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REVIEW

Advancements in Stimulus-Responsive Co-Delivery Nanocarriers for Enhanced Cancer Immunotherapy

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Abstract: Cancer immunotherapy has emerged as a novel therapeutic approach against tumors, with immune checkpoint inhibitors (ICIs) making significant clinical practice. The traditional ICIs, PD-1 and PD-L1, augment the cytotoxic function of T cells through the inhibition of tumor immune evasion pathways, ultimately leading to the initiation of an antitumor immune response. However, the clinical implementation of ICIs encounters obstacles stemming from the existence of an immunosuppressive tumor microenvironment and inadequate infiltration of $CD8^+$T cells. Considerable attention has been directed towards advancing immunogenic cell death (ICD) as a potential solution to counteract tumor cell infiltration and the immunosuppressive tumor microenvironment. This approach holds promise in transforming "cold" tumors into "hot" tumors that exhibit responsiveness to antitumor. By combining ICD with ICIs, a synergistic immune response against tumors can be achieved. However, the combination of ICD inducers and PD-1/PD-L1 inhibitors is hindered by issues such as poor targeting and uncontrolled drug release. An advantageous solution presented by stimulus-responsive nanocarrier is integrating the physicochemical properties of ICD inducers and PD-1/PD-L1 inhibitors, facilitating precise delivery to specific tissues for optimal combination therapy. Moreover, these nanocarriers leverage the distinct features of the tumor microenvironment to accomplish controlled drug release and regulate the kinetics of drug delivery. This article aims to investigate the advancement of stimulus-responsive co-delivery nanocarriers utilizing ICD and PD-1/PD-L1 inhibitors. Special focus is dedicated to exploring the advantages and recent advancements of this system in enabling the combination of ICIs and ICD inducers. The molecular mechanisms of ICD and ICIs are concisely summarized. In conclusion, we examine the potential research prospects and challenges that could greatly enhance immunotherapeutic approaches for cancer treatment.

Keywords: antitumor therapy, immunogenic cell death, co-delivery, immune-checkpoint inhibitors, stimulus-responsive nanocarriers

Introduction

Cancer, being a substantial global public-health concern, is projected to 28.4 million cases worldwide by the year 2040.[1] In recent decades, cancer immunotherapy has made noteworthy strides. In recent decades, cancer immunotherapy has made significant progress. Currently, it predominantly focuses on two domains. The first is the activation of key components within the immune system, including cancer vaccines,[2] cytokine therapy,[3] and adoptive T-cell therapy.[4] The second domain involves the suppression of immune-checkpoint molecules, such as immune-checkpoint blocking (ICB).[5,6] Immune-checkpoint molecules refer to the small proteins produced by immune cells in the body that regulate effector function. Tumor cells evade and survive the body's immune system by overactivating immune-checkpoint molecules. Immune-checkpoint inhibitors (ICIs) can prevent the overactivation of immune checkpoint inhibitors,

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allowing immune cells to eliminate cancer cells. ICIs exert their antitumor effects mainly through PD-1/PD-L1 inhibitors.[7] PD-1/PD-L1 inhibitors include PD-1 antibodies and PD-L1 antibodies, which can bind to PD-1 and PD-L1 respectively, preventing the binding of cancer cells and T cells. Then promoting the T cell-mediated killing and clearance of tumors. However, numerous tumors exhibit a poor response to the use of PD-1/PD-L1 checkpoint inhibitors alone.[8–10] This is due to the fact that the tumors are mostly "cold" tumors, which are manifested as a low immunogenicity of the tumor cells. Furthermore, the immunosuppressive tumor microenvironment (ITM) significantly impedes the infiltration and function of cytotoxic lymphocytes (CTLs), which contributes to sustained tumor growth.

Researchers have shown that ICD could activate $CD8^+$T cells, thereby improving the tumor microenvironment.[11] ICD represents a type of cell death capable of transforming "cold" tumors into "hot" ones. The process of "cold tumors" becoming "hot tumors" is essentially a process of increasing the immune-inflammatory response to the tumor.[12–14] Thus, the combined treatment of ICD inducers with PD-1/PD-L1 inhibitors can enhance the antitumor effects. However, the drug administrations of certain ICD inducers, such as chemotherapy drugs, are commonly delivered systemically, resulting in adverse side effects and limited bioavailability. Thus design targeted approaches for locally stimulating and enhancing tumor immune therapy is necessary. Moreover, the combination of ICD inducers and PD-1/PD-L1 inhibitors faces challenges such as uncontrolled drug release due to the immediate release of drugs upon entering the medium. Hence, there is an urgent need for searching a reliable drug-delivery platform to enhance targeting and achieve controlled drug release.

Nanocarriers possess numerous advantageous attributes, such as their small size, extensive surface area, convenient modifiability and the ability to co-deliver ICD inducers and PD-1/PD-L1 inhibitors. Stimulus-responsive nanocarriers are fabricated by introducing different internal and external stimulus-responsive materials on the basis of the original nanocarriers.[15,16] Stimulus-responsive nanocarriers possess favorable attributes for the construction of a drug-delivery platform through the combination of ICD inducers and PD-1/PD-L1 inhibitors. Attributes as follows: (i) introduction of stimulus-responsive materials to reconstruct TEM, which is conducive to the acquisition of long-term immune memory after the release of ICD inducers and PD-1/PD-L1 inhibitors;[17] (ii) unifying ICD inducers and PD-1/PD-L1 inhibitors with different distributions and different targets in vivo in nanocarrier to obtain better synergistic antitumor effect;[18] (iii) avoiding the systemic toxic side effects of ICD inducers and PD-1/PD-L1 inhibitors alone;[19] and (iv) controlling the release of ICD inducers and PD-1/PD-L1 inhibitors and exerting synergistic antitumor effects.[20] In the past few years, our group has published several papers in the field of stimulus-responsive nanocarriers and accumulated some experience, which effectively provided technical support for the writing of this review.[21,22]

This article centers its attention on the progress of stimulus-responsive co-delivery nanocarriers that rely on ICD inducers and PD-1/PD-L1 inhibitors. It provides an overview and analysis of recent advancements in the utilization of these co-delivery nanocarriers within the realm of tumor immunotherapy. Furthermore, novel insights into the realm of efficient tumor immune treatment will be offered.

Overview of ICD and ICIs

ICD

ICD is a process in which tumor cells mediate the generation of adaptive immune responses in the body under external or internal stimuli. Its hallmarks are the release of tumor-associated antigens (TAAs) and damage-associated molecular patterns (DAMPs).[23,24] Inducers are required before ICD, as described in detail in the following text.

Mechanism of ICD

Under external or internal stimuli, certain apoptotic tumor cells can induce immunogenic proteins and then trigger the body's antitumor immune response. CTLs are activated to more effectively kill tumor cells, finally achieving a more desirable antitumor effect. This phenomenon is known as tumor-cell ICD. Various types of DAMPs are released, including calreticulin protein (CALR) exposed on the cell surface, heat-shock proteins (HSPs), high mobility group box 1 (HMGB1), adenosine triphosphate (ATP), and type I interferons (IFN-I).[25–27]

CALR is usually located in the endoplasmic reticulum and acts as a multifunctional protein involved in various intracellular immune processes, such as protein folding and maintaining calcium homeostasis.[28,29] Diseases such as

kidney fibrosis and tumors are closely associated with it.[30,31] Following induction by ICD, CALR undergoes translocation and exposure on the cell membrane mediated by EIF2S1 inactivation phosphorylation.[32] On the cell membrane, it forms complexes with partner proteins like ERp57, serving as "eat me" signals that promote the engulfment of dying cells by dendritic cells (DCs) and enhance antigen presentation by antigen-presenting cells (APCs), particularly immature DCs.[33] ATP is generally located inside cells and is an important component of DAMPs. Extracellular ATP participates in purinergic signaling and inflammatory response and is closely associated with diseases such as tumors, ischemic injury, post-heart transplantation, and rejection reactions[34,35] Innate and adaptive immunity are also activated by ATP through a series of reactions.[36,37] Karen M Dwyer's team found that blocking CD39 and CD73 is beneficial for the treatment of acute and chronic kidney diseases.[38] HMGB1, located in the cell nucleus, is extensively involved in processes such as inflammation and tumors. It is associated with diabetic nephropathy and primary thrombocytopenia.[39,40] Under stimulations by inducers, HMGB1 is released from the cell membrane.[41] On one hand, HMGB1 stimulates innate immune cells by binding to TLR2 and TLR4.[42] On the other hand, it forms complexes with CXCL12. With the help of chemokine receptor CXCR4, HMGB1 recruits immune cells to tumor cells.[43] HSPs could also be released upon external or internal stimuli, and present tumor antigens to T cells, leading to the killing and elimination of tumor cells.[44,45]

During the ICD, DAMPs and pattern-recognition receptors interact to activate innate immune responses.[46] DAMPs can also bind to antigen-presenting cells, promoting the maturation of DCs, phagocytosis of dead-cell antigens, and presentation of TAAs to CTLs and thus activating adaptive immunity.[47] In addition to these advantages, pro-inflammatory cytokines are released in ICD, enhancing the activation of T cells and the immune stimulatory effects on tumor infiltration (Figure 1).[48,49]

Different Inducers to Induce ICD

Inducers are required for ICD. Certain chemotherapy drugs (such as doxorubicin (DOX), cyclophosphamide, anthracyclines like mitoxantrone, curcumin, oxaliplatin, and platinum-based chemotherapy drugs like cisplatin),[50–52] as well as radiotherapy,[53] induce antitumor immune responses by inducing ICD in tumor cells. Several physical stimuli can also trigger ICD, such as photodynamic therapy (PDT)[54] and photothermal therapy (PTT), which activate $CD8^+$T cell responses through ER exposure, thereby initiating a cascade of ICD. In addition to these, lysosomes,[55] nanopulse stimulation and oncolytic viro-therapy[56] can induce ICDs.

Oxaliplatin, a commonly used chemotherapy drug, can increase the infiltration of immune cells such as $CD8^+$T cells and promote DC maturation.[57] Li used oxaliplatin as an inducer of ICD, and studied the efficacy of oxaliplatin in the

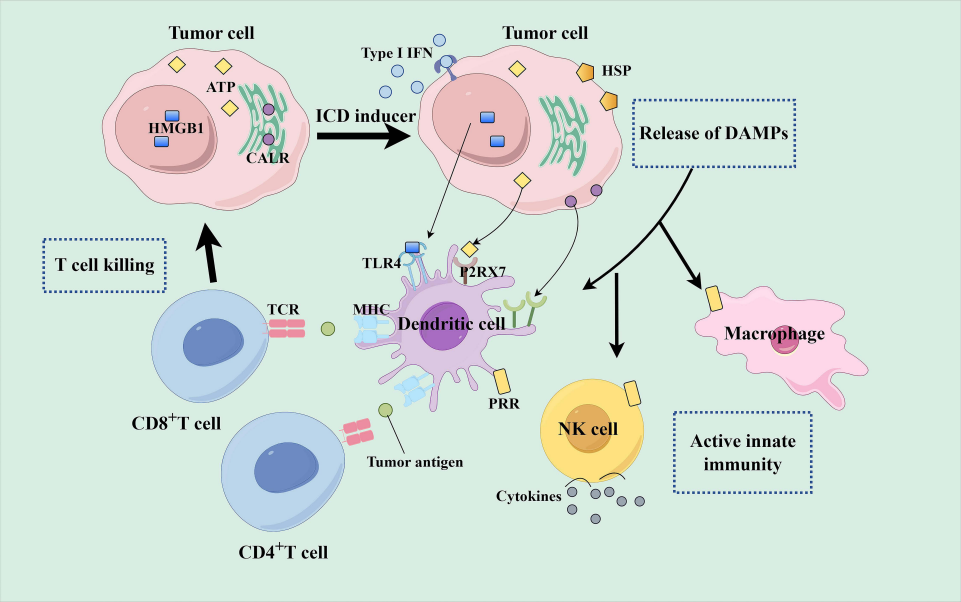

Figure 1 Mechanisms of ICD (by Figdraw).

treatment of lung cancer. Results showed that the ICD induced by oxaliplatin provided an immunogenic microenvironment and enhanced the therapeutic effect of Lewis lung cancer.[58] PDT primarily induces cellular toxicity through the generation of reactive oxygen species, requiring the synergistic effects of photosensitizers, light, and molecular oxygen. Kensuke Kaneko's experiments demonstrated that the sole injection of photosensitizer HS201 or laser irradiation does not significantly inhibit the growth of E0771 breast tumors. This finding implied that PDT's tumor-killing effects required the involvement of photosensitizers and light.[58] PTT selectively kills cancer cells by converting light energy into heat using an external light source.[59] Wu used iron-based ternary chalcogenide nanoparticles, known as AGFES2, for the treatment of triple-negative breast cancer. AGFES2 acts as an ICD inducer, triggering an immune response by generating heat and promoting the release of tumor-specific antigens.[60] In addition, ICD can be induced by radiotherapy. Li developed a nanoscale metal-organic framework that responds to radiation therapy in 2018. The radiodynamic therapy can trigger robust antitumor immune responses. The combination of the framework, X-ray and anti-PD-L1 (aPD-L1) therapy can amplify the antitumor immunotherapy and effectively prevent the growth and metastasis of osteosarcoma.[61] ICD can be induced by these inducers in tumor cells to elicit antitumor immune responses.

ICIs

Tumor immunotherapy can be primarily classified into two categories: cellular immunotherapy and ICIs therapy. Currently, available ICIs include CTLA-4 inhibitors and PD-1/PD-L1 inhibitors.[62,63] CTLA-4 expression is predominantly found on T cells, while PD-1/PD-L1 expression is more widespread.[64,65] In the early stages of immune response, CTLA-4 inhibits T cell activity, whereas PD-1/PD-L1 regulates immune responses in peripheral tissues or tumor sites. CTLA-4 inhibitors, being a pioneering target for immunotherapy, have been extensively researched but still face challenges such as low response rates and the occurrence of autoimmune side effects. Therefore, this section primarily focuses on PD-1/PD-L1 inhibitors.

Mechanism of ICIs

ICIs block immune checkpoints to exert their antitumor effects. Under normal physiological conditions, PD-1 is expressed on activated T cells, B cells, NK cells, monocytes, and DCs. It interacts with PD-L1, PD-L2, and other molecules expressed on the surface of APCs to inhibit the excessive activation of T cells and maintain immune homeostasis in the body.[66] In many types of tumors, PD-L1 molecules have abnormally high expression in tumor cell on their surface. These molecules bind to PD-1 molecules on tumor-infiltrating T lymphocytes, thereby inhibiting the normal activation of T cells, evading tumor cell killing by T cells, and ultimately achieving tumor immune escape.[67] Anti-PD-1 (aPD-1) or a-PD-L1 antibodies can block the binding between tumor PD-L1 or tumor PD-1, eliminating this immunosuppressive effects. T cells are then reactivated, allowing them to recognize and kill cancer cells.[68] At the tumor site, aPD-1 antibodies can also bind to Fcγ receptors on the surface of macrophages, mediating the depletion of regulatory T cells, thereby increasing the proportion of activated T cells and enhancing antitumor ability (Figure 2).[69]

Type of ICIs

Currently, PD-1/PD-L1 inhibitors can be classified into two distinct categories: PD-1 antibodies and PD-L1 antibodies. The Food and Drug Administration (FDA) has thus far granted approval to 7 ICIs that target the PD1/PD-L1 pathway, consisting of 4 PD-1 blocking antibodies and 3 PD-L1 blocking antibodies.[70] The PD-1 antibodies encompass dostarlimab, nivolumab, pembrolizumab, and cemiplimab, while the PD-L1 antibodies comprise atezolizumab, durvalumab, and avelumab.[65] As of November 2022, China has a total of 16 ICIs available in the market. Among these, there are 8 domestically developed PD-1 monoclonal antibodies (Toripalimab,[71] Sintilimab,[72] Camrelizumab,[73] Tislelizumab,[74] Penpulimab,[75] Zimberelimab,[76] Srullimab, Puterimab), 2 domestically developed PD-L1 monoclonal antibodies (Envafolimab,[77] Suglizumab), and 1 domestically developed dual antibody (PD-1/CTLA4) known as Cadonilimab.[78] Additionally, there are 2 imported PD-1 inhibitors (Nivolumab,[79] Pembrolizumab[80]), 2 imported PD-L1 inhibitors (Atelizumab,[81] Durvalumab[82]), and 1 imported CTLA-4 monoclonal antibody (Ipilimumab).[83] The availability of these drugs brings newfound optimism for cancer patients in China.

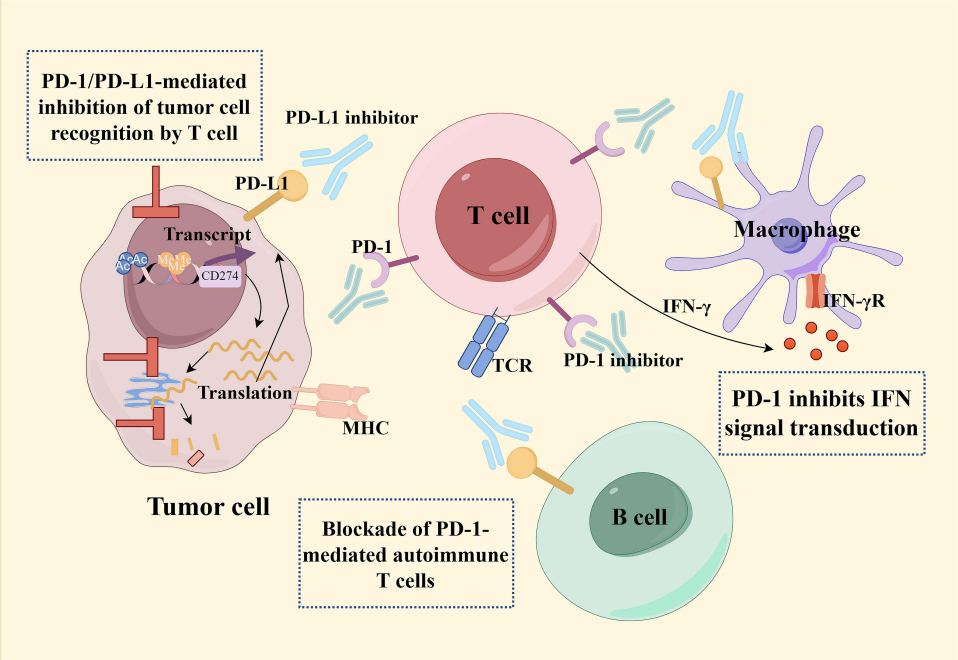

Figure 2 Mechanism of PD-1/PD-L1 inhibitors (by Figdraw).

Advantages of Combination of ICD Inducers and PD-1/PD-L1 Inhibitors

ICD inducers and PD-1/PD-L1 inhibitors have the potential to enhance antitumor immunity. ICD inducers themselves present certain limitations, including the occurrence of severe toxic side effects caused by chemotherapy drugs that effectively induce ICD. Moreover, these drugs exhibit inadequate pharmacokinetics and tissue penetration, as well as weak targeting capabilities.[84] PD-1/PD-L1 inhibitors encounter challenges associated with low immunogenicity and an immunosuppressive microenvironment.[85,86] To solve these issues, the utilization of responsive nanocarriers as co-delivery vehicles can effectively harmonize the physicochemical properties of ICD inducers and PD-1/PD-L1 inhibitors. When PD-1/PD-L1 inhibitors combined with ICD inducers, they can increase $CD8^+$T cell infiltration and convert "cold" tumors, which have low responsiveness to immunotherapy, into "hot" tumors with high immunotherapy responsiveness.

In a systematic review and meta-analysis of randomized controlled trials investigating ICIs monotherapy, ICIs plus chemotherapy, and chemotherapy alone for non-small cell lung cancer (NSCLC), the greatest survival benefit with the highest safety is observed in patients receiving pembrolizumab combined with platinum-based chemotherapy. This finding suggested that chemotherapy, as an ICD inducer, can synergize with PD-1/PD-L1 inhibitors to exert a combined antitumor effect.[87] Although promising results have been achieved with the use of ICD inducers in combination with ICIs, many failures still occurred. In a similar trial, 297 patients treated with pembrolizumab and chemotherapy showed no statistically significant improvement.[88] Additionally, in a clinical trial that received paclitaxel liposomal chemotherapy in combination with a PD-1/PD-L1 inhibitor as a first-line therapeutic agent, treatment-related adverse events of any grade were still observed in 25 patients, and adverse events of grade 3 or worse were observed in 9 patients.[89] Therefore, the cocktail combination of ICD inducers with ICIs are not universally applicable in clinical practice.

Stimulus-Responsive Nanocarriers

Excellent specificity is possessed by nanocarriers. The passive targeting is achieved through the EPR effect, whereas active targeting is achieved through the surface modification of nanocarriers. Stimulus-responsive nanocarriers regulate drug release in response to exogenous or endogenous stimuli, and achieve rapid and precise responses.[90] Exogenous stimulus-responsive and endogenous stimulus-responsive nanocarriers are separated from stimulus-responsive nanocarriers (Table 1). Photothermal stimulation and magnetic fields are exogenous stimuli, whereas redox reactions, pH, and

Table 1 Latest Progress of Research on the Use of Single Stimulus-Responsive Nanocarriers for the Co-Delivery of ICD Inducers and PD-1/PD-L1 Inhibitors

Nanoparticles	ICD Inducer	PD-1/PD-L1 Antibody	Targeting Therapy	Effects
Silica nanoparticles	Bengal rose	Atezolizumab	Lung cancer	Inhibited the effective accumulation of bone marrow metastasis; prolonged retention time[94]
Graphene quantum dots	ZnPC	aPD-L1	Oral squamous cell carcinoma	Reversed the immunosuppressive tumor microenvironment; enhanced type I interferon-mediated innate immunity[95]
Mesoporous polydopamine nanoparticles	OTX +IDOi@MPDAs	BETOTX015	Breast cancer	Promoted CTLs activation; reversed immune suppression[96]
CeNB	Ce6	BMS-1	Breast cancer	Suppressed the tumor growth and metastasis[97]
Ce6/ MLT@SAB	Ce6	aPD-L1	Breast cancer	Controlled of distant tumors; strengthen the antitumor ability[98]
Gold nanostar nanoparticles	Photothermal ablation	aPD-L1	Colorectal cancer	Reversed the immunosuppressive tumor microenvironment[99]
PLGA-PEG	IR780	PD-L1 antagonist peptide	Colonic carcinoma	Prolonged the survival of the mice[100]
HSA-BMS@ CAP-ILTSL	Hyperthermia	BMS-202	Pancreatic cancer	Suppressed the tumor growth and metastasis[101]
FVIO	Mild magnetic hyperthermia	aPD-L1	Breast cancer	Inhibited the potential metastatic spread and the growth of distant tumor[102]
$CoFe_2O_4$@ $MnFe_2O_4$	Magnetic hyperthermia	aPD-L1	Breast cancer	Ablation of primary tumors; abscopal antitumor effect[103]
IONC-AAPH	AMF	aPD-1	Adenocarcinoma of colon	Inhibition of deep tumor growth; Induced long-term immune memory[104]
BiGC@PNA	RF	αPD-1	Breast cancer	Inhibited tumor metastasis and recurrence[105]
Liposome	DOC	αPD-L1 inhibitors	Colorectal cancer	Enhanced innate; adapted antitumor immune responses[106]
PD-NPs	DOX	aPD-L1	Breast tumor	Suppressed tumor advancement[107]
Bionanoparticle	λ phage vaccine	aPD-1	Hepatocellular carcinoma/ triple-negative breast cancer tumors	Suppressed primary hepatic or mammary tumor growth[108]
Liposome	TNF-α	aPD-L1	Osteosarcoma	Increased bioavailability; reduced drug toxicity[109]
Nanovesicles	DOX	aPD-L1	Melanoma	Induced antitumor T cell response[110]
Self-assembled nanoparticles	DOX	D-PPA	Colon cancer	Achieved effective accumulation at the tumor site[111]
PEG/PEI/CAD nanoparticles	DOX	aPD-1	Breast tumor	Blocked tumor immune escape; maintained the antitumor immunity[112]
ShPD-L1/Spam1 dual drug-loaded nanoparticles	DOX	pshPD-L1	Chromoma	Triggered immune memory effect; inhibited tumor metastasis[113]
CUR-BMS1166 @ZIF-8@PEG-FA	Curcumin	BMS1166	Osteosarcoma	Antitumor effect; immune memory effect[114]
IMS	Indocyanine green	aPD-1	Melanoma	Suppressed primary and distant tumors; prolonged the survival of mice[115]
MDP NPs	DOX, adriamycin	aPD-1	Melanoma	Suppressed primary; distant tumors[116]
MDHPs	Mitochondrial dysfunction	αPD-L1	Colonic adenocarcinoma	Regressed tumor growth; prevented lung metastasis[117]
FGL1/PD-L1 siRNA	ROS	siPD-L1	Lewis lung cancer	Alleviated the immunosuppressive microenvironment[118]

enzymes are endogenous ones.[91–93] Dual-stimulus responsive nanocarrier can play a synergistic role in the two stimuli to promote the release of anticancer drugs and improve the therapeutic effect (Table 2). Utilizing stimulus-responsive nanocarriers as drug-delivery vehicles, combined with ICD inducers and ICIs, can maximize the antitumor effects.

The Benefits of Stimulus-Responsive Nanocarriers in Facilitating the Combination of ICIs and ICD Inducers

Tumor immunotherapy targets a variety of TME components, including tumor cells, tumor-associated macrophages (TAMs), DCs, T cells, and various myeloid suppressor cells.[128,129] On-demand release of tumor immunotherapeutic agents is crucial to achieving effective antitumor immunity while minimizing side effects. In recent years, with advances in nanoscience and materials chemistry, "smart" platforms for stimulating responses have shown great potential for addressing cancer immunotherapy (Table 3).[130]

Passive targeting in targeted therapy is mainly realized by adjusting the size, morphology, charge and other physicochemical properties of the carriers, while active targeting is mainly realized by modifying peptides, antibodies or antibody fragments on the surface of the nanocarriers.[131] For different drugs and intracellular environments, different types of nanocarriers can be designed according to passive and/or active targeting, and then combined with stimulus-responsive materials to deliver payloads on demand. This greatly improves therapeutic efficacy and reduces adverse effects.

Exogenous Stimulus-Responsive Nanocarriers

Photo-Responsive Nanocarriers

Photo-responsive nanocarriers (Figure 3A) are constructed by combining photosensitizers with PD-1/PD-L1 inhibitors on nanocarriers, inducing potent ICD and enhancing targeting. Photosensitizers are substances that react when exposed to ultraviolet, visible, or infrared light. They are used to construct stimulus-responsive nanocarriers and to induce ICD through PDT. Photo-responsive nanocarriers combine photosensitizers with PD-1/PD-L1 inhibitors to achieve the combined therapy of ICD and immunotherapy.[132]

Table 2 Latest Progress of Research on the Use of Dual Stimulus-Responsive Nanocarriers for the Co-Delivery of ICD Inducers and PD-1/PD-L1 Inhibitors

Nanoparticles	ICD Inducer	PD-1/PD-L1 Antibody	Targeting Therapy	Effects
Nanoemulsion	DOX	HY19991	T1 tumor bearing	Inhibited the primary tumor and distant tumor; prolonged the survival time of mic[119]
Manganese oxide cross-linked BSA/HA nanoparticles	DOX	aPD-L1	Hepatocellular carcinoma	Inhibited tumor recurrence and metastasis[120]
TAF Nanocomplexe	DOX	aPD-L1	Melanoma	Alleviated the immunosuppressive microenvironment; prevented immune escape[121]
UCNPs@Cu-Cys-GOx	CDT	aPD-L1	Breast cancer	Inhibited the distant tumor[122]
Iron oxide nanoparticles	Protopor-phyrin	aPD-L1	Breast cancer	Improved cell survival rate; inhibited liver and lung metastasis[123]
Double hydroxide nanoparticles	LDHs	aPD-L1	Colorectal cancer	Inhibited the progression of primary hepatocellular carcinoma[124]
MPSNs	PDT and PTT	aPD-L1	Breast cancer	Eradicated primary tumors; inhibited distant metastasis[125]
Micellar nanocarrier	PTX	aPD-1	Melanoma	Extended the circulation time[126]
Liposomes	DOX	Melanoma	Melanoma	Induced robust immune responses; inhibited cancer metastasis[127]

Table 3 Stimulus Response Sites of Stimulus-Responsive Nanocarriers

Stimulus	Nanoparticles	Stimulus Response Sites
Exogenous stimulus	Photo-responsive nanocarriers	Bengal rose[94]
		ZnPC[95]
		Indoleamine 2, 3-dioxygenase[96,97]
		Chlorin e6[98]
		Gold nanostar[99]
		IR780[100,101]
	Magnetic-responsive nanocarriers	Magnetic vortex nanoring[102]
		2,3-dimercaptosuccinic acid[103]
		Magnetic iron oxide[104]
		Gold nanocluster[105]
Endogenous stimulus	Enzyme-responsive nanocarriers	Indoleamine 2.3-dioxygenase[106]
		Cathepsin B[107]
		Aspartate β-hydroxylase[108]
		Lactate dehydrogenase[109]
		Poly(ADP-ribose) polymerase[110]
	pH-responsive nanocarriers	Hydrophobic stearyl chain[111]
		Polyethylene glycol shielding[112]
		PshPD-L1-loaded aldehyde[113]
		Imidazolate Framework[114]
	Redox-responsive nanocarriers	SeSe bonds[115]
		Metal phenolic coordination[116]
		Helical polypeptide[117]
		Thioketal and cis-aconitate[118]
Dual stimulus	pH and redox dual-responsive nanocarriers	Pickering nanoemulsion[119]
		Hydrazone linkage and electrostatic interactions[120]
		Tannic acid-Fe network[121]
		ROS and hydrogen bonding[122]
	pH and light dual-responsive nanocarriers	Protoporphyrin IX and alginate gelation[123]
		Layered double hydroxide and PEG-DMMA[124]
		Imiquimod and mesoporous structure of silicon shell[125]
	pH and enzyme dual-responsive nanocarriers	Matrix-protease and a sheddable PEG layer[126]
		Polymer anchoring moiety and matrix metalloproteinase[127]

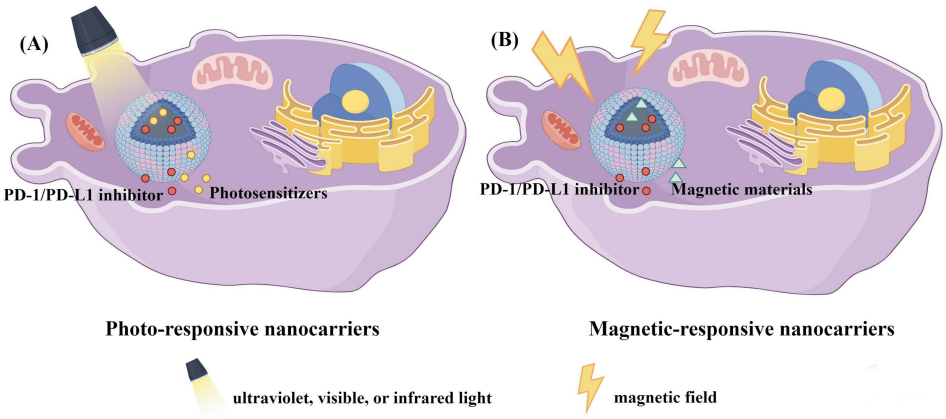

Figure 3 Schematic diagram of the release of exogenous stimulus-responsive nanocarriers under stimulus. (**A**) Photo-responsive nanocarriers. (**B**) Magnetic-responsive nanocarrier. (by Figdraw).

Researchers constructed a mesoporous silica nanocarrier (MSNs) capable of responding to light, which loaded with the photosensitizer Rose Bengal, peptide vaccine AL-9, and PD-1/PD-L1 inhibitors for the treatment of bone metastasis in lung cancer in 2021.[94] Another research attempted to improve antitumor immunity by further optimizing the nanoparticles size. Researchers developed a photo-sensitive, targeted nuclear nanoparticle delivery system using 5-nm graphene quantum dots to co-deliver the photosensitizer zinc phthalocyanine (ZnPc). This system effectively inhibited distant oral squamous cell carcinoma.[95] Tian designed a photothermal-responsive mesoporous polydopamine nanocore with dual-mode magnetic resonance/photoacoustic imaging effect in 2023. It achieved precise release and reversed the immunosuppressive effects of PD-L1/CD47/Tregs.[96] Zheng constructed a photo-sensitive, self-delivered nanodrug based on the photosensitizer Ce6, the IDO inhibitor NLG919, and the PD-1/PD-L1 inhibitor BMS-1. The drug platform can activate the cascade immune processes in photodynamic immunotherapy of metastatic tumors. And it was confirmed that the CeNB tremendously suppressed the tumor growth and metastasis.[97] Liu designed a serum albumin (SA)-coated thin bauxite scaffold that can be loaded with chlorine e6 (Ce6), photosensitizers, and honey bee venom melittin (MLT). The Ce6/MLT@SAB with PD-1 inhibitor provided more effective control of distant tumors by aPD−1 therapy.[98] PTT is also an effective method for tumor treatment. Xiao combined PD-1/PD-L1 inhibitors with photothermal ablation and developed PDA/GNS@aPD-L1 nanoparticles, gold nanostars modified with bio-inspired polydopamine functionalization. Photothermal ablation can induce ICD and reverse the ITM, providing a new strategy for colorectal cancer treatment.[99] Yu developed a synthetic photo-sensitive nanoparticle, NP@IR780, which incorporated PD-L1 blockade for the purpose of cancer photothermal-immunotherapy. The utilization of PLGA-PEG nanoparticles loaded with IR780 resulted in significant photothermal effects and the induction of robust antitumor immunity.[100] In order to address pancreatic cancer, a combination strategy involving mild hyperthermia and BMS-202 treatment was devised, utilizing size-adjustable thermo- and fibrotic matrix-sensitive liposomes. The results of antitumor analysis proved that subthermal therapy combined with ICB inhibited tumor growth and reduced the risk of tumor metastasis in subcutaneous.[101]

Magnetic-Responsive Nanocarriers

Magnetic-responsive nanocarriers (Figure 3B) hold great promise for targeted drug delivery, imaging, and chemothermal therapy for cancer.[133] The nanoparticles can selectively attach onto functional molecules and allow transportation to target locations under an external magnetic field induced by an electromagnet or permanent magnet.[134–136] Magnetothermal therapy (MHT) refers to the induction of tumor cytotoxicity by a magnetic thermal agent. This agent is capable of generating a large amount of heat when exposed to an applied alternating magnetic field (AMF). Compared with other thermotherapy methods, MHT has the unique advantage of high tissue penetration.[137] A magnetic hyperthermia-responsive nanocarrier was prepared by Liu using ferromagnetic vortex-like iron oxide (FVIO) nanorings in 2023. FVIO-mediated mild magnetic hyperthermia combined with PD-L1 blockade can inhibit the potential metastatic spread and growth of distant tumors.[102] Hu designed a superparamagnetic nanoparticle $CoFe_2O_4$@$MnFe_2O_4$ nanoparticle by increasing the saturation magnetization value in response to the magnetic environment. This nanoparticle combined magnetic hyperthermia with αPD-L1 treatment. The immunotherapy strategy has

shown its efficacy in achieving complete ablation of the primary tumor. Moreover, it has a significant distant antitumor effect on distant simulated metastases.[103] Zhang constructed a magnetic field mediated nanoplatform IONC-AAPH. This nanoplatform exhibited the capability to generate localized heat and carbon-centered free radicals. The combination of IONC-AAPH under alternating magnetic field with aPD-1 dramatically suppressed the growth of untreated distant tumors in deep tissue.[104] Radiofrequency (RF)-responsive biGCs was synthesized by Zhang activating sequential redox reactions of LA and NaBH4. The integration of RF-responsive biGC@PNA nanoplatforms with decitabine induced a potent ICD effect and significantly inhibited tumor metastasis and recurrence.[105]

Endogenous Stimulus-Responsive Nanocarriers

Enzyme-Responsive Nanocarriers

Enzymes possess specific substrate selectivity and distinct bio-interactions, making them advantageous biological targets.[138] In addition, enzyme-responsive nanocarriers (Figure 4A) can control drug release by targeting bio-enzymes that are only found in specific tissues in the body to achieve drug accumulation at the target site.[139] The tumor microenvironment is a very rich environment in which many enzymes are overexpressed, such as matrix metalloproteinase (MMP2 and MMP9), esterase, alpha-amylase and Cathepsin B. Wang's team constructed an enzyme-responsive camptothecin nanovesicles to the tumor microenvironment. Nanovesicles take advantage of the lipid bilayer cross-over ability of the ICD inducer DOX to coload the indoleamine 2, 3-dioxygenase inhibitor indolemod into their interior, triggering a powerful immune response.[106] A prodrug nanoparticles (PD-NPs) that is enzyme sensitive in response to the tumor microenvironment was proposed by Moon, combined with aPD-L1 peptide, cathepsin B-specific cleavable peptide and DOX. DOX can induce ICD and aPD-L1 peptide induces immune-checkpoint blocking. The findings indicated that the utilization of PD-NPs for the targeted delivery of aPD-L1 and DOX effectively suppresses tumor advancement while minimizing adverse effects.[107] A λ phage vaccine based on bionanoparticles was administered to mice with syngeneic HCC, in combination with PD-1 inhibition. Compared with control group, combination therapy (Vaccine+PD-1 inhibitor) significantly suppressed primary hepatic or mammary tumor growth.[108] Zhu developed a lactate dehydrogenase (LDH)-responsive nanoplatform using TNF-α-loaded liposomes. Then approach that enhanced aPD -1/PD-L1 antitumor immunity.[109] Wang developed an enzyme-sensitive nanovesicles as a novel delivery system for DOX and siRNA, achieving synergistic effects between PD-L1 blockade and DOX, finally leading to a potent therapeutic antitumor T cell response in melanoma mice.[110]

pH-Responsive Nanocarriers

Liposomes possess high biocompatibility and enhance the stability of certain drugs due to the protective effect of the bilayer structure. pH-sensitive nanocarrier systems (Figure 4B) are typically designed with a variety of pH-sensitive chemical bonds or chemical groups that undergo dissociation with changes in environmental pH. Thus, these chemical bonds or groups can release loaded therapeutic drugs in the target tumor area.[140,141]

Zhu developed amphiphilic DCS nanoparticles through the pH-sensitive linker hydrophobic stearyl chain, which effectively released loaded DOX and D-PPA in response to the slightly acidic tumor environment, blocked PD-1/PD-L1,

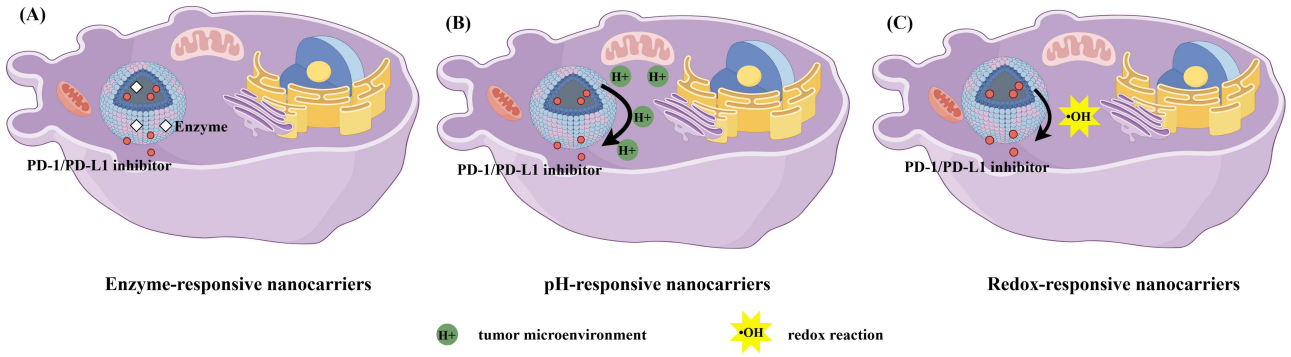

Figure 4 Schematic diagram of the release of endogenous stimulus-responsive nanocarriers under stimulus. (**A**) Enzyme-responsive nanocarriers. (**B**) pH-responsive nanocarriers. (**C**) Redox-responsive nanocarriers. (by Figdraw).

avoided immune escape, and triggered an enhanced immune response.[111] A pH-responsive DOX delivery nanosystem was designed and further combined with DOX and aPD-1 for antitumor. PEG/PEI/CAD nanoparticles can be stable during somatic circulation, and after entering mildly acidic tumors, they can escape the PEG shielding and effectively release the co-delivered drug.[112] The researchers first utilized a PEG derivative to encapsulate DOX and second loaded two plasmids to form shPD-L1/Spam1 dual drug-loaded nanoparticles. While under acidic environment, this Schiff base fragment can easily be altered resulting in the dissociation of the nanosystem to release plasmids. This novel therapy effectively increased the degree of T-cell infiltration, triggering an immune memory effect and thus inhibiting tumor metastasis.[113] Ge synthesized a pH-sensitive autophagy controlling nanocarrier. After entering tumor cells, nanocarrier induced autophagy and reduced intracellular pH, which in turn promoted the release of curcumin and enhanced autophagic activity. It finally showed satisfactory antitumor effect and strong immune memory effect.[114]

Redox-Responsive Nanocarriers

By modifying nanocarriers with redox sensitive bonds and/or linkers (such as disulfide bonds), oxidation-reduction reactions can be triggered to release therapeutic drugs encapsulated within the nanocarriers. Redox-responsive nanocarriers (Figure 4C) decorated with disulfide-based bonds and/or linkers can be cleaved by glutathione (GSH), enabling oxidation-reduction reactions for therapeutic responses.[142,143] Xu developed a GSH/reactive oxygen species dual-responsive nanogel system (IMS) that actively targeted cancer cells overexpressing mannose receptors. Combined with a PD-1, it can effectively suppress primary and distant tumors and prolong the survival of mice.[115] Xie's group fabricated a phenolic ICD inducer that enhances ROS-dependent cell death, assembling DOX, a phenolic manganese dioxide nanoreactor, iron, and polyethylene glycol polyphenol (MDP NP). It effectively improved the tumor response to PD-1 checkpoint blockade immunotherapy and overcame immunosuppression.[116] Jeong developed an oxidative stress-responsive peptide fluorinated and co-treated with αPD-L1. This peptide is able to target mitochondria and trigger mitochondrial dysfunction, thereby inducing oxidative stress-mediated ICD. The experiment significantly regressed tumor growth and prevented lung metastasis.[117] A novel strategy was proposed to combine tumor-penetrating peptide iRGD with ROS-sensitive nanoparticles. The ROS-sensitive nanoparticles loaded FGL1 siRNA and PD-L1 siRNA. This project increased infiltration of effector $CD8^+$T cells and effectively alleviated the immunosuppressive microenvironment of the tumor.[118]

Dual-Stimulus-Responsive Nanocarriers

pH and Redox Dual-Responsive Nanocarriers

pH and redox dual-responsive nanocarriers (Figure 5A), which combine redox-responsive with pH-responsive, playing a synergistic role to amplify the anticancer drug release and ultimately improving the therapeutic effect. The Pickering nanoemulsion (PNE) was designed using a redox-sensitive nanogel. PD-1/PD-L1 inhibitor HY19991, the core of PNE, and shell DOX were effectively released in response to the tumor microenvironment. The result showed that D/

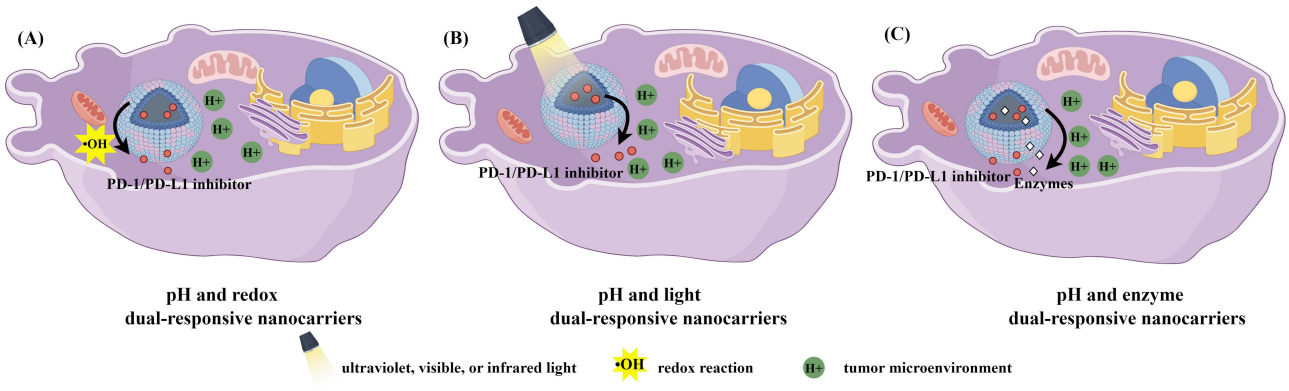

Figure 5 Schematic diagram of the release of dual-stimulus-responsive nanocarriers under stimulus. (**A**) pH and redox dual-responsive nanocarriers. (**B**) pH and light dual-responsive nanocarriers. (**C**) pH and enzyme dual-responsive nanocarriers. (by Figdraw).

HY@PNE enhanced tumor penetration behavior and triggered potent antitumor effects.[119] A pH and redox-sensitive nanocarrier was designed utilizing manganese ions and hydrazine functionalized macromolecules. Manganese oxide crosslinked bovine serum albumin/hyaluronic acid nanoparticles (BHM) can effectively alleviate tumor hypoxia and achieve complete eradication of liver cancer by loading DOX and ICG.[120] Researchers constructed a fibronectin (FN)-coated Metal Phenolic Networks that combined pH and redox reactions. This system utilized the modification of FN to promote the targeting of drug delivery. Moreover, it achieved enhanced ICD and effective drug aggregation at the tumor site.[121] Scientists have designed an upconversion nanoparticle UCNPs@Cu-Cys-GOx (UCCG) based on tumor microenvironment response. This system combined nanozymes to amplify ROS production in situ. Combined treatment with a PD-L1 antibody effectively inhibited the growth of primary tumors and tumor metastasis.[122]

pH and Light Dual-Responsive Nanocarriers

pH and light dual-responsive nanocarriers (Figure 5B), combining a degradable photosensitizer with a pH stimulator, could achieve the effects of synergistic therapeutic effect. A tumor microenvironment and near-infrared light dual-responsive prodrug hydrogel was developed by Ding. The alginate hydrogels released oxidized iron modified with PPIX and PD-L1 antibody prodrug nanoparticles, which can generate a large amount of reactive oxygen species and effectively treat breast cancer in a 4T1 mouse model.[123] Other researchers designed a pH-responsive nanoplatform based on siRNA-loaded layered double hydroxides (LDHs). The photothermal effect generated by LDHs altered the "cold" immune microenvironment, promoting synergistic immunity and effectively inhibited the progression of primary hepatocellular carcinoma.[124] Yue designed a light and pH-sensitive mesoporous silica nanocarrier MPSNs@R837. MPSNs@R837 induced high-efficiency ICD and promoted the maturation of dendritic cells, thereby inducing tumor-specific immune responses. Once combined with PD-1/PD-L1 inhibitor, the system significantly inhibited primary and metastatic tumors.[125]

pH and Enzyme Dual-Responsive Nanocarriers

The combination of pH-sensitive and enzyme-responsive (Figure 5C) have a combined effect on drug release. Su prepared a pH- and enzyme-responsive micellar nanocarrier by PEG layer and matrix protease modification. The weak acidity of the tumor microenvironment and the enriched matrix metalloproteinase-2 (MMP-2) triggered PEG shedding and aPD-1 release, respectively, promoting nanoparticles into cancer cells to play a synergistic antitumor effect.[126] Liu constructed polymer-liposomes containing MMP and pH-responsive polymer chains. The polymeric liposomes promoted the release of aPD-L1 peptide and DOX under the stimulation of the tumor microenvironment, effectively disrupting the PD-1/PD-L1 interaction and enhancing the antitumor effect.[127]

New Horizons

On the basis of stimulus-responsive nanocarriers delivering ICD inducers and PD-1/PD-L1 inhibitors, we proposed some novel strategies to further improve the system, including further refining the nanocarriers, recommending a multimodal synergistic strategy, and taking into account the effects of drug combination ratio and population heterogeneity on experimental results in hopes that it will serve as valuable references for future research.

New Horizons on Nanocarrier Co-Delivery Systems

Considering the complexity of ICD and the synergy of immunotherapy, adjusting the size,[144] morphology, surface charge, surface chemical modifications, and surface topological structures of nanocarriers can enhance the cellular uptake and internalization capabilities of co-delivery systems.[145–147] This adjustment is also beneficial for in vivo tissue distribution and metabolism.

New Horizons on Multimodal Synergistic Enhancement of Antitumor Immunity

In the face of genetic mutations, immune evasion, invasion, and distant metastasis that may occur in cancer treatment, multimodal synergistic therapy demonstrates tremendous therapeutic potential. Combinatorial approaches involving ICD inducers and PD-1/PD-L1 inhibitors, together with gene therapy, local microwave hyperthermia, immunomodulatory

adjuvants, natural products,[148] and so forth, might result in remarkable superadditive effects. This may become a new research direction for synergistic therapy.[149]

New Horizons on Drug-Combination Ratios

Existing studies have indicated that combination anticancer treatments generally depend on the molar ratio of different drugs used in combination. In particular, such effects generally depend on the specific release proportions of these drugs within tumor tissues after systemic administration, which critically influence the therapeutic efficacy.[148] So it is important to control precise ratios of ICD inducers and PD-1/PD-L1 inhibitors in nanocarriers to achieve the best antitumor immunity and greatest synergy.

New Horizon on the Heterogeneity of Patient Populations

The response to synergistic therapy may vary among different types of tumors, different patients with the same type of tumor, and even different regions within the same tumor. Research has found that tumor patients with enhanced oxidative metabolism exhibit poor response to PD-1 blockade therapy, but they are apparently more sensitive to oncolytic virus therapy.[150] Thus, integrating these information and using them to design immunotherapy strategies that target a patient's tumor-specific metabolism is one of the new directions for the future.

Future Prospects and Challenges

The activation and maturation of T-cells are facilitated by ICIs. However, the widespread distribution of T-cell populations throughout organs makes ICIs capable of inducing immune-related adverse events (irAEs) with varying frequencies and severities.[151] These adverse events can impact virtually any organs due to the diverse characteristics of T-cells and their ability to infiltrate tissues. To ensure effective management of patients receiving ICIs, it is imperative to implement personalized monitoring strategies that align with the individual risk profile of each patient. This advancement will empower physicians to customize their approach accordingly. Furthermore, the augmented accumulation of immunotherapeutic agents at the tumor site may potentially result in the onset of autoimmune disorders, thereby exacerbating the incidence of irAEs. In addition, the intricate design of responsive drug delivery systems poses significant challenges for pharmaceutical companies in terms of scaling up production and facilitating commercialization. It is anticipated that future research endeavors, encompassing diverse interdisciplinary advancements, will significantly advance the progress of stimulus-responsive nano-co-delivery platforms, ultimately facilitating their translation into clinical practice.

Conclusion

In conclusion, the combination of immune checkpoint inhibitors with ICD represents a novel direction in the realm of immunotherapy. The induction of ICD can enhance the infiltration of tumor cells and modify the immunosuppressive microenvironment of tumors, addressing the limitations of PD-1/PD-L1 therapy. The recent advancements in stimulus-responsive nanocodelivery carriers offer a promising platform for effectively combining ICD inducers and inhibitors. Nevertheless, the successful application of stimulus-responsive nanocarriers in clinical settings is hindered by considerable challenges arising from intricate manufacturing procedures and inevitable drug seepage. Consequently, the development of drug delivery platforms that possess straightforward formulation, well-established preparation techniques, and feasible industrial-scale production is still an urgent problem for researchers to solve. By proposing the effect of modified nanocarrier, multi-modal synergies, drug combination rates, and population heterogeneity on the experimental results, we hope to provide valuable references for future research. This review provides a generic stimulus-responsive nanoplatform for combining ICD inducers and PD-1/PD-L1 inhibitors to achieve enhanced antitumor immunity for cancer immunotherapy. In a word, immunotherapy still has a long way to go in the field of cancer treatment, and stimulus-responsive co-delivery nanocarriers play a crucial role in harnessing their unique advantages.

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Disclosure

The authors report no conflicts of interest in this work.

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