The TME is complex, thus, designing a multistimuli-responsive DDS can produce a cascade of responses to precisely deliver more drugs to melanoma cells, reduce side effects and enhance the effects of melanoma immunotherapy. In contrast to drug release in response to a single stimulus, drugs can be released from multistimuli-responsive DDSs in a programmed manner.[69]

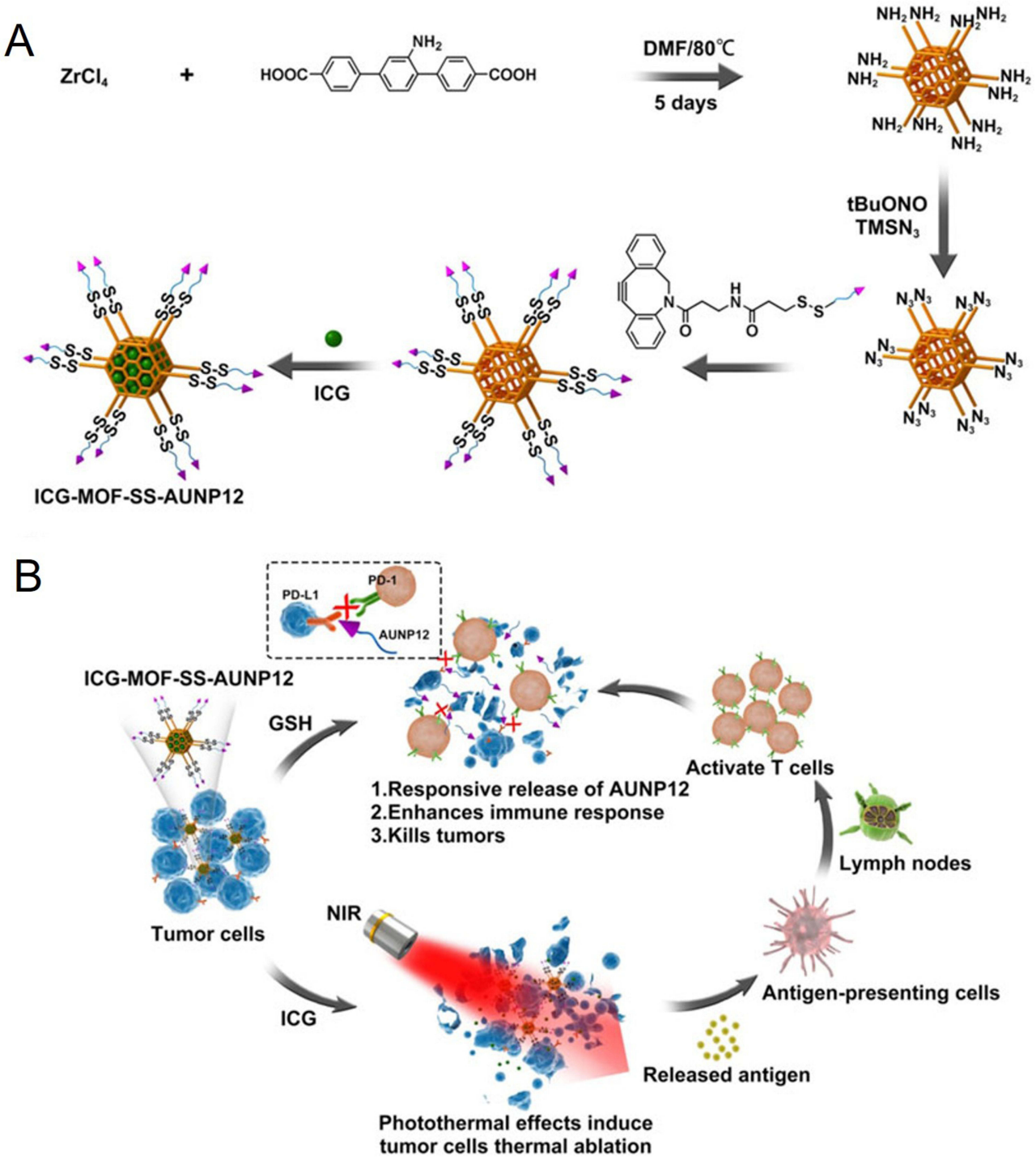

Figure 5 GSH-responsive DDS. The schematic diagram of (**A**) the construction and (**B**) the anti-tumor activity of ICG-MOF-SS-AUNP12 nanoparticles for synergistic photothermal and immunotherapy. Image reproduced with permission from Hao Y, Liu T, Zhou H et al. The GSH responsive indocyanine green loaded PD-1 inhibitory polypeptide AUNP12 modified MOF nanoparticles for photothermal and immunotherapy of melanoma. *Front Bioeng Biotechnol.* 2023;11:1294074.Copyright © 2023 Hao, Liu, Zhou, Peng, Li and Chen. CC-BY.[31]

The multistimuli responses reported in the literature for melanoma immunotherapy include pH-binding ROS,[35,70] pH-binding enzymes,[36,37] pH-binding GSH,[38,39] GSH-binding enzyme,[40] and GSH-binding ROS.[41] Low pH and excess ROS are two important features of the melanoma TME, and multistimuli-responsive DDSs with both pH- and ROS-responsive properties more effectively improve the efficiency of melanoma immunotherapy.[71] Dai et al[72] prepared a pH/ROS cascade-responsive

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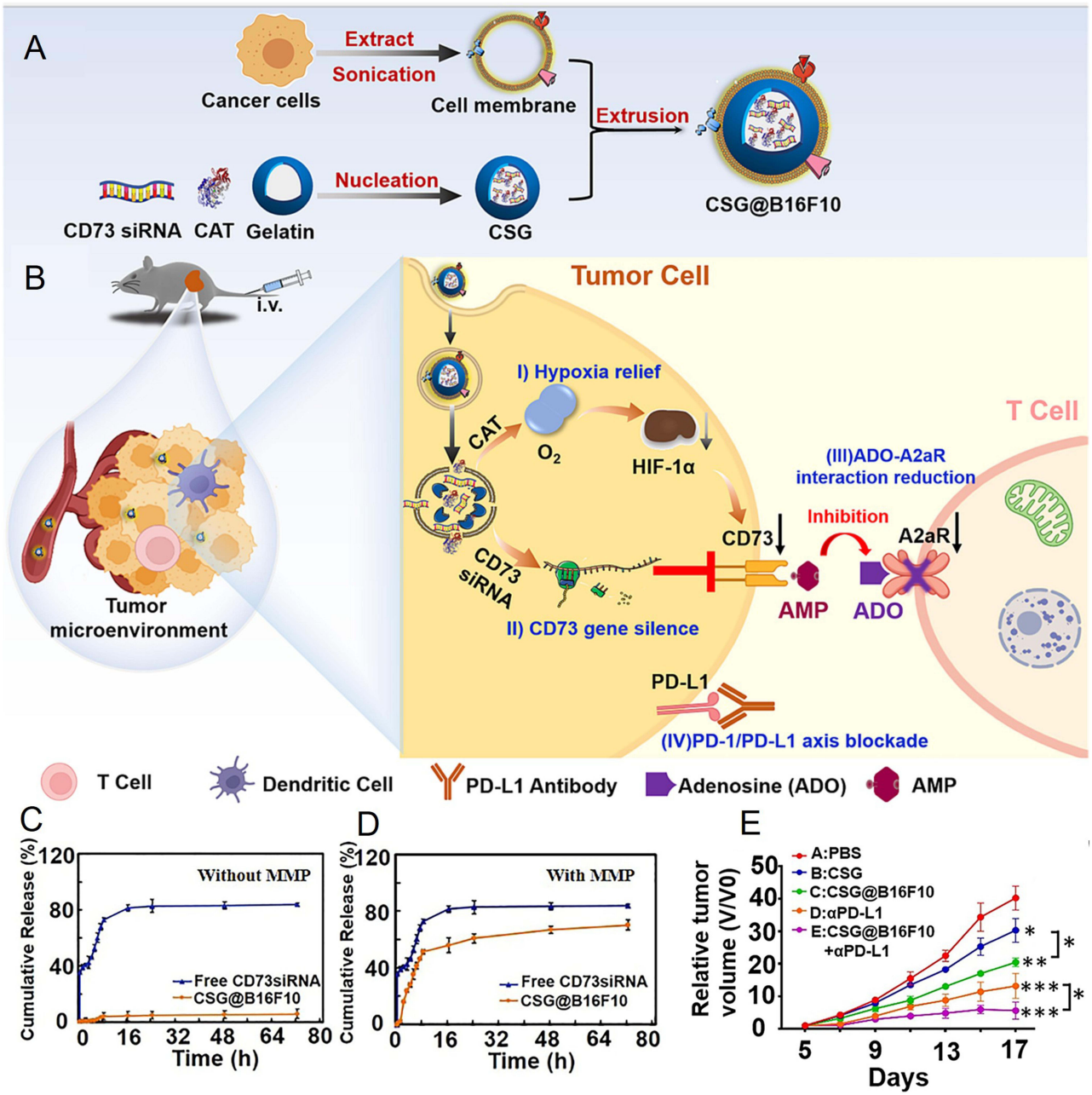

Figure 6 Enzyme-responsive DDS. (**A**) Protocol for the preparation of CSG@B16F10. (**B**) Anti-tumor therapeutic scheme illustration of CSG@B16F10 via intravenous administration. (**C**) In vitro CD73siRNA release profiles of CSG@B16F10 from 0 h to 72 h in physiological saline solution in the absence (C)/presence (**D**) of MMP. (**E**) Curves showing tumor volumes of mice after various treatments. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. Images A and B reproduced with permission from Yuan CS, Teng Z, Yang S et al. Reshaping hypoxia and silencing CD73 via biomimetic gelatin nanotherapeutics to boost immunotherapy. *J Control Release*. 2022;351:255–271. © 2022 Elsevier B. V. All rights reserved.[34]

prodrug micellar nanosystem (P(HCPT-DTDA)-PEI(HCPT)) for chemoimmunotherapy and synergistic remodeling of the TME. These nanoparticles (NPs) were covalently grafted with many 10-hydroxycamptothecin (HCPT) molecules into P-based (HCPT-DTDA) copolymers via ROS-cleavable linkers. Polyethylenimine (PEI) molecules were then introduced into P(HCPT-DTDA) to form the appropriately sized, positively charged core NP PHDP. Acid-responsive charge reversal polyanionic PEG-encapsulated poly(L-lysine)-modified dimethylmaleic anhydride (PEG-PLL-DMMA; PPD) was finally used to modify the surface of the core NPs via electrostatic interactions, which were loaded with siTGF-β to form PPD/PHDP@siTGF-β NPs (Figure 7A). The acid TME triggered the shedding of the PPD shell from the PPD/PHDP@siTGF-β

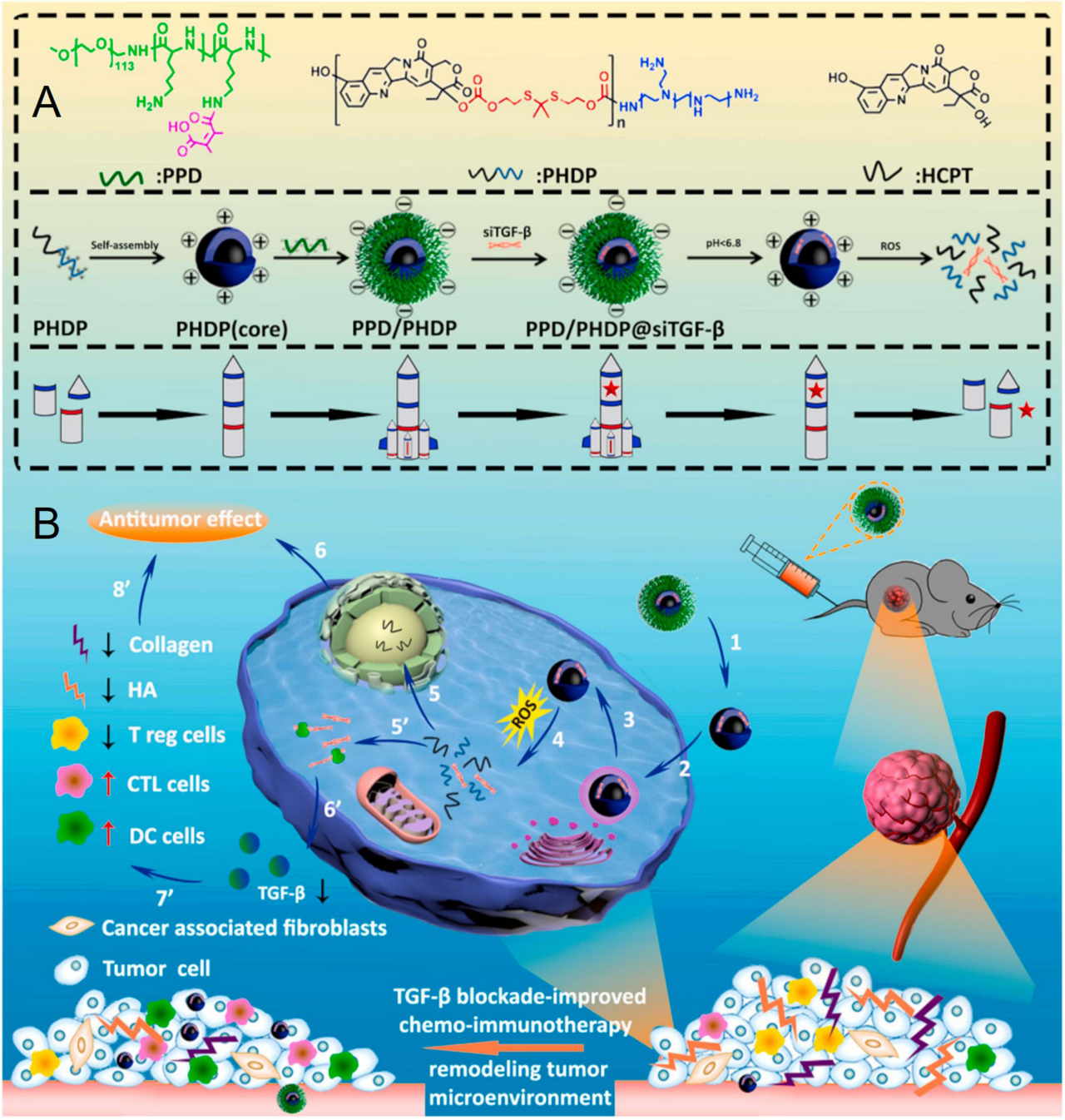

Figure 7 Multi-stage-responsive DDS. (**A**) Synthesis routes and disassembly mechanism of PPD/PHDP@siTGF-β micelleplexes. (**B**) illustration of PPD/PHDP@siTGF-β drug delivery system for tumor therapy in vivo. Image reproduced with permission from Dai L, Li X, Zheng X et al. TGF-β blockade-improved chemo-immunotherapy with pH/ROS cascade-responsive micelle via tumor microenvironment remodeling. *Biomaterials*. 2021;276:121010. © 2021 Elsevier Ltd. All rights reserved.[72]

NPs, thereby exposing the cationic PHDP core. Subsequently, under elevated ROS conditions, the ROS-cleavable crosslinked core underwent cleavage, leading to rapid co-release of HCPT and siTGF-β. This dual payload synergistically eliminated melanoma cells and activated antimelanoma immunity, ultimately achieving enhanced therapeutic efficacy through potent immune modulation (Figure 7B). Compared with single stimuli-responsive DDSs, these multistimuli-responsive DDSs could improve the accuracy of drug release.

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However, the complex synthesis steps needed to generate multistimuli-responsive DDSs may increase the toxicity of the product, thus, constructing rationally responsive DDSs for the particular application is important for facilitating melanoma immunotherapy.

Exogenous Stimuli-Responsive DDSs

Owing to the dense stroma and the dynamic TME of melanoma, endogenous stimuli-responsive DDSs may not be able to respond in a timely manner in the TME, resulting in immunotherapy failure.[73] Exogenous stimuli-responsive DDSs can precisely control drug release at the melanoma site. External stimuli include light, temperature, ultrasound, magnetic and electrical stimuli.[74] Unlike endogenous stimuli-responsive DDSs, exogenous stimuli are not affected by physiological or pathological factors, can adapt to the complex and dynamic physiological environment, and can regulate the immune response via remote control.

Light-Responsive DDSs

Light, a sensitive exogenous stimulus, offers the advantage of remote control, allowing for precise adjustments to the irradiation power and exposure time to selectively target local tumors.[75] Light-responsive molecules, such as PSs and photothermal agents, are key components of light-responsive DDSs. Upon light irradiation, these active substances undergo energy transfer, structural rearrangement, or chemical cleavage, generating ROS and heat, which in turn trigger drug release.[42,43] Moreover, ROS and heat cause a strong inflammatory response, thereby inducing neutrophils to quickly infiltrate the tumor site, improving the tumor response rate and enhancing immunotherapy.[76] Phototherapies, including PDT and photothermal therapy (PTT), utilize the photosensitization of PSs to produce ROS via intersystem crossing (ISC) or heat via nonradiative decay, effectively inducing ICD and thus stimulating the immune system.[77] Wang et al successfully prepared a light-responsive DDS integrating PDT, PTT and immunotherapy (RH@PSN@Lip) (Figure 8).[44]

