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Review

# Unleashing the Potential of Metal Ions in cGAS-STING Activation: Advancing Nanomaterial-Based Tumor Immunotherapy

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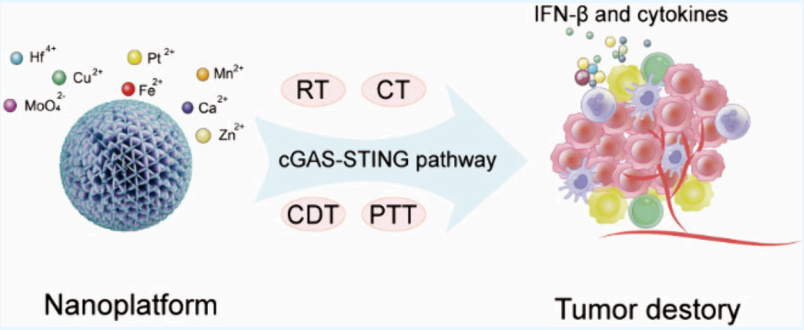


**ABSTRACT:** Immunotherapy is a critical modality in cancer treatment with diverse activation pathways. In recent years, the stimulator of interferon genes (STING) signaling pathway has exhibited significant potential in tumor immunotherapy. This pathway exerts notable antitumor effects by activating innate and adaptive immunity and regulating the tumor immune microenvironment. Various metal ions have been identified as effective activators of the STING pathway and, through the design and synthesis of nanodelivery platforms, have been applied in immunotherapy as well as in combination therapies, such as chemotherapy, chemodynamic therapy, photodynamic therapy, and cancer vaccines. Metal nanomaterials showcase unique advantages in immunotherapy; however, there are still aspects that require optimization. This review systematically examines existing metal-based nanomaterials, elaborates on the mechanisms by which different metal ions activate the STING pathway, and discusses their application models in tumor combination therapies. We also provide a comparative analysis of the advantages of metal nanomaterials over other treatment methods. Our exploration highlights the broad application prospects of metal nanomaterials in cancer treatment, offering new insights and directions for the advancement of tumor immunotherapy.

## 1. INTRODUCTION

Despite continuous increases in the global incidence of malignant tumors, some of which already have high incidence and mortality rates, the effectiveness of traditional treatment methods is limited due to severe side effects, drug resistance, and the fact that many patients do not respond to current therapies.[1,2] In recent years, with the rise of immunotherapy, from antibody-based immunomodulators to cell-based therapies to other emerging technologies, remarkable progress has been made in cancer treatment.[3−6] Immunotherapy has completely changed the treatment landscape for various types of tumors. In the context of tumor immunotherapy, the stimulator of interferon genes (STING) signaling pathway promotes various aspects of innate and adaptive immunity and is considered a key target for immunotherapy.[7,8] However, STING-targeted strategies are hindered by low delivery efficiency and systemic toxicity, leading to inconsistent therapeutic responses.[9] Although various types of STING agonists have been developed, their poor stability and specificity in vivo limit their practical applications and overall efficacy.[10−12] Systemic administration of STING agonists can unintentionally activate STING pathways in nontarget tissues, causing excessive release of pro-inflammatory cytokines like IFN-$\beta$ and triggering systemic inflammation.[13] Prolonged activation may lead to chronic inflammatory diseases, such as lupus, and increase tumor metastasis risk.[14] Traditional cyclic dinucleotide-based STING agonists are rapidly degraded by extracellular phosphodiesterases, limiting their efficacy and requiring intratumoral delivery, which is unsuitable for metastatic tumors.[15] Their negative charge and hydrophilic nature further hinder cytoplasmic delivery, resulting in low efficiency.[12] Additionally, small-molecule agonists must exhibit high pathway specificity to avoid interfering with other cellular

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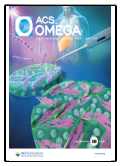

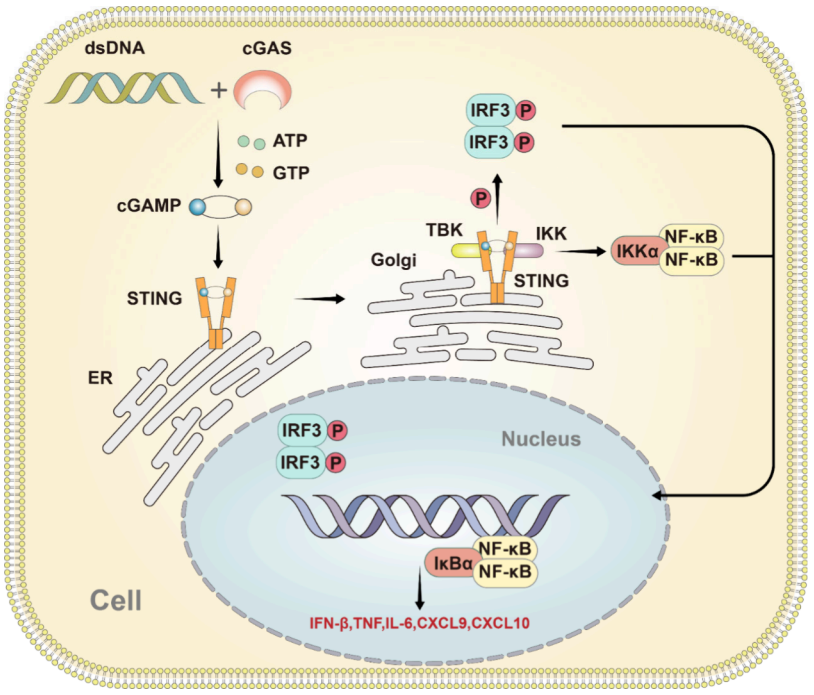


**Figure 1.** The cGAS-STING pathway. cGAS is activated upon recognizing free cytoplasmic DNA from host or foreign sources, using ATP and GTP to synthesize cGAMP. cGAMP binds to STING on the ER, triggering its activation and conformational change. Activated STING then moves to the Golgi, where it recruits and activates TBK1 and IKK, leading to the activation of IRF3 and NF-κB pathways, which induce the expression of interferons and cytokines, thereby enhancing the immune response.

processes.[14] In contrast, newly discovered metal ions capable of activating the STING pathway demonstrate greater therapeutic potential due to their unique properties. Metal ions induce cell death through mechanisms such as disrupting osmotic pressure, activating immune pathways, and promoting oxidative stress, offering broad potential in tumor therapy.[16] They also enhance the antigen-presenting abilities of dendritic cells and macrophages[17,18] and increase the cytotoxicity of natural killer cells, thereby promoting nonspecific immunity. Furthermore, some metal ions can stimulate the activation and proliferation of specific immune cells, such as $CD8^+$ T cells, enhancing tumor cell recognition and clearance, which strengthens the overall antitumor immune response.[19] However, the systemic delivery of metal ions can lead to toxic side effects. For example, nonspecific distribution of manganese can cause neurotoxicity.[20] Copper accumulation may lead to liver toxicity,[21] and excess iron can induce oxidative stress and tissue damage.[22] Additionally, low cellular uptake rates and short circulation half-lives further limit the effective activation of the STING pathway in vivo.[23,24] Improving agonist targeting and reducing systemic toxicity have therefore become research focuses. In this context, using nanomaterials for agonist delivery may be an effective strategy to enhance their bioavailability and therapeutic efficacy.[25] By incorporating metal ions into these platforms, metal-based nanomaterials can be developed for tumor immunotherapy,[26,27] enabling precise spatiotemporal regulation of the STING pathway.[28−30]

This review explores the therapeutic potential of metal ions and nanodelivery platforms within the context of cancer immunotherapy, examining their underlying mechanisms of action and emphasizing their roles in combination treatment strategies. Through an in-depth analysis, we offer critical insights to inform the optimization of metal-based nanomaterials in advancing future cancer immunotherapeutic approaches.

## 2. THE STING PATHWAY

Owing to genomic instability, oxidative stress, and intense metabolism in tumor cells, DNA leakage frequently occurs.[31] As a crucial step in the activation of innate immunity, the recognition of cytoplasmic DNA is particularly important. As a cytosolic DNA sensor, cyclic GMP-AMP synthase (cGAS) can directly recognize double-stranded DNA (dsDNA) in the cytoplasm, including DNA from pathogens or self-DNA.[32,33] It catalyzes the synthesis of cyclic GMP-AMP (cGAMP) from ATP and GTP, which act as second messengers to activate STING, a protein located in the endoplasmic reticulum.[34,35] Activated STING is transported to the Golgi apparatus, during which it undergoes a conformational change, leading to the recruitment of TANK-binding kinase 1 (TBK1) and its own autophosphorylation.[36] Subsequently, STING recruits and phosphorylates interferon regulatory factor 3 (IRF3), enabling its translocation to the nucleus and initiating the transcription of type I interferons.[37,38] Additionally, STING can stimulate IκB kinase (IKK) and mediate the production of inflammatory genes driven by NF-κB[39,40] (Figure 1). Notably, the cGAS-STING pathway interacts with other immune pathways. For example, signal crosstalk with Toll-like receptors (TLRs) and the RIG-I/MAVS pathway can significantly enhance the immune response.[41] The synergistic activation of these pathways not only significantly enhances the release of pro-inflammatory cytokines but also boosts T cell immunological activity, further amplifying the antitumor immune response.[42,43]

DNA damage within the tumor microenvironment (TME), such as the accumulation of cytosolic DNA induced by treatments like radiotherapy and chemotherapy, can signifi-


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cantly increase the activation frequency of the cGAS-STING pathway.[44] This pathway generates various immune-stimulatory molecules, such as type I interferons,[45] stimulates the maturation of dendritic cells (DCs), accelerates the migration of DCs to lymph nodes,[46] activates tumor-specific $CD8^+$ T cells,[47] promotes the polarization of antitumor macrophages,[48] activates natural killer (NK) cells,[49] and drives the expression of various chemokines (such as CXCL9 and CXCL10), which are necessary for the migration and infiltration of cytotoxic T lymphocytes (CTLs). These processes mediate the elimination of tumors by the immune system. Additionally, tumor DNA is transferred to the cytoplasm of DCs and macrophages through an undefined mechanism.[50,51] The accumulation of tumor DNA activates the STING-IRF3-induced IFN signaling pathway, which promotes tumor antigen presentation on DCs and subsequently cross-priming of $CD8^+$ T cells, thereby initiating antitumor immunity[52] (Figure 2).

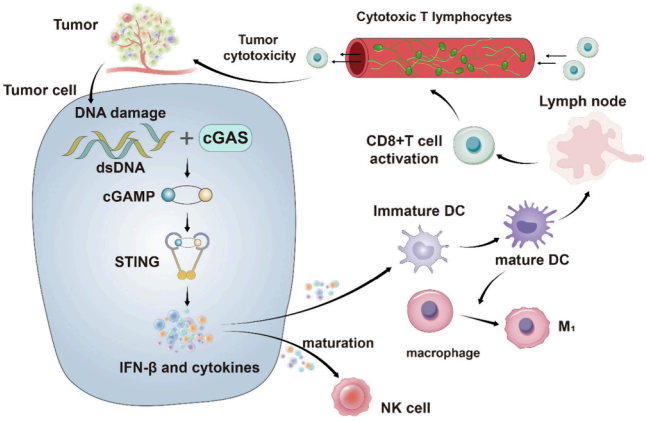


**Figure 2.** The antitumor immunity effects of the cGAS-STING pathway. The activation of the STING signaling pathway in tumor cells induces the expression of IFN and other inflammatory factors, which stimulate the maturation of DC cells, accelerate the migration of DC cells to lymph nodes, promote the polarization of antitumor macrophages and activate tumor-specific $CD8^+$ T cells, activate NK cells, drive the expression of various chemokines, and promote the infiltration of cytotoxic T lymphocytes.

The multifaceted role of the cGAS-STING pathway in the TME extends beyond immune cells to include nonimmune cells. For instance, STING activation in endothelial cells contributes to the normalization of tumor vasculature, alleviating hypoxia in tumor regions, thereby promoting immune cell infiltration into the tumor and increasing the efficiency of drug delivery.[53] Through the aforementioned pathway, the STING pathway reshapes the tumor immune microenvironment and activates antitumor immunity in the body.

However, in certain circumstances, the STING pathway may also promote tumor progression.[54] Sustained activation of the cGAS-STING pathway may lead to chronic inflammation, where excessive activation of the NF-$\kappa$B signaling pathway produces an overabundance of pro-inflammatory cytokines, promoting tumor growth rather than inhibiting it.[55,56] Additionally, the STING-IL-35 axis in B cells is thought to inhibit the proliferation and activity of NK cells, thereby weakening the NK cell-mediated antitumor effect.[57] Additionally, the interaction between cGAS-STING pathway activation and autophagy plays a critical role in tumor immune evasion.[58] For instance, the activation of autophagy can diminish the activity of the cGAS-STING pathway by clearing cytosolic DNA, which, in turn, may partially suppress the host's antitumor immune response.[59] Moreover, strategies that combine activation of the cGAS-STING pathway with immune checkpoint inhibitors show promising potential.[53] By enhancing antigen presentation and T cell infiltration, activation of the cGAS-STING pathway can convert "cold" tumors into more immunologically active tumors, increasing their sensitivity to immune checkpoint inhibitors and thereby enhancing antitumor efficacy.[60,61]

## 3. DIFFERENT METAL-BASED PLATFORMS THAT ACTIVATE cGAS-STING FOR IMMUNOTHERAPY

Metal-based materials possess the advantages of easy synthesis and high porosity, making them highly effective for drug loading and enabling controlled, sustained release.[62,63] Some metal-based nanodelivery platforms not only serve as drug carriers in cancer immunotherapy but can also directly or indirectly activate the STING signaling pathway.[64] Additionally, metal−organic frameworks (MOFs), as emerging porous materials, have demonstrated great potential in drug delivery (Table 1). MOFs can efficiently deliver STING agonists or other immune modulators to activate the cGAS-STING pathway, enhancing immune responses and improving antitumor efficacy.[65,66]

**3.1. Specific Metal Ion Platforms.** Metal ions are essential in biological processes like membrane excitability, signal transduction, metalloprotein catalysis, and cell death regulation,[67] each with unique physiological roles. By influencing key cellular processes such as oxidative stress, DNA damage, and immune cell activation, metal ions can serve as direct activators or enhancers of the STING signaling cascade. Metal-based nanomaterials show significant potential in activating the STING pathway and modulating tumor immunity, advancing cancer immunotherapy, and providing a basis for exploring new antitumor mechanisms. Common metal-based nanodrug delivery systems include iron-, zinc-, platinum-, and manganese-based platforms, with manganese-based systems standing out due to their widespread application and significant effects.

*3.1.1. Manganese Ion Platform.* Manganese is a common metal in mammalian tissues, serving as a component of metalloenzymes and an activator of certain enzymes.[68] $Mn^{2+}$ enhances the activity of the cGAS-STING pathway through multiple mechanisms, significantly promoting anticancer immune responses. Under steady-state conditions, $Mn^{2+}$ is predominantly sequestered in membrane-enclosed organelles, preventing its interaction with cytosolic immune sensors.[69] However, during viral infection or other stress conditions, $Mn^{2+}$ is released into the cytosol, where it can directly activate monomeric cGAS independently of dsDNA.[69−71] $Mn^{2+}$ also induces conformational changes in cGAS, enhancing its affinity for dsDNA, while dsDNA further increases cGAS's affinity for $Mn^{2+}$.[69] This cooperative interaction lowers the activation threshold of the STING pathway, allowing even low levels of DNA to amplify the signal and promote efficient cGAMP production.[70,72] In addition to accelerating the catalytic efficiency of cGAS in generating cGAMP from ATP and GTP, $Mn^{2+}$ may also enhance the binding affinity of cGAMP to STING, although this requires further validation.[73,74]

Upon direct intratumoral injection of $Mn^{2+}$, free $Mn^{2+}$ is rapidly metabolized or cleared within a matter of minutes.[75]


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**Table 1. Metal-Based Nanodelivery Platforms Stimulate cGAS-STING Activation for Enhanced Immunotherapy in Tumors**

| metal | mechanism | nanodelivery platform | tumor type | therapy | reference |
|---|---|---|---|---|---|
| $Mn^{2+}$ | binds directly to cGAS, enhancing its affinity for dsDNA and lowering the activation threshold of the STING pathway | manganese-phenolic network platform (TMPD) | breast cancer | chemotherapy; CDT; immunotherapy | 77 |
| | accelerates cGAMP synthesis and increases its binding efficiency to STING | Mn(III)-doped and Prussian blue-based photothermal nanoparticle (PBM) | breast cancer | photothermal therapy; immunotherapy | 84 |
| | activates TBK1 and NF-κB signaling pathways, inducing the production of IFNs and pro-inflammatory cytokines | manganese zinc sulfide nanoparticles (PPIR780-ZMS) | melanoma | immunotherapy | 85 |
| | | manganese-silica nanoplatform (MnOx@HMSN) | colorectal carcinoma | cancer vaccines | 220 |
| | | G5-pBA/OVA@Mn | melanoma | cancer vaccines | 186 |
| | | Mn-enriched photonic nanomedicine (MnPB-MnOx) | breast cancer | photothermal therapy; immunotherapy | 172 |
| | | ONc-Mn-A-malF127 | colorectal carcinoma | photothermal therapy; immunotherapy | 221 |
| | | BSA-Man@$Mn^{2+}$-Ft@Lap | breast cancer | immunotherapy | 29 |
| | | TMA-NPs | breast cancer | radiation therapy; immunotherapy | 145 |
| | | $MnO_2$-melittin nanoparticles (M-M NPs) | melanoma | cancer vaccines | 222 |
| | | Vir-ZM@TD | breast cancer | immunotherapy | 30 |
| | | NanoMn-GOx-PTX | breast cancer | CDT; immunotherapy | 164 |
| | | MnP@Lip | colorectal carcinoma; breast cancer | chemotherapy; immunotherapy | 223 |
| | | CDN−$Mn^{2+}$ particle, CMP | colorectal carcinoma | immunotherapy | 224 |
| | | PL/APMP-DOX NPs | breast cancer | chemotherapy; immunotherapy | 90 |
| | | lipopolysaccharide-decorated manganese(II)-phenolic networks (LMP vaccine) | melanoma | cancer vaccine | 225 |
| | | Bio-MnSe@Dox | breast cancer | immunotherapy | 226 |
| | | $MnO_2$ NPs | breast cancer | immunotherapy | 227 |
| | | MnIR@NS | breast cancer | photothermal therapy; immunotherapy | 86 |
| | | Mn-LDH | breast cancer; colorectal carcinoma | immunotherapy | 228 |
| | | Mn@BSA NC and Mn@BSA NW | melanoma | immunotherapy | 229 |
| | | PLHM | glioblastoma | immunotherapy | 230 |
| | | CM NPs | melanoma | immunotherapy | 201 |
| MOFs | serve as drug carriers that deliver STING agonists, dsDNA mimetics, or immune modulators directly to the cytosol, activating the cGAS-STING pathway | SR@PMOF NPs | breast cancer | photothermal therapy; immunotherapy | 65 |
| | enhance ROS production and DNA damage through incorporated metal ions such as $Mn^{2+}$, $Zn^{2+}$, and $Cu^{2+}$, further amplifying STING activation | TZM | osteosarcoma | radiation therapy; immunotherapy | 116 |
| | stimulate immunogenic cell death through PDT/RDT, releasing DAMPs and enhancing immune cell recruitment | RBC@Mn-MOF/PPI | breast cancer | immunotherapy | 66 |
| | | MOF-CpG-DMXAA | hepatoma | immunotherapy | 231 |
| | | cGAMP/MOL | colorectal carcinoma | radiation therapy; immunotherapy | 124 |
| | | TPP@CoTCPP | bone metastatic tumors | sonodynamic-ionic immunotherapy | 130 |
| | | DHA@MIL-101 | lung cancer | immunotherapy and ferroptosis-targeted therapy | 154 |



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**Table 1. continued**

| metal | mechanism | nanodelivery platform | tumor type | therapy | reference |
|---|---|---|---|---|---|
| | | PMZH | breast cancer | immunotherapy | 203 |
| $Zn^{2+}$ | enhances cGAS phase separation and enzymatic activity, accelerating cGAMP production | ZnS@BSA | hepatoma | immunotherapy | 96 |
| | induces ROS generation, promoting tumor cell death and forming a positive feedback loop with the STING pathway | ZCCG | melanoma | immunotherapy | 97 |
| | restores cGAS-STING functionality by promoting degradation of mutant p53, which suppresses the pathway | Zn-LDH | melanoma | immunomodulating adjuvant | 232 |
| | | zinc-phenolic nanocapsule (RMP@Cap) | breast cancer | pyroptosis-targeted therapy and immunotherapy | 233 |
| | | ZIF-8@$MnO_2$ | breast cancer | immunotherapy | 126 |
| | | $ZnFe_2O_4$-PTX@CCM | melanoma | chemotherapy; immunotherapy | 234 |
| | | zinc−Mn−CDN particle (ZMCP) | melanoma; colorectal carcinoma | immunotherapy | 235 |
| $Cu^{2+}$ | induces mitochondrial metabolic disruption and cuproptosis, releasing mtDNA to activate the cGAS-STING pathway | PEG-polyphenol-chlorin e6 | breast cancer | immunotherapy | 99 |
| | increases oxidative stress, leading to ICD and tumor antigen release | Gel@M/$CuO_2$/DOX/STING | breast cancer | CDT; immunotherapy | 236 |
| | | Cu/ZIF-8@U-104@siNFS1-HA (ZCUNH) | osteosarcoma | ferroptosis-targeted therapy and immunotherapy | 237 |
| $Fe^{3+}$ | generates ROS through Fenton reactions, inducing ICD and exposing dsDNA to activate the STING pathway | MF@SOR | hepatocellular carcinoma | immunotherapy | 98 |
| | inhibits autophagy defense mechanisms in tumor cells, enhancing immune cell infiltration | OMV/SaFeFA | colorectal carcinoma | ferroptosis-targeted therapy and immunotherapy | 238 |
| $Ca^{2+}$ | triggers pyroptosis in tumor cells, releasing dsDNA and inflammatory cytokines, thereby activating the STING pathway | MCSP | cervical cancer | pyroptosis-targeted therapy and immunotherapy | 239 |
| $Hf^{4+}$ | induces nuclear DNA damage during radiotherapy, releasing DNA into the cytoplasm to activate the STING pathway | Hf-nIm@PEG (HNP) | colorectal carcinoma | radiation therapy; immunotherapy | 104 |
| $HfO^{2-}$ | enhances cGAS sensitivity to dsDNA through radiosensitization. | $HfO_2$@$MnO_2$-PAH/PAA/HA(HfMnH) | colorectal carcinoma | radiation therapy; immunotherapy | 149 |
| Au | induces mitochondrial damage, generates ROS, releases mtDNA, and triggers ICD, activating the cGAS-STING pathway | NHC-gold(I)-alkyne-GA-TPP complexes | hepatoma | chemoimmunotherapy | 240 |
| ruthenium | induces DNA damage, which results in the release of cytosolic dsDNA and subsequent activation of the cGAS-STING pathway | Ru1 NPs | breast cancer | photodynamic therapy; immunotherapy | 241 |
| | generates ROS under PDT conditions, enhancing ICD and amplifying the tumor antigen presentation process | | | | |
| platinum | induces mitochondrial or nuclear DNA damage, causing cytoplasmic accumulation of dsDNA and activating the STING pathway | NP2 | colorectal carcinoma | chemotherapy; immunotherapy | 109 |
| | | PtII complexes (Pt1/Pt2) | cervical cancer; breast cancer; lung cancer | immunotherapy | 108 |
| | | glutathione-responsive nanoparticle (NP2) | bladder cancer | chemotherapy; immunotherapy | 242 |
| | | $NP^{PDT}$-56MESS | melanoma | chemotherapy; immunotherapy | 243 |
| lanthanide | utilizes unique optical and magnetic properties for guided drug delivery while enhancing type I IFN responses | Ln-GAMP-NPs | melanoma | immunotherapy | 107 |
| | | NaGdF4:Nd@NaLuF4@PEG-polyphenol/Mn (DSPM) | breast cancer | radiation therapy; immunotherapy | 244 |
| $MoO_4^{2-}$ | depletes tumor GSH and inhibits GPX4, triggering lipid peroxidation and ferroptosis to activate the STING pathway | MMP NDs | colorectal carcinoma; breast cancer; melanoma | immunotherapy | 105 |
| | | $MoO_X$-PEG NPs | colorectal carcinoma; breast cancer | immunotherapy | 189 |



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The development of nanoparticle-based delivery systems not only significantly prolongs the retention time of $Mn^{2+}$ within the tumor microenvironment but also enhances its local bioavailability, thereby improving antitumor therapeutic efficacy.[75,76] Pang's team developed a manganese-phenolic network platform that leverages $Mn^{2+}$ to upregulate STING-associated proteins, thereby promoting antitumor immune responses at the tumor site.[77] pH-sensitive release technology uses the acidic tumor microenvironment for targeted drug release, enhancing efficacy and reducing systemic toxicity.[78−80] $MnO_2$-based nanovaccines dissociate in low pH, releasing $Mn^{2+}$ to activate the STING pathway and improve tumor targeting through antigen-mimicking properties.[81] Manganese-based nanoparticles can also serve as MRI contrast agents, enabling imaging-guided tumor therapy and highlighting the potential of manganese-based nanoplatforms in immunotherapy applications.[81,82] Membrane biomimetic technology further enhances the tumor accumulation of manganese-based nanomaterials, improving targeting specificity and in vivo stability.[83] This approach enables more precise MRI tumor labeling and monitoring, advancing integrated diagnosis and therapy. Moreover, $Mn^{3+}$-doped nanosystems exhibit exceptional functionality in photothermal ablation. By inducing dsDNA leakage in tumor cells through localized heating, they activate the cGAS-STING pathway, while $Mn^{3+}$ is converted to $Mn^{2+}$, amplifying the STING pathway activation. This transformation not only strengthens immune responses but also elevates the local temperature within the tumor microenvironment, facilitating tumor cell eradication.[84] In addition, the thermosensitive micelle system optimizes the synergy between thermal ablation and $Mn^{2+}$. Through temperature-sensitive release of $Mn^{2+}$, it not only induces dsDNA leakage via thermal ablation but also utilizes $Mn^{2+}$-mediated chemodynamic therapy (CDT) to generate hydroxyl radicals (·OH), directly killing tumor cells.[85] Meanwhile, thermosensitively released $Mn^{2+}$ further activates the cGAS-STING pathway, promoting the production of type I interferons such as IFN-$\beta$, enhancing immune infiltration at the tumor site.[86]

Notably, manganese-based nanomaterials also exhibit unique functionalities in modulating the tumor microenvironment. Specifically, $Mn^{2+}$ can also modulate the tumor microenvironment by polarizing tumor-associated macrophages (TAMs) from an immunosuppressive M2 phenotype to a pro-inflammatory M1 phenotype, further enhancing antigen presentation and increasing cytotoxic T lymphocyte (CTL) infiltration into tumors.[87] Additionally, manganese-based nanomaterials can generate oxygen in the acidic tumor environment, alleviating tumor hypoxia and reducing the expression of hypoxia-inducible factor HIF-1$\alpha$ and vascular endothelial growth factor (VEGF), thereby further disrupting the immunosuppressive characteristics of the tumor microenvironment.[88] Furthermore, $Mn^{2+}$ activates TBK1 and p65 through a STING-independent pathway, inducing the NF-$\kappa$B signaling cascade and increasing the production of type I interferons.[74] Not only does it activate $CD8^+$ T cells and natural killer (NK) cells, but it also promotes macrophage maturation and antigen presentation, thereby significantly enhancing immune recognition and clearance of tumors.[89] Meanwhile, manganese-based nanomaterials effectively promote the release of inflammatory cytokines, such as TNF-$\alpha$ and IL-6, which not only enhance the local immune response but also activate STING-independent pathways to further boost immune clearance efficiency.[90]

Manganese-based nanoplatform immunotherapy shows great potential for clinical application; however, there is a notable lack of research on its safety. Thorough investigation of its metabolic pathways and potential toxicity in vivo is crucial for broader use. Given the role of $Mn^{2+}$ in sensitizing cGAMP and directly activating cGAS, there are significant opportunities to design innovative combination therapies to improve therapeutic outcomes. Additionally, whether $Mn^{2+}$ possesses other immunoregulatory functions within the cGAS-STING pathway remains an important area for further research, potentially opening new avenues for advancing immunotherapy strategies.

*3.1.2. Other Metal Ion Platforms.* Beyond manganese, many other metal ions also play indispensable roles in various cellular processes. For example, $Zn^{2+}$ supports cell proliferation and differentiation via enzyme activation;[91] $Cu^{2+}$ aids energy metabolism and antioxidant defense,[92] and molybdenum cofactor (Moco) acts as a critical cofactor in sulfur and nitrogen metabolism.[93] Additionally, rare metals like lanthanides possess distinctive optical, magnetic, and catalytic properties, making them ideal for imaging and targeted drug delivery.[94,95] These unique characteristics of metal ions highlight their versatility and potential in developing innovative platforms for cancer treatment.

$Zn^{2+}$-containing nanoclusters have been developed for immunotherapy, showing significant bioactivity by promoting cGAS phase separation in the presence of cytoplasmic DNA, enhancing cGAS enzymatic activity, and accelerating cGAMP production to activate the STING pathway.[96] This process induces ROS generation, leading to tumor cell death and damaged DNA release, creating a positive feedback loop within the cGAS-STING signaling pathway.[97] $Fe^{3+}$-based nanovaccines induce immunogenic cell death (ICD), releasing immunogenic factors that promote dendritic cell maturation and dsDNA exposure, thus activating the STING pathway and strengthening antitumor immune responses.[98] $Cu^{2+}$-based nanomaterials induce cuproptosis by disrupting mitochondrial metabolism, releasing mtDNA, and activating the STING pathway. Yu designed a nanoinitiator coloaded with $Cu^{2+}$ and a mitochondrial autophagy inhibitor, where excess $Cu^{2+}$ triggers cuproptosis and mtDNA release, enhancing antitumor immunity through the mtDNA-cGAS-STING axis.[99] Mitochondria, as metabolically active organelles, can accumulate misfolded proteins, leading to proteotoxic stress that activates innate immunity through inflammatory signaling pathways.[100,101] $Cu^{2+}$-loaded nanomaterials induce DLAT aggregation, suppress mitochondrial respiration, and cause oxidative damage, releasing mtDNA that activates the STING pathway.[102] Copper-induced cuproptosis not only results in mitochondrial damage but also upregulates PD-L1 expression on the surface of tumor cells. When combined with anti-PD-L1 therapy, this approach can convert immune "cold tumors" into "hot tumors", thereby enhancing the efficacy of immunotherapy.[103] $Hf^{4+}$ nanomaterials also activate the STING pathway, promoting dendritic cell maturation and cytokine production, including type I interferons.[104]

Certain metal anions have shown specific immunoregulatory potential in activating the STING pathway, broadening the use of metal ions in tumor immunotherapy. Lei et al. found that $Mn^{2+}$ and $MoO_4^{2-}$-based nanomaterials activate the cGAS-STING pathway by depleting glutathione in tumors and inhibiting GPX4, leading to ferroptosis and dendritic cell maturation, which in turn activates $CD8^+$ T cells. These T cells secrete interferon-$\gamma$ (IFN-$\gamma$), further promoting lipid perox-


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idation-mediated ferroptosis and establishing a therapeutic "cycle".[105] Lanthanide-based nanomaterials leverage their unique optical and magnetic properties to enable precise imaging and targeted drug delivery in tumor immunotherapy.[106] By activating the STING pathway, they enhance type I interferon responses, further promoting dendritic cell maturation and antigen presentation, effectively stimulating $CD8^+$ T cell and CTL infiltration, thus optimizing antitumor immune responses.[107] Platinum-based nanomaterials activate the STING pathway indirectly by inducing mitochondrial or nuclear DNA damage,[108] leading to the accumulation of cytoplasmic double-stranded DNA and activation of the cGAS-STING signaling pathway, triggering a potent antitumor immune response.[109,110] Their application in combined chemotherapy and photodynamic therapy not only strengthens immune responses but also offers multimodal treatment potential, making them suitable for more precise immunotherapy strategies.[111,112]

**3.2. Metal−Organic Frameworks (MOFs).** MOFs are composed of metal ions or metal clusters coordinated with organic ligands, and their structure can be precisely tuned to meet specific needs.[113] As a type of porous material, MOFs offer significant advantages, such as high surface area, large pore volume, easy synthesis, good thermal stability, and adjustable framework sizes.[114] This allows MOFs to load and release a wide variety of drugs.[115] Additionally, MOFs can activate the STING signaling pathway, further enhancing tumor immunotherapy by triggering the innate immune response. Therefore, they are well-suited to serve as drug carriers in chemotherapy, immunotherapy, and photodynamic therapy (PDT).[116]

The immunosuppressive tumor microenvironment often hinders the therapeutic efficacy of cancer immunotherapy.[117] Zhou et al. proposed polymeric MOF nanoparticles loaded with the STING agonist as well as meso-tetra(carboxyphenyl)-porphyrin (TCPP).[65] TCPP is a porphyrin-based photosensitizer that can coordinate with metal ions to form an MOF structure without requiring additional modifications.[118] Upon light irradiation, TCPP generates singlet oxygen, inducing apoptosis and releasing fragmented DNA and tumor-associated antigens.[119] The released STING agonist synergizes with PDT to activate the STING pathway, reversing the immunosuppressive tumor microenvironment and enhancing antitumor immunity.[120] In addition to light irradiation, TCPP within the MOF structure can also be indirectly activated through an energy transfer mechanism, particularly facilitated by high atomic number elements like Ta and Zr.[116] These elements efficiently capture X-ray energy and transfer it nonradiatively to TCPP, allowing its activation without external light. This approach leverages the penetrating power of X-rays to achieve effective treatment of deeper tumors and is referred to as radiodynamic therapy (RDT).[121] Through the activation of the cGAS-STING pathway, RDT induces immunogenic cell death, promotes dendritic cell maturation, and upregulates the expression of PD-L1, ultimately triggering a robust antitumor immune response.[122,123] Additionally, certain MOFs can independently achieve immunomodulation without ligand modification. Luo et al. developed a 2D nanoplatform with cGAMP that maximizes surface area for enhanced radiosensitization. Under X-ray irradiation, it induces cancer cell death through RDT and activates the STING pathway, promoting immunostimulatory factor release and immune cell infiltration, effectively reversing the immunosuppressive tumor microenvironment.[124]

In over 50% of human cancers, mutant p53 (mutp53) is a prevalent genetic alteration that suppresses the cGAS-STING pathway by interacting with TANK-binding kinase 1 (TBK1). This interaction prevents the formation of a trimeric complex between TBK1, STING, and IRF3, which is essential for IRF3 activation. Consequently, this mechanism reduces the sensitivity of cGAS to cytosolic DNA, thereby inhibiting innate immune activation.[125] $Zn^{2+}$-based nMOFs restore cGAS-STING pathway function by promoting the ubiquitin-mediated degradation of mutp53.[126] Additionally, they release $Zn^{2+}$ in the acidic tumor microenvironment, triggering oxidative stress, regulating tumor metabolism, and enhancing immune activity.[127] Other types of nMOFs have shown efficacy in enhancing immune function: $Fe^{2+}/Fe^{3+}$-based nMOFs produce ROS through Fenton reactions under acidic conditions, inhibiting tumor cell autophagic defenses and promoting T cell infiltration, thereby enhancing the effectiveness of immunotherapy.[128] $Mn^{2+}$-based MOFs increase the sensitivity of cGAS to cytosolic dsDNA and generate ROS, which strengthens immune cell recruitment in the tumor microenvironment and further enhances antitumor immunity.[129] Additionally, Co-based MOFs enhance radiotherapy sensitivity via cGAMP-dependent STING activation, providing sustained ROS production to promote tumor clearance.[130] Further studies indicate that Ti-based MOFs, under near-infrared light irradiation, leverage their photocatalytic properties to produce ROS, combining photothermal and photodynamic therapy to boost immune recognition and attack on tumors.[131] Cu-based MOFs produce ·OH via Fenton-like reactions and, when combined with immune checkpoint blockade, increase tumor cell sensitivity to photodynamic therapy (PDT), further enhancing overall immune response.[132]

The complex tumor microenvironment may affect the delivery efficiency, targeting specificity, and stability of MOFs in drug delivery, thereby limiting their clinical effectiveness.[133] Surface functionalization can significantly enhance the targeting specificity and biocompatibility of MOFs. For example, modifying the MOF surface with targeting molecules, such as folic acid, enables active targeting of cancer cells and responsive drug release, thereby improving therapeutic efficacy.[134] Additionally, by tuning the particle size and surface chemistry of MOFs, stability and drug-loading control in vivo can be further optimized, achieving more precise treatment outcomes.[135] MOF materials show great potential in optimizing drug delivery, enhancing targeting specificity, and modulating the STING pathway. Through rational surface functionalization and structural tuning, MOFs are expected to achieve more efficient drug delivery and immune activation in cancer treatment, offering innovative, multifunctional solutions for antitumor therapies.

Metal-based nanomaterials influence the "fate" of cancer cells by modulating cellular signaling pathways, inducing programmed cell death processes such as ferroptosis, cuproptosis, or immunogenic cell death, thereby enhancing antitumor immune responses. Despite their potential in remodeling the tumor microenvironment and overcoming immune suppression, clinical application faces challenges related to biocompatibility, toxicity, targeted delivery efficiency, and stability in vivo.[136] Structural optimization and formulation improvements are needed to enhance therapeutic efficacy and reduce side effects.


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## 4. METAL-BASED PLATFORMS INDUCE SYNERGISTIC THERAPEUTIC STRATEGIES FOR ENHANCED IMMUNOTHERAPY

The application of metal-based nanoplatforms in tumor combination therapy represents a significant breakthrough in the current cancer treatment strategies. By integration of traditional therapies such as immunotherapy, chemotherapy, and radiotherapy, these platforms achieve multifaceted antitumor effects. Metal ions not only directly mediate oxidative stress responses in tumor cells, generating ROS to kill cancer cells, but also enhance immune cell recognition of tumors by activating the cGAS-STING signaling pathway.[137,138] MOFs, with their highly diverse structures, serve as ideal drug delivery vehicles. They not only facilitate the loading of immune modulators such as STING agonists but also enable the precise control of drug release, thereby enhancing the accumulation of therapeutic agents in tumor regions and minimizing side effects on normal tissues.[139,140] This combination therapy demonstrates significant synergistic effects while effectively overcoming resistance issues that may arise with single therapies.[141,142] Metal-based nanoplatforms hold great promise for application in tumor combination therapy, with the potential to play a crucial role in precision medicine and personalized treatment in the future.

**4.1. Radiation Therapy and Immunotherapy.** In radiotherapy (RT), radiation-induced DNA damage that leaks into the cytoplasm can trigger the host's antitumor immune response.[143] However, due to the limited capacity of cGAS to detect cytoplasmic DNA, the response rate is suboptimal, and cytoplasmic DNA may be neutralized by host DNases.[144] Metal ions, such as $Mn^{2+}$ and $Zn^{2+}$, can significantly enhance the activation of the cGAS-STING pathway. Corelease of $Mn^{2+}$ promotes the accumulation of cytoplasmic DNA, markedly strengthening the antitumor immune response induced by radiotherapy.[75] Additionally, $Mn^{2+}$ alleviates hypoxia in the tumor microenvironment, increases reactive oxygen species (ROS) production, and activates the cGAMP-STING axis, achieving a synergistic antitumor effect with radiotherapy.[145] High atomic number metal nanomaterials, such as yttrium and tantalum, offer significant advantages in radiosensitization, enhancing antitumor efficacy by increasing local X-ray energy absorption.[146] These materials are ideal for radiotherapy due to their stability under high-dose radiation and their ability to increase ROS production within cells, thereby enhancing cGAS-STING signaling.[147] Another emerging material is zirconium-based compounds, such as hafnium dioxide ($HfO_2$), which are efficient in activating the cGAS-STING pathway by generating cytoplasmic dsDNA while maintaining biocompatibility and low toxicity.[148] $HfO_2$ nanoparticles, as radiosensitizers, not only generate more cytoplasmic DNA but also trigger the cGAS-STING pathway, thereby modulating the tumor microenvironment and enhancing antitumor immunity.[149] The introduction of these metal nanomaterials helps to improve the tumor microenvironment by increasing cytoplasmic DNA accumulation and immune cell infiltration, achieving antitumor effects through both radiotherapy and immunotherapy.

**4.2. Chemotherapy and Immunotherapy.** In cancer treatment, the combination of chemotherapy and immunotherapy can significantly enhance the therapeutic efficacy. Metal-based nanomaterials, in particular, have shown potential to boost tumor immune responses by activating the cGAS-STING pathway.[150] In various tumor models, metal-based nanoparticles, such as manganese, iron, and copper, not only enhance the efficacy of chemotherapeutic drugs but also promote immunogenic cell death by upregulating the expression of interferons and pro-inflammatory cytokines.[137] Additionally, these metal-based materials can modulate the tumor microenvironment, inhibiting tumor growth and metastasis through oxidative stress and the release of pro-inflammatory cytokines.[151,152] Nanoparticles coloaded with manganese ions ($Mn^{2+}$) and chemotherapeutic drugs enable tumor microenvironment-responsive drug release, enhancing targeted drug distribution, achieving higher drug accumulation at the tumor site, and improving therapeutic efficacy while reducing side effects.[153] The chemotherapeutic agents enhance antitumor effects by inducing DNA damage within the tumor, while $Mn^{2+}$ boosts immune responses by activating the cGAS-STING pathway in response to the damaged DNA.[90] MOFs, with their high surface area and tunable properties, serve as excellent drug delivery platforms, capable of transporting cGAS-STING agonists or chemotherapeutic drugs to tumor sites to further activate the immune system.[98] Other metal-based nanomaterials also demonstrate unique advantages in combined chemotherapy and immunotherapy. Iron-based nanomaterials effectively regulate the tumor microenvironment (TME) by promoting reactive oxygen species (ROS) generation, which significantly activates the STING signaling pathway and boosts antitumor immunity.[154] Calcium-based nanomaterials improve the mildly acidic tumor microenvironment by depleting lactate in the tumor region, thereby modulating the immunosuppressive microenvironment within tumors and enhancing the responsiveness to other immunotherapeutic approaches.[155,156] These metal-based nanomaterials work synergistically through multiple mechanisms in tumor immunotherapy, not only directly destroying tumor cells but also inhibiting tumor recurrence and metastasis through immune activation.[157] Although their biocompatibility and targeting still require further optimization, numerous studies have demonstrated their significant effectiveness in combined chemotherapy and immunotherapy.

**4.3. Chemical Dynamic Therapy and Immunotherapy.** Chemodynamic therapy (CDT) is a treatment based on the Fenton reaction or similar processes, catalyzing $H_2O_2$ to produce highly reactive hydroxyl radicals (·OH) that kill tumor cells. By leveraging the acidic conditions and high $H_2O_2$ concentration in the tumor microenvironment, CDT can specifically generate ROS at the tumor site, inducing oxidative stress and achieving targeted therapy.[158−160] Metal ions such as $Fe^{3+}$, $Mn^{2+}$, and $Cu^{2+}$ play a crucial role in catalyzing the decomposition of $H_2O_2$, thereby enhancing the efficiency of the Fenton reaction and boosting the antitumor efficacy of CDT.[161−163] A manganese-based multifunctional nanoplatform leverages a cascade-like Fenton reaction to directly destroy tumor cells, while $Mn^{2+}$ activates the STING pathway, significantly inducing the production of IFNs and pro-inflammatory cytokines, triggering innate immune responses and promoting immunogenic cell death in tumor cells.[164] Additionally, the incorporation of nanocarriers, such as metal−organic frameworks (MOFs), further optimizes the efficacy of CDT. MOFs can load metal ions to enhance ROS generation efficiency and can be surface-functionalized for targeted delivery, thereby reducing side effects on normal tissues.[165] Combining MOFs with copper or manganese produces a dual-pathway STING activation effect, effectively enhancing the


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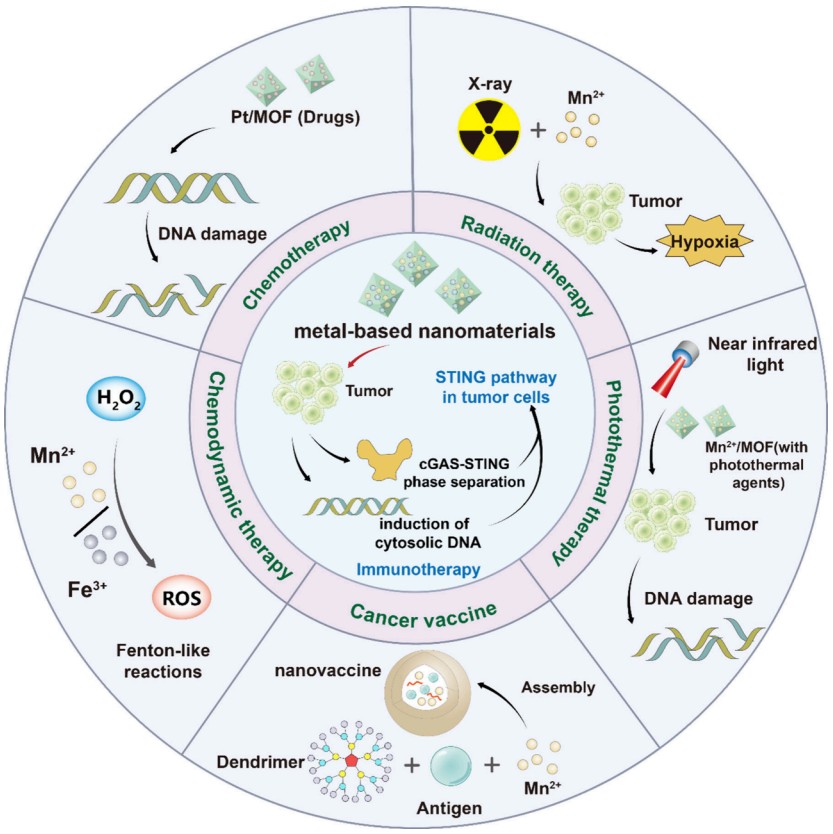


**Figure 3.** Metal-based platforms induce synergistic therapeutic strategies for enhanced immunotherapy. In addition to activating tumor immunotherapy triggered by the cGAS-STING pathway, metal nanomaterials can also be combined with chemotherapy, radiotherapy, