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Nanoparticle-Mediated STING Activation for Cancer Immunotherapy

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As the first line of host defense against pathogenic infections, innate immunity plays a key role in antitumor immunotherapy. The cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) (cGAS-STING) pathway has attracted much attention because of the secretion of various proinflammatory cytokines and chemokines. Many STING agonists have been identified and applied into preclinical or clinical trials for cancer immunotherapy. However, the fast excretion, low bioavailability, nonspecificity, and adverse effects of the small molecule STING agonists limit their therapeutic efficacy and in vivo application. Nanodelivery systems with appropriate size, charge, and surface modification are capable of addressing these dilemmas. In this review, the mechanism of the cGAS-STING pathway is discussed and the STING agonists, focusing on nanoparticle-mediated STING therapy and combined therapy for cancers, are summarized. Finally, the future direction and challenges of nano-STING therapy are expounded, emphasizing the pivotal scientific problems and technical bottlenecks and hoping to provide general guidance for its clinical application.

1. Introduction

Immunotherapy is one of the most prospective therapeutic strategies employing both the innate and adaptive immune systems against cancer cells.[1] As the first line of host defense against pathogenic infections, innate immunity receptors recognize various pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs) via germline-encoded pattern recognition receptors (PRRs) including toll-like receptors (TLRs), nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), retinoid acidinducible gene I (RIG-I)-like receptors (RLRs), and cytosolic DNA sensors.[2] Cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING) pathway is an important cytosolic DNA sensing pathway that activates the expression of some genes (e.g., interferon regulatory factor 3 (IRF3)) as well as generation of special signal molecules (type I interferon) to assist cell-to-cell communication, resulting in the inhibition of infectious pathogens invasion.[3] Although the role of cGAS-STING pathway in pathogen detection is well verified, its importance in cancer immunity has merely recently begun to emerge.[4]

In recent years, many STING agonists have been identified and applied to preclinical or clinical trials for cancer immunotherapy.[5] However, the failure of STING therapy appeared in patients due to the fast excretion, low bioavailability, nonspecificity, and adverse effects of the small molecule STING agonists.[6] Nanomedicines have a great potential to improve the efficacy of STING therapy.[7] To date, nanodelivery systems with appropriate size (10–300 nm), surface charge and targeting group have been widely used to improve the solubility and stability of STING agonists, decrease the systemic toxicity, and improve tumor accumulation.[7,8]

The diversity, complexity, and heterogeneity of tumors greatly limit the efficiency of monotherapy.[9] Therefore, it is preferential to develop multimodal therapeutic strategies to enhance the antitumor effect.[10] Growing evidence has suggested that the STING therapy is capable of boosting current cancer treatments, such as surgery, radiotherapy (RT), chemotherapy (e.g., doxorubicin (DOX), cisplatin (Pt)), phototherapy (e.g., photodynamic therapy (PDT), photothermal therapy (PTT)), and immunotherapy (e.g., immune checkpoint blockade (ICB), and chimeric antigen

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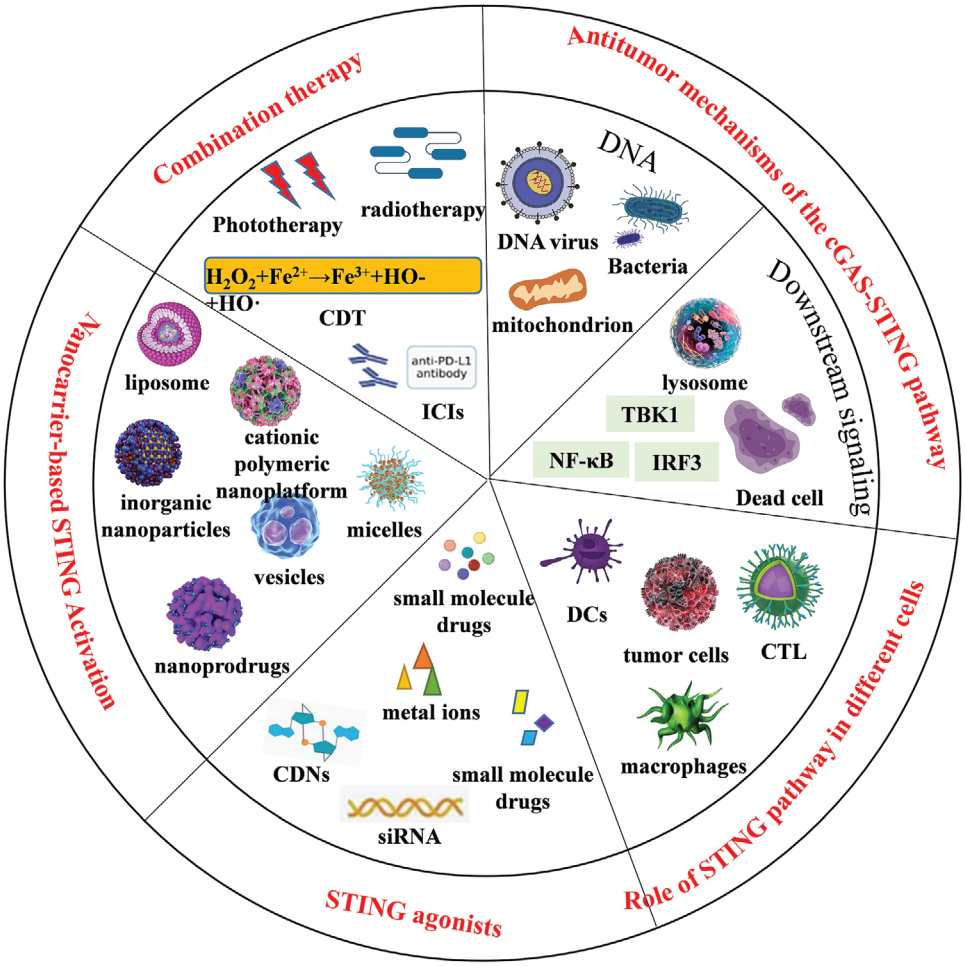

Figure 1. Outline of this review on STING activation for cancer immunotherapy.

receptor T-cell immunotherapy (CAR-T)).[11] The combination of STING therapy with other treatments can not only maximize the positive aspects, but also minimize the negative impacts of STING therapy. In this review, we will discuss the mechanism of cGAS-STING pathway, introduce the cGAS-STING pathway within different cell types, summarize the STING agonists, focus on the nanoparticle mediated STING therapy and combination therapy, and point out future direction and challenges of nano-STING therapy (**Figure 1**).

2. Antitumor Mechanisms of the cGAS-STING Pathway in Cells

Once infected, amounts of intracellular double stranded DNA (dsDNA) are recognized and bonded with cyclic GMP-AMP synthase (cGAS), accompanied by conformational change and cyclic GMP-AMP (cGAMP) production using adenosine triphosphate (ATP) and guanosine triphosphate (GTP) as the second messenger.[12] cGAMP is then bonded with STING, an endoplasmic reticulum (ER)-resident transmembrane dimer protein with its C-terminal tail facing to cytosol.[13] The activated STING protein turns into oligomerization and initiates downstream signaling. Besides cGAMP, cyclic dinucleotides (CDNs) can also bind and activate STING.[14] Moreover, ER stress mediated STING shift is another way to activate STING.[15] We will focus on the DNA sources, STING mediated downstream signals, and STING pathway roles in different cells in the following.

2.1. The DNA Sources

cGAS is activated by interacting with double-stranded DNA (dsDNA) (**Figure 2**A). The DNA sources mainly contain: 1) Microbial DNA from viruses, retrovirus, and bacteria. At present, it has been found that many DNA viruses can induce the response of STING pathway. In addition to DNA viruses (e.g., vaccinia virus, herpes simplex virus), RNA viruses (e.g., HIV, dengue virus, influenza virus) have also been found to promote the release of mtDNA to incite cGAS-STING pathway.[16] Bacterial DNA (e.g., chlamydia trachomati, francisella novicida) and bacterial CDNs are another ones to trigger the cGAS-STING pathway.[17] 2) Leaked self-DNA from nucleus, lysosome, and mitochondria. Leaked self-DNA can enter the cytosol via exosomes or endocytosis. For example, tumor-derived DNA coming from the dying cells, cell debris, exosomes, and microvesicles can activate the cGAS-STING pathway in dendritic cells (DCs); 3) Mitochondrial

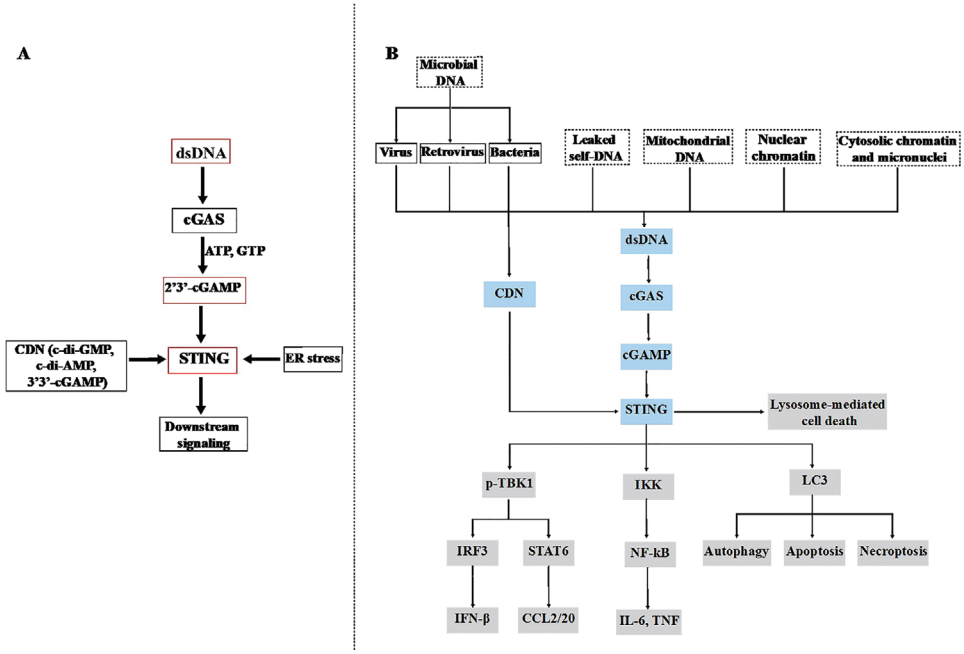

Figure 2. The mechanism of STING activation. A) Schematic diagram of cGAS-STING pathway activation. B) DNA source of activation of STING pathway and STING-mediated downstream signal activation.

DNA. Mitochondrial stress triggered by radiation, toxicant, microorganism, gene, ROS, and so on induces mtDNA leakage into the cytoplasm, in which the mtDNA binds to cGAS to sensitize STING pathway.[18] 4) Nuclear chromatin. Recently, longer reconstituted nucleosomal arrays imply cGAS activated by chromatin in vitro, suggesting the nucleosomes as the STING agonists.[19] However, it is also DNA or residual free DNA link to cGAS not the nucleosomes.[20] 5) Cytosolic chromatin and micronuclei. Cytosolic micronuclei, chromatin, DNA resulting from defective DNA replication, repair, and mitosis as well as dysfunctional telomeres are cell intrinsic self-DNA capable of detected by cGAS.[21]

2.2. STING Initiates Downstream Signal

The activated STING proteins turn into oligomerization and translocate to the Golgi apparatus via autophagosome, leading to a series of responses (Figure 2B). They mainly contain: 1) Interferon regulatory factor 3 (IRF3) activation. When STING is activated, it moves from ER to the periphery of the nucleus with TANK-binding kinase 1 phosphorylation (p-TBK1). p-TBK1 can catalyze IRF3, which further translocates to the nucleus and upregulates type I interferons such as interferon-β (IFNβ).[22] 2) STAT6 activation. Activated STING excites signal transducers and activators of transcription 6 (STAT6) to ER, leading to STAT6 phosphorylation by p-TBK1, secreting chemokines (CCL2/20).[23] 3) NF-κB and MAPK pathway activation. Phosphorylation of IκB kinase (IKK) recruits NF-κB to the nucleus, in which it activates transcription of genes encoding proinflammatory cytokines (e.g., IL-6, tumor necrosis factor (TNF)).[24] 4) Autophagy, apoptosis, and necroptosis. STING signaling also activates lipidation and autophagosome of the microtubule-associated protein 1A/1B-light chain 3 (LC3), leading to autophagy, apoptosis, and necroptosis.[25] (5) Lysosome mediated cell death. In the progress of translocation, STING is internalized to lysosome, in which the STING accumulation leads to lysosomal membrane permeabilization, resulting in a lytic form of cell death.[26]

2.3. STING Activation Rate

STING is located on the ER and traffics to the Golgi upon activated, where the following signals take place.[13a] Thus, the displacement between ER and Golgi is the rate-limiting step in STING activation. It was reported that the Ca^{2+} sensor STIM1 deficiency accelerated the activation rate of STING resulting from its lingering in the ER membrane.[27] Besides promoting STING activation, CDNs also induced UNC-51-like kinase (ULK1) activation to phosphorylate STING with the STING activation rate decrement because of the negative feedback.[28] Inactive rhomboid protein 2 (iRhom2) recruited the translocation-associated protein TRAPβ into the STING complex to facilitate the transport of STING from the ER to perinuclear microsome.[29] Sorting nexin 8 (SNX8) collected VPS34, a Class III phosphatidylinositol 3-kinase, to STING to speed up the activation rate of STING.[30] The ubiquitin regulatory X domain-containing proteins 3B (UBXN3B) interacted with STING and its E3 ligase TRIM56 to promote STING transportation.[31] Transmembrane emp24 protein transport domain containing 2 (TMED2) regulated STING activation rate by transporting ER to the perinuclear region.[32] STING ER exit protein (STEEP) for CxORF56 also had been reported to be beneficial to the transfer of STING between organelles. However, there is limit application of nanotechnology to amplify its activation rate.

Table 1. Immune responses regulated by STING agonists in different cell types.

Cell type	Role in cell	Refs.
Tumor cell	Type I IFN; BAX; Senescence/Apoptosis	[33]
T cell	Type I IFN; Stall growth; Highest in Th1 and $CD8^+$ T cells	[34]
B cell	The number of regulatory B cells; IL-35; BCR activation	[35]
Dendritic cell	Type I IFN; Cross-presentation; Lymph node-homing; Th1 chemokines	[36]
Macrophage	Type I IFN, inflammatory cytokines, chemokines; Maturation, activation, and polarization	[37]
Endothelial cell	Type I IFN; Vascular normalization	[38]
NK cell	Granzyme; Recruitment and cytotoxiciy	[39]

2.4. Role of STING Pathway in Different Cell Types

The cGAS-STING pathway is able to be activated in both immune (e.g., DC, macrophage, T cell, and natural killer (NK) cell) and tumor cells (**Table 1**). Compared with other cells, the sensitivity of cGAS-STING pathway in DCs is more than 100 folds higher mainly eliciting DCs maturation and antigen cross-presentation followed with stimulation of cytotoxic T lymphocytes and NK cells. Moreover, cGAS-STING pathway can polarize macrophages from M2 to M1 types. In addition, the up-regulation expression of chemokines (CXCL9 and CXCL10) during STING pathway activation is important for effector T cell infiltration. Endothelial cells in the tumor microenvironment also affect tumor vasculature via cGAS-STING pathway. Unfortunately, STING activators increase the number of regulatory B cells (a type of white blood cells), which secrete an immunosuppressive molecule interleukin-35 (IL-35). Due to the different effects of STING in cells, it is necessary to precisely control the STING activation. Nanotechnology with modifiable physical and chemical properties are utilized to activate STING in different cells. For example, pH hypersensitive (pH 6.8) nanoparticles released drugs into TME, while those with pH responsive at the pH value of 5.0 was able to release drugs only after internalization by tumor cells. In addition, the particle size and mode of administration are also related to the target of STING activation.

3. STING Agonists

The recent years have seen rapid development of various STING agonists such as CDNs and analogues, chemodrugs, metal ion, small molecule inhibitors, small molecule drugs, and siRNA (**Figure 3**).

3.1. CDNs and Analogues

The mainly existing STING agonists are natural CDNs, including cGAMP (2' 3'-cGAMP, 3' 3'-cGAMP, 3' 5'-cGAMP, and 2' 5'-cGAMP), c-di GMP and c-di AMP (**Figure 4**).[40] They bind to STING proteins and stimulate type I interferon secretion.[41] However, the relatively large molecular weight and strong polarity of natural CDNs make it difficult to penetrate cell membranes, insufficient uptake by cells. Its phosphodiester bond is easily hydrolyzed by enzymes, and its metabolism is unstable. These shortcomings limit its clinical application to some extent.[42] Therefore, a large number of structural modifications were made to the phosphodiester bond, ribose, and base components of natural CDNs, in order to improve their poor membrane permeability, cellular uptake, and metabolic instability, thereby enhancing their biological activity. Optimized CDNs exhibit more favorable pharmacokinetic characteristics, and several of these compounds have entered clinical trials, such as ADU-S100 (also known as ML RR-S2 CDA, a phosphodiesterase-resistant CDN),[43] IACS-8779 (phosphorothioate CDNs), IACS-8803 (phosphorothioate CDNs),[44] ML RR-S2 CDG (phosphodiesterase-resistant CDN),[45] and MK-1454.[46] However, all these STING agonists currently in clinical trials are only administered by intratumoral injection, which is adverse to their application. In order to treat a wider range of cancers, stable STING agonists that can be administered systematically and preferentially target to tumors remain to be the focus of future research.

3.2. Chemodrugs

Recent studies have shown that 7-ethyl-10-hydroxycamptothecin (SN38) promotes the STING pathway in DCs by leaked self-DNA (**Figure 5**).[47] Similar chemodrugs that can activate STING include chlorhexidine, hydroxy chlorhexidine, doxorubicin, daunorubicin,[48] and platinum drugs (e.g., cisplatin, carboplatin, and oxaliplatin).[49] Taxol,[50] docetaxel, and 5-FU[51] induce cytosolic chromatin and micronuclei to activate cGAS. Photothermal therapy,[52] photodynamic therapy,[53] radiotherapy,[54] and carbonyl cyanide m-chlorophenyl hydrazine (CCCP) activate STING pathway via mtDNA. Metformin enhances STING expression by inhibiting the AKT pathway. Dimeric aminobenzimidazole (diABZI) is another developed STING agonist with unclear mechanism.[55] Among of them, chemodrugs confirmed as cGAS-STING agonists are few but attractive due to their great tested in humans.

3.3. Metal Ion

Metal ions manganese (Mn^{2+}), zinc (Zn^{2+}), calcium (Ca^{2+}), iron (Fe^{2+}), and magnesium (Mg^{2+}) are essential micronutrients, participating in various functional enzymes, and play important roles in host immune system. Mn^{2+} has been reported to cause cGAS conformation change, increase the sensitivity of cGAS to cytoplasmic DNA, and enhance the binding affinity between cGAMP and STING proteins.[56] The zinc finger domain in

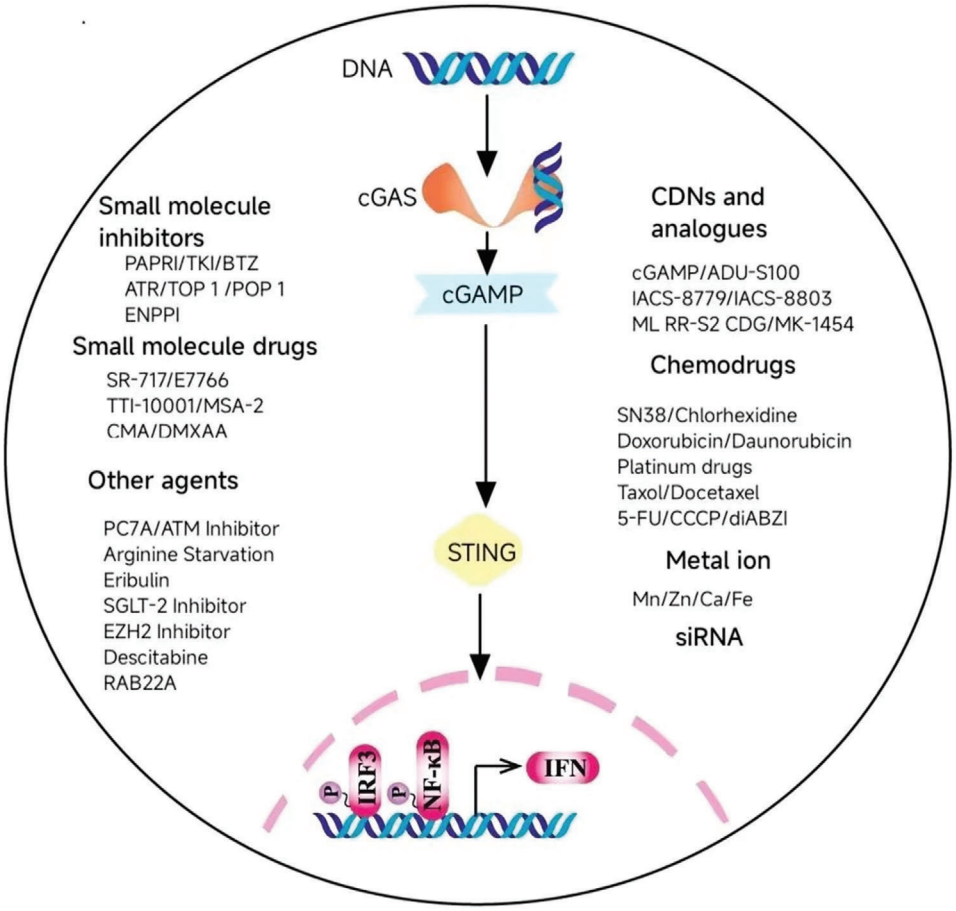

Figure 3. Overview of the STING agonists.

cGAS and DNA binding region enables it to recognize dsDNA. Thus, Zn^{2+} also plays an important role in the cGAS-STING pathway.[57] As a multifunctional second messenger, recent study reported that the IFN-β induced by vadimezan (also known as 5, 6-dimethylxanthenone 4-acetic acid (DMXAA)) was able to be inhibited by Ca^{2+} chelator,[58] implying the positive correlation of STING pathway and Ca^{2+}. In another research, ferric ammonium citrate treatment in vitro and in vivo increased the secretion of IFN-β. The expression of genes involved in iron metabolism and STING pathway were upregulated, suggesting the participant of Fe^{2+} in STING pathway.[59] In all, varieties of metal ions reveal robust immune function via STING pathway which broadens their huge application potential. The absence and accumulation of metal ions can induce cell damage, which facilitates the ion interference therapy development. The regulation of metal ions on immune cells promotes tumor immunotherapy into the age of metal immunotherapy.

3.4. Small Molecule Inhibitors

Some small molecule inhibitors involved in DNA activity can also affect the STING pathway. For example, poly-(ADP-ribose) polymerase (PAPR) inhibitors (e.g., talazoparib, olaparib, and niraparib) lead to the reduction of DNA repair and the accumulation of intracellular dsDNA, stimulating cGAS/STING signal and the downstream immune response.[60] Tyrosinase inhibitor (e.g., osimertinib, anlotinib) leads to tumor cell apoptosis, increases macrophage infiltration via inositol-requiring-enzyme (IRE1α)-dependent HER3 up-regulation, and activates cGAS in cancer cells to generate cGAMP, which is transported to macrophages followed by STING activation.[61] Protease inhibitor (*e. g.*, bortezomib, BTZ) induces genomic instability and inhibits DNA repair, resulting in accumulation of the cytosolic DNA sensor cGAS and activation of STING pathway.[62] ATR and topoisomerase 1 (TOP1) inhibitor activates the STING pathway by micronuclei.[63] RNA polymerase I (POL I) CX-5461 is one of the most promising POL I inhibitors being studied at present. Treatment with CX-5461 can induce rapid accumulation of cytosolic DNA, leading to the up-regulated transcription of STING.[64] Ecto-nucleotide pyrophosphatase/phosphodiesterases 1 (ENPP1 or NPP1) located on the cell surface has been reported to negatively regulate the STING pathway via cyclic 2′3′-cGAMP hydrolysis. Hence, its inhibition attracts attention for cancer immunotherapy.[65] Compared with other STING agonists, small molecule inhibitors have the advantages of high selectivity and low side effects. However, their applications still face some challenges, such as drug resistance caused by tumor gene mutation, the generation of some toxic side effects and drug interactions, the balance between multitarget inhibition and

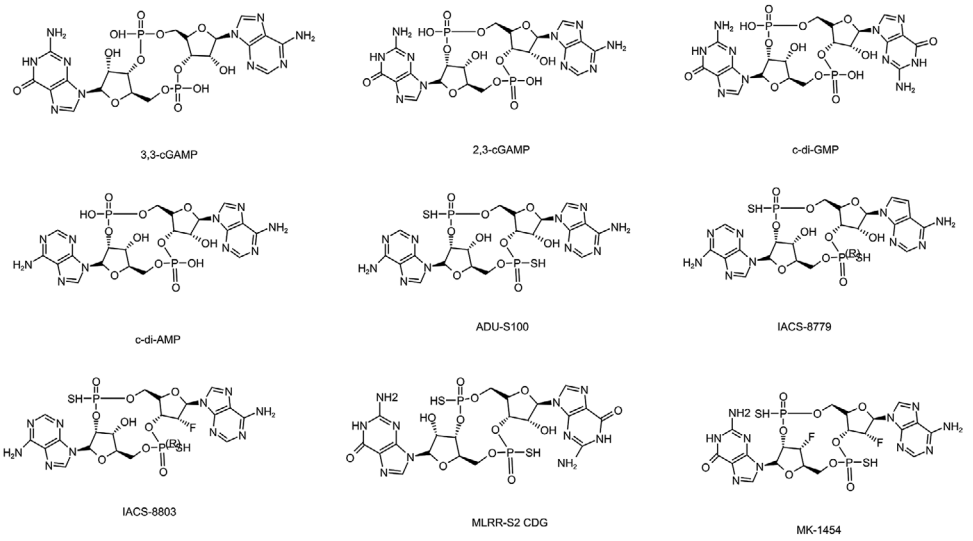

Figure 4. Structures of cyclic dinucleotide and synthetic CDN analogues.

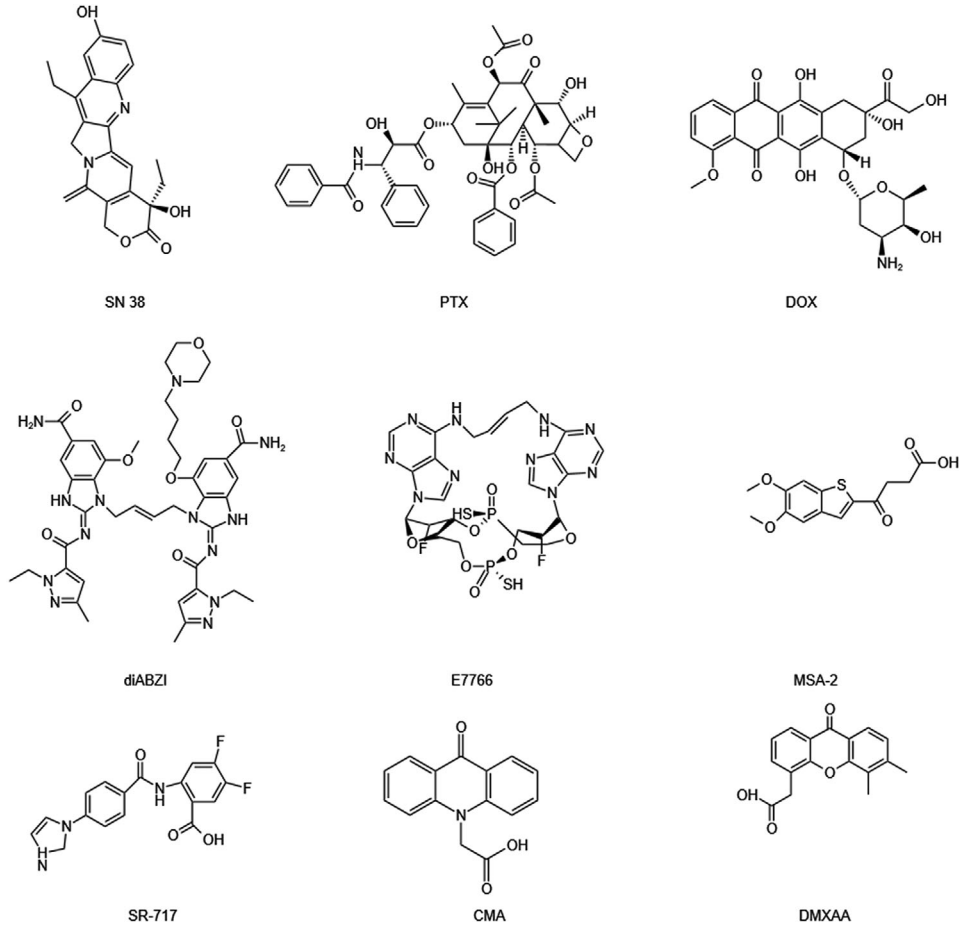

Figure 5. Structures of non-CDN STING agonists.

inhibitor selectivity, and the accuracy of chemodrugs before clinical trials.

3.5. Small Molecule Drugs

Small molecule drugs are another type of STING agonists (Figure 5). For example, SR-717 is a novel systemic cGAMP analog, which can induce STING with the closed conformation.[66] E7766 is a macrocyclic bridged STING agonist (MBSA), with pangenotypic and superior activity.[67] TTI-10001, a new non-CDN small molecule STING agonist, has strong activity to five hSTING alleles and mSTING.[68] MSA-2 is a potent and orally available non-nucleotide STING agonist which can be bounded to STING as a noncovalent dimer with nanomolar affinity.[4c] 10-carboxymethyl-9-aridinone (CMA) is a specific murine STING agonist similar to DMXAA.[69]

3.6. siRNA

Compared with other therapies, gene therapy is a fundamental treatment, which can replace the mutated pathogenic genes, change the gene structure of the tumor cells, and introduce functional genes that can enhance the immune ability of the body. It has high efficiency, minimal side effects, great tolerance, and high specificity. In recent years, gene therapy has rapidly developed and achieved certain clinical success. For antitumor immunotherapy, knockdown of anti-TBK1 by siRNA has shown to enhance the STING pathway in GBM cells.[70] Because of its specificity, rapid, reliable, and simple operation, siRNA has become a new expectation for tumor immunotherapy. The application of siRNA technology to inhibit oncogene expression, mutation, over-expressed growth factors and receptors, overexpression of cyclin, cell invasion, and metastasis have made gratifying research results. Some studies have been transferred from in vitro to in vivo experiments. Especially, the application of siRNA technology to solve the resistance of chemotherapy has a very high practical value in the treatment of malignant tumors. However, siRNA technology, as a new technology to be applied in clinic, still has many problems: 1) siRNA technology is highly specific, even a single base mismatch will reduce the efficiency of siRNA; 2) Not all genes can be used as the target sequence of siRNA interference, and whether the RNA of noncoding region is sensitive to siRNA remains to be studied; 3) How to safely and effectively guide siRNA into human cells and stably express it in them, a large number of tests are still needed to pave the way for clinical application; 4) Whether siRNA can specifically target overexpressed protein genes in cancer tissue in animal tests without affecting the same gene that is normally expressed; 5) Because cancer is a polygenic disease, siRNA can target multiple genes without interfering with each other. Therefore, the application of siRNA technology in tumor immunotherapy needs to be further studied.

3.7. Other Agents

PC7A containing a seven-membered ring with tertiary amine is a multivalent STING agonist that activates innate immunity through STING-PC7A condensate formation. Compared with natural CDNs, PC7A stimulates the long-term production of pro-inflammatory cytokines.[71] The ataxia telangiectasia mutation (ATM) inhibitor effectively activates the STING pathway by down-regulating mitochondrial transcription factor A.[72] Arginine starvation leads to chromatin leakage and STING activation via epigenetic silencing of metabolic and DNA-repair genes.[73] Eribulin activates the STING pathway via the cytoplasmic accumulation of mtDNA.[74] Sodium-dependent glucose transporters 2 (SGLT-2) inhibitor activates the STING pathway via repressing the AKT pathway.[75] EZH2 inhibitor can induce H3K27 to change from trimethylation to acetylation, resulting in STING pathway activation.[76] Descitabine, an inhibitor of DNA methyltransferase, reduces methylation at the cg16983159 site and increases STING expression. Rafeesome (RAB22A regulated nonclinical autophagosome fused with early endosome) mediates the extracellular secretion of activated STING and plays an antitumor immune function. These agents extend the range of STING agonists beyond classic STING activations and may therefore be useful in patients for whom are unresponsive to typical agonists.

4. Nanocarrier-Based STING Activation

As discussed above, the fast excretion, low bioavailability, nonspecificity, and adverse effects of the small molecule STING agonists limit their therapeutic efficacy and in vivo application. Nanodelivery systems with appropriate size, charge, and surface modification are capable of addressing these dilemmas (**Table 2**).[77] The generally used nanocarriers include liposome, cationic polymeric nanoplatform, inorganic nanoparticle, micelle, vesicle, exosomes, and nanoprodrug.[78]

4.1. Liposome

Liposomes are bilayer hollow spherical vesicles mainly formed by phospholipids, which are used to deliver hydrophilic and hydrophobic drugs.[105] Liposomes could enhance the targeting of chemodrugs, decrease the side effects, avoid degradation, and prolong circulation time. Thus, various drug delivery systems based on liposomes have been applied into STING therapy. For example, Dane et al. designed a polyethylene glycol (PEG)-liposome when cGAMP was coupled with PEG-liposome through a cleavable disulfide bond. After intravenous injection, the nanoparticles activated STING pathway in tumors, and induced strong immune response in vivo (**Figure 6**A).[87b] In another example, Mooney et al. used cationic liposomes for electrostatic adsorption of 2', 3'-cGAMP (Figure 6B). Compared to free cGAMP, NPs showed a high level of cellular uptake, leading to excellent inhibitory effect on tumor growth and metastasis. According to the results, not only the cGAMP but also the liposome itself can activate the innate immunity and adaptive immunity, a secondary responsiveness in the same tumor cells.[42] Distinct from traditional methods of administration, Zhao et al. reported an inhalable phosphatidylserine coated liposomes loading with cGAMP (NP-cGAMP). The results demonstrated that inhalation of aerosolized NP-cGAMP enabled rapid distribution

Table 2. Nanodelivery systems with STING agonists.

Nano formulations	STING agonist	Target cells	Tumor model	Refs.
Prussian blue (PB)/Mn, H-MnO_2, Bio-MnO_2 NPs, PPIR780-ZMS, MnO_2 NPs, MnO@mSiO_2-iRGD NPs, Vir-ZM@TD, OVA/MnO_2, NanoMn-GOx-PTX, MnP@Lip, Mn/$CaCO_3$@PL/SLC NPs, M@P@HA, MDPMH, GSMM, Nd@$NaLuF_4$	Mn^{2+}	CT26, 4T1, B16F10, NSCLC, B16, BMDCs/BMDM, DC2.4, Raw 264.7, MC38/MLE-12, A549 cells	CT26, 4T1, B16F10, LLC, B16, MC38, MB49, B16-OVA	[79]
Naphthalocyanine/Mn/ABZI	Mn^{2+}/ABZI	BMDCs	CT26	[80]
Zn-LDH	Zn^{2+}	B16F10, 4T1-luc	B16F10, 4T1-luc	[81]
ZnS@BSA		HCC	Hepa1-6	[82]
$mPEG_{2k}$DSPE/CPT-Pt(IV)	CPT-Pt (IV)	CT26	CT26	[11d]
MPCO	Olaparib	4T1, BMDC	4T1	[83]
LP-cGAMP, STING-NP, hNVs, nanoSTING-vax, NS (cGAMP), NGC-gels/ αTIM-3, MF-Fe-STING NPs, NP-cGAMP, STING-NPs, cGAMP-siinfekl-STINGΔTM	cGAMP	DC2.4, B16-F10, RAW264.7, RAW-Blue ISG, TAM, BMDC, CT26, Hepal-6, 4T1, L929, BMDM, AM, Neuro 2a,9464D, HEK293T, MC38	V600E BRAF, B16F10/ E0771 YUMM1.7, B16F10, 4T1, B16-OVA, CT26, Hepal-6, 4T1-Luc, Neuro 2a, 9464D	[84]
DNPs	cGAMP, cdi-GMP	/	NOD	[85]
mPEG-NP, STING-LNP, Immuno-NP, CSiNPs, c-di-GMP-PNT, PmTriTNE@CDA	cdGMP	RAW264.7, B16F10, 4T1	4T1, B16F10, Panc02, B16-OVA, 4T1 CDX/PDX	[86]
Cationic lipid/CDN, LDN-CDN, PEGMA-*co*-DEAEMA-*co*-BMA, CDN PBAE, ATN-MPTX/CPs-CDN	CDN	RAW-Lucia ISG, RAW-ISG, MC38, THP1-Blue ISG reporter cells, CDN PBAE, 4T1, BMDC, BMDM	E0771, MC38, 4T1, B16F10	[87]
CDA@bMSN, NP Vacc	CDA	BMDC/B16F10, BMDCs	B16F10, B16F10-OVA,MC38	[88]
CPs-CDN, SA-NTL/SA-TL	ADU-S100	BMDC/BMDM, MC38, B16F10, RAW264.7, THP1-Dual cells	B16F10, MC38,	[89]
NAcp@CD47, cdG@RMSN-PEG-TA	CDG	GL261 GBM, RAW 264.7	GBM, 4T1	[90]
PLGA	ONP-302	Myeloid cells	MC38, B16F10	[91]
CC-6td NP	6-thio-dG	MC38/BMDC	MC38	[92]
UPs-4T1/EPB, IDP@O_2	DMXAA	4T1/WT, 4T1/EPB, 4T1, BMDC	4T1/WT, 4T1/EPB, 4T1	[93]

(*Continued*)

Table 2. (Continued).

Nano formulations	STING agonist	Target cells	Tumor model	Refs.
Au-CZTS/Asp	aspirin	4T1, L02, MCF-7, DC, RAW264.7	4T1	[94]
SN38-NPs	SN38	E0771, BMDCs	E0771	[47]
STING ADC	IMSA172	/	B16F10 B16-EGFR	[95]
HI@PWY	HCPT	4T1, BMDC	4T1	[96]
LV-sHDL	Vadimezan	4T1, BMDC	4T1	[97]
SA@VitC hydrogel	SA	CT26	CT26	[98]
125I-VNP/131I-VNP	IRT	CT26/BMDC RAW264.7	4T1, CT26,	[54a]
TMA-NPs	RT/TMA-NPs	/	4T1	[99]
NBTXR3	RT	HCT116-DUAL	/	[93b]
IO-PG-GLU-Ce6	Damaged DNA	LLC	LLC	[100]
Mn_3O_4@Au-dsDNA/DOX	dsDNA	B16F10, 4T1, RAW 264.7	B16F10	[101]
CS/αPD-L1	CS	Caco-2, BMDC	B16F10	[102]
SR717@RGE-HFn NPs	SR717	RAW, THP-1 Luc-GL261, G422	Luc-GL261 G422	[103]
TBK1si/rGO-PEG	TBK1si	U251, GBM	/	[104]

of NP-cGAMP to lesions and subsequent uptake by APCs to stimulate STING signaling (Figure 6C).[106] All of the results illustrate the good property of liposomes as STING agonist carrier, among of which the cationic liposomes has huge advantages.

4.2. Cationic Polymeric Nanoplatform

The cationic polymers such as polyamidoamine (PAMAM), polyethylenimine (PEI), polypeptides, and chitosan have great potential in drug delivery because of their versatile structure, multifunctionality, easy modification, and tailorable physicochemical properties.[107] Similar to the cationic liposomes, cationic polymers also have great advantages as STING agonist carriers and immune adjuvant. Luo et al. constructed a branched polymer-pyropheophorbide a (Ppa) conjugate (BGSSP) that self-assembled into a compact structure with AZD2281 encapsulation in the core (AZD@BGSSP). AZD@BGSSP degraded to Ppa and triggered AZD2281 release in the highly expressed cathepsin B and glutathione tumor cells. Combination with PDT and AD2281, cytosolic dsDNA accumulated to activate the STING pathway for immunity activation.[108] In another research, Chen et al. reported a tumor-targeted lipid-dendrimer-calcium-phosphate (TT-LDCP) nanocarrier with thymine-functionalized dendrimers which exhibited both gene delivery capacity and immune adjuvant properties via STING pathway activation (**Figure 7**A).[109]

4.3. Inorganic Nanoparticles

Inorganic nanomaterials can be divided into metal nanomaterials (MnO_2, ZnO_2, Fe_2O_3, $CaCO_3$, CaO_2) and nonmetal nanomaterials (SiO_2, C_3N_4). Due to their excellent physicochemical properties, inorganic nanomaterials have been developed rapidly for antitumor therapy.[110] For example, Park et al. developed biodegradable mesoporous silica nanoparticles (bMSN) with larger pore diameter (5–10 nm) for efficient drug loading and delivery, where thinner Si–O–Si matrix endowed rapid degradation under physiological conditions. The surface of bMSN was modified with amine ($–NH_2$), thus promoting the cellular delivery of negatively charged CDN. Significant therapeutic efficacy of bMSN carrying STING agonists was observed in two murine melanoma models, highlighting the potential of bMSN in cancer immunotherapy (Figure 7B).[88a] Compared to the nonmetal nanomaterials, the metal ones not only improve the targeted delivery ability of drugs, but also decompose into ions serving as a drug to participate in tumor therapy. For example, Zhou et al.

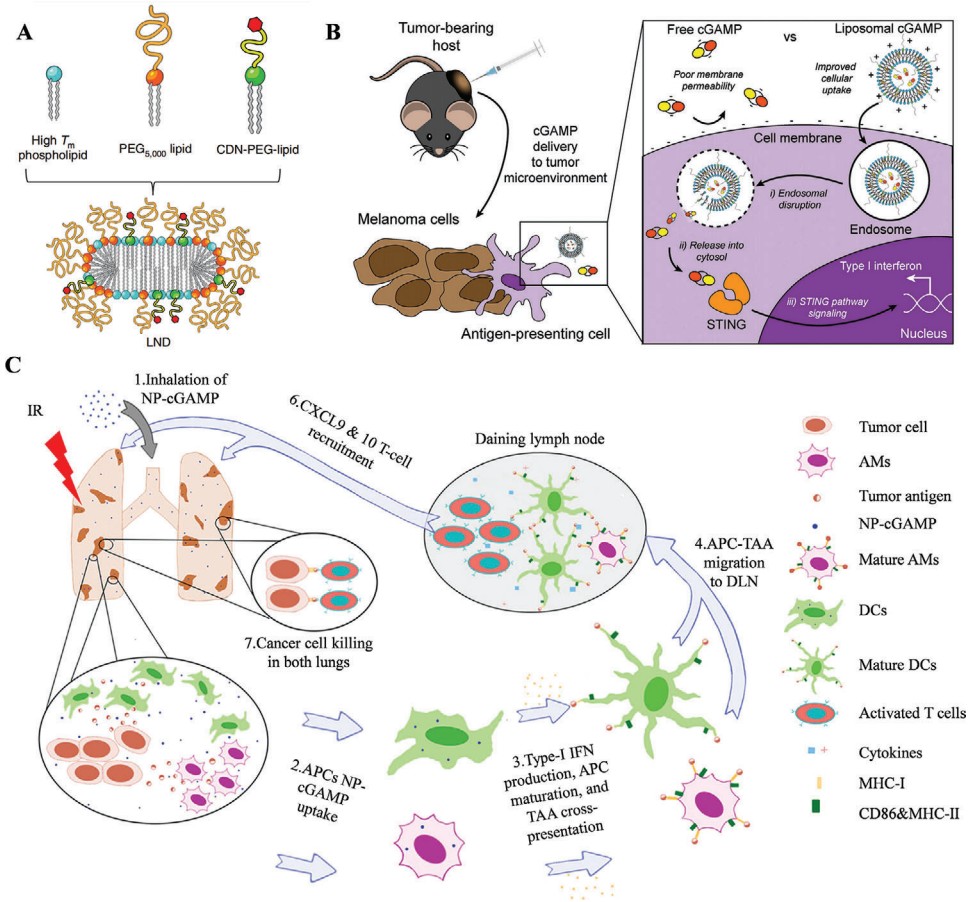

Figure 6. Liposome-based CDN delivery for cancer immunotherapy. A) Chemical structures of CDN-PEG-lipid. Reproduced with permission.[87b] Copyright 2019, Springer Nature. B) Schematic of liposomal cGAMP structure and therapeutic strategy. Reproduced with permission.[42] Copyright 2017, Wiley-VCH GmbH. C) Schematic of the mode of action of the inhalable NP-cGAMP for enhancing antitumor immunity against lung metastases. Reproduced with permission.[106] Copyright 2019, Springer Nature.

designed a tumor microenvironment (TME) responsive MnO_2-melittin nanoparticles (M–M NPs) which consumed glutathione with •OH and Mn^{2+} production, specifically induced tumor cell death and activated cGAS-STING pathway.[79e] Cai et al. synthesized ZnS@BSA (bovine serum albumin) nanoclusters, where BSA was used as the matrix to ensure the overall stability of zinc and sulfur ions in the physiological conditions. The nanoclusters can release zinc ions in tumor acidic environment, thereby activating the cGAS-STING pathway and producing ROS. The produced H_2S gas further promoted the generation of ROS by inhibiting the catalase in cancer cells. The results showed that the nanoclusters could obviously inhibit tumor growth and elicit intense immune response.[82] Zhang et al. developed membrane fusogenic lipid-coated nanoparticles with the inner polyplex core composed of Fe(II) ions and cGAMP (Fe-STING NPs). Fe^{2+} and cGAMP released in the acidic tumor cells led to Fenton reaction and STING activation to potentiate apoptosis. Then antigen-presenting cells (APCs) engulfed the tumor-cell-derived apoptotic bodies (ABs) loaded with neoplastic cGAMP, contributing to being a Trojan horse to impart high immunogenicity (Figure 7C).[84g]

4.4. Micelles

Polymeric micelles are characterized by simple preparation, simultaneous multiple drugs encapsulation, and easy surface modification. Generally, the hydrophobic chemodrugs were encapsulated via hydrophobic interactions, donor–acceptor interactions, and hydrogen bonding. Due to their appropriate particle size and easy penetration into lymph nodes, which are beneficial to the delivery of tumor antigens and immune adjuvants, polymeric micelles have been widely studied in antitumor immunotherapy.[111] For example, a metal micellar nanovaccine was constructed by the self-assembly of Mn, ABZI, naphthalocyanine (ONc) coordinated nanoparticles (ONc-Mn-A), and maleimide-decorated Pluronic F127 (malF127) micelles. The ONc-Mn-A-malF127 micelles activated the STING pathway, matured DC, and eventually killed tumor cells by cytotoxic $CD8^+$ T cells and NK cells (**Figure 8**A).[80] In another research, Wang et al. developed a thermally sensitive micelle (mPEG-*b*-PHEP) that incorporated IR780 and manganese zinc sulfide nanoparticles (ZMS) (PPIR780-ZMS). Mn^{2+}-mediated chemodynamic and STING therapy synergistically suppressed the primary tumor growth and pulmonary

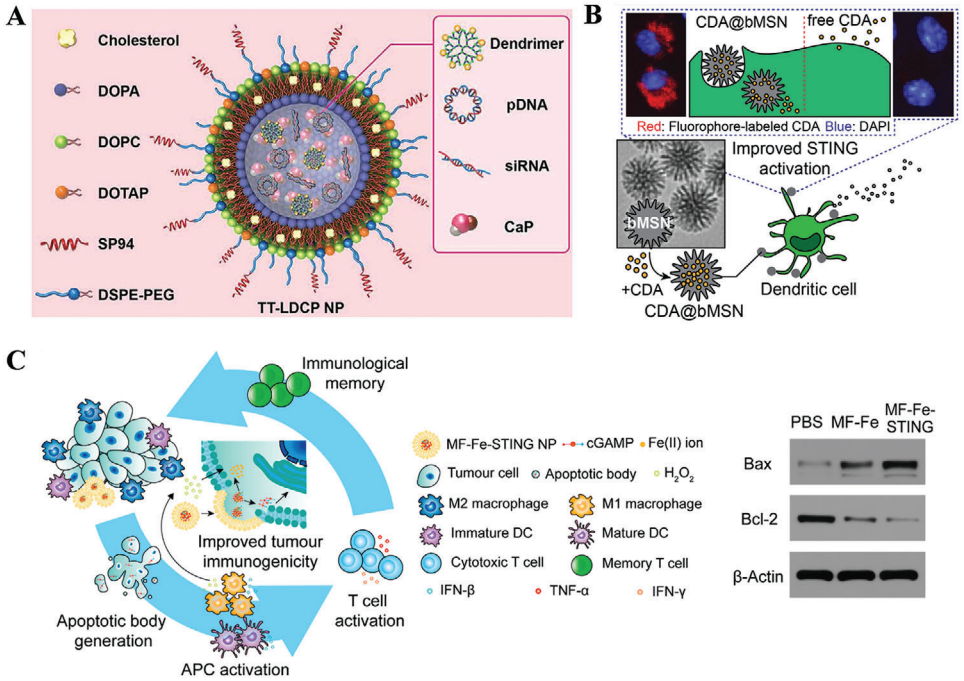

Figure 7. Inorganic nanoparticles-based STING agonists delivery for cancer immunotherapy. A) Schematic representation of the mechanism of immunogene therapy by TT-LDCP NPs containing siRNA against the immune checkpoint PD-L1 and pDNA encoding the immunostimulating cytokine IL-2. Reproduced with permission.[109] Copyright 2020, The American Association for the Advancement of Science (AAAS). B) Schematic illustration of bMSN for delivery of STING agonists. Reproduced with permission.[88a] Copyright 2020, Wiley-VCH GmbH. C) Schematic illustration of the intracellular STING nanovaccine delivery. Reproduced with permission.[84g] Copyright 2022, American Chemical Society.

metastases with systemic cytokine expression in a safe level (Figure 8B).[79d]

4.5. Polymeric Vesicles

Polymeric vesicles are novel nanodrug delivery systems. Compared with other small molecule surfactant vesicles, polymer vesicles are biodegradable, biocompatible, stable, and multifunctional, in which the membrane properties can be regulated by the type and length of polymeric blocks. During drug encapsulation, polymer vesicles can not only physically encapsulate drugs, but also have a variety of functional groups in their blocks that can be connected to drug molecules through more stable covalent bonds, so as to better control drug loading, encapsulation efficiency, and drug release. These advantages make polymer vesicles are widely used for cancer therapy. Wilson et al. synthesized a series of poly(beta-amino ester) (PBAE) polymers (PEG-*b*-DEAEMA-*co*-BMA-*co*-PDSMA), forming vesicles to encapsulate RR-c-di-AMP or RR-c-di-GMP via electrostatic interaction. STING NPs increased the biological potency of cGAMP, enhanced STING signaling, and converted immunosuppressive tumors to immunogenic ones, leading to the enhanced therapeutic efficacy of cGAMP (**Figure 9**A).[84d] Zhong et al., reported a reduction-responsive biodegradable polymeric vesicles loaded with ADU-S100 for STING therapy in melanoma (CPs-CDN).[89a] The results showed that CPs-CDN prolonged the circulation time of CDN and enhanced its accumulation in tumor site. Boosting STING pathway were confirmed in tumor draining lymph nodes, resulting in significantly antitumor effect in combination with low-dose fractionated radiation. Jaklenec et al. developed microfabricated PLGA nanoparticles that remained at the site of injection and released cGAMP at predetermined time points via pulses that mimicked multiple injections over days to weeks. They found that decreasing the number of injections could directly benefit current STING therapy by reducing risk of metastasis.[112] In addition to electrostatic and hydrophobic interaction, the specific host–guest strategy in nanodrugs displayed longer circulation time and could be effectively enriched in tumor sites, showing a highly effective effect of inhibiting tumor growth. A supramolecular delivery system based on calixarene CDN encapsulation via host–guest was established (CAlixarene-STING) (Figure 9B). CAlixarene-STING efficiently enhanced the immunostimulatory potency of CDGSF to against tumor recurrence. CAlixarene-STING also displayed a superior adjuvant activity on SARS-CoV-2 recombinant vaccines.[113]

4.6. Exosomes

Exosomes are vesicles released from living cells with dynamic size changing from 50 to150 nm. The nanospheric membrane of exosomes is formed by lipids and proteins derived from the parent cells. With further understanding, its clinical application has attracted more and more attention. One of the most useful properties of exosomes is the ability to cross barriers, such as the plasma membrane and the blood/brain barrier, to deliver molecules. Thus, exosomes have great potential in the delivery

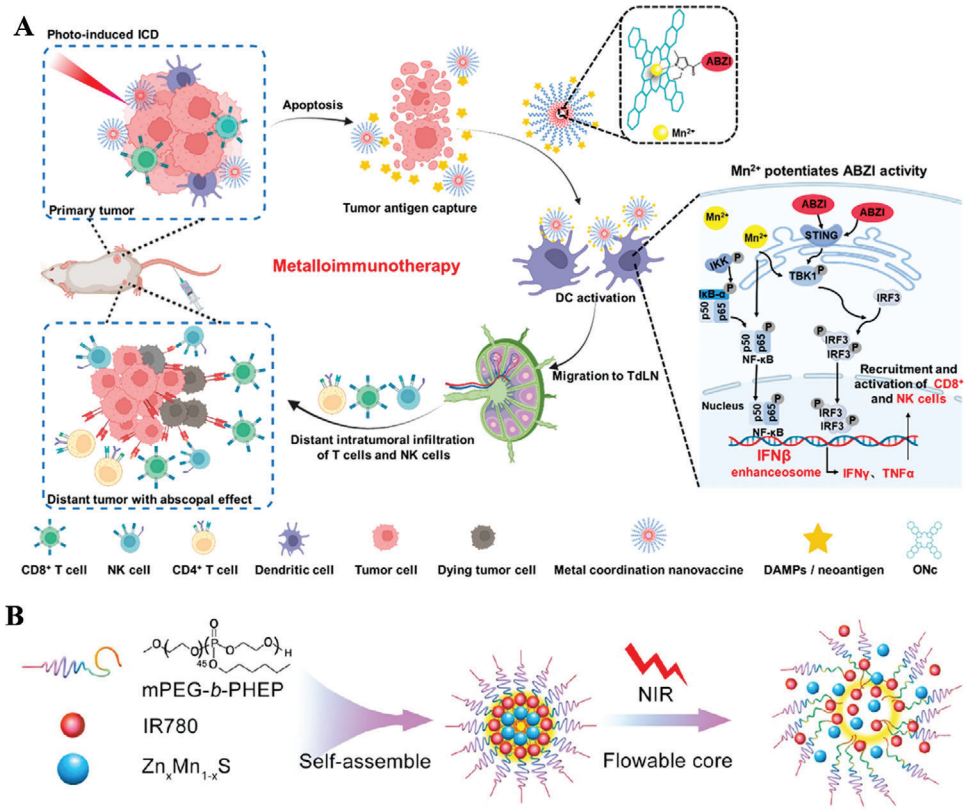

Figure 8. Micelles-based STING agonists delivery for cancer immunotherapy. A) Schematic illustration of manganese coordination micelles for PTT-mediated ICD and STING therapy. Reproduced with permission.[80] Copyright 2022, American Chemical Society. B) Schematic illustration of the amphiphilic polymer mPEG-*b*-PHEP for STING therapy. Reproduced with permission.[79d] Copyright 2022, American Chemical Society.

of various chemodrugs, proteins, and nucleic acids. Kalluri et al. engineered exosomes to deliver cyclic GMP-AMP (iExoSTINGa) (**Figure 10**A). Compared with STINGa alone, iExoSTINGa selectively targeted the STING pathway in APCs with superior potency in B16F10 tumor growth suppression (Figure 10B).[114] This study highlighted the potential of exosomes in antitumor immunotherapy.

4.7. Nanoprodrugs

Nanoprodrugs are compounds that have pharmacological effects only after being transformed in vivo. The precursor drug itself has no biological activity or very low activity, and becomes an active substance after metabolism in the body. The purpose of this process is to increase the bioavailability of the drug, strengthen the targeting, and reduce the toxicity and side effects. Zhou et al. designed an acid activated DMXAA nanoprodrug using amphiphilic diblock copolymer PEG-*b*-PDPA. The nanovaccine activated the STING pathway in DCs by releasing DMXAA in pH 6.0, while not at pH 7.4 (Figure 10C).[115] Zhao et al. designed a SN38 nanoprodrug based on poly(L-glutamic acid)-*g*-methoxy poly(ethylene glycol) (PLG-*g*-mPEG). After injection of nanoprodrug into the tumor bearing mice, the leaked DNA caused by SN38 transferred from tumor cells to DCs through exosomes, activating STING pathway to inhibit tumor growth (Figure 10D).[47] Cao et al. designed a ROS responsive hybrid platinum (IV) prodrug composed of cisplatin and topoisomerase I inhibitor camptothecin (CPT) (CPT-Pt (IV)). The CPT-Pt (IV) released cisplatin and CPT in tumor cells, and activated the STING-IRF3-TBK1 axis via DNA damages.[11d] This study showed that DNA damaging drugs have potential of efficiently activating cGAS-STING pathway through the nanodelivery system (Figure 10E).

4.8. Biomimetic Nanoparticles

A large number of organic, inorganic, or organo–inorganic hybrid materials with complex structure and superior properties have been synthesized. These materials have special physical properties compared to conventional materials, which allow organisms to perform all sorts of strange functions. With the development of nanotechnology, it has been found that many special abilities of organisms are closely related to nanotechnology. Nature is an advanced synthetic factory, churning out organisms with exotic functions. The realization of these functions often depends on the ordered or disordered assembly of basic material units on a microscale. The exploration and research of these materials have opened up a new way for people to biomimetics on the microscale. The goal of biomimetic nanomaterials is to develop a "living" material with functions similar to those of living organisms. Zhang et al. developed a new biomimetic

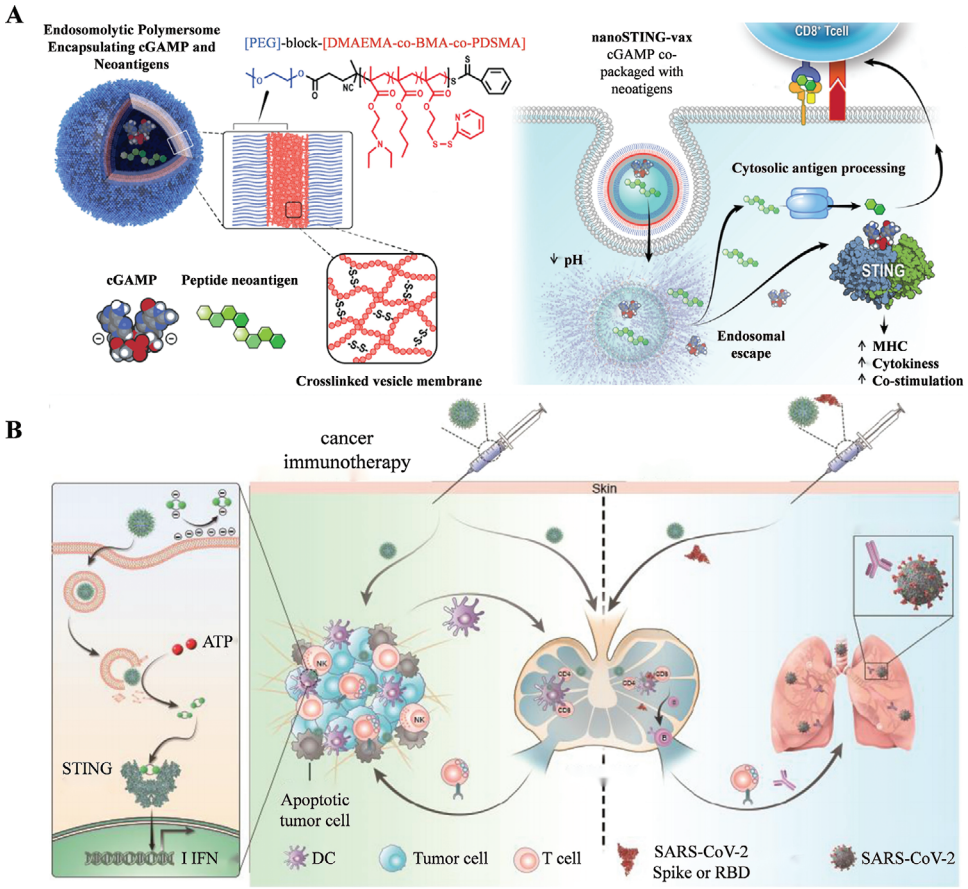

Figure 9. Vesicles-based STING agonists delivery for cancer immunotherapy. A) Schematic of nanoSTING-vax structure. Reproduced with permission.[84d] Copyright 2020, American Chemical Society. B) Schematics of CASTING preparation. Reproduced with permission.[113] Copyright 2022, Chinese Chemical Society.

nanoparticles with dual targeting function for the first time (SR717@RGE-HFn NPs). The results demonstrated that the bionic nanocarrier successfully spanned BBB and delivered STING agonist to brain glioma lesions, effectively activating STING pathway and triggering immune regulation. Thus, the growth of brain glioma was effectively inhibited and the survival rate of brain glioma bearing mice was improved. In addition, the biomimetic nanodrug had no obvious adverse effects on blood biochemical indexes and major organ pathology, and had excellent biocompatibility, which provided a promising immunotherapy strategy for brain glioma patients.[103] Gao et al. designed a bionic cancer cell membrane (EPBM) coated nanovaccine (PLGA/STING@EPBM) to deliver STING agonists and tumor antigens to Clec9a$^+$ DCs. They found that STING agonists significantly stimulated the secretion of type I interferon (IFN) in Clec9a$^+$ DCs, generated strong antitumor effects in tumor models that are responsive to or resistant to anti-PD-1 therapy, without significant cytotoxicity.[116]

4.9. Other Nanoparticles

Compared to synthetic materials, protein-based nanoparticles attract numerous attentions owing to their biocompatibility, amenability to genetic engineering, and intrinsic capacity to form well-defined structures. For example, a protein delivery system via genetic fusion was engineered for the recombinant STING spontaneously penetrating cells to deliver CDNs (**Figure 11**A).[117] Luo et al. described a bovine serum albumin (BSA)/ferritin-based nanoagonist incorporating Mn and β-lapachone, which synergistically activated cGAS-STING pathway in DCs with robust adaptive antitumor immunity (Figure 11B).[118]

5. Combination Therapy Based on Nanotechnology

The combination of STING therapy with other treatments has great application in antitumor therapy. They mainly included surgery, chemotherapy and CDT, radiotherapy, phototherapy (PTT and PDT), immune checkpoint inhibitors (ICIs), adoptive transfer of chimeric antigen receptor (CAR)-modified T cells therapy, vaccines, and other combination (IDOi and TLR9 agonists).

5.1. Surgery

As the most common intervention, although surgery can completely eliminate benign tumors, there is still a risk of recurrence and metastasis for malignant tumors. Thus, surgery is

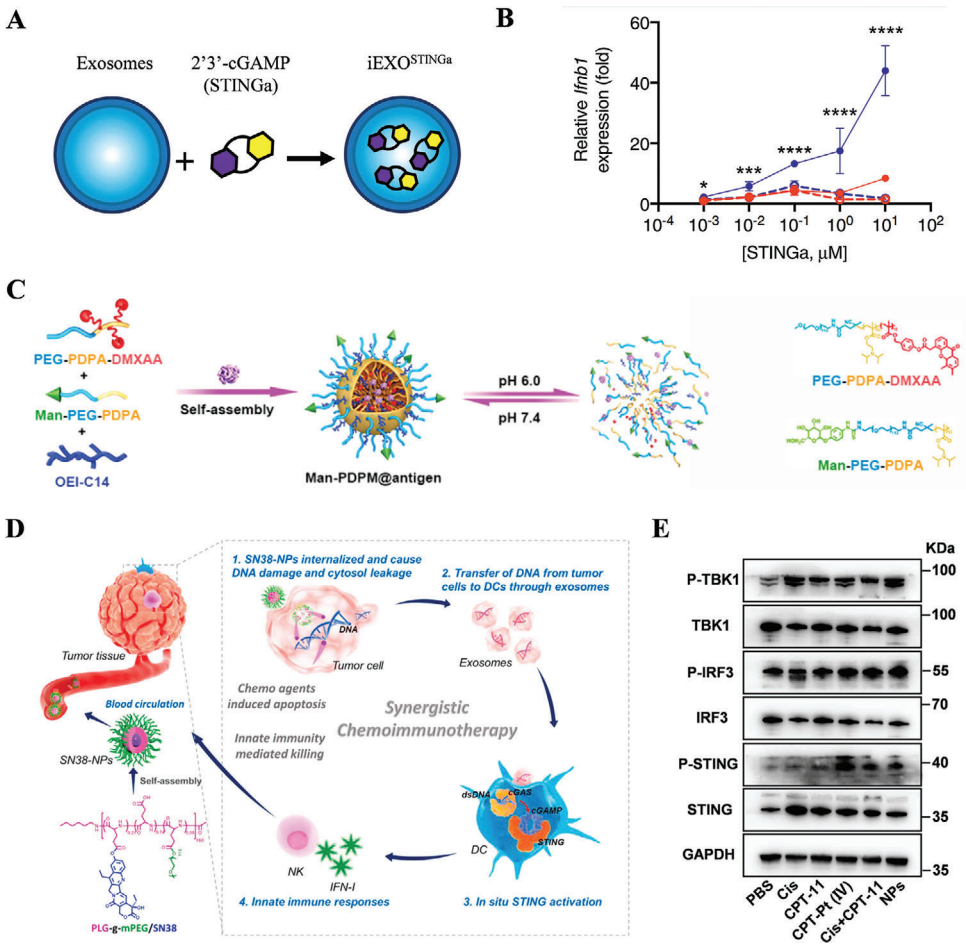

Figure 10. A) Exosomes enriched from the culture supernatant of HEK293T cells were loaded with cGAMP. B) BMDCs treated with iExoSTINGa also showed increased expression of Ifnb1 when compared with cells treated with STINGa. Reproduced with permission.[114] Copyright 2021, Elsevier. C) The nanovaccine was constructed from an acid-activatable micellar nanoparticle, neoantigen, and DMXAA. Reproduced with permission.[115] Copyright 2020, American Chemical Society. D) Schematic illustration of SN38-NPs for in situ activating STING pathway and cancer chemoimmunotherapy. Reproduced with permission.[47] Copyright 2021, Elsevier. E) The proteins expression in the cGAS-STING pathway of tumors treated with different drugs for 24 h. Reproduced with permission.[11d] Copyright 2022, Elsevier.

often assisted with chemotherapy, radiotherapy, immunotherapy, and so on. Recently, Baird et al. combined STING therapy with tumor resection in a range of head and neck squamous cell carcinoma (HNSCC) murine tumor models.[119] Surprisingly, tumors treated with STING-loaded biomaterials were cured. These data demonstrated the possibility of STING therapy in tumorous personalized immunotherapies. Another preclinical research showed that setting hydrogel STING NPs at the excisional site could prevent tumor recurrence and metastasis via systemic immune response.[120] This combined application implied the possibility of STING therapy in HNSCC surgery to prevent the malignancy of tumors.

5.2. Chemotherapy and CDT

Chemotherapy is a treatment that targets and attacks tumor cells. It acts on all cells in the body, both normal and tumorous. These effects last only as long as the treatment continues. Immunotherapy targets the patient's immune system to activate a stronger immune response. Immunotherapy often takes more time to have an effect, but these effects may last long after the treatment is over. Recent studies have found that some chemodrugs can also play an important role in immunotherapy.[121] Mao et al. designed two PtII complexes (Pt1 and Pt2) for chemotherapy, pyroptosis, and cGAS-STING therapy in cancer cells, inhibiting tumors in vitro and in vivo (**Figure 12**A).[122] Ge et al. engineered a ferrocene-containing polymersome coloaded glucose oxidase (GOD) and DiABZI, in which enhanced STING therapy and chemodynamic-immunotherapy were obtained in primary tumors and distant tumors (Figure 12B).[123]

Chemodynamic therapy (CDT) taking advantage of Fenton and Fenton-like reactions for in situ cytotoxic hydroxyl radicals and O_2 generation, has emerged as a potential antitumor therapy. Compared with traditional chemotherapy, metal elements in CDT can also play a key role in immune regulation. For example, a leukemia cell membrane (LCM)-coating hollow MnO_2 nanoplatform (HM) with doxorubicin (DOX)

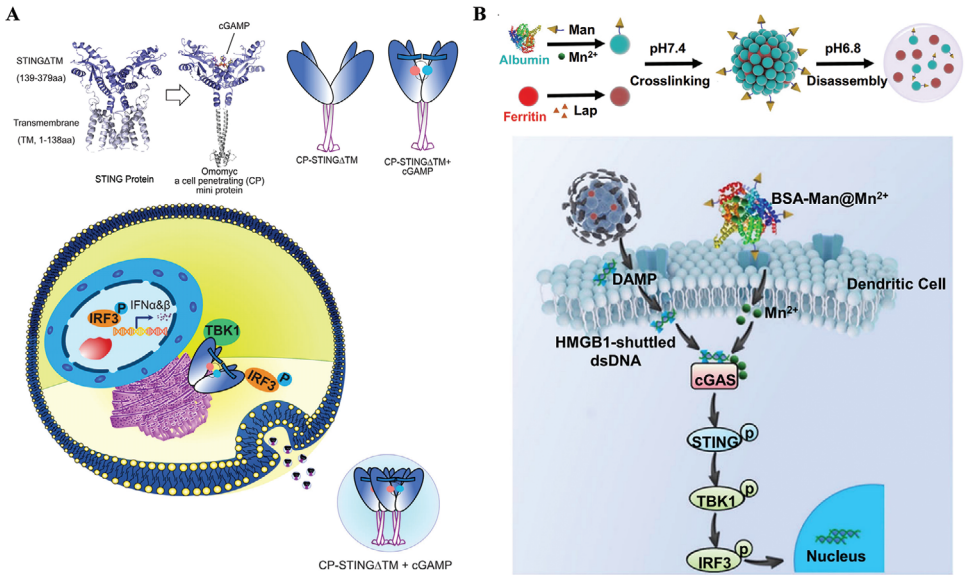

Figure 11. Other nanoparticles-based STING therapy. A) Schematic of using recombinant cell-penetrating (CP)-STINGΔTM as a biologically functional platform for cGAMP delivery. Reproduced with permission.[117] Copyright 2021, Wiley-VCH GmbH. B) Schematic of a biocompatible and TME-responsive protein-based nanostructure activating cGAS/STING signaling of DCs. Reproduced with permission.[118] Copyright 2022, Springer Nature.

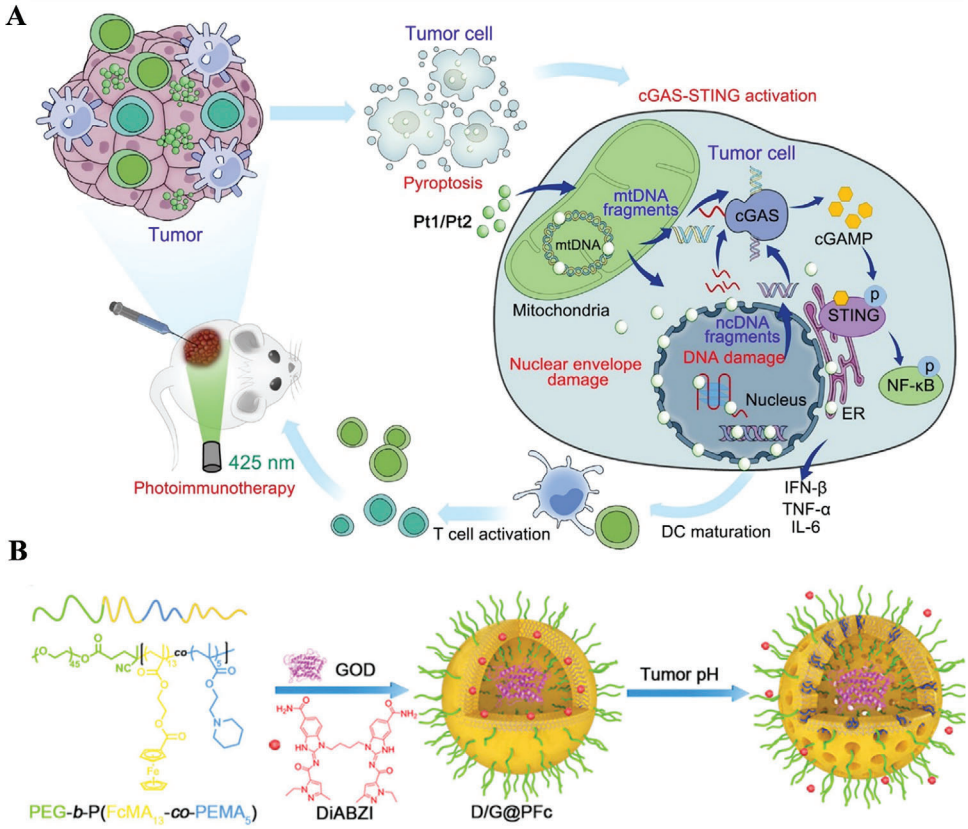

Figure 12. The combination of chemotherapy, CDT, and STING therapy. A) Pt1/Pt2 activated cGAS-STING pathway and pyroptosis for anticancer immunotherapy. Reproduced with permission.[122] Copyright 2022, Wiley-VCH GmbH. B) Schematic illustration of the polymersome nanoreactors by coloading GOD and DiABZI (D/G@PFc) for antitumor immunotherapy. Reproduced with permission.[123] Copyright 2021, Wiley-VCH GmbH.

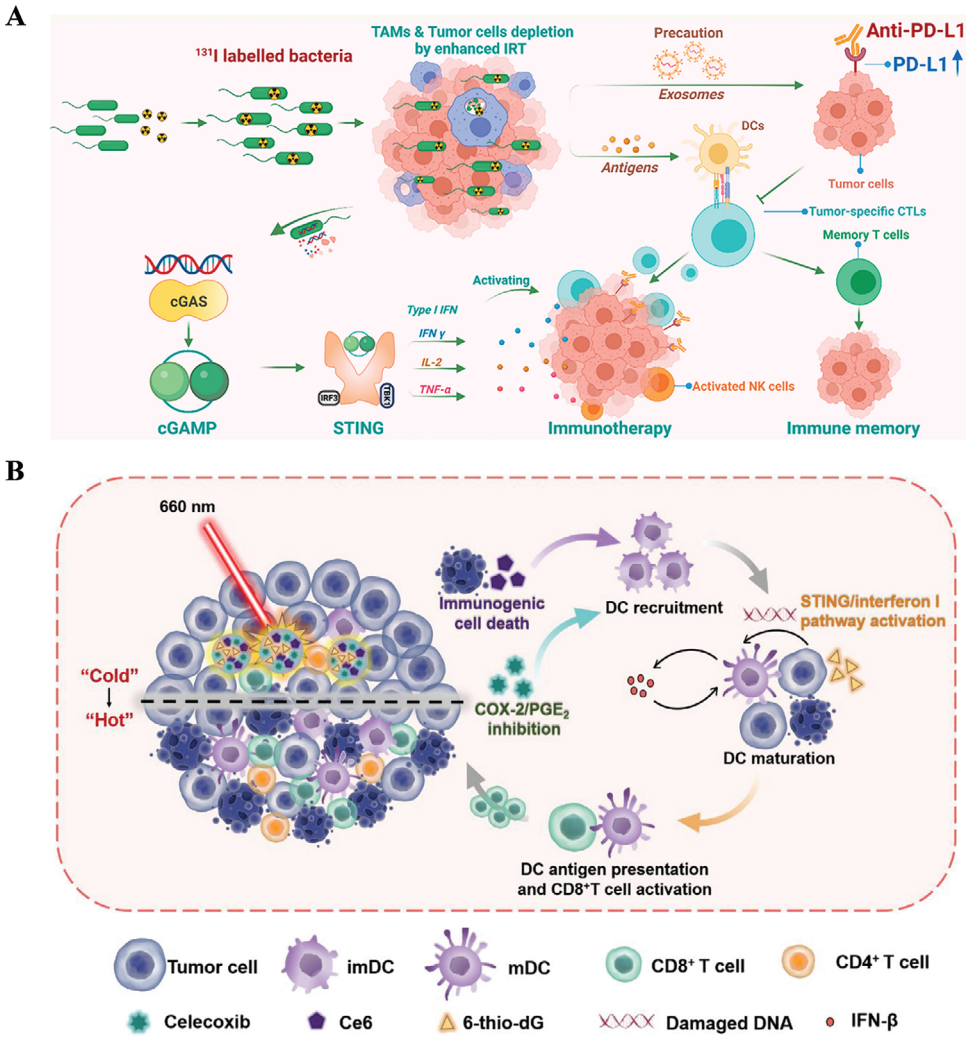

Figure 13. A) Schematic diagram of radio-immunotherapy induced by radiolabeled bacteria. Mechanism of inactivated bacteria to boost multiple antitumor immune responses for radio-immunotherapy. Reproduced with permission.[54a] Copyright 2022, American Chemical Society. B) Illustration of preparation of carrier-free CC-6td NPs and schematic illustration for the mechanism of CC-6td NPs enhancing dendritic cell function. Reproduced with permission.[92] Copyright 2022, Elsevier.

encapsulation (LHMD) was constructed to activate STING pathway and sensitize cGAS to recognize the dsDNA breaks induced by DOX.[8c] In another research, an amphiphilic thermally sensitive polymer mPEG-*b*-PHEP was chosen to incorporate IR780 and manganese zinc sulfide nanoparticles (ZMS) (PPIR780-ZMS), in which Mn^{2+}-mediated CDT and cGAS-STING activation by photothermal boosted the antitumor effect of this nanoplatform, providing a practical strategy for the application of Mn-based nanostructures.[79d]

5.3. Radiotherapy

Besides surgery and chemotherapy, radiotherapy (RT) has also been utilized in cancer therapy for decades. Preclinical and clinical trials show that the immune response mediated by RT can effectively suppress tumor volume growth.[124] An inactivated bacteria vector with $^{125}I/^{131}I$ labeling (^{125}I-VNP/^{131}I-VNP) was built to achieve efficient internal radioisotope therapy (IRT) in primary tumor and revealed robust systemic antitumor immune activity via cGAS-STING pathway activation by dsDNA induced by IRT.[54a] After combination with ICIs (αPD-L1), ^{131}I-VNP led to the inhibition of tumors growth and rechallengement (**Figure 13**A). In another example, Dai et al. proposed a radiosensitization cooperation with STING pathway activation approach by constructing a novel lanthanide-doped radiosensitizer-based metal-phenolic network, named as $NaGdF_4$:Nd@$NaLuF_4$@PEG-polyphenol/Mn (DSPM).[125] These work showed radiotherapy could serve as an important methodology synergistic with STING therapy for high antitumor immune response.

5.4. Phototherapy

PDT and PTT are two types of phototherapy widely investigated in antitumor therapy, in which photosensitizer molecules absorb

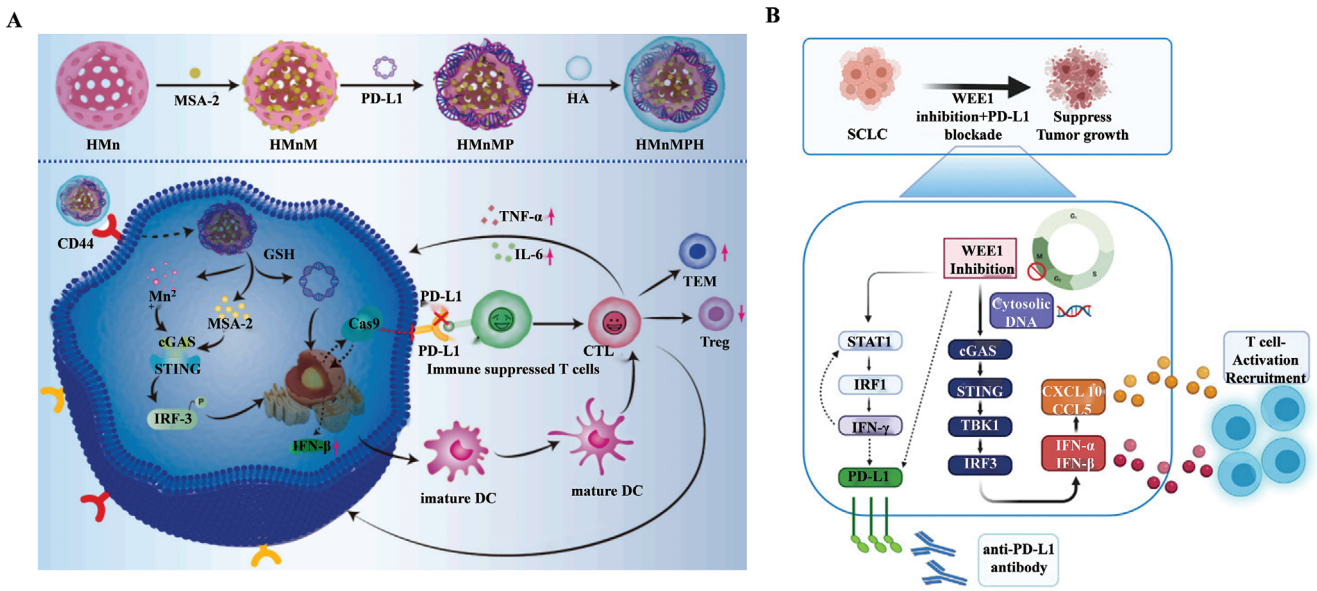

Figure 14. A) Design and immunotherapeutic functions of HMnMPH. Reproduced with permission.[129] Copyright 2022, Elsevier. B) Schematic of effective treatment of Small cell lung cancer (SCLC) with a WEE1 inhibitor in combination with PD-L1 antibody. Reproduced with permission.[130] Copyright 2022, Elsevier.

light and convert it into ROS or heat to kill tumor cells and induce robust immunity response.[126] A nanodrug designed by chlorin e6 (Ce6), celecoxib, and 6-thio-2'-deoxyguanosine (6-thio-dG) was applied to treat tumors by PDT and STING therapy, in which Ce6 enabled PDT, celecoxib down-regulated the prostaglandin E2 (PGE2), and 6-thio-dG triggered DNA damages to activate STING pathway in DCs (Figure 13B).[92] Similarly, a hollow mesoporous organosilica nanoparticle coloaded with platinum nanoparticle (Pt-NPs) and IR820 (HMON@IR820/Pt-NPs) was used to inhibit primary and distant gastric cancer (GC) via enhanced chemotherapy, PDT, PTT, and STING therapy.[127] The NPs were able to trigger intracellular H_2O_2 decomposition to O_2 by surface Pt-NP modification to enhance the PDT effect. Additionally, the release of Ox-mitoDNA and nDNA induced by IR820 and Pt-NPs, respectively, stimulated the cGAS/STING pathway. Thus, STING activation combination with phototherapy could notably improve cancer immunotherapy efficacy which has emerged huge potential in tumor eradication.

5.5. ICIs

Immune checkpoint inhibitors (ICIs) mainly target cytotoxic T lymphocyte-associated protein 4 (CTLA4) and programmed cell death 1 (PD-1), or its main ligand PD-L1.[128] Numerous evidences show that the efficacy of immunotherapy depends on the tumor immunogenicity, antigen expression, and immunoinfiltration. Most immune checkpoint blockade therapy in clinical trials failed because of low immunogenicity of patients. To enhance ICB therapeutic efficiency, increasing tumor immunogenicity and infiltration of immune cells in tumor tissues are necessary. Excitingly, STING agonists have great potential of improving the immunogenicity of the tumor via promoting antigen presentation, DCs maturation, and T cells activation to reverse immune "cold" tumor to "hot" tumor. For example, a TME responsive nanoplatform consisted of hollow manganese dioxide (HMn), MSA-2, CRISPR-Cas9/sg-PD-L1 plasmid, and hyaluronic acid (HA) (HMnMPH) had been proven to inhibit the primary and distal cancers via the long-term immunity (**Figure 14**A).[129] Small cell lung cancers (SCLCs) have high mutation which leads to relatively unresponsive to ICIs. Combined WEE1 inhibition (AZD1775), a STING agonist and anti PD-L1 antibody induced remarkable T cells antitumor response to inhibit tumor growth (Figure 14B).[130]

5.6. CAR-T therapy

In the field of immunotherapy, chimeric antigen receptor T (CAR-T) cell therapy has also attracted a lot of attention but been restrained by limited infiltration of immune cells. In an example, CAR-T cells generated from Th/Tc17 cells treated with DMXAA or cGAMP greatly suppressed tumor, due to the recruitment of CAR-T cells through a chemokine milieu.[131] The results suggest new approaches to enhance CAR-T therapy in solid tumors. In another study, the efficacy of CD70 CAR-T cells in renal carcinoma cells (RCCs) immunotherapy was enhanced by the PARPi treatment activating STING pathway (**Figure 15**A).[132]

5.7. Vaccines

Vaccine is a revolutionary strategy for cancer therapy.[133] However, cancer vaccines are hindered by tumor immunosuppressive microenvironment. STING-activating DNA nanovaccines (STING-NVs) are developed to elicit potent antitumor immune responses in a murine melanoma model.[134] STING-NVs have been designed by PLA-*b*-PEG coloaded cytosine (C)-rich i-motif

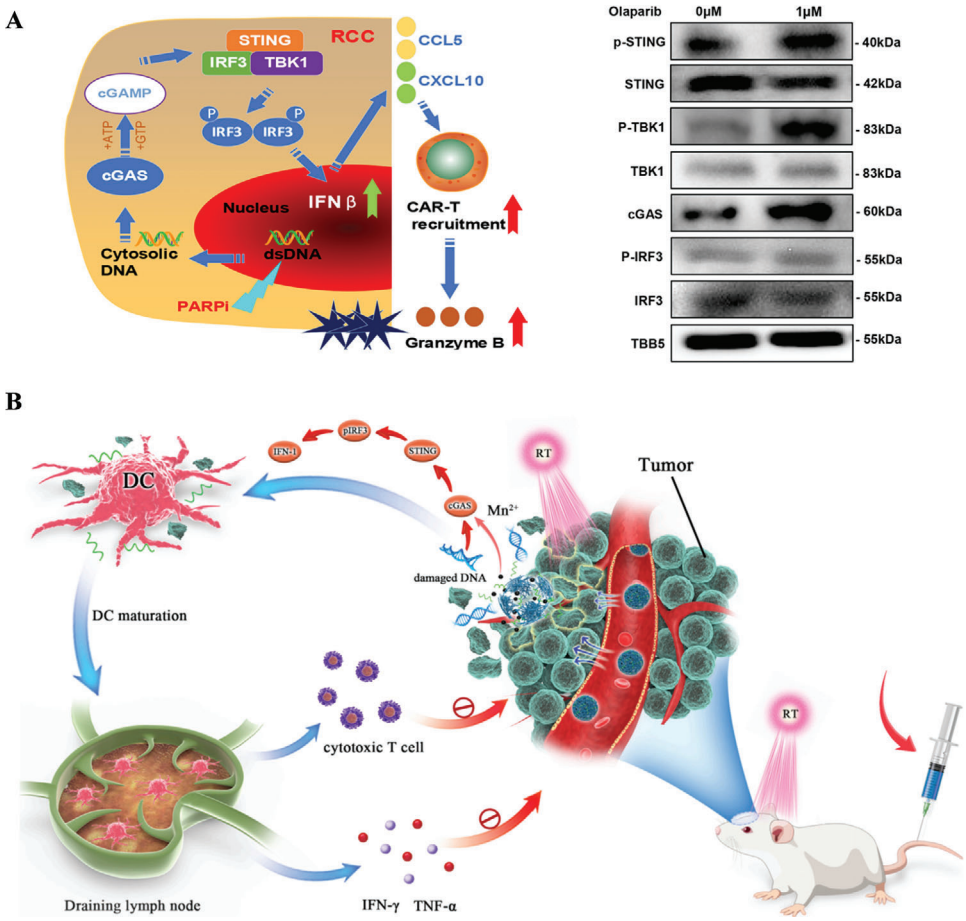

Figure 15. A) Model for cGAS-STING pathway activation in response to DDR targeting in RCC. Reproduced with permission.[132] Copyright 2021, Springer Nature. B) Schematic illustration of the combination therapy of orthotopic glioblastoma monitored by MRI. Reproduced with permission.[138] Copyright 2021, Elsevier.

DNA and CDG.[135] Under acidic tumors, CDG release potentiated antitumor immunity resulting in repolarization of immunosuppressive M2-type macrophages into antitumor M1-type macrophages. In a poorly immunogenic murine melanoma model, intralesional STING-NVs outperformed liposomal CDG and fluoride-CDG therapeutic efficacy. Moreover, Gao et al. designed an ultra-pH-sensitive (UPS) cancer vaccine via PEG-PC7A and model antigen ovalbumin (OVA).[71a] The nanovaccine demonstrated significant suppression effect on melanoma, colon cancer, and human papilloma virus-E6/E7. All of these results suggest the huge potential of STING-NVs in cancer immunotherapy.

5.8. Ion Interference Therapy

Ion interference therapy is a new strategy to use bioactive nanomaterials to reverse the ion distribution in tumor cells with lethality, such as ferroptosis, cuproptosis, and calcoptosis. Due to its unsaturated hybrid orbital, manganese ion is often the active center of cellular REDOX, which can produce Fenton-like reaction and cause ferroptosis. Moreover, the optical absorption of manganese ion can be used for photothermal and photodynamic therapy. The activation of manganese ion in STING has promoted the application of manganese ion in immunotherapy. Huang et al. found that $MnCl_2$ caused lipid peroxidation in tumor cells and increased mitochondrial ROS level, led to ferroptosis. In addition, $MnCl_2$ enhanced the phosphorylation levels of STING, TBK1, and IRF3, and up-regulated the expression of IFN produced by the cGAS-STING pathway.[136]

5.9. Other Combination Therapy

Indoleamine 2, 3-dioxygenase (IDO) has negative immune regulation associated with tryptophan metabolism. Recent findings reveal that IDO can be triggered in the progress of innate immunity or T cell activation. As an important innate immunity, the cGAS-STING pathway activation was also accompanied by IDO enhancement. Thus, a nanoprodrug coupling MSA-2 and NLG-919 (an IDO inhibitor) was designed to explore the ability of tumor growth inhibition and antitumor immune response activation.[137] Outcomes of this study may provide guidance for preclinical trials of STING therapy.

Besides STING agonists, TLR9 agonists are the common immune adjuvants for cancer vaccines, though their clinical

applications are disappointing because of the weak IFN inducer and undesired type 2 immunity. Yet, combination therapy of TLR9 and STING agonists could address these limitations by simultaneously inducing innate and adaptive IFN-γ mediated immune response, suppressing type 2 immunity, and exerting robust antitumor activities in GBM models (Figure 15B).[138]

6. The STING Therapy in Clinical

At present, STING agonists have made great progress in the development of antitumor drugs, and a number of drugs have been studied in clinical, such as IMSA-101owned by ImmuneSensor Therapeutics, GSK3745417 owned by GlaxoSmithKline, BMS-986301 owned by Bristol-Myers Squibb, SB-11285 a unit of Spring Bank Pharmaceuticals and MK-1454 a unit of Merck. However, they are mainly targeted at solid tumors not the nonsolid tumors. Excitingly, MK-1454 is being developed for lymphoma. From the perspective of molecular structure, STING agonists currently under research can be divided into five categories: 1) Cyclic dinucleotides: as binding ligands of STING, cyclic dinucleotides play a direct role in the activation of STING. ADU-S100 is the first cyclic dinucleotide STING agonist to enter clinical trials. 2) Aminobenzimidazoles: This class of molecules was first developed by GlaxoSmithKline and a series of aminobenzimidazole STING agonists have been obtained by using radiolabeled cGAMP to competitively bind to the CTD region of STING. Xanthone and xanthone. 3) Xanthone and xanthone. 4) Benzothiophene: Merck pioneered the patent protection of STING agonists; 5) Benzophenylenes: These molecules were also originally obtained by high-throughput screening. It provides a new prospect for STING agonist development. Due to poor stability, the first generation of small molecule STING agonists can only be administered by intratumoral injection, which brings certain difficulties to drug development and clinical application. The new generation of small molecule STING agonists can be administered systemically throughout the body or intratumoral, meeting the clinical therapeutic requirements of patients with different tumors. Nowadays, STING agonists continue to emerge, and great progress has been made in the treatment of various diseases, especially in the field of tumor immunotherapy. We believe that with the in-depth research in the future, the progress will be faster and faster. We look forward to the early market of the STING agonists for the benefit of patients.

7. Conclusion and Perspective

In recent years, immunotherapy has emerged robust momentum in the field of tumor therapy. Drugs based on immunotherapy have rapidly entered clinical trials, and tumor treatment has achieved a breakthrough in immunotherapy, bringing good news to patients. STING signal as one of immunotherapy can initiate innate immunity via foreign DNA recognition through the cGAS pathway or damaged DNA release. On the other hand, STING stimulates antigen presentation and elicits T cell provocation by activating dendritic cell, which is an important linker between innate and adaptive immunity. In this review, we summarized the existing mechanisms of STING activation, when the detailed mechanisms about DNA-mediated innate immunity remain the focus of future research. In addition, why cGAS-STING is not activated by DNA from host itself is still a puzzle. There are many STING agonists, such as CDN, DNA damaged chemodrugs, non-CDN small molecules, metal ion, and small molecule inhibitors. However, they either have negative charge for inferior internalization, poor water solubility, and short half-life in vivo for low bioavailability, or have systemic toxicity and poor targetability for serious side effects. Therefore, therapeutic efficacy is limited if we directly use free STING agonists through intravenous injection, oral and other systematic administration. In patients with multiple heterogeneous distal tumors, it is difficult to achieve STING agonist distribution within the distal tumor in a concentration that can stimulate an immune response. Intratumoral injection may present certain difficulties in drug development and application in different indications. cGAS-STING pathway has different functions in different cells. For example, it can induce apoptosis in tumor cells, while activate immunity in immune cells. Therefore, the location and dosage of STING agonists should be accurate in vivo.

To maximize the STING therapy, a better solution is to deliver STING agonists using nanocarriers. Nanocarriers encapsulation with these agonists enter the capillaries through blood circulation or enter the lesions through the endothelial cell space which are then absorbed by tumor cells in different ways, such as phagocytosis, macropinocytosis, caveolae/raft, and clathrin, to achieve high targetability and bioavailability. Nanocarriers with small size and high specific surface can embed hydrophilic and hydrophobic substances, improve their targeability via enhanced permeation and retention (EPR effect). After modification by the targeting group, the precise delivery of the agonists from nanocarrier can be achieved, which can reduce the drug dosage and weak side effects. Compared with free STING agonists, nanocarriers can prolong their circulation time, reduce their administration frequency and systemic toxicity, and improve their therapeutic efficacy. Meanwhile, nanocarriers with specific decoration can resolve delivery barriers, such as blood–brain barrier, transmembrane barrier, so that the STING agonists can aggregate in the lesion and improve efficiency. Moreover, nano-STING combination with radiotherapy, chemotherapy, tumor vaccine, immune checkpoint inhibitors, CAR T cell therapy, and other novel therapeutic methods can not only reduce the dosage of STING agonists, but also synergistically enhance the antitumor effect, overcome the tolerance of tumor therapy, and achieve the best therapeutic effect.

Although a number of nano-STING therapies have amazing antitumor effect, there are still some directions should be explored in the future study. First, as for in vivo delivery through systemic administration, more efficient nanocarriers need to cope with the cascade of physiological barriers including tumor targetability, cellular internalization, and STING agonist release. The reported nanocarriers generally resolved one or two barriers, while neglected the others. Thus, nanocarriers that give consideration to all the barriers should be developed in future. Second, the combination of different treatments with STING therapy into one nanocarrier should be optimized with efficient delivery and improved with a simpler preparation procedure in a large-scale for the possibility of clinical translation. All in all, more efforts should be made for STING therapy as one of important immunotherapy approaches in clinical trials.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

cancer immunotherapy, cGAS-STING pathway, combination therapy, drug delivery, nanoparticles

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