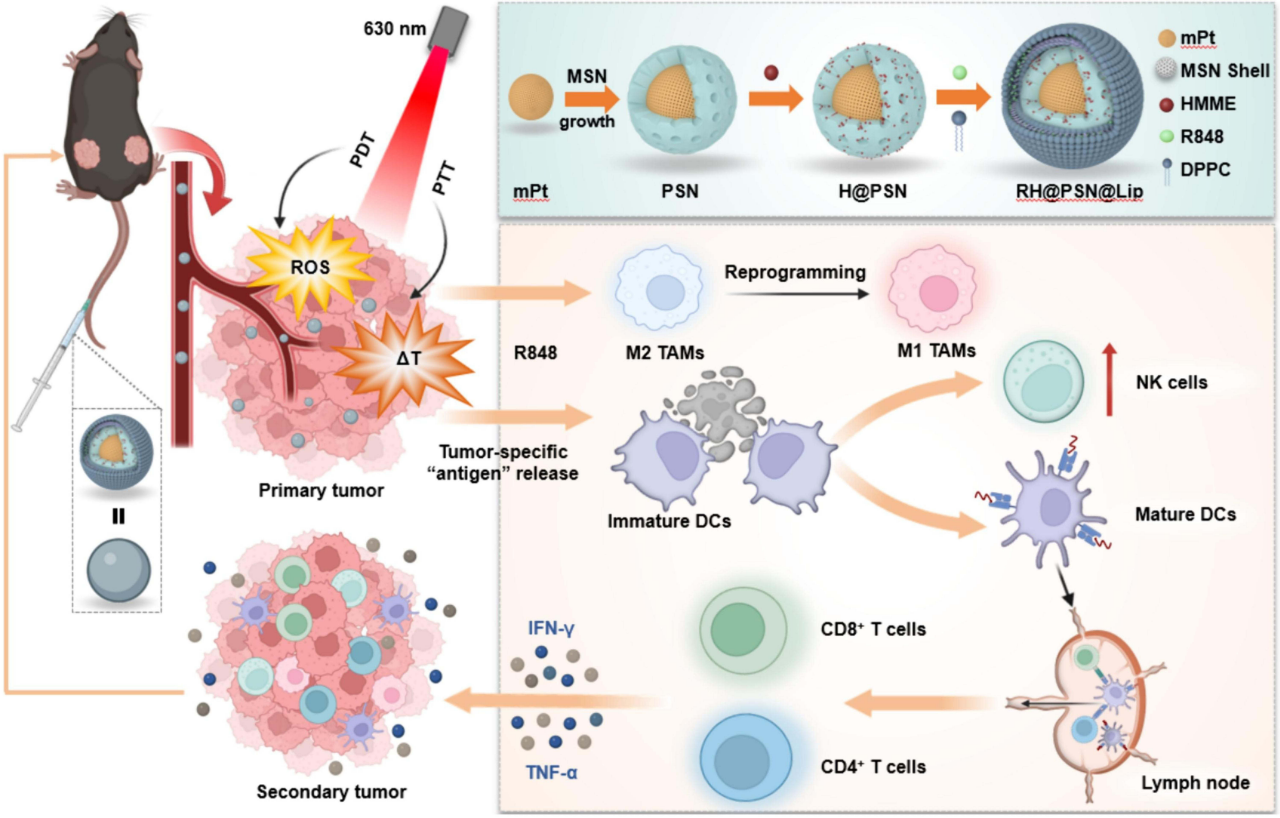

Figure 8 Schematic illustration of the fabrication process and working mechanisms of synergistic PDT/PTT/immunotherapy for cancer treatment. Image reproduced with permission from Wang X, Zhong X, Xie Z et al. A trinity Strategy: Mesoporous platinum nanoparticles serve as a photoenhanced nanoplatform for tumor immunotherapy. *Chem Eng J*. 2024:153365. © 2024 Elsevier B.V. All rights are reserved, including those for text and data mining, AI training, and similar technologies.[44]

H@PSN was obtained by coupling mesoporous platinum (mPt) NPs with the PS hematoporphyrin monomethyl ether (HMME). The surface of the H@PSNs was coated with liposomes composed of 1, 2-dipalmitoylphosphatidylcholine (DPPC) containing resiquimod (R848). Upon exposure to visible red laser irradiation, the PS HMME produced ROS, and efficient photothermal conversion was achieved by the HMME and mPt of RH@PSN@Lip. R848 was subsequently released from the thermally sensitive DPPC layer when the temperature increased, thus promoting DC maturation, increasing cytotoxic T lymphocyte (CTL) infiltration, and stimulating immune responses. Moreover, Pt has CAT-like activity and can catalyze the decomposition of the endogenous H_2O_2 into O_2, promote the production of ROS, further stimulate the systemic immune response, and effectively eradicate melanoma cells.

Despite significant advances in the fabrication and application of light-responsive DDSs, many challenges remain, such as overheating during PTT,[78] chemotherapeutic resistance,[79] and PDT resistance under hypoxic conditions.[80] To address these limitations, more powerful combined therapeutic systems need to be developed. Multifunctional materials should be designed, multiple therapeutic agents should be integrated with imaging agents, and different light-triggered therapies should be combined within a single platform.

Multistimuli-Responsive DDSs

Although external stimuli can provide an additional boost to allow drugs to reach their maximum release potential, external stimuli cannot autonomously reach the tumor site and do not have good biosafety.[81] Internal stimulation combined with external stimulation (such as light, temperature, or mechanical stimulation) can enhance the active tumor targeting and biosafety of multistimuli-responsive DDSs to produce a greater immune response and reduce adverse effects.[82]

pH-sensitive chemical bonds can be used to link a light-responsive moiety to the drug carrier, and when such a DDS enters the acidic melanoma microenvironment, the chemical bonds are partially cleaved, and the drugs are more easily released under light irradiation.[83] Such a light-responsive system combined with pH stimulation can achieve the targeted and timely release of drugs according to the specific pH of melanoma tissue. For example, Chen et al[48] synthesized a pH-responsive iron oxide NP (FGR) for PTT-enhanced chemodynamic immunotherapy using the iron oxide NPs as the core with a dextran-coupled Toll-like receptor (TLR) agonist (R848) coated on the surface via acid-sensitive bonds. In the acidic TME, the acid-sensitive bonds within FGR were hydrolyzed, which specifically released R848 to activate the TLR-7/8 pathway and promote the maturation of DCs. Moreover, FGR exerted a PTT-enhanced chemodynamic therapy (CDT) effect under near-infrared (NIR) laser irradiation, which mediated tumor cell apoptosis and ICD and significantly inhibited tumor growth and metastasis in a mouse model of melanoma.

Ultrasound, a clinically established imaging tool, also exhibits immunomodulatory potential to enhance cancer therapy, which therapeutic mechanisms include four modalities: high-intensity focused ultrasound (HIFU), low-intensity focused ultrasound (LIFU), ultrasonic cavitation (UC), and sonodynamic therapy (SDT).[84] In addition, ultrasound can help to precisely deliver immune agents to a sufficient depth. Ultrasound-responsive nanomaterials can help drugs cross the penetration barrier, improve tumor targeting, overcome the obstacles of immunotherapy, enhance tumor immunogenicity, and produce better immunotherapy effects.[45] For example, Zhao et al constructed a pH- and ultrasound-responsive fusion membrane biomimetic nanoliposome (lipop-Ce6/TPZ@MH) to enhance ICD and activate antitumor immunity.[49] The acoustic sensitizer chlorin e6 (Ce6) and the chemical drug tirapazamine (TPZ) were loaded into pH-sensitive liposomes coated with a hybrid red blood cell–platelet membrane (MH). Owing to the specific targeting function of the hybrid membrane, these liposomes accumulated at the tumor site, and the acid-sensitive lipid DOPE caused the dissolution of the liposomes to release Ce6 and TPZ in response to the acidic microenvironment. In the in vitro release experiments, the cumulative release of TPZ after 60 h at pH 5.5 was 50% greater than that at pH 7.4. Moreover, under local ultrasound stimulation, Ce6 produced many toxic ROS, leading to severe hypoxia at the tumor site, which then activated TPZ to induce further tumor cell apoptosis. The in vivo results revealed that approximately 53.2% of the calreticulin (CRT) was exposed upon lipop-Ce6/TPZ@MH treatment, which was significantly greater than its exposure in the other treatment groups. Moreover, almost no high mobility group 1 (HMGB1) was detected in the nucleus, indicating a significant improvement in ICD efficiency.

Magnetic fields are a common external stimulus, and traditional magnetic nanomaterials contain magnetic elements such as iron[46] and manganese (Mn).[47] Magnetic NPs can be used to deliver drugs for immune functions, for instance, Mn-based

nanomaterials can be used as biocompatible nanocarriers to deliver immunotherapeutic agents and activate the host immune system. Moreover, these nanomaterials can also act as immune adjuvants to increase antigen uptake and presentation, regulate the TME and promote the immune response.[85] Given their reactivity and biosafety in vivo, many magnetic NPs have been designed to also be responsive to pH.[86] The magnetic NPs are destabilized in the acidic environment of melanoma tumors. This prevents damage to normal tissue and enhances the degradation of the magnetic NPs, further ensuring their biosafety in vivo.[87] Sun et al prepared hollow mesoporous silica-coated MnO_2 NPs (MnO@mSiO_2-iRGD NPs) using the tumor-homing peptide iRGD (CRGDKGPD) for magnetic resonance imaging (MRI)-guided tumor immuno-chemokinetic combination therapy.[50] Under acid TME conditions, MnO@mSiO_2-iRGD NPs dissociate to achieve MRI-guided tumor-specific release of Mn^{2+}. This process triggers three synergistic therapeutic effects: competitive blockade of PD-1/antibody interactions, enhanced CTL infiltration and dual suppression of melanoma progression and metastasis.

The Mechanism by Which Stimuli-Responsive DDSs Enhance Melanoma Immunotherapy

Melanoma employ sophisticated immune evasion strategies, including impaired antigen presentation, recruitment of immunosuppressive cells, and metabolic reprogramming, fostering an iTME that drives tumor immune escape and reduces immunotherapy efficacy.[88] This section presents how stimuli-responsive DDSs enhance melanoma immunotherapy through three key mechanisms: remodeling the iTME, inducing ICD, and synergizing with multimodal therapies (chemotherapy, phototherapy, and other treatment modalities) to amplify antitumor immune responses.

Remodeling the TME

The microenvironment of melanoma tumors is a complex and multifaceted interaction network composed of tumor cells, immune cells, stromal cells, the extracellular matrix, secretory factors, blood vessels and lymphatic vessels.[89] In this microenvironment, numerous metabolic pathways are activated in response to the elevated nutritional demands of cancer cells, resulting in oxygen consumption and the production of various metabolites, including glucose, lactic acid, amino acids, and adenosine.[90] These metabolites further promote the growth of tumor cells while enhancing the inhibitory function of Tregs, weakening T-cell activity, and ultimately forming an iTME.[91] Hypoxia and other factors can also accelerate the polarization of macrophages into tumorigenic macrophages and intensify immunosuppression in melanoma.[92] Moreover, the antigen presentation ability of immune cells determines the effectiveness of the immune response, and the absence of antigen presentation in melanoma tumors reduces the T-cell activation, which induces immunosuppression.[93] In view of these characteristics of the iTME, the use of stimuli-responsive DDSs to regulate the metabolic pathways of melanoma cells, induce the polarization of M2 macrophages into M1 macrophages, and increase antigen presentation is expected to reshape the iTME and enhance melanoma immunotherapy efficacy.

Deactivation of Melanoma Cell Metabolic Pathways

Metabolic reprogramming is one of the key features of melanoma that results in alterations in glycolysis. Melanoma cells rely primarily on glycolysis for energy production. The aberrant metabolism of glucose depletes essential nutrients in immune cells and results in the production of immunosuppressive metabolites, leading to a hypoxic and acidic microenvironment and promoting immune evasion.[94] Therefore, inhibiting glucose metabolism in melanoma cells to improve the TME is an effective anticancer treatment strategy. Currently, strategies to inhibit glucose metabolism in the TME include inhibiting the glycolytic activity of tumor cells, targeting lactate in the TME, alleviating hypoxia in the TME, and targeting the PI3K/AKT/mTOR signaling pathway.[95–97] As an immunomodulatory factor in the iTME, tumor-derived lactate is a highly promising target for melanoma immunotherapy.[98] By targeting the lactate transporter monocarboxylate transporter (MCT) and lactate dehydrogenase (LDH) to inhibit the production of lactic acid in the TME or neutralizing lactic acid with proton pump inhibitors, the low pH of the TME can be raised, ultimately increasing immunotherapy efficacy.[99] Commonly used drugs for the melanoma immunotherapy include lactate oxidase (LOD),[100] MCT inhibitors,[101] and LDH inhibitors.[102] However, these drugs lack targeting. Stimuli-responsive DDSs can target the melanoma TME by responding to endogenous stimuli and inhibiting only glycolysis. In a previous study, Hu et al developed a smart GSH-responsive nanoparticle, MOF@LOD-siRNA@Lips-FA (MLSLF), to modulate lactate metabolism and promote effective antitumor immunotherapy (Figure 9A). [103] LOD and a siRNA against

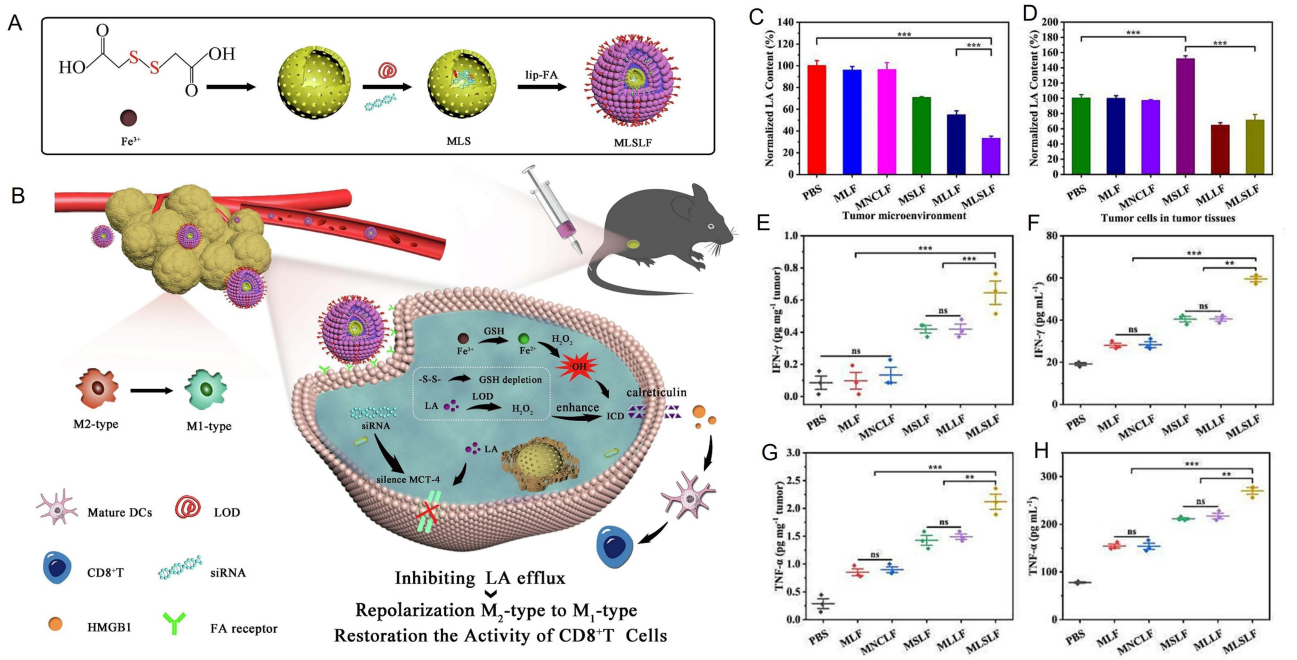

Figure 9 GSH-responsive DDS for reprogramming the immunosuppressive microenvironment. (**A**) Schematic illustration of Preparation of MLSLF. (**B**) Schematic illustration of therapeutic mechanism of MLSLF for efficient antitumor immunotherapy. (**C**) Normalized extracellular LA content of TME. (**D**) Normalized intracellular LA content of B16F10 tumor tissues. Cytokine levels of IFN-γ in tumor tissues (**E**) and in secretion (**F**). Cytokine levels of TNF-α in tumor tissues (**G**) and in secretion(**H**) after different treatments. $^{**}P < 0.01$, $^{***}P < 0.001$, ns: no significance. Data are expressed as means SD (n = 5). Image reproduced with permission from Hu H, Dai Z, Zhang F et al. Metal organic frameworks based intelligent nanoadjuvants for boosting tumor immunotherapy through enhanced ICD and lactic acid regulation. *Chem Eng J*. 2024;479:147464. © 2023 Elsevier B.V. All rights reserved.[103]

MCT4 were loaded into the Fe-MOF and modified with folate liposomes (FA-lips) to yield MLSLF. In the GSH-overexpressing melanoma microenvironment, the disulfide bonds in MLSLF are cleaved in response to endogenous GSH, releasing LOD and the siRNA (Figure 9B). siRNA-mediated downregulation of MCT4 effectively silenced MCT4, thereby inhibiting lactate efflux (Figure 9C), while LOD catalyzed the conversion of intracellular lactate (Figure 9D), effectively blocking lactate metabolism in melanoma cells. The In vivo results show MLSLF significantly elevates proinflammatory cytokines interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α) levels in tumors and systemic circulation versus controls (Figure 9E–H), demonstrating systemic immune activation for enhanced therapeutic efficacy.

In addition to glucose metabolism, melanoma cells can also obtain energy and substances through other metabolic pathways, such as amino acid metabolism. Elevated levels of the amino acids tryptophan (Trp) and arginine (Arg) are common TME markers and clinical manifestations of melanoma.[104] The immunosuppressive effects of IDO are related to Trp metabolism, making IDO an effective target for melanoma immunotherapy. IDO1 can enzymatically convert tryptophan, which is essential for T-cell function, into kynurenine (Kyn), leading to immunosuppression. This mechanism significantly reduces the efficacy of immune checkpoint blockade (ICB). Small-molecule inhibitors of IDO, such as epacadostat (EPA) and NLG919, have been utilized to inhibit this pathway.[105,106] However, EPA demonstrated limited efficacy in inhibiting IDO at tumor sites in Phase III clinical trials, which may be due to poor pharmacokinetics and an inappropriate dosage.[107] Consequently, an increasing number of researchers are investigating the application of reactive nanocarriers for the delivery IDO inhibitors, aiming to improve their targeted delivery and effective penetration within the TME.[108] Dai et al[109] constructed dual pH/redox-responsive micelles to codeliver NLG919 and curcumin (CUR) for IDO-mediated immunotherapy. In the acidic melanoma microenvironment, the 2-propionic-3-methylmaleic anhydride (CDM) linkers of the vesicles were cleaved, and the PEG layers dissociated, causing the particle size to decrease and the charge to reverse, subsequently, the micelles were more easily endocytosed by melanoma cells. The endocytosed vesicles rapidly released CUR and NLG919 upon GSH hydrolysis in the cell (Figure 10A). The in vivo results revealed that these pH/redox-responsive micelles significantly reduced the Kyn/Trp ratio, effectively regulated amino acid metabolism,

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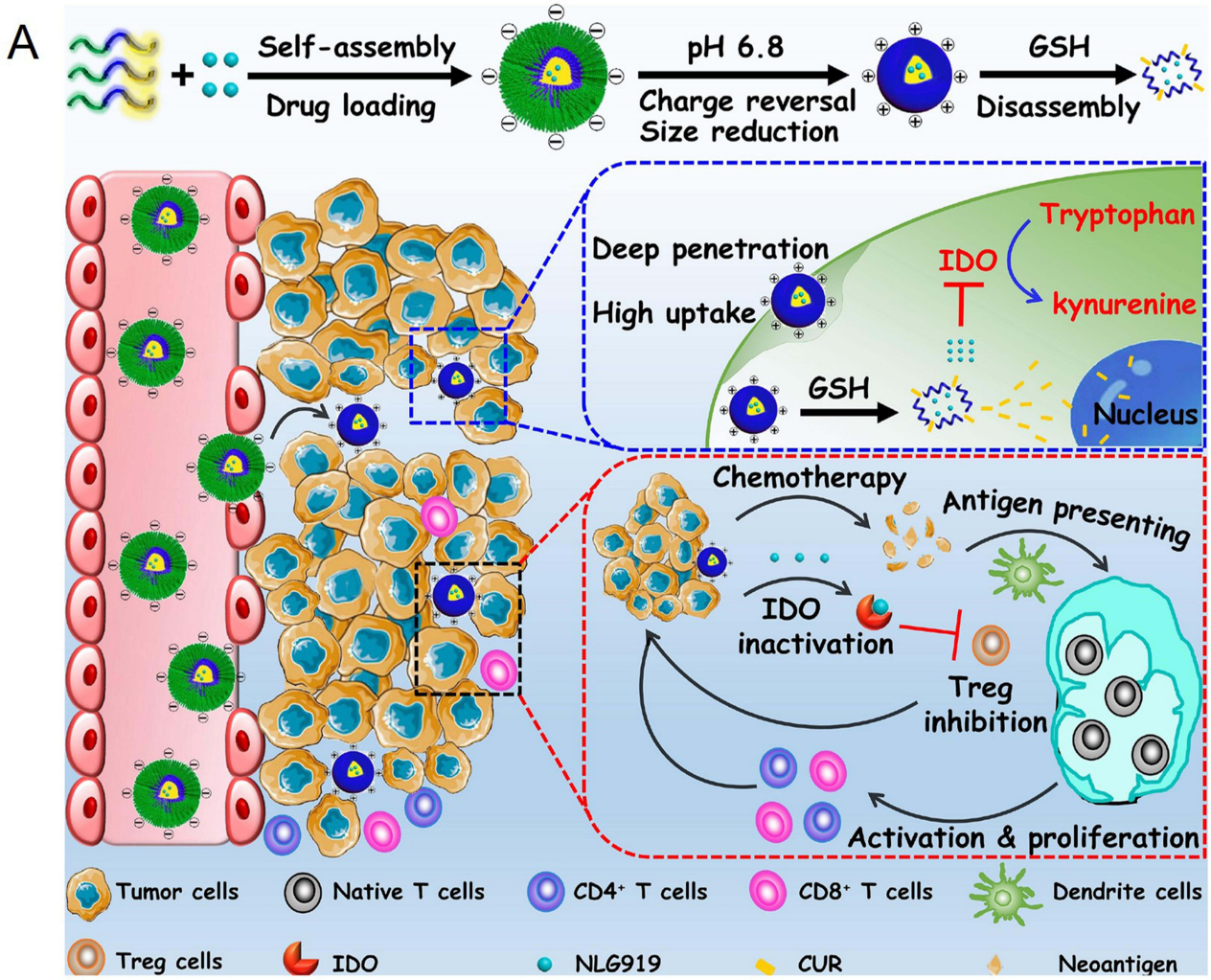

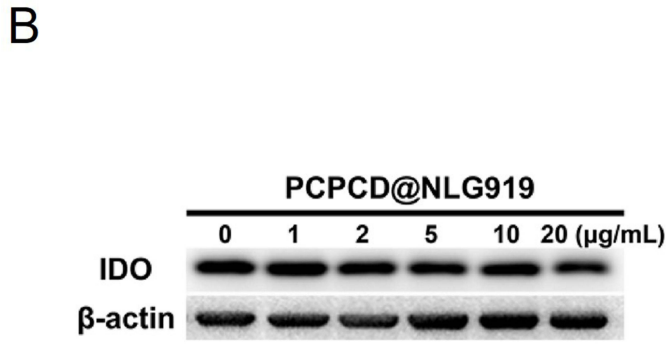

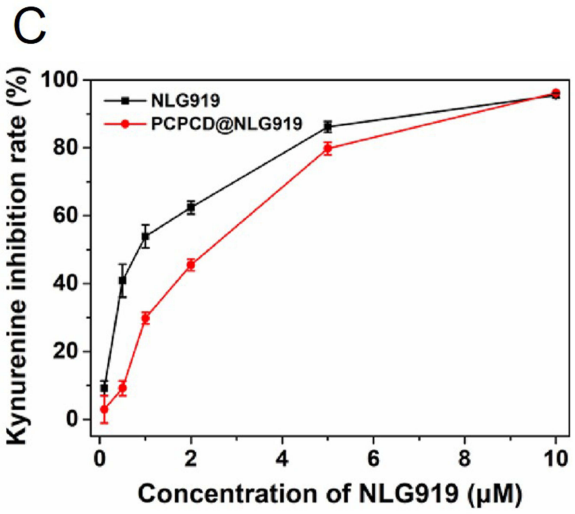

Figure 10 Dual-responsive DDS for reprogramming amino acid metabolism to enhance ICD. (**A**) Illustration of size-shrinkable and charge-reversal PCPCD system for tumor chemo-immunotherapy in vivo. (**B**) Effect of PCPCD@NLG919 on the expression of IDO after treatment. (**C**) In vitro inhibitory activity of IDO of B16F10 cells after culture with free NLG919 or PCPCD@NLG919 micelles plus IFN-γ. Image reproduced with permission from Dai L, Li X, Yao M et al. Programmable prodrug micelle with size-shrinkage and charge-reversal for chemotherapy-improved IDO immunotherapy. *Biomaterials*. 2020;241:119901. © 2020 Elsevier Ltd. All rights reserved.[109]

increased the maturation of DCs, and promoted the recruitment of CTLs, helper $CD4^+$ T cells, and natural killer (NK) cells to the tumor, alleviating immunosuppression (Figure 10B–C).

Repolarization of TAMs

TAMs are prevalent in the melanoma microenvironment and significantly influence melanoma growth and metastasis. TAMs exhibit plasticity, dynamically transitioning between M1-like and M2-like phenotypes. M1-like TAMs, characterized by their secretion of proinflammatory mediators, contribute to the elimination of melanoma cells.[110] Conversely, M2-like TAMs directly block T-cell activity or inhibit T-cell proliferation through indirect pathways, thereby abolishing the antitumor functions of T cells and NK cells and ultimately promoting the formation of an iTME.[111] Methods exploiting TAMs to relieve immune suppression and improve immunotherapy efficacy against melanoma have been reported in many studies.[112] For example, blocking CSF1R signaling to deplete or reprogram TAMs, inducing M2-to-M1 macrophage polarization, inhibiting CCL2/CCR2-mediated TAM recruitment to TME, and enhancing TAM-mediated phagocytosis of cancer cells through CD47/SIRPα axis blockade.[113] Accumulating evidence indicates that reprogramming macrophages from an M2 phenotype to an M1 phenotype is pivotal in eliciting robust antimelanoma immune responses.[114] Several immunomodulators, including type I interferons (such as IFN-α and IFN-β), type II interferons (such as IFN-γ), COX-2 inhibitors (such as celecoxib) and IL-1β inhibitors, have been reported to repolarize TAMs.[115] These drugs are generally not tumor specific, have low bioavailability and lack high affinity.[116] Hence, it is necessary to use stimuli-responsive DDSs to ensure the precise delivery of these drugs to melanoma tissue. Tang et al designed a GSH-responsive nanogel to remodel the TAM phenotype and improve the melanoma TME to enhance immunotherapy.[117] The disulfide bond in nanogel acts as a GSH response switch, triggering the release of metformin in the presence of high concentrations of GSH, which effectively polarizes M2 macrophages to M1 macrophages via the AMPK–NF-kB signaling pathway. Furthermore, Song et al engineered an IL4RPEP-1-targeted pH-sensitive nanoplatform (A&C IPP NPs) to reprogram M2 macrophages to M1 macrophages and remodel the TME in melanoma (Figure 11A).[118] The NPs utilized targeted peptide IL4RPep-1 to selectively target melanoma cells overexpressing IL-4 receptors. Under acidic TME conditions, the NPs exhibited triggered release of afuresertib (ASB, an AKT inhibitor) and celecoxib (CXB) (Figure 11B). In vivo analyses demonstrated that A&C IPP NPs significantly elevated IL-12 levels compared to free drug formulations (Figure 11C), and the M2 macrophage marker CD206 was downregulated and the M1 macrophage marker CD86 was upregulated in tumors treated with A&C IPP NPs (Figure 11F), confirming TAM repolarization from immunosuppressive M2 to antitumor M1 phenotypes. Concurrently, robust increases in TNF-α and IFN-γ secretion were observed (Figure 11D and E), collectively indicating potent antitumor immune activation. These findings underscore the dual capacity of A&C IPP NPs to remodel the TME and suppress melanoma progression through enhanced immunomodulation.

Promotion of Antigen Presentation

T cells can be effectively reactivated using monoclonal antibodies designed to target specific immune checkpoints. Such reactivation allows the immune system to resume its attack on melanoma cells by recognizing and consistently and effectively destroying them.[119] However, owing to the extreme adaptability and resilience of melanoma cells, they are prone to developing resistance to immune checkpoint inhibitors.[120] A key factor contributing to this resistance is the inadequate expression or presentation of tumor-associated antigens (TAAs). When TAAs are poorly expressed or effectively evade immune surveillance, T cells are unable to recognize and target melanoma cells. Several hypomethylating agents (HMAs), including 5-azacytidine (AC), 5-aza-2′-deoxycytidine (DAC), zebularine (Zeb), and 5-fluor-2′-deoxycytidine (5-F), have been reported to effectively promote TAA presentation.[121] Owing to the lack of targeting functions, stand-alone HMA therapies require relatively high doses and may cause adverse reactions.[122] Thus, the use of stimuli-responsive nanocarriers can allow low doses of HMAs to be delivered in a targeted manner, increasing TAA expression, enhancing sensitivity to ICB, and delivering ICB agents to improve immunotherapy efficacy. To this end, a dual bioresponsive gel depot was designed by Ruan et al to codeliver an anti-PD1 antibody (aPD1) and Zeb.[35] The aPD1 was encapsulated in a ROS-responsive hydrogel (Zeb-aPD1-NP-Gel) along with Zeb after being loaded into pH-sensitive calcium carbonate NPs ($CaCO_3$ NPs). Zeb increased the expression of MAGE-E1, TRP1 and CD146 to promote TAA presentation, improved immunogenicity against melanoma cells, and enhanced the capture of tumor antigens by

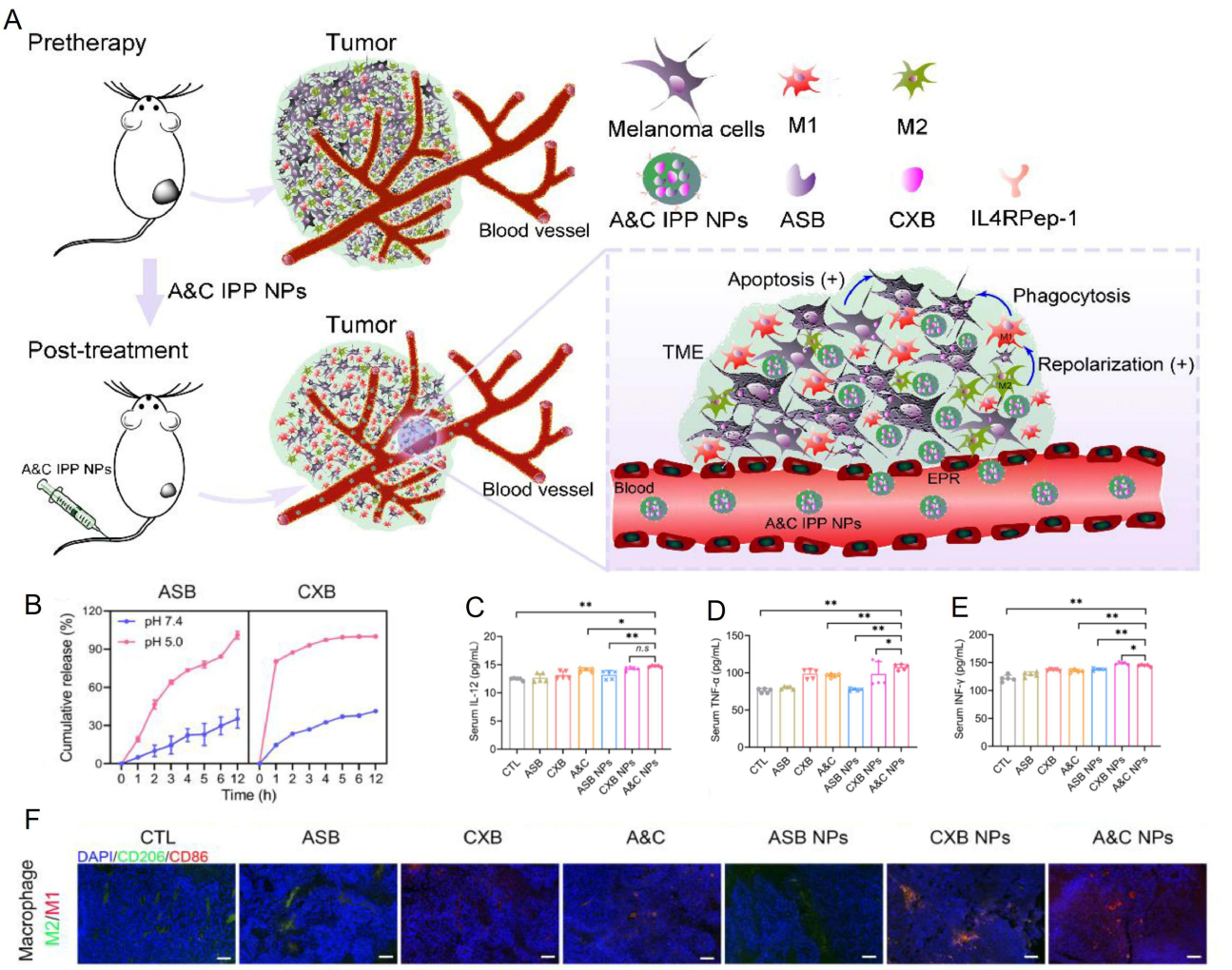

Figure 11 pH-responsive DDS for Repolarizing TAMs. (**A**) Schematic Illustration of the use of IPP NPs for enhanced in vivo tumor chemo-immunotherapy therapy. (**B**) The cumulative release profile of ASB and CXB from IPP NPs. (**C**–**E**) Serum IL-12, TNF-α, and INF-γ levels. (**F**) Representative immunofluorescence staining images show the distribution of $CD206^+$ M2-type macrophages (green) and $CD86^+$ M1-type macrophages (red) in tumor tissues after different treatments (scale bars: 50 μm). NPs: IPP NPs. $^*P < 0.05$, $^{**}P < 0.01$, n.s: no significance. Data were presented as mean ± SD (n = 5). Image reproduced with permission from Song M, Zhu B, Qiu S et al. Codelivery of afuresertib and celecoxib by IL4RPep-1-targeting nanoparticles for effective treatment against melanoma. *Applied Materials Today.* 2023;33:101868. Copyright 2023 Elsevier.[118]

antigen-presenting cells. Zeb also upregulated PD-L1 in B16F10 tumors, increasing tumor sensitivity to PD-1/PD-L1 checkpoint blockade therapy and effectively enhancing immune system activation, leading to a robust immune response to melanoma.

STING is an important signal transduction pathway in innate immunity and one of the most important components of the cGAS-STING pathway. Activation of the cGAS-STING pathway can enhance antitumor antigen presentation, induce the release of type I interferon I (IFN-I) and other inflammatory cytokines, promote T-cell infiltration, and enhance immune-mediated killing activity, giving STING great potential in tumor immunotherapy.[123] Epigenetically silenced STING in melanoma drives immune escape, making its activation a promising therapeutic strategy. The use of cGAS antagonists, STING agonists and STING antagonists can effectively regulate the cGAS-STING pathway and activate the immune response. However, the efficacy of these immunomodulators is limited by several factors, including rapid immune clearance, inadequate cytoplasmic delivery, a lack of specific cell targeting, and a systemic inflammatory response, which impede their use in immunotherapy.[124] Stimuli-responsive DDSs can protect these immunomodulators from enzymatic degradation and promote their delivery. Li et al designed GSH-responsive dendritic mesoporous silicone nanoparticles (DMONs) that respond to the TME.[29] GSH-responsive disulfide bonds in DMONs enable tumor-specific

biodegradation, releasing encapsulated dsDNA to trigger IFN-I production, DC maturation, and T-cell activation in B16F10 melanoma models.

Induction of Immunogenic Death

ICD is a specific mode of tumor cell death that can trigger a tumor-specific immune response through the release of damage-associated molecular patterns (DAMPs) and TAAs in the TME.[125] ICD-induced immunotherapy holds great promise for the complete eradication of melanoma tumors and the establishment of long-lasting protective antimelanoma immunity.[126] Common ICD induction strategies for melanoma include chemotherapeutic agents, PTT, PDT, and radiotherapy, which can activate adaptive immune responses.[127] However, nonspecific delivery of these inducers can lead to significant systemic toxicity and compromise the host immune system.[128] To precisely control drug release at the tumor site to promote antimelanoma immunogenicity and minimize systemic adverse effects, stimuli-responsive DDSs have been used to improve melanoma immunotherapy by enhancing ICD of melanoma cells.[129]

Stimuli-responsive DDSs can be used for the targeted delivery of chemotherapeutic agents, including doxorubicin (DOX), cyclophosphamide, methotrexate, and oxaliplatin.[130] This class of medications can induce apoptosis in nonendoplasmic reticulum (ER)-targeted cells under moderate ER stress conditions. This process leads to the release of CRT as well as DAMPs and the activation of immune cells.[77,131] Zhang et al employed aromatic thione (ATK) as a ROS-sensitive linker to conjugate DOX and cutaneous dextran sulfate (DS) to construct a ROS-responsive nanodrug delivery system (DOX/ADS NPs) (Figure 12A).[132] In a murine B16F10 melanoma model, the melanoma-targeted DS-based nanoinducers (DOX/ADS NPs) exhibited superior DOX release and more significant suppression of B16F10 tumor cells than did free DOX and the nonfunctionalized nanomedicine DOX/UDS NPs (Figure 12B–E). Furthermore, the DOX/ADS NPs effectively induced the translocation of CRT to the cell membrane in vivo, facilitating DC maturation and T-cell proliferation, increasing the infiltration of CTLs, raising the CTL-to-Treg ratio, elevating the levels of cytotoxic cytokines, and activating the immune response against melanoma (Figure 12F). The responsive nanocarriers demonstrated superior drug loading capacity and responsiveness to release cues, were able to deliver drugs in a targeted manner to melanoma sites via their homing properties, and mitigated the adverse reactions associated with DOX. Thus, stimuli-responsive DDSs hold great promise in revolutionizing the design of precision nanocarriers for the effective delivery of ICD agents to bolster melanoma immunotherapy.

PSs, including porphyrin and nonporphyrin PSs (such as ICG and methylene blue (MB)), are widely used in melanoma treatment.[133] Photosensitization is generally divided into two types: Type I is electron/hydrogen transfer which generating superoxide anions ($O^{2-\bullet}$), H_2O_2 and hydroxyl radicals (·OH) and Type II is energy transfer which converting nontoxic triplet oxygen ($^3O_2$) into cytotoxic singlet oxygen ($^1O_2$).[134] These generated ROS may cause apoptosis, necrosis, pyroptosis, and microvascular damage to tumor cells. These dying tumor cells subsequently induce ICD by releasing DAMPs, tumor-specific antigens, and proinflammatory cytokines, which may lead to increased immunogen exposure and immune system activation.[135] However, melanin is an antioxidant and ROS scavenger that leads to resistance to PDT in melanoma. In addition, the heterogeneous proliferation of melanoma cells leads to hypoxia, which impedes the induction of ICD.[136] Furthermore, PSs are often highly cytotoxic, so the effectively delivering them in a safe manner is a significant challenge. It has been reported that some metal NPs in hydrogen peroxide-responsive DDSs can catalyze the conversion of H_2O_2 to oxygen.[137] When loaded with PSs, these stimuli-responsive DDSs can provide oxygen to tumors to improve the efficacy of PS-induced ICD, ultimately alleviating the toxic side effects and drug resistance of the PSs. Qin et al chose a series of reductively cleavable polymeric micelles (PMs) assembled from amphiphilic poly(ε-caprolactam)-ss-poly(ethylene glycol)-ss-poly(ε-caprolactam) (PCL-ss-PEG-ss-PCL) to deliver MnO_2 and ICG.[138] Upon internalization, the disulfide bonds in the HTIM-PMs were cleaved, releasing MnO_2 and ICG due to the acidity, high GSH expression and high H_2O_2 contents in the TME. ICG promotes ROS production and hence tumor cell death. MnO_2 synergistically enhances phototherapy by catalytically decomposing endogenous hydrogen peroxide to elevate tumor oxygenation while maintaining biosafety, thereby potentiating ROS production and photo-immunotherapy efficacy.

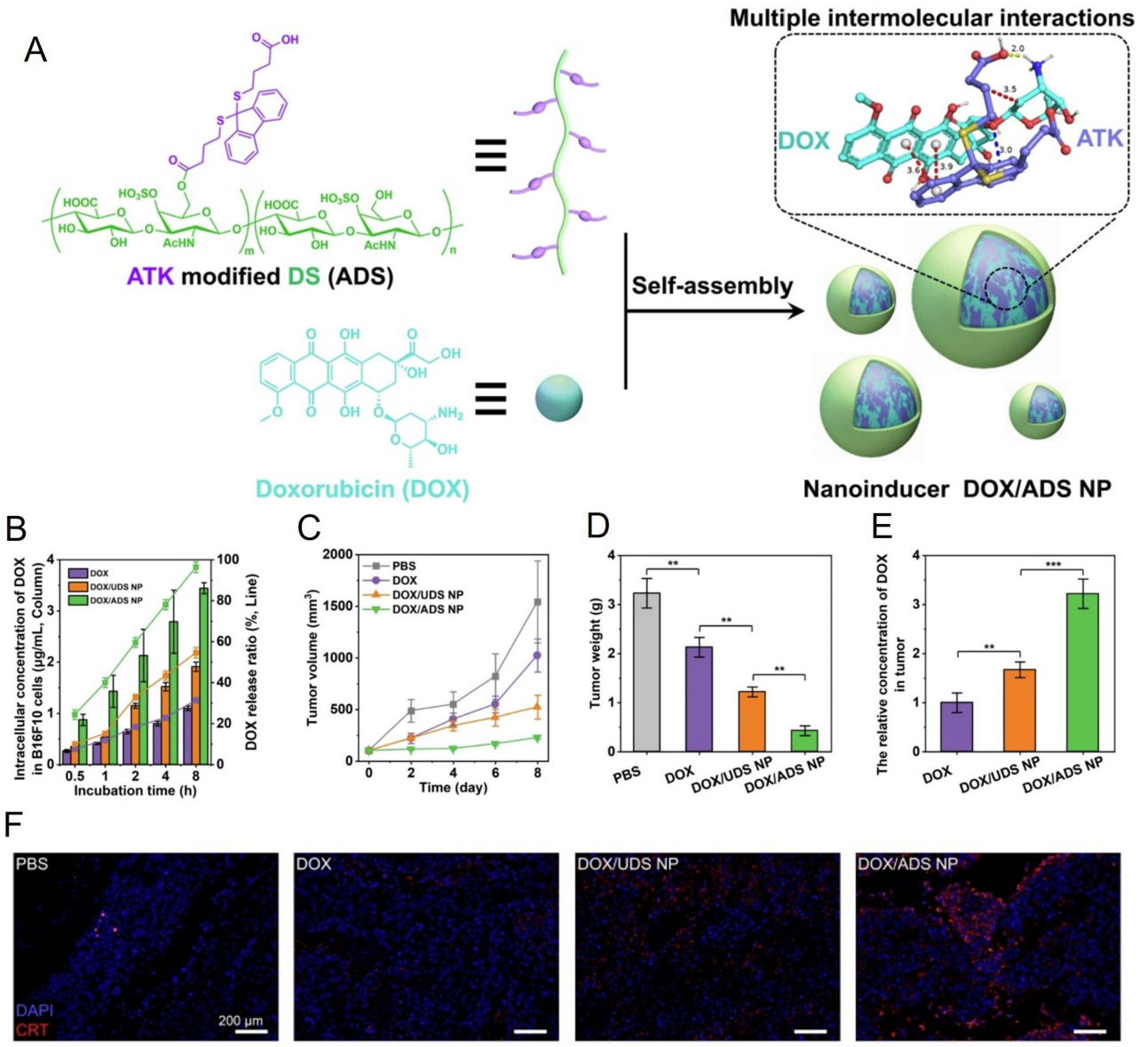

Figure 12 Bionic delivery system for Adriamycin-enhanced ICD delivery. (**A**) Schematic illustration of nanoinducer (DOX/ADS NP) based on aromatic thioketal-modified dermatan sulfate (ADS). (**B**) The intracellular DOX concentration and release ratio after incubation of DOX, DOX/UDS NP or DOX/ADS NP (equivalent to 3.5 μg/mL DOX) with B16F10 cells for different time. (**C**) Growth curves of B16F10 tumors after various treatment. (**D**) Average tumor weights in different groups at the end of treatment. (**E**) The relative concentration of DOX in tumor at the end of experiment. (**F**) The expression level of CRT in tumor sections. Image reproduced with permission from Zhang Q, Li S, Ren J et al. ROS-triggered nanoinducer based on dermatan sulfate enhances immunogenic cell death in melanoma. All data are presented as mean ± SD (n = 6). $^{**}P < 0.01$, $^{***}P < 0.001$. *J Control Release*. 2022;348:22–33. © 2022 Elsevier B.V. All rights reserved.[132]

Enhancement of Immunotherapy Through Multiple Pathways

The immune response involves multiple stages, including antigen presentation, lymphocyte activation, proliferation and differentiation, and tumor elimination.[139] Failure at any stage could reduce the efficiency of melanoma immunotherapy. Thus, combining immunotherapy with other therapeutic modalities, such as chemotherapy, phototherapy, or thermotherapy,[140] could promote the immune response against melanoma. Stimuli-responsive DDSs are structurally flexible and adaptable, so they can load multiple immunomodulators and therapeutics. The different immune activation stages involve different targets, thus, different immunomodulators or therapeutics need to be delivered to different targets. Stimuli-responsive DDSs can effectively utilize different types of stimulation in the TME for programmed drug release, which leads to the more accurate delivery of different immunomodulators or therapeutics to the target to produce the best immunotherapy effects.

Studies have shown that chemotherapy can increase tumor immune responses, with a significant cumulative effect.[141] The combination of conventional chemotherapy and immunotherapy has gradually become a trend in recent clinical research. Many patients with poor immune responses may respond to chemotherapy/immunotherapy, and some melanoma patients with low PD-L1 expression and poor ICB responses may respond to chemical immunotherapy.[142] The combination of chemotherapy and immunotherapy is the most common approach to increase melanoma immunotherapy efficacy.[143] Du et al assembled Ce6-coupled hyaluronic acid, dextro-1-methyltryptophan (1-mt)-coupled polylysine (PM), and an aPD-L1 into a cascade-responsive nanodelivery platform (aPD-L1@HC/PM NPs) (Figure 13A).[144] In vitro studies in a simulated melanoma microenvironment revealed its stepwise drug release mechanism. Hyaluronidase-sensitive hyaluronic acid-Ce6 (HC) was

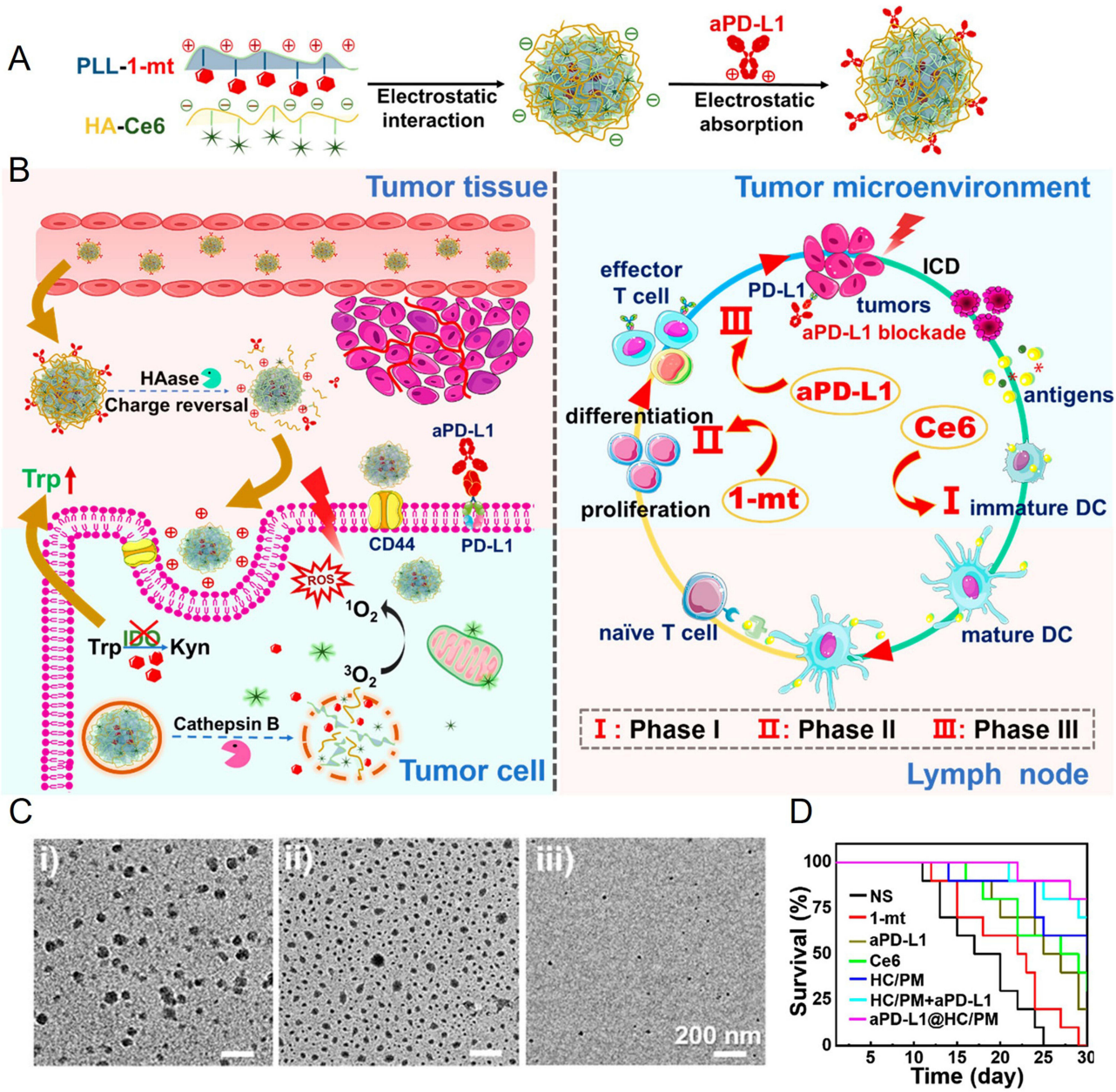

Figure 13 The three-in-one immunotherapy nanoplatform (aPD-L1@HC/PM NPs) for manipulating the three stages of the cancer immune cycle to enhance immunotherapy. (**A**) Assembly strategy for aPD-L1@HC/PM NPs. (**B**) Illustration of the step-by-step detached release behavior of aPD-L1, Ce6, and 1-mt and the immunotherapy capability via the cascade-amplifying cancer-immunity cycle. (**C**) TEM images of (i) the aPD-L1@HC/PM NPs and the (ii) aPD-L1@HC/PM NPs after incubation with HAase for 4 h without papain and (iii) with papain. (**D**) Survival ratio of differentially treated groups. Image reproduced with permission from Li Q, Zhang D, Zhang J et al. A three-in-one immunotherapy nanoweapon via cascade-amplifying cancer-immunity cycle against tumor metastasis, relapse, and postsurgical regrowth. *Nano letters*. 2019;19(9):6647–6657. Copyright 2019 American Chemical Society.[144]

https://doi.org/10.2147/DDDT.S517331

degraded by hyaluronidase into smaller HC fragments, exposing the positively charged PLL layer while simultaneously releasing the aPD-L1 (Figure 13B). In a papain-rich environment at pH 5.0, the PLL layer subsequently underwent amide bond cleavage, leading to the controlled release of 1-mt. Transmission electron microscopy confirmed the gradual collapse of the NP structure under these varying conditions, indicating the ability of the aPD-L1@HC/PM NPs to structurally transform in a step-by-step manner within the melanoma microenvironment, which facilitated on-demand drug delivery (Figure 13C). The cascade mechanism coordinates a tripartite attack: Ce6-mediated PDT induces ICD in B16F10 cells to enhance antigen presentation, free 1-mt blocks IDO-mediated immunosuppression to increase T-cell proliferation and differentiation, while aPD-L1 checkpoint inhibition amplifies effector T-cell cytotoxicity through PD-1/PD-L1 axis blockade, synergistically eradicating tumors. In vivo studies demonstrated the effectiveness of this approach, with 75% of the mice in the aPD-L1 @HC/PM NP treatment group surviving for more than one month, which was better than that in the control group (Figure 13D). This synergistic cascade release mechanism effectively enhances the immune response to melanoma, leading to a significant therapeutic effect.

Conclusions and Prospects

The advancement of nanotechnology and stimuli-responsive materials has provided novel strategies for melanoma immunotherapy. DDSs engineered with chemical or biological responsiveness, exploit TME properties or external triggers to precisely regulate immune cell activity, thereby amplifying therapeutic efficacy. Although preclinical studies in melanoma-bearing models demonstrate that such systems significantly enhance drug targeting, most remain confined to proof-of-concept stages, with <5% advancing to clinical trials. Critical barriers persist in translating these innovations into melanoma immunotherapy practice, particularly in addressing three pivotal challenges.[145] Firstly, the biosafety of stimuli-responsive DDSs represents a critical challenge that must be addressed for clinical translation. For instance, non-degradable polymers (eg, polyacrylates) and non-biodegradable inorganic nanoparticles (eg, mesoporous silica) may result in long-term retention within tissues, and the incorporation of responsive bonds or groups might increase synthetic complexity and safety concerns, all of which contribute to significant toxicity. For example, residues of cetyltrimethyl ammonium bromide (CTAB) which was used to synthesize gold nanorods, damage cell membranes, leading to hemolysis and apoptosis.[146] And in a clinical trial (NCT03077607), residue of the crosslinking agent glutaraldehyde used in some pH-responsive polymers was found to induce an immune response. Therefore, the use of biocompatible or biomimetic materials should be prioritized in the design of nanomedicines. Naturally derived materials such as extracellular vesicles, hyaluronic acid, chitosan, and collagen exhibit superior biocompatibility compared to synthetic alternatives and can be engineered to respond to specific stimuli. Additionally, simplifying synthesis procedures and rigorously evaluating biosafety are essential considerations. Furthermore, during clinical trials, potential adverse host immune responses, as well as the metabolism and systemic clearance of the employed biomaterials, must be thoroughly investigated. Overall, the rational design of biomaterial-based platforms that take into account biological effects is critical to improve immunotherapy efficacy and safety in melanoma for clinical translation.[147] Secondly, stimuli-response materials have shown significant targeted delivery effects in preclinical animal model studies. However, there are large differences between patients, including changes in cell gap size, material organ permeability, and complex stress states, and NPs has potential off-target effects in normal cell tissues and in blood.[148–150] And there are huge differences between animal models and human physiology. Therefore, it is necessary to make rational use of different stimuli, cut or destroy the stimuli-response DDSs at different locations, and release each drug in steps at specific locations to maximize the activation of different immune pathways. In addition, the discovery of new melanoma-specific stimuli will further improve the accuracy of the timing and sequence of drug release of stimuli-responsive DDSs. Although the current preclinical results are promising, clinical trials have yet to verify the feasibility of stimuli-response DDSs in humans, combined with AI systems to analyze targeting effects, reducing the cost of early trial and error. Thirdly, responding to the complex preparation of DDSs is difficult for clinical conversion. Most stimuli-response DDSs are designed with complex structures and formulations that are difficult to scale up for industrial production. At the same time, due to the huge differences between patients and tumor heterogeneity, it requires a lot of optimization and improvement experiments to transform each stimulus from preclinical experimental model to routine clinical practice. Therefore, in the development of stimuli-responsive DDSs, attention should be paid to advanced methods that can precisely control the

preparation process to produce nanomedicine with the required characteristics and industrial scale-up feasibility.[152] These issues also require sustained efforts and ongoing research to advance the clinical transformation of stimuli-responsive DDSs in the future and promote the further development of melanoma immunotherapy.

Abbreviations

iTME, immunosuppressive tumor microenvironment; TME, tumor microenvironment; DDSs, drug delivery systems; MM, malignant melanoma; ICD, immunogenic cell death; ROS, reactive oxygen species; PS, photosensitizer; IDO, indoleamine 2.3-dioxygenase; IND, indoximod; PDT, photodynamic therapy; TAMs, tumor-associated macrophages; O_2, oxygen; NOX, NADPH oxidase; GSH, glutathione; ICG, indocyanine green; DCs, dendritic cells; MMPs, matrix metalloproteinases; EMT, epithelial-mesenchymal transition; ECM, extracellular matrix; CAT, oxygen-producing catalase; H_2O_2, hydrogen peroxide; Tregs, regulatory T cells; NPs, nanoparticles; HCPT, 10-hydroxycamptothecin; PEI, polyethylenimine; PTT, photothermal therapy; ISC, intersystem crossing; mPt, HMME, mesoporous platinum; hematoporphyrin monomethyl ether; DPPC, 1,2-dipalmitoylphosphatidylcholine; R848, resiquimod; CTL, cytotoxic T lymphocyte; TLR, Toll-like receptor; CDT, chemodynamic therapy; NIR, near-infrared; HIFU, high-intensity focused ultrasound; LIFU, low-intensity focused ultrasound; UC, ultrasonic cavitation; SDT, sonodynamic therapy; TPZ, tirapazamine; CRT, calreticulin; HMGB1, high mobility group 1; MCT, monocarboxylate transporter; LDH, lactate dehydrogenase; LOD, lactate oxidase; IFN-γ, proinflammatory cytokines interferon-γ; TNF-α, tumor necrosis factor; Trp, amino acids tryptophan; Arg, arginine; Kyn, kynurenine; ICB, immune checkpoint blockade; EPA, epacadostat; CUR, curcumin; CDM, 2-propionic-3-methylmaleic anhydride; NK, natural killer; ASB, afuresertib; CXB, celecoxib; DOX, doxorubicin; TAAs, tumor-associated antigens; HMAs, hypomethylating agents; AC, 5-azacytidine; DAC, 5-aza-2′-deoxycytidine; Zeb, zebularine; 5-F, 5-fluor-2′-deoxycytidine; aPD1, anti-PD1 antibody; IFN-I, type I interferon I; DAMPs, damage-associated molecular patterns; ER, endoplasmic reticulum; ATK, aromatic thione; DS, dextran sulfate; $O^{2-\bullet}$, superoxide anions; ·OH, hydroxyl radicals; $^3O_2$, nontoxic triplet oxygen; $^1O_2$, cytotoxic singlet oxygen; 1-mt, dextro-1-methyltryptophan; EPR, enhance permeability and retention. OVA, ovalbumin; LMWH, low molecular weight heparin; GA gambogic acid; Oxa, oxaliplatin; Sia, sialidase; CA, cinnamaldehyde; PA, pheophorbide A; Cas9-Cdk5, CRISPR/Cas9-Cdk5 plasmid; PTX, paclitaxel; pOVA, plasmid ovalbumin; 2-BP, 2-bromopalmitate; CPT, camptothecin; IMDQ, imidazoquinoline.

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Author Contributions

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

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Disclosure

The authors declare no conflicts of interest in this work.

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