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REVIEW

Nanodelivery Strategies for STING Agonists: Toward Efficient Cancer Immunotherapy

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Abstract: cGAS-STING (cyclic GMP-AMP synthetase-interferon gene stimulator) signaling pathway has great potential in tumor treatment, and its superior performance in tumor treatment makes it a new method for tumor treatment. However, the delivery of STING agonists alone has some limitations, such as easy degradation and low bioavailability. Moreover, STING agonists are usually injected intratumorally to avoid systemic side effects caused by strong immune responses, which is not suitable for metastatic lesions. Using nanocarriers to deliver STING agonists can overcome these limitations to some extent. This review explores the collaborative foundation between nanodelivery systems and the STING signaling pathway. It systematically summarizes the existing types of STING agonists and the types of nanoscale delivery systems and analyzes the delivery strategies of STING agonist delivery systems from multiple aspects, including the tumor microenvironment (TME), tumor cell targeting, multifunctional integrated drug delivery systems, and novel biomaterial. The review elaborates on the practical applications of these strategies as well as the challenges and problems they face. Finally, it analyzes and discusses the potential future directions of STING nanodelivery systems, aiming to provide references for research in related fields and to promote the efficient application of STING agonists in cancer therapy.

Keywords: cGAS-STING, Anti-tumor therapy, Drug delivery system, Synergistic basis, Delivery strategy

Introduction

Currently, the treatment methods for tumors are diverse, including traditional surgery, radiotherapy, chemotherapy, as well as the rapidly developing immunotherapy and targeted therapy in recent years. These treatment methods have achieved significant progress in tumor therapy, but still have certain limitations. For example, compared with traditional treatment methods, immunotherapy has milder side effects, but it can cause the immune system to become overly active, causing damage to normal tissues.[1] Immunotherapy works by removing the "constraints" of the host immune system on cancer cells. But this process may stimulate the immune system to misidentify and attack normal cells and tissues, thereby causing adverse reactions.[2] The infiltration of immune cells in solid tumors is limited by the immunosuppressive tumor microenvironment (TME).[3] Targeted drug delivery offers several benefits in tumor treatment, including improved permeability, the Enhanced Permeability and Retention (EPR) effect, minimized side effects, and accurate targeting of tumor cells.[4] Improved permeability refers to Nanoparticles boost drug passage through biological membranes, aiding in reaching target sites. The EPR effect refers to the phenomenon in solid tumors where large molecules or nanoparticles enter tumor tissue via leaky blood vessels and stay there due to poor lymphatic drainage. However, during targeted therapy, cancer cells may evade the suppression of drugs through genomic alterations, changes in signaling pathways, and other means, leading to drug resistance.[5] Hence, it remains highly challenging to design and develop more advanced methods for tumor treatment.

The superior performance of STING pathway in tumor treatment has made it a novel method for tumor therapy. Activating STING pathway can boost the development of dendritic cells (DC) and enhance antigen presentation, which in turn initiates T cell-mediated immune reactions.[6] However, the use of STING agonists in tumor therapy are rarely stemming from their poor stability and rapid clearance. Nanoparticle delivery systems can encapsulate STING agonists,

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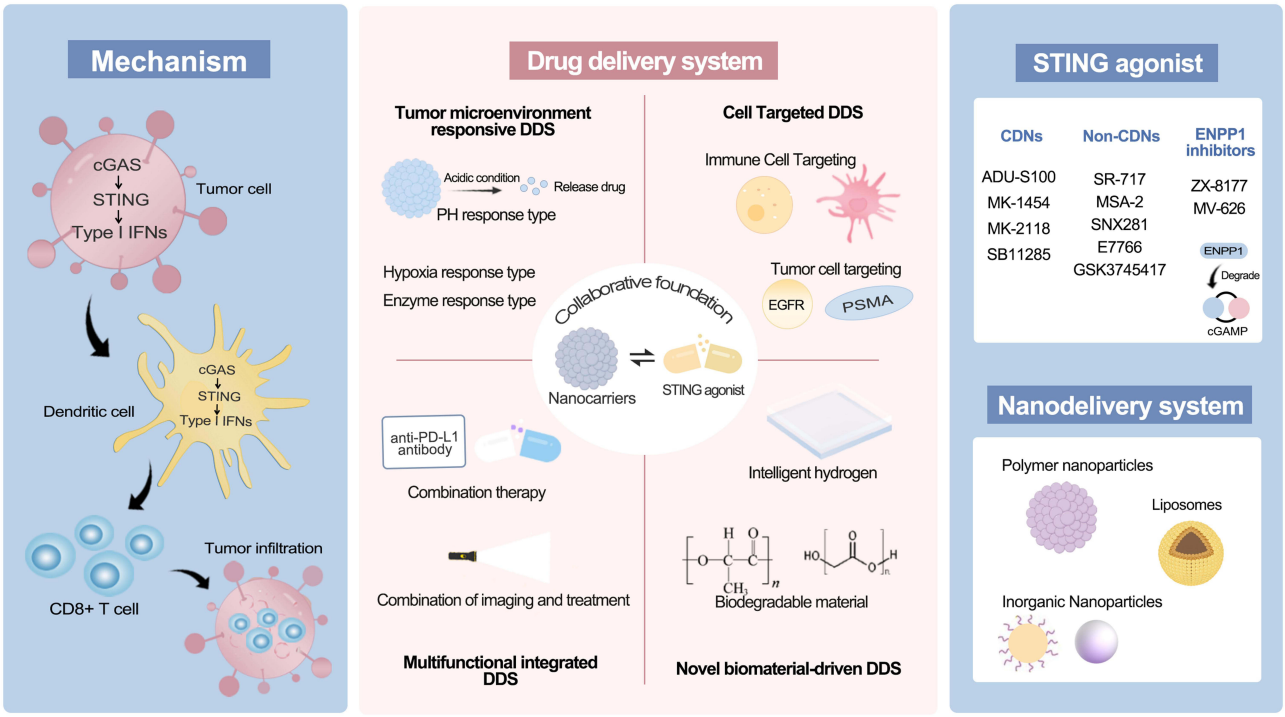
Graphical Abstract



significantly improving their stability, bioavailability, and cellular uptake efficiency. Moreover, nanoparticle delivery systems can precisely deliver STING agonists to tumor sites, achieving targeted drug delivery and reducing side effects on normal tissues.

In this review, we summarize the existing types of STING agonists, the types of nanoscale delivery systems and analyze the strategies and challenges of STING agonist delivery systems in terms of TME, tumor cell targeting, multifunctional integrated drug delivery systems, and novel biomaterials. We also analyze and predict the future development directions based on the current research status and challenges.

STING Signaling Pathway: A Powerful Target for Tumor Immunotherapy

STING is a crucial immunoregulatory protein that acts as a pivotal component in innate immune responses. STING is composed of 379 amino acids,[7] STING consists of five parts: four transmembrane helices in the N-terminal transmembrane domain (NTD), namely TM1 (residues 21–41), TM2 (47–67), TM3 (87–106), and TM4 (116–136), as well as a globular C-terminal domain (CTD, residues 157–379).[8] The N-terminal transmembrane region anchors STING to the endoplasmic reticulum membrane or the membranes of other organelles.[9] CTD, which is exposed in the cytoplasm, contains a ligand-binding domain (LBD) and a C-terminal tail (CTT).[10] LBD interacts with cGAS (cyclic GMP-AMP synthase), which is responsible for converting intracellular double-stranded DNA into the second messenger 2′,3′-cyclic GMP-AMP (cGAMP), thereby activating STING. In the reSTING state of the cell, the dimerized conformation of STING predominantly resides within the endoplasmic reticulum (ER) membrane system.[11] Upon stimulation, the STING protein initiates intracellular translocation, beginning its journey from the endoplasmic reticulum membrane system and subsequently progressing toward the Golgi, facilitated by the coat protein complex II.[9,12]

The structure of STING enables it to sense DNA that abnormally exists within cells. Pharmaceutical agents designed to target genomic material induce structural DNA lesions in the cytoplasmic compartment of malignant cells. This biochemical alteration subsequently triggers the generation of chromatin fragments, which undergo specific recognition by the cyclic

GMP-AMP synthase (cGAS) detection pathway.[13] This recognition triggers the production of cGAMP.[14] STING becomes activated upon binding to cGAMP and subsequently translocated from the endoplasmic reticulum to the Golgi apparatus.[15] As STING relocates, it recruits TANK-binding kinase 1 (TBK1) and phosphorylates it.[16] Subsequently, the CTT domain of STING facilitates the recruitment of IRF3, which subsequently undergoes phosphorylation.[17] Phosphorylated IRF3 promotes the production of type I interferons (IFN-I), and IRF3 also stimulates the production of pro-inflammatory cytokines together with activated NF-κB.[18,19] The cGAS-STING pathway generates interferons and pro-inflammatory cytokines, creating an inflammatory microenvironment that makes tumor cells more susceptible to recognition and attack by the immune system.[20] Dendritic cells (DCs) take up DNA derived from tumor cells through phagocytosis, activating the cGAS-STING pathway in DCs to produce type I IFN.[21] This promotes the maturation of DCs. The mature DCs then facilitate the clonal expansion of effector T cells, which go on to kill tumor cells.[22]

Upon activation of the STING signaling pathway, tumor cells and immune cells produce large amounts of IFN-I, which possess multiple antitumor functions. Interferon can recruit immune cells and activate dendritic cells. It can also increase the number and activity of cytotoxic T cells (CD8+T) and natural killer cells (NK), thus enhancing the immune system's attack on tumors.[23,24] Figure 1 shows the mechanism of activing the cGAS-STING signaling pathway for anti-tumor therapy.

Classification of STING Agonist Nanodelivery Systems

Polymer Nanoparticles

Polymeric nanoparticles are typically composed of natural or synthetic polymer materials that serve as carriers, with drugs loaded internally or on the surface to deliver drugs and enhance their bioavailability.[25] The carrier materials of

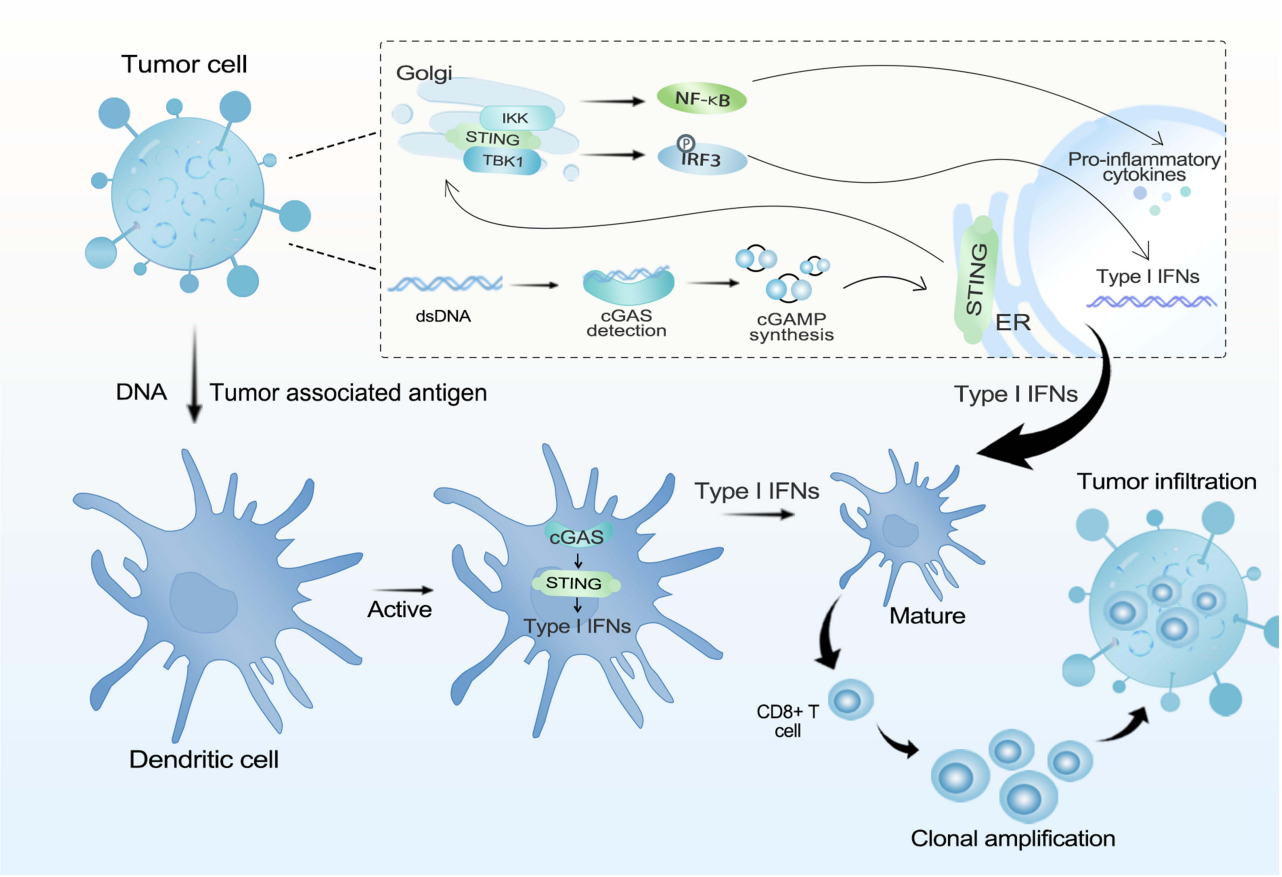


Figure 1 The mechanism of activing the cGAS-STING signaling pathway for anti-tumor therapy.

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polymeric nanoparticles generally exhibit good biocompatibility and can be safely metabolized and degraded in the body, thereby reducing toxicity to the organism.[26] Moreover, polymeric nanoparticles can improve the solubility and stability of drugs, thereby enhancing their bioavailability in the body.[27] However, during the preparation process of polymeric nanoparticles, some impurities or residues may be introduced, which can affect biological safety.[28] Additionally, the preparation process of nanoparticles is complex and it is difficult to achieve large-scale production and quality control.

Liposomes

Liposomes are nanovesicles composed of a phospholipid bilayer.[29] The composition of liposomes is similar to that of biological membranes, which gives them good biocompatibility.[30] They can encapsulate drugs to prevent degradation and promote drug penetration into cells. However, the phospholipid components of liposomes are prone to oxidation, which can affect the stability and drug encapsulation efficiency of liposomes during long-term storage.[31] Moreover, the encapsulation rate of liposomes is relatively low, leading to insufficient drug loading capacity.[32]

Inorganic Nanoparticles

Inorganic nanoparticles are nanoscale particles made from inorganic materials. They commonly include silica, metal oxides, and metallic nanoparticles.[33] Compared with organic nanoparticles such as liposomes and polymeric nanoparticles, inorganic nanoparticles have several distinct features, including good controllability of size and shape, and a large specific surface area.[34] However, some heavy metal components in inorganic nanoparticles have potential toxicity, and their accumulation in the body may lead to organ damage.[35] Additionally, inorganic nanoparticles generally have low solubility.[35] Table 1 lists the advantages and disadvantages of different nanodelivery systems.

Synergistic Basis of Nanodelivery System and STING Signal Pathway

Characteristics and Delivery Requirements of STING Agonists

Cyclic dinucleotide (CDN) agonists are natural ligands or analogs of STING that can directly bind to the STING receptor, activate the STING protein and trigger downstream signaling pathways, and promote the production of IFN-I, initiating a critical immune response cascade for antitumor activity.[36] ADU-S100, being the initial STING agonist, can induce the activation of the STING pathway through intratumoral injection, which induces the generation of CD8+ T cells that are tumor-specific. Cardin et al[37] synthesized a carbon cyclopyrimidine compound CDN (15a), which can activate the STING pathway via intravenous injection, thereby promoting cytokine secretion and the activation of CD8+ cytotoxic T cells, producing adaptive immune response.

Unlike traditional CDN agonists, non-CDN agonists do not rely on imitating the natural cyclic dinucleotide structure. Compared with CDN agonists, Non-CDN agonists have higher metabolic stability in vivo and are not easily degraded, so

Table 1 Advantages and Disadvantages of Different Nanodelivery Systems

Category	Advantages	Disadvantages
Polymer nanocarriers	The carrier material of polymer nanoparticles has good biocompatibility, which can be safely metabolized and degraded in vivo, reducing biological toxicity.[26] It can also improve the solubility and stability of drugs and enhance the bioavailability in vivo[27]	During the preparation of polymer nanoparticles, some impurities or residues may be introduced, which may affect the biological safety.[28]
Liposomes	Liposomes are similar in composition to biomembrane, and have good biocompatibility, which can contain drugs to prevent degradation and promote them to enter cells.[30]	Phospholipids in liposomes are easily oxidized, which affects their long-term storage stability and drug encapsulation efficiency,[31] and the encapsulation efficiency is low and the drug loading capacity is insufficient.[32]
Inorganic nanocarriers	Compared with organic nanoparticles (such as liposomes and polymeric nanoparticles), inorganic nanoparticles have good controllability in size and shape, as well as a large specific surface area.[34]	Some heavy metal components of inorganic nanoparticles are potentially toxic, which can cause organ damage in vivo and have low solubility.[35]

they are more suitable for systemic administration.[38] Non-CDN agonists include aminobenzimidazole, xanthone, acridone, and benzothiophene classes. Unlike CDNs, non-CDN agonists activate the STING pathway through a distinct mechanism, and the binding mechanisms of different agonists vary. For example, SR-717 can act as a cGAMP mimic, directly activating the STING pathway and enhancing the activation of CD8+ T cells and DCs within associated tissues;[39] MSA-2 induces conformational changes in STING, converting it to an active state and thereby activating the STING pathway.[40]

ENPP1 inhibitors have been developed as novel STING agonists. ENPP1 is a transmembrane phosphodiesterase that downregulates cGAS-STING pathway signaling by degrading cGAMP.[41] Cells lacking ENPP1 exhibit higher capacity for activating STING with cGAMP, and inhibiting ENPP1 enhances signaling through the cGAS-STING pathway.[42] Li et al[43] discovered an effective ENPP1 inhibitor, ZX-8177, which prevents ENPP1 from hydrolyzing cGAMP, thereby increasing the expression level of IFN-β in vivo. This inhibitor significantly inhibits tumor growth and enhances antitumor immune responses. Table 2 lists the types and route of delivery of some STING agonists.

STING agonists face many challenges in cancer treatment.[44] For example, CDN-derived STING agonists have significant effects in activating STING. However, they have poor stability in vivo, are prone to degradation, have a short half-life, and have difficulty crossing the cell membrane barrier.[45,46] This limits their effective duration of action in the body and affects the therapeutic effect. Non-CDN STING agonists have overcome the above limitations to a certain extent, but they have poor water solubility, and injection administration often leads to systemic toxicity and significant adverse reactions.[47] Therefore, STING agonists are mainly administered by intratumoral injection, but this mode of administration is not suitable for metastatic lesions and tumors that are located in hard-to-reach deep organs or in the central nervous system.[48,49] For example, CDN-based STING agonists such as ADU-S100 require intratumoral injection,[50,51] which not only limits their therapeutic effect on deep-seated tumors or metastatic lesions, but also increases the complexity of clinical operations and the pain of patients. The use of STING agonists can also lead to serious toxic and side effects, such as rheumatoid arthritis, non-alcoholic fatty liver disease, systemic lupus erythematosus and other autoimmune diseases, which limit their widespread clinical application.[52–54]

In the in vivo environment, STING agonists are prone to hydrolysis, nanocarriers can enhance the stability of drugs and improve the water solubility of poorly soluble drugs, so as to increase their bioavailability in vivo.[55,56] In addition, STING agonists need to be specifically delivered to target cells such as tumor cells or immune cells. Nanocarriers can deliver STING agonists to target diseased tissues and alleviate the side effects and reduce the impact of drugs on normal tissues.[57] The application of nanocarriers can also increase the drug concentration in tumors, thus the efficacy of cGAS-STING agonist is enhanced to some extent.[58]

Table 2 Clinical Stages and Types of STING Agonists

Drug Name	Molecular Type	Delivery Route	Phase	NCT Number
ADU-S100	CDN analog	Intratumoral injection (i.t).	Phase I / II	NCT03937141
MK-1454	CDN analog	i.t.	Phase I / II	NCT04220866
MK-2118	CDN analog	i.t.	Phase I	NCT03249792
SB11285	CDN analog	Intravenous injection (i.v).	Phase I	NCT04096638
TAK-676	CDN analog	i.v.	Phase I / II	NCT04879849
BMS-986301	CDN analog	i.t.	Phase I	NCT03956680
BI-1387446	CDN analog	i.t.	Phase I	NCT04147234
SNX281	non-CDN molecule	i.v.	Phase I	NCT04609579
GSK3745417	non-CDN molecule	i.v.	Phase I	NCT03843359
E7766	non-CDN molecule	i.t.	Phase I	NCT04144140
HG-381	non-CDN molecule	/	Phase I	NCT04998422
TXN10128	ENPP1 inhibitor	/	Phase I	NCT05978492
SR-8541A	ENPP1 inhibitor	/	Phase I	NCT06063681
RBS2418	ENPP1 inhibitor	/	Phase I	NCT05270213

Regulatory Potential of Nanodelivery System on STING Signaling Pathway

Nanodelivery systems have the potential to boost the effectiveness of STING agonist immunotherapy. Shaji et al[59] compared the antitumor effects of cGAMP encapsulated in lipid nanoparticles (LNPs) and free cGAMP using a mouse model. The study demonstrated that the administration of cGAMP encapsulated in LNPs to mice effectively suppressed tumor growth.

Nanodelivery systems can also modulate immunosuppressive cells. Nanoparticles can be modified on their surface or loaded with specific drugs to modulate immunosuppressive cells within the TME.[60] For instance, nanocarriers carrying immunomodulatory agents can boost the percentage of CD8+ T cells within tumors and diminish the infiltration of immunosuppressive cells into tumors.[61]

Additionally, the properties of nanomaterials themselves (such as surface charge, chemical composition, and topological structure) may have direct or indirect effects on the STING signaling pathway. Some nanomaterials can act as agonists to directly activate the STING pathway. Zhang et al[62] found that MnO_2 nanomaterials, by converting to Mn^{2+}, show potential as cGAS agonists. Mn^{2+} not only boosts the DNA-sensing capability of cGAS and the formation of cGAMP, but also enhances STING's affinity for cGAMP, thus efficiently activating the cGAS-STING pathway.[60] Cheng et al[63] merged exosomes from M1 macrophages and tumor cells that were genetically modified to overexpress CD47, designing and synthesizing gene-engineered hybrid exosomes (gHE). To activate the STING pathway, they further encapsulated DNA-damaging chemotherapeutic agent SN38 coupled with MnO_2 nanoparticles. In the acidic TME, MnO_2 nanoparticles decompose into Mn^{2+}, which, together with cytoplasmic DNA produced by immunogenic cell death induced by the therapeutic efficacy of SN38 in chemotherapy, synergistically activates cGAS-STING pathway.

Nanomaterials can also indirectly promote the intracellular action of STING agonists by regulating cell uptake and endosomal escape mechanisms, revealing their intrinsic synergy. For example, Shae et al[64] designed STING-activating nanoparticles (STING-NPs) that can respond in the acidic endosomal environment, releasing polymer fragments that disrupt the endosomal membrane, and promote the intracellular release of cGAMP, thereby enhancing the activation of the STING pathway and the antitumor immune response.

Design Strategy of Drug Delivery System

Drug Delivery System Based on Tumor Microenvironment Response

Tumor Specific Enzyme Activation

The aberrant expression of enzymes such as matrix metalloproteinases (MMPs), cathepsins, phospholipases and redox enzymes in TME is due to the faster proliferation of tumor cells compared to normal tissues, which requires more enzymes to provide functional support.[65] MMPs are enzymes that promote tumor invasion and metastasis.[66] MMPs degrade the extracellular matrix (ECM), compromising its structural integrity and facilitating tumor invasion and metastasis.[67] Additionally, MMPs can promote tumor angiogenesis by degrading the ECM.[68] The degradation of the ECM and vascular basement membrane by MMPs creates space for the formation of new blood vessels, allowing endothelial cells to proliferate and extend toward the tumor.[69] Hyaluronic acid (HA) is a high-molecular-weight polysaccharide that is widely present in the ECM and plays a significant role in tumor development and progression.[70] HA engages with cell surface receptors and activates signal pathways that enhance the proliferation, migration and invasion of tumor cells.[71] Hyaluronidase can degrade hyaluronic acid, thereby improving the TME, inhibiting tumor growth, and enhancing the penetration of antitumor drugs into the tumor.[72] Cathepsin B (CtsB) is a lysosomal cysteine protease capable of directly degrading ECM components, including collagen and fibronectin.[73] It also indirectly promotes tumor invasion and metastasis by activating MMPs. Moreover, CtsB can degrade specific ECM components such as tenascin-C, which promotes angiogenesis and thus supports tumor growth.[74]

Therefore, key enzymes in the TME can be designed as enzyme-responsive nanoparticles to inhibit tumor growth. By designing prodrug structures that can be cleaved by specific enzymes (such as MMPs, and hyaluronidase, HAase), the specific release of STING agonists in the TME can be achieved. Using nanoparticles as carriers to encapsulate STING agonists and incorporating enzyme-responsive linkers can enable targeted drug release. For example, Zhu et al[75] designed an enzyme-responsive STING agonist nanoparticle (NEs@STING-Mal-NP) that is responsive to hyaluronidase

(Figure 2A). This nanoparticle uses neutrophils as carriers to actively penetrate tumor tissues and release the STING agonist in response to hyaluronidase. This nanoparticle significantly enhances the tumor penetration of the STING agonist, activates the STING pathway, and improves the immunosuppressive TME. Li et al[76] developed a multilayer liposome (HLHC) based on the physical cross-linking of HA and lipid molecules for efficient delivery of the STING agonist cGAMP (Figure 2B).

Immune cells in TME can be activated by the release of STING agonists from enzyme-responsive drug delivery systems, which enhances the efficacy of immunotherapy. Although there are currently few studies on the combination of enzyme-responsive drug delivery systems and STING agonists, this strategy holds significant potential for clinical application and is worthy of further research and exploration. In the future, personalized drug delivery regimens could be tailored based on the enzyme expression profiles in a patient's TME, further improving therapeutic outcomes.

PH Response Mechanism

Tumor cells primarily generate energy through glycolysis, a metabolic process that leads to the generation of substantial quantities of lactic acid.[77] Lactic acid is an acidic metabolic byproduct, and its accumulation significantly reduces the extracellular pH, thereby establishing a microenvironment that is acidic.[78] This acidic microenvironment within tumors facilitates the invasion of tumor cells while stimulating their colonization and expansion at metastatic sites.[79] This acidic microenvironment can inhibit the function of immune cells by inhibiting the differentiation of monocytes into dendritic cells and the anti-tumor activity of natural killer cells and cytotoxic T cells, thus promoting the immune escape of tumor cells.[80] Moreover, an acidic pH can promote the formation of premetastatic niches in distant organs, creating favorable conditions for tumor cell metastasis.[79] A pH-sensitive cationic polymer modified lipid nanoparticle (LNP-B) loaded with CDNs has been developed.[81] Figure 3A shows the preparation process of LNP-B. In order to efficiently encapsulate the negatively charged CDNs, a distinctive functional phospholipid known as DSPE-PCB+ was synthesized, featuring multiple positive charges at one end.[81] This enhances the ability of CDNs to load drugs in the lipid nanoparticles. In an acidic environment, DSPE-PCB+ experiences hydrolysis, promoting the release of CDNs from the lipid nanoparticles, thereby enhancing immunogenic cell death (ICD) in tumor cells. Compared with free CDNs, LNP-B prolonged the circulation of CDNs and enhanced their accumulation in tumors. Wang et al[82] designed a nanomicelle formulation called D-SAM, encapsulating the STING agonist cGAMP within micelles of another STING agonist, PC7A. The PC7A in D-SAM contains ultra-pH-sensitive tertiary amines that can be protonated under weakly acidic conditions, creating a proton sponge effect. This buffers the lysosomal pH to delay the degradation of STING, allowing the agonist to be released and activate STING more sustainably. Compared with the classical STING agonist ADU-S100, D-SAM not only effectively prolonged the activation and infiltration of CD8-positive T cells but also avoided T cell exhaustion and apoptosis (Figure 3B).

Currently, pH-responsive drug delivery systems still face many challenges in practical applications. Many pH-responsive materials have poor stability and are prone to degradation. For example, some biopolymer carriers are easily degraded by enzymes in the body, leading to premature drug release.[84] Moreover, pH-responsive carriers in the body may be interfered with by blood components, metabolic products, and other factors, which can affect their responsive performance.[85]

Hypoxia Response

The hypoxic condition within tumor tissues is a key feature of the TME.[86] The formation of a hypoxic environment in tumors is caused by processes such as the incomplete structure and poor permeability of tumor blood vessels.[87] The STING signaling pathway is inhibited by tumor hypoxia.[88] Improving the hypoxic state helps to restore the normal function of the STING signaling pathway and boosts the immune response against tumors. Some nanoparticles can carry oxygen or substances that can generate oxygen, thereby improving the hypoxic environment of tumor tissues. For example, Zhou et al[83] developed a metal-organic framework (MOF) nano-system, which was composed of Mn2+, CaCO3, a prodrug of barnesonone (AQ4N) and STING agonist SR-717 (AMSC MOFs). Figure 3C shows the preparation process and mechanism of AMSC MOFs. CaCO3 consumes lactic acid in TME to alleviate immunosuppression caused by hypoxia. The nanosystem effectively activates the STING pathway through SR-717 and CaCO3 consuming

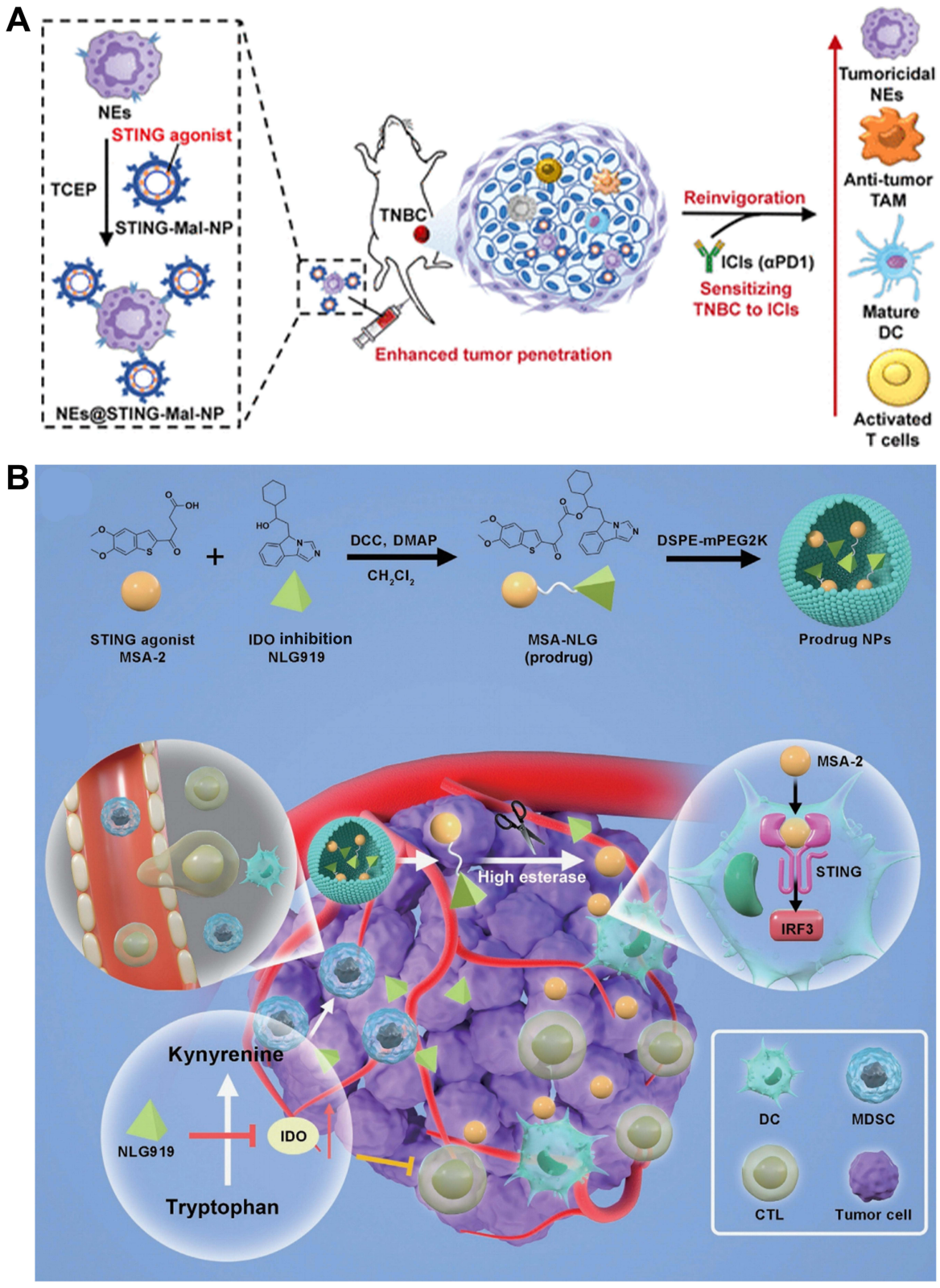

Figure 2 (**A**) The design strategy of NEs@STING-Mal-NP. Reproduced from Hao M, Zhu L, Hou S, Chen S et al. Sensitizing tumors to immune checkpoint blockage via STING agonists delivered by tumor-penetrating neutrophil cytopharmaceuticals. ACS nano. 2023;17(2):1663–1680. Copyright © 2023 American Chemical Society.[75] (**B**) Preparation process of multilayer liposomes based on physical crosslinking of hyaluronic acid and lipid molecules for delivering STING agonist cGAMP. Reproduced from Yu J, Li X, Li J, Sun N, Cheng P et al. Single-Dose Physically Cross-Linked Hyaluronic Acid and Lipid Hybrid Nanoparticles Containing Cyclic Guanosine Monophosphate–Adenosine Monophosphate Eliminate Established Tumors. ACS nano. 2024;18(43):29,942–29955. Copyright © 2024 American Chemical Society.[76]

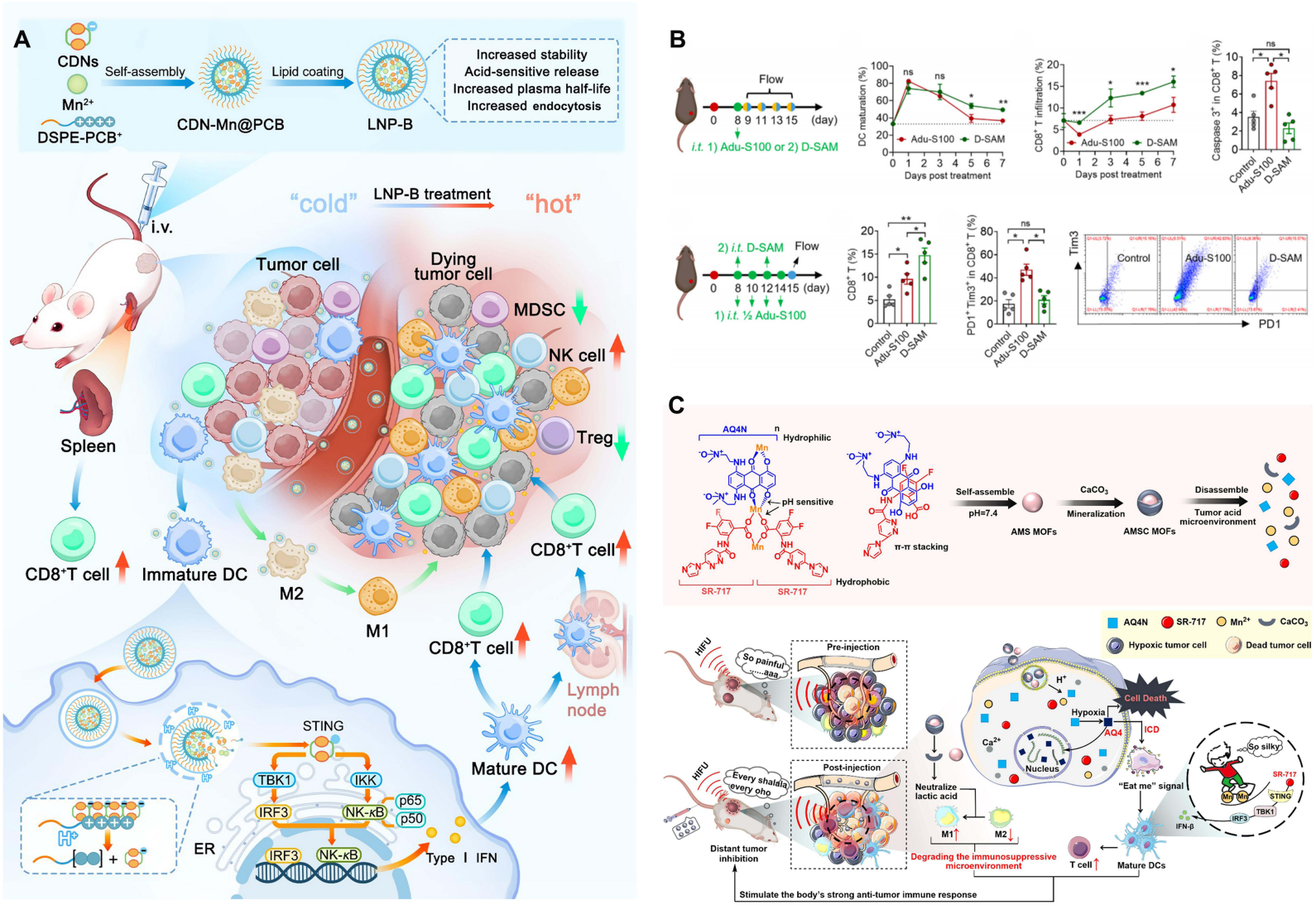

Figure 3 (**A**) Preparation of pH-sensitive polycationic polymer modified lipid nanoparticles (LNP-B) system for tumor delivery of intravenous CDNs. Reproduced from He Y, Zheng K, Qin X, Wang S, Li X, Liu H, Liu M, Xu R, Peng S, Pang Z. Intravenous delivery of STING agonists using acid-sensitive polycationic polymer-modified lipid nanoparticles for enhanced tumor immunotherapy. Acta Pharm Sin B. 2025 Mar;15(3):1211–1229. © 2025 The Authors. CC BY-NC-ND license.[81] (**B**) D-SAM extends the activation duration and infiltration period of CD8-positive T cells. (Some data in this paper are expressed by mean standard deviation (SD). The significant difference analysis method of each group data is one-way ANOVA. Reproduced from Wang J, Wang X, Xiong Q, Gao S, Wang S, Zhu S, Xiang S, Li M, Xie H, Li S. A dual-STING-activating nanosystem expands cancer immunotherapeutic temporal window. Cell Rep Med. 2024 Nov 19;5(11):101,797. © 2024 The Author(s). CC BY-NC-ND license.[82] The degree of difference between each group is marked as: n.s., and there is no obvious difference; *P<0.05; **P<0.01; ***P<0.001) (**C**) Synthesis and Mechanism of AMSC MOFs. Reproduced from Zhou Y, Huang X, Wu D, Xie X et al. HIFU postoperative hypoxia enables metal-organic frameworks amplifying banoxantrone and STING activation for enhanced immunotherapy. Chem Eng J. 2025;159,704. © 2025 Elsevier B.V. All rights are reserved, including those for text and data mining, AI training, and similar technologies.[83]

lactic acid. Yu et al[89] developed a high-valence bismuth nanoparticle platform NaBiVO3-PEG, which can generate of reactive oxygen species (ROS). Because tumor hypoxia can inhibit the activation of STING signaling pathway, the nano-platform has the potential to trigger the STING signaling pathway, thereby enhancing the anti-tumor immune response. Table 3 lists some design strategies of drug delivery system based on TME reaction.

Cell Targeted Drug Delivery System

Immune Cell Targeting

The STING signaling pathway is an essential component of innate immunity, capable of activating immune responses by recognizing intracellular DNA damage and pathogen DNA. Additionally, activation of the STING pathway can enhance the TME and boost the infiltration of immune cells.[60] The activation of STING promotes the maturation of DCs and enhances their antigen-presenting ability, thereby activating T cells.[93] It also promotes the secretion of chemokines, guiding T cells to infiltrate the tumor site.[94] STING activation can transform an immunosuppressive TME into an immunosupportive one.[95] For example, activation of STING can induce the polarization of tumor-associated macrophages (TAMs) from the M2 phenotype, which is immunosuppressive, to the immunostimulatory M1 phenotype.[96]

DCs, as antigen-presenting cells,[97] play a crucial role in both innate and adaptive immunity and are central to antitumor immunity. DCs are capable of capturing and processing tumor antigens, activating cytotoxic T cells and natural killer (NK) cells, and thus play an essential role in antitumor immune pathways.[98] After recognizing tumor cells, DCs present processed tumor antigens to T cells via antigenic peptides bound to major histocompatibility complexes as the first signal for activation.[99] The upregulation of costimulatory molecules such as CD80 and CD86 on the surface of DCs provides the second signal for activation.[100] Naive T cells, stimulated by these two signals, become specific cytotoxic T lymphocytes (CTLs),[101] thereby exerting targeted antitumor effects. DCs can release a variety of chemokines, such as CXCL9, CXCL10, and CCL5.[101,102] These chemokines recruit T cells expressing CXCR3 to infiltrate the tumor and also recruit NK cells. Activated NK cells leave the lymph nodes and travel to the tumor site to kill cancer cells.[103] Within the tumor microenvironment (TME), macrophages exhibit functional heterogeneity and are principally categorized into two distinct subtypes: pro-inflammatory M1 macrophages and immunomodulatory properties M2 macrophages. M1 macrophages can secrete a variety of pro-inflammatory cytokines and chemokines.[104] These cytokines and chemokines can activate T cells and enhance antitumor immune responses. M2 macrophages have anti-inflammatory properties and can release immunosuppressive factors, which can promote tumor progression, angiogenesis, and immune evasion.[104,105]

Targeting nanoparticles to immune cells is a feasible design strategy. By selecting appropriate nanomaterials, such as mannosylated liposomes and nanoparticles conjugated with anti-CD11c antibodies, precise targeting and recognition of immune cells can be achieved. Additionally, optimizing the drug loading and release patterns to match the intracellular environment of immune cells can optimize the performance of drug delivery.

Table 3 Drug Delivery System Based on Tumor Microenvironment (TME) Response

Composition of Nanodelivery System	TME type of Response	Experimental Result	Refers
First, the STING agonist MSA-2 and the indoleamine-2,3-dioxygenase (IDO) inhibitor NLG 919 were coupled to obtain a TME esterase-responsive prodrug. Then, the prodrug was wrapped in the polymer DSPE-mPEG2K to obtain nanoparticles.	Esterase response type	This nanomedicine can cleave and release both drugs at esterase-rich tumor sites, thereby activating the tumor immunity in situ and exerting a high efficiency antitumor effect.	[90]
PH-responsive polymer encapsulating STING agonist ASA404 and chemotherapy drug HCFU.	Ph response type	The encapsulated drug is released in the tumor, which effectively improves the bioavailability of the drug and the anti-tumor effect.	[91]
Self-assembled nanoparticles containing dysprosium ions and manganese ions (Dy/Mn-P)	Hypoxia response type	Dy/Mn-P nanoparticles increased the level of endogenous ROS in tumor and significantly enhanced the activation of STING pathway, thus triggering anti-tumor immune response.	[92]

Mannose is a type of sugar ligand that can be recognized and endocytosed by mannose receptors on the exterior of immune cells like macrophages and dendritic cells, and then enter the lysosomes within the cell. Mannose-modified liposomes can achieve precise targeting of immune cells through specific binding to mannose receptors. Liao et al[106] developed D-mannose-modified nanoliposomes (MLipo@OVA) for the targeted delivery of ovalbumin (OVA) to macrophages. This type of liposome significantly increased the uptake efficiency of macrophages. Studies have shown that mannose-modified liposomes can be efficiently absorbed by DCs, promote the maturation of DCs, and significantly inhibit tumor metastasis in vivo.[107] Although there are currently relatively few research examples of using mannitol-modified nanoparticles to target immune cells to activate the STING pathway, this method shows great potential in terms of both theory and application prospects. CD11c is an antigen primarily expressed on the surface of dendritic cells. Nanoparticles conjugated with anti-CD11c antibodies can achieve precise targeting through specific binding to the CD11c antigen on the surface of dendritic cells. Zhang et al[108] synthesized mannose-modified stearic acid grafted chitosan micelles (M-CS-SA) and cooperated with oxaliplatin. The nano-micelle can target dendritic cells, activate cGAS-STING signal pathway in cooperation with oxaliplatin, and enhance the anti-tumor effect. Figure 4A shows a schematic diagram of the synergy between oxaliplatin and M-CS-SA.

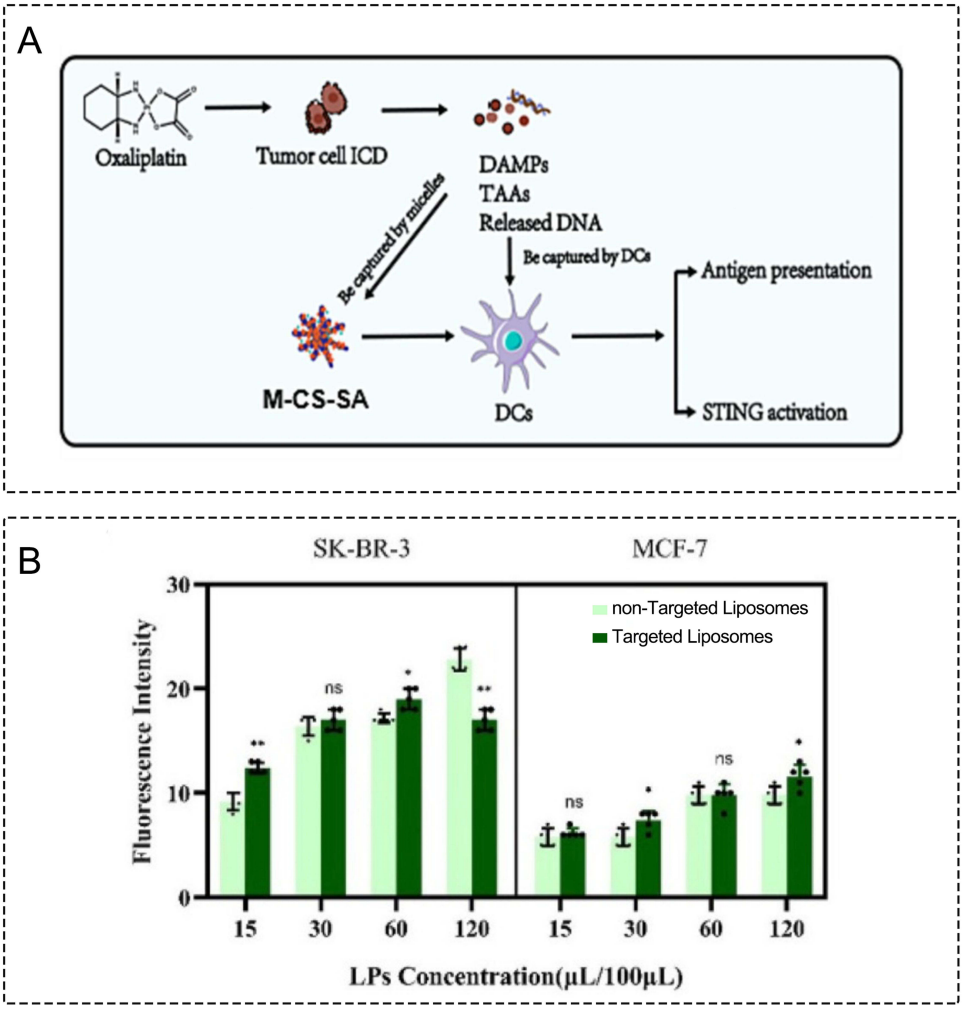

Figure 4 (**A**) Schematic diagram of synergy between oxaliplatin and M-CS-SA. Reproduced from Nguyen NT, Le XT, Lee WT, Lim YT, Oh KT, Lee ES, Choi HG, Youn YS. STING-activating dendritic cell-targeted nanovaccines that evoke potent antigen cross-presentation for cancer immunotherapy. Bioact Mater. 2024 Sep 6;42:345–365. © 2024 The Authors. CC BY-NC-ND license.[109] (**B**) Compared the fluorescence intensity between targeted liposomes and non-targeted liposomes, the targeted liposomes showed higher uptake. Reproduced from Wu YT, Fang Y, Wei Q, Shi H, Tan H, Deng Y, Zeng Z, Qiu J, Chen C, Sun L, Chen ZJ. Tumor-targeted delivery of a STING agonist improvescancer immunotherapy. Proc Natl Acad Sci U S A. 2022 Dec 6;119(49):e2214278119. Copyright © 2022 the Author(s). Published by PNAS. Creative Commons Attribution License 4.0 (CC BY).[110] (The degree of difference between each group is marked as: n.s., and there is no obvious difference; *P<0.05; **P<0.01).

Although immune cell targeting has shown remarkable potential for the therapy of neoplasms and infectious illnesses, it also faces many challenges. For example, immunosuppressive cells and metabolic products in TME can weaken the capacity of immune cells and promote drug resistance.[111] Moreover, the heterogeneity and mutability of tumor cell surface antigens present obstacles for immune cells to exactly recognize and target tumor cells.[112] To address these issues, immune cell therapies that can target multiple tumor antigens simultaneously can be developed to enhance targeting specificity. Additionally, combining multiple therapies to eliminate immunosuppressive cells can reduce drug resistance.

Tumor Cell Targeting

Tumor cells express a variety of specific receptors on their surface, which have a major impact on occurrence, development, metastasis, and treatment of tumors. The number of epidermal growth factor receptors (EGFR) is significantly increased in various tumor cells.[113] The EGFR signaling pathway is crucial for regulating cell proliferation, differentiation, survival, and development. Upon activation, it promotes cell proliferation, survival, migration, and angiogenesis through downstream signaling pathways such as Ras-Raf-MEK-ERK and PI3K-Akt-mTOR.[114]

Human epidermal growth factor receptor 2 (HER2) is overexpressed in several cancers, including breast, gastric, and ovarian cancers.[115] HER2 forms heterodimers with other HER family members to activate the PI3K-Akt-mTOR and Ras-Raf-MEK-ERK pathways, thereby promoting cell proliferation, survival, migration, and invasion.[116]

Prostate-specific membrane antigen (PSMA) is highly expressed in malignant prostate epithelial cells, with expression levels increasing as the malignancy of prostate cancer progresses.[117,118] PSMA activates the PI3K-Akt pathway and intracellular calcium release by stimulating the glutamate receptor (mGluR), upregulating the mTOR pathway to promote cell proliferation and survival.[119] PSMA inhibitors can target its binding sites to delay or even terminate the proliferation of prostate cancer cells.[120,121]

The abnormal expression and signaling mechanisms of these receptors on the surface of tumor cells are important factors in the occurrence, development, and malignant transformation of tumors, and have become key targets for cancer therapy. Sun et al[122] developed HER2-targeted nanoliposomes for co-delivering viral peptides and the STING agonist diABZI. By targeting HER2 specifically, diABZI was delivered specifically to tumor cells. Figure 4B shows a comparison of the fluorescence intensity between targeted and non-targeted liposomes, with the targeted liposomes demonstrating superior uptake.

Targeted therapy for tumor cells is of significant importance in cancer treatment but also faces many challenges. Targeted drugs for tumor cells can specifically recognize antigens on the surface of cancer cells, but drug'efficiency entry into cancer cells is still limited.[123] For example, the TME is complex, containing a variety of cells and extracellular matrix components.[124] These components form physical and chemical barriers that hinder the penetration and uptake of drugs.[125] Currently, innovative drug delivery systems are being developed to improve the efficiency of drug entry into tumor cells. Moreover, as treatment progresses, tumor cells may develop drug resistance through genetic mutations, reducing the effectiveness of treatment. Table 4 lists some design strategies of cell targeted drug delivery system.

Table 4 Cell Targeted Drug Delivery System

Composition of Nanodelivery System	Targeted Cell Type	Experimental Result	Refers
A nanoparticle with metal-organic framework (MOF) gating and hyaluronic acid (HA) modification is capable of carrying cisplatin (CDDP) and SR-717.	Tumour cell	After being internalized by tumor cells, the acid/reduction-responsive gated MOF will rapidly decompose to release SR-717 and CDDP. CDDP induces double strand DNA (dsDNA) damage in cancer cells, activates the cGAS-STING pathway, and enhances antitumor immune responses.	[126]
Stimulated dendritic cell targeted nanovaccine (Si9GM) combined with anti-CD11c antibody	CD11c	This vaccine, in combination with anti-CD11c antibodies, targets conventional dendritic cells type 1 (cDC1), reduces the number of tumor regulatory T cells (Tregs), and enhances antitumor immunity.	[109]

Multifunctional Integrated Drug Delivery System

Combination of Imaging and Treatment

Nanoplatforms can integrate therapeutic drugs and imaging contrast agents into one entity, enabling simultaneous diagnosis and treatment. This integrated design not only allows for precise localization of the tumor's position, size, and boundaries but also enables real-time monitoring of treatment efficacy.[127,128] Nanoplatforms can also carry targeting molecules that specifically bind to receptors or antigens outer membrane of tumor cells, thereby achieving tumor targeting and reducing distribution of drugs in normal tissues, which in turn reduces toxicity to normal tissues.[129] The imaging function of nanoplatforms can monitor in real-time the distribution, release of the drug, and the tumor's response.

Biosensors constructed via nanotechnology can monitor in real-time the changes in STING pathway and the body's immune reaction during tumor therapy.[130,131] A fluorescent molecular probe designated as BN-O was developed by Song er al.[132] through structural optimization of an N-oxide framework. This engineered compound demonstrates hypoxia-responsive characteristics, enabling simultaneous generation of both near-infrared II (NIR-II) region fluorescence emissions and photoacoustic detection signals under oxygen-deficient microenvironmental conditions (Figure 5A). This mechanism additionally stimulates cGAS-STING pathway, thereby facilitating the secretion of damage-associated molecular patterns along with inflammatory cytokines from neoplastic cells. This, in turn, enhances the development of dendritic cells and the activation of T cells, ultimately accomplishing precise tumor diagnosis and effective therapy.[133,134] Sun et al[135] designed a NIR-II photoactivatable immunotheranostic nanoparticle (SAPTN) based on a STING agonist. SAPTN has high spatial and temporal resolution deep tissue NIR-II imaging capabilities, which can clearly diSTINGuish tumor margins from surrounding tissues, thereby guiding phototherapy.

Nanoplatforms integrating imaging and therapeutic functions hold significant importance in tumor treatment. They can significantly improve diagnostic accuracy, enhance therapeutic efficacy, improve the TME, reduce side effects, and support personalized treatment. However, the preparation of nanoplatforms faces numerous complex challenges. For instance, the extremely small size of nanoplatforms necessitates highly precise control techniques during the preparation process. Moreover, the preparation process of nanoplatforms is often quite complex. Overcoming the limitations of nanoplatforms is an important direction for the future development of precision oncology.

Combination Therapy and Synergistic Administration

Cancer cells exhibit significant heterogeneity in their genetics, phenotype, and function, and different cells have varying sensitivities to treatment. Monotherapy may fail to cover all cancer cells comprehensively, leading to the survival of some cells and subsequent drug resistance. Moreover, monotherapy is often insufficient to address the complexity of tumors.[137] Immunotherapy, such as PD-1/PD-L1 inhibitors, relies on the infiltration and activation of immune cells in the TME. However, some tumors are characterized as "immune-cold" tumors, meaning that immune cells have difficulty infiltrating the tumor tissue, resulting in poor efficacy of immunotherapy.[138,139] Chemotherapy and radiotherapy, while capable of directly killing cancer cells, also have significant toxicity to normal tissues and are prone to inducing drug resistance.[140,141]

Monotherapy has many limitations in cancer treatment, while combination therapy can act on cancer cells through multiple mechanisms, making it difficult for cancer cells to develop resistance mutations to multiple drugs simultaneously, thereby significantly improving treatment efficacy. For example, radiotherapy can induce immunogenic cell death (ICD), releasing tumor antigens to activate the immune system.[142] Immunotherapy, on the other hand, can further increase the local bioavailability of the drug, thereby enhancing the efficacy of immunotherapy.[143] Sun et al[144] significantly enhanced the antitumor immune response through local radiotherapy combined with dual-immune-activating nanoadjuvants (STING-TLR9). The dual-immune-activating nanoadjuvants were able to counteract the immunosuppressive effects associated with radiotherapy, and this combination therapy achieved full eradication of tumors and metastatic lesions in various syngeneic mouse tumor models. The combined administration of PD-1 and CTLA-4 immune checkpoint inhibitors with intralesional ADU-S100 delivery exhibited significant therapeutic efficacy, inducing persistent tumor volume reduction in 71% of treated neoplastic lesions.[136] The efficacy of the combination therapy was superior to that of PD-1 antibody monotherapy. Figure 5B shows the effect of intratumoral injection of STING alone on tumor treatment compared with systemic α-PD-1 and/or α-CTLA-4 treatment combination. Hao et al[145] also used the combination of photodynamic therapy and STING agonist to treat colorectal cancer and experimentally

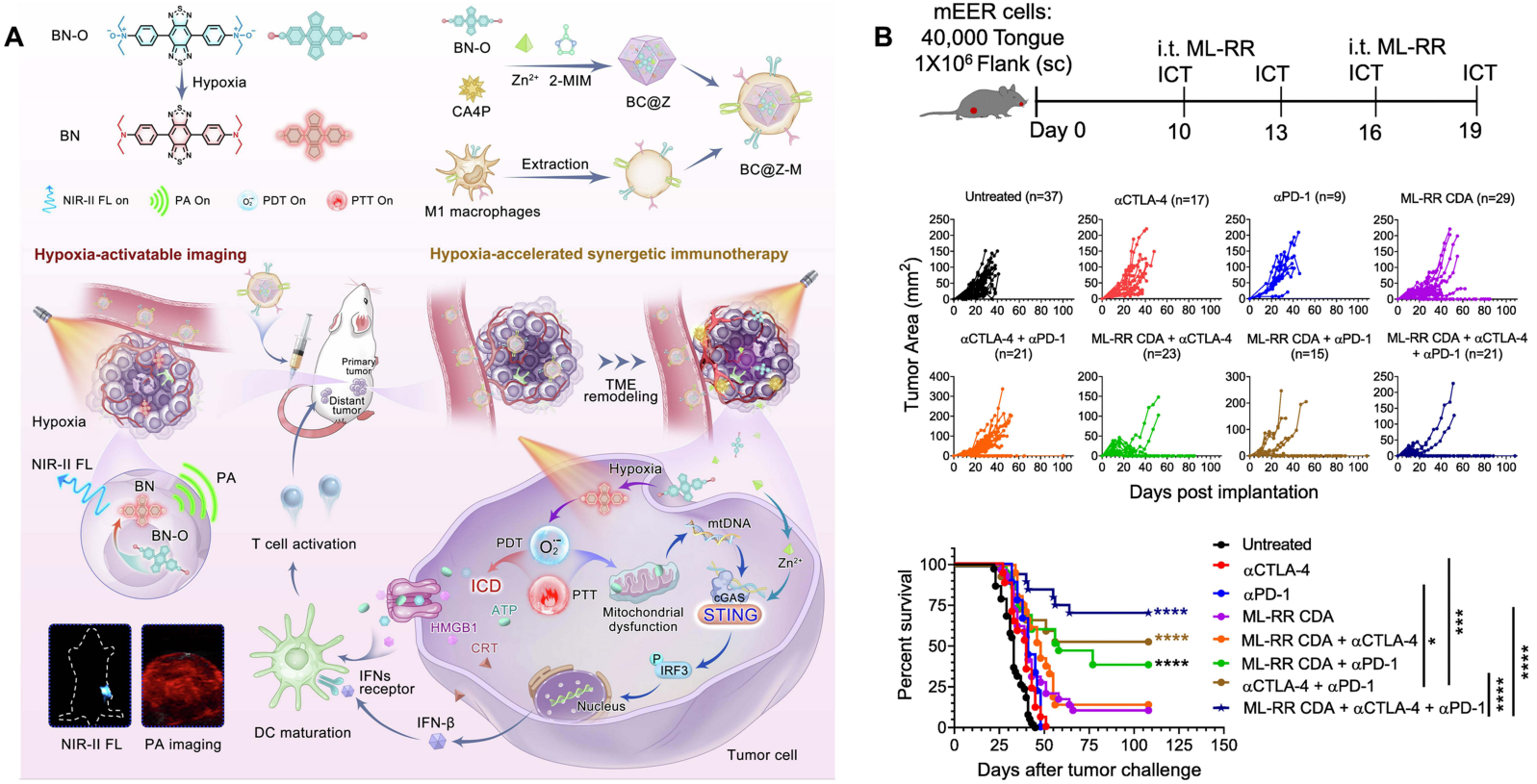

Figure 5 (**A**) Schematic diagram of nano-platform that can be activated in low oxygen environment, which is used to start NIR-II fluorescence imaging, photoacoustic imaging and enhance cancer immunotherapy. Reproduced from Song, J., Wang, H., Meng, X. et al. A hypoxia-activated and microenvironment-remodeling nanoplatform for multifunctional imaging and potentiated immunotherapy of cancer. Nat Commun 15, 10,395 (2024). Creative Commons Attribution 4.0 International License.[132] (**B**) Effect of intratumoral injection of STING alone on tumor treatment by the fusion of systemic α-PD-1 and/or α-CTLA-4 therapies. Reproduced from Dorta-Estremera S, Hegde VL, Slay RB, Sun R, Yanamandra AV, Nicholas C, Nookala S, Sierra G, Curran MA, Sastry KJ. Targeting interferon signaling and CTLA-4 enhance the therapeutic efficacy of anti-PD-1 immunotherapy in preclinical model of HPV$^+$ oral cancer. J Immunother Cancer. 2019 Sep 18;7(1):252. © The Author(s). 2019. Creative Commons Attribution 4.0 International License.[136] (The degree of difference between each group is marked as: *P<0.05; ***P<0.001; ****P<0.0001).

validated that the efficacy of the combined therapy was significant and superior to that of monotherapy. It is also possible to achieve a synergistic antitumor effect by combining metal-based nanosystems that can activate the STING pathway with other therapeutic modalities such as chemotherapy, radiotherapy, and immune checkpoint inhibitors.[146]

Moreover, due to the synergistic effects of combination therapy, the required dosage of each drug can be appropriately reduced, which helps to mitigate toxic side effects. For example, the combination of targeted therapy with chemotherapy or immunotherapy can inhibit tumor growth at multiple stages, thereby reducing the risk of drug resistance. The combination of the STING agonist MSA-2 with PD-1 antibodies can reduce the likelihood of resistance.[147] Table 5 lists some design strategies of multifunctional integrated drug delivery system.

Novel Biomaterial-Driven Drug Delivery System

Biodegradable Material

Natural biodegradable materials are mainly derived from renewable natural resources and possess excellent biocompatibility and environmental friendliness. Common natural biodegradable materials include starch-based materials, cellulose and lignin, and protein-based materials. These natural biodegradable materials can rapidly absorb moisture from blood, promoting coagulation, and can be used as hemostatic materials. Wu et al[151] developed a novel starch-based hemostatic sponge incorporating serotonin (SLS sponge) by integrating serotonin into a starch matrix through esterification and amidation reactions. The SLS sponge is able to quickly set off the coagulation cascade, promote the grouping of red blood cells and platelets, and enhance platelet activation. Natural biodegradable materials can also be used as scaffold materials to guide cell growth and tissue repair. Cordeiro R et al[152] tested the porosity, mechanical properties and biocompatibility of different types of cellulose (including microcrystalline cellulose, methylcellulose, and corn core cellulose) and found that the addition of cellulose can promote cell adhesion and proliferation. Xun et al[153] developed a macroporous bacterial cellulose (BC) scaffold crosslinked by calcium ions for cranial bone regeneration. Natural biodegradable materials such as starch-based nanomaterials, owing to their small size, high specific surface area, and biocompatibility, have been used to develop precision drug delivery systems that can actively recognize cancer cells and achieve targeted drug release.[154] Jeong et al[155] developed a urease-powered nanomotor (STING@nanomotor) using chitosan, a natural biodegradable material, as the base material. The biocompatibility and mucosal adhesion of chitosan

Table 5 Multifunctional Integrated Drug Delivery System

Composition of Nanodelivery System	Function of the System	Experimental Result	Refers
mRNA-LNP encoding IL-12 is used in combination with STING agonists.	Combination therapy and synergistic administration	The activation of STING agonists promotes the migration of non-exhausted T cells to the tumor site. Cytokines delivered by mRNA-LNP can activate the cytotoxic function of CD8+ T cells. The synergistic effect of these two mechanisms can transform the tumor immune microenvironment from a suppressive state to an activated state.	[148]
A macromolecular prodrug of poly(lactic acid) (PLA) conjugated with gemcitabine (GEM) was first designed and modified with PD-L1 antibodies on its surface. In addition, the STING agonist was integrated into the GEM-loaded nanoparticles to generate triple-combination immunogenic nanovesicles.	Combination therapy and synergistic administration	Surface modification with PD-L1 antibodies enables tumor-specific targeted delivery, while also combining PD-L1 blockade to enhance overall efficacy. The integration of the STING agonist can further enhance the immunotherapeutic effect.	[149]
Hafnium dioxide (HfO_2) nanoparticles (radiation sensitizer) and 7-ethyl-10-hydroxy camptothecin (SN38, a STING agonist) were integrated into a polydopamine (PDA)-coated core-shell nano-platform (HfO_2@PDA/Fe/SN38) to achieve the synergistic effect of radiochemotherapy and immunotherapy.	Combination of imaging and treatment	The complex exhibits favorable imaging properties and, by activating the cGAS-STING pathway, enhances the effectiveness of radiotherapy, inhibiting the growth of both primary and abscopal tumors in tumor-bearing mice.	[150]

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enable it to effectively bind to and penetrate the mucus layer on the bladder wall, thereby increasing retention time of the nanomotor in the bladder and the efficiency of drug delivery. Figure 6A shows the fabrication method of a nano-motor driven by urease and loaded with a STING agonist. Wang et al[156] fused different glioma targeting parts to ferritin nanoparticles (RGE-HFn NPs), and wrapped or bound STING agonist SR717 in nanoparticles (SR717@RGE-HFn NPs). Although the research and application of natural biodegradable materials such as cellulose in the delivery of STING agonists are relatively few, these materials show great potential for diverse applications in the field of STING agonist delivery because of their biodegradability and environmental friendliness.

In the sphere of medication delivery system development, synthetic biodegradable materials like polylacticacid (PLA), polyglycolicacid (PGA), and their copolymer PLGA are utilized. These materials can encapsulate drugs and achieve targeted drug delivery and sustained release in the form of nanoparticles, microspheres, or films. For example, PLGA nanoparticles have been used to encapsulate STING agonists, significantly improving drug delivery efficiency and immune activation. Wilson et al[157] used biodegradable poly (β-amino ester) (PBAE) nanoparticles to deliver CDNs, effectively inhibiting tumor growth (Figure 6B). PBAE nanoparticles possess excellent biocompatibility and degradability and can naturally degrade in the body, avoiding the risk of immune reactions arising from prolonged retention. Gu et al[158] integrated the cGAS-STING-activating vascular disrupting agent DMXAA with poly (ethylene glycol)-grafted poly (lactic-co-glycolic acid) copolymer (PLGA-PEG) to obtain PLGA-PEG/DMXAA (PPD) nanoparticles to induce

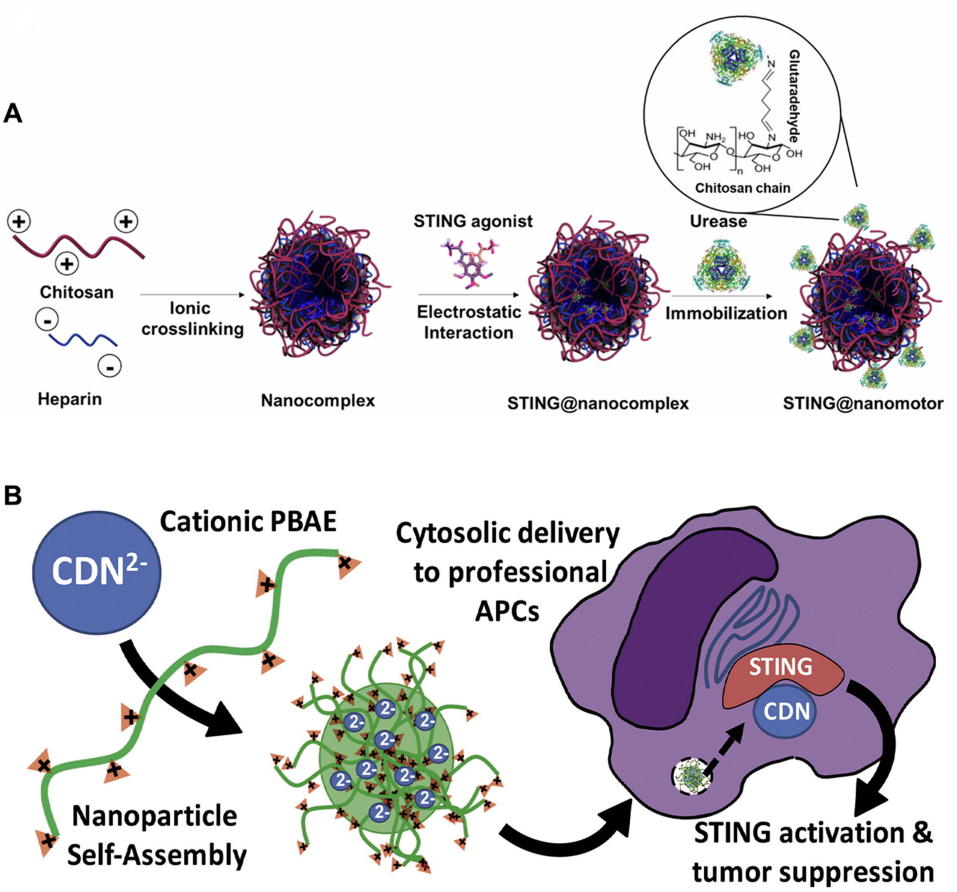

Figure 6 (**A**) The fabrication procedure of the urease-driven nano-motor incorporating a STING agonist. Reproduced from Choi H, Jeong SH, Simó C, Bakenecker A, Liop J, Lee HS, Kim TY, Kwak C, Koh GY, Sánchez S, Hahn SK. Urease-powered nanomotor containing STING agonist for bladder cancer immunotherapy. Nat Commun. 2024 Nov 15;15(1):9934. © The Author(s) 2024. Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.[155] (**B**) PBAE nanoparticles deliver CDNs and act on STING signaling pathway. Reproduced from Wilson DR, Sen R, Sunshine JC, Pardoll DM, Green JJ, Kim YJ. Biodegradable STING agonist nanoparticles for enhanced cancer immunotherapy. Nanomedicine: Nanotechnology. Biology and Medicine. 2018;14(2):237–246. *© 2017 Elsevier Inc. All rights reserved.*[157]

tumor-specific vascular destruction, which was used for multiple synergistic treatment of cancer. Although biodegradable materials generally have good biocompatibility, the intermediate products generated during their degradation in the body may trigger immune responses in the organism, thus limiting their applications.[159]

Intelligent Hydrogel

Intelligent hydrogels are a type of polymeric material featuring a three-dimensional network structure, which enables them adapting to these shifts in the surrounding environment,[160] such as temperature, pH, light, pressure, etc. Intelligent hydrogels can be categorized based on their response mechanisms into several types, including temperature-sensitive hydrogels, pH-sensitive hydrogels, redox-sensitive hydrogels, enzyme-sensitive hydrogels, electric field-sensitive hydrogels, light-sensitive hydrogels, and those that are multi-responsive.[161,162] Wang et al[163] developed a ROS-responsive hydrogel system (GEM-STING@Gel), which was used to co-deliver gemcitabine and STING agonist DMXAA. GEM-STING@Gel can form in situ at the tumor site and release drugs in response to ROS stimulation, thereby achieving targeted drug release and long-term treatment. A temperature-responsive hydrogel encapsulating STING agonist and a photothermal agent has been developed.[164] This hydrogel can rapidly release drugs upon near-infrared phototherapy, which prompts rapid heating. The release of the STING agonist activates the STING pathway, promoting the release of IFN-I and further enhancing the immune response. Due to the small pore size of the hydrogel network, the transport of biomacromolecules is relatively difficult. Therefore, the response of intelligent hydrogels to biomacromolecules is slow, which restricts their widespread application.[165] Table 6 lists some design strategies of the novel biomaterial-driven drug delivery system.

In addition, we summarize the advantages and disadvantages of various drug delivery systems in Table 7.

Table 6 Novel Biomaterial-Driven Drug Delivery System

Composition of Nanodelivery System	Mechanism of Action	Experimental Result	Refers
cGAMP is encapsulated in a micelle matrix composed of polymer PSC7A to form the polymer (PolySTING).	Structural changes of polymers at specific pH	This polymer undergoes structural changes at specific pH levels, thereby enabling the encapsulation and targeted release of the STING agonist.	[166]
Injectable hydrogel ALG @ MSA-2 was formed by loading STING agonist MSA-2 with calcium ion responsive sodium alginate as carrier.	Forming intelligent hydrogel	ALG@MSA-2 optimized the therapeutic effect of STING agonist MSA-2 and enhanced the anti-tumor effect.	[167]

Table 7 The Advantages and Disadvantages of Various Drug Delivery Systems

Drug Delivery system	Advantage	Disadvantage
Drug delivery system based on tumor microenvironment response	Releasing drugs at specific parts to improve the bioavailability of drugs.	Many response materials are unstable and easy to degrade and easily interfered by blood components, metabolites and other factors.[85]
Cell Targeted Drug Delivery System	Accurately acts on target cells and reduces the toxicity to normal cells.	Immunosuppressive cells and metabolic products in TME can weaken the capacity of immune cells and promote drug resistance[106]
Multifunctional integrated drug delivery system	They can significantly improve diagnostic accuracy, enhance therapeutic efficacy, improve the TME, reduce side effects, and support personalized treatment.	The preparation process of nano-platform is often complicated.
Novel biomaterial-driven drug delivery system	It has good biocompatibility and environmental friendliness.	The long-term stability of some biomaterials in vivo remains to be verified.

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Prospects for STING Agonist Nanodelivery

Nanotechnology has effectively enhanced the piling up of STING agonists at neoplastic sites, while the triggering effect on the STING pathway has strengthened immune response to combat tumors.[168] However, the exiSTING delivery systems all have certain limitations. By optimizing nanomaterials or developing nanomaterials with higher stability, the stability and effectiveness of drug delivery systems can be improved, thereby improving therapeutic potency of drugs. For example, biodegradable nanoparticles can be employed in combination with metal ions through coordination, which leverages the charge-shielding effect to alter the surface properties of the nanoparticles.[169] This approach enhances the stability of the particles and regulates the targeting ability of the nanocarriers, thereby achieving precise treatment. Additionally, biomimetic cell membrane nanoparticles can be utilized. By mimicking the structure and function of cell membranes, these nanoparticles can evade clearance by the immune system and prolong the circulation time of the drug within the body.

The properties of STING agonists has the potential to be optimized to improve therapeutic efficacy. The physicochemical properties of STING agonists may limit their loading efficiency in nanocarriers, thereby affecting their performance in cancer immunotherapy. Chemical modification or structural remodeling of STING agonists can enhance their properties,[170] such as introducing groups at specific sites of the STING agonist or by modifying the chemical bonds, making them more readily loaded by nanocarriers, not only can their cellular uptake efficiency be increased, but also their bioavailability can be enhanced, thus fully exerting their therapeutic effects in inhibiting tumor growth.

In addition to optimizing materials and drugs themselves, exploring more effective combination therapy strategies is also an important direction for enhancing therapeutic efficacy. For example, combining nanomedicine with radiotherapy. For example, nanomedicine can be used as a radiosensitizer linked to selenide bonds that are sensitive to X-rays.

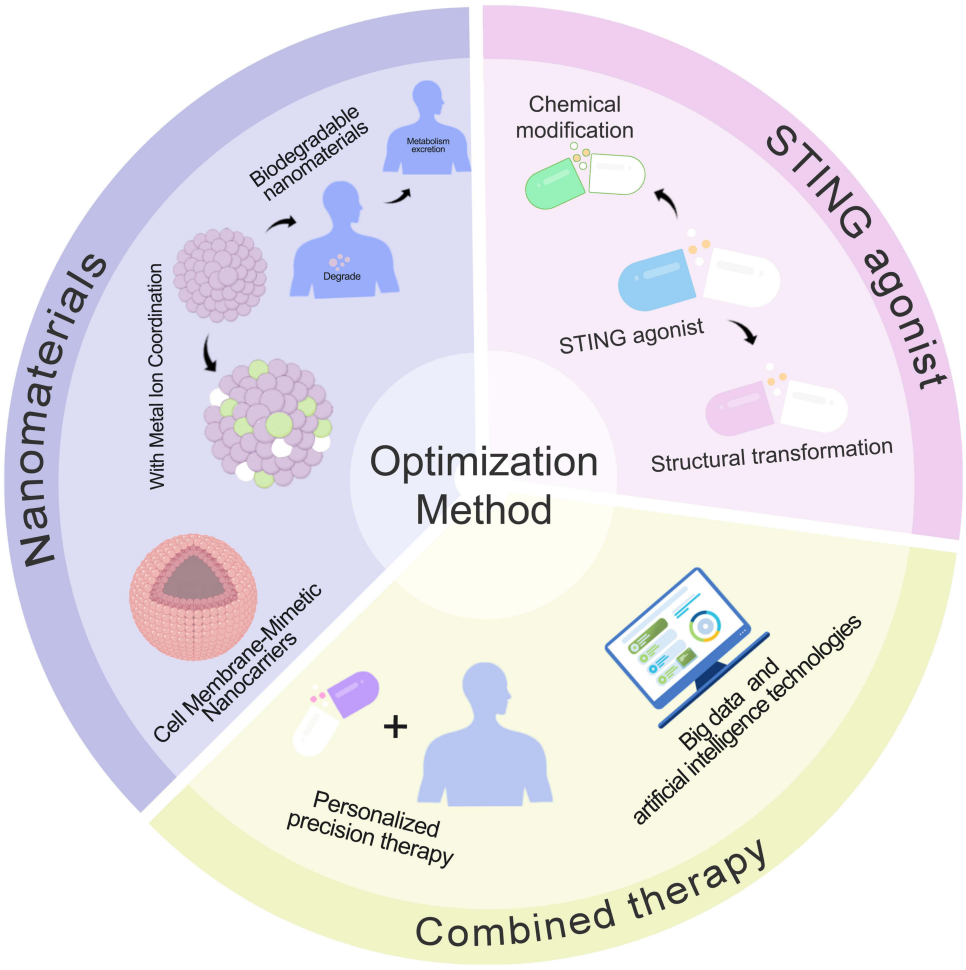

Figure 7 The methods that can improve the limitations of the combination of STING agonists and nanodelivery systems.

Through the triple dynamic phase shift effect induced by X-rays, precise treatment can be achieved.[171] Moreover, big data and artificial intelligence technologies can be utilized to conduct in-depth analyses of patients' clinical data and treatment responses, enabling the customization of the most suitable treatment plans for each individual patient and realizing personalized precision therapy. Figure 7 illustrates the methods that can improve the limitations of the combination of STING agonists and nanodelivery systems.

Conclusion

Currently, there are a variety of methods for treating tumors, including traditional surgery, radiotherapy, chemotherapy, as well as immunotherapy and targeted therapy, which have developed rapidly in recent years. These treatment methods have made significant progress in tumor therapy, but still have some limitations. The approach of delivering STING agonists via nanodelivery systems has brought a new direction to tumor treatment. Nanodelivery systems for STING agonists can not only overcome the problems of poor stability and rapid clearance of STING agonists, but also precisely deliver STING agonists to tumor sites, achieving targeted drug delivery and reducing side effects on normal tissues.

The synergistic approach of nanodelivery systems and the STING signaling pathway has shown significant advantages in tumor treatment. In this review, we explored and analyzed the design strategies of several types of drug delivery systems for STING agonists. Nanotechnology was used to effectively increase the accumulation of STING agonists at tumor sites, while the activation of the STING signaling pathway enhanced the antitumor immune response. However, the existing drug delivery systems all have certain limitations. For example, nanocarrier materials may have potential toxicity and side effects, the synergistic mechanisms between STING agonists and other drugs in combination therapy are not fully understood, and the stability of nanocarriers is difficult to ensure. Future research needs to explore new therapeutic strategies to overcome these limitations.

In summary, we hope that these strategies will not only bring new hope to cancer patients but also provide new ideas and orientations for the future vision of overcoming cancer challenges and offer some forward-looking guidance for subsequent research.

Data Sharing Statement

No data was used for the research described in the article.

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Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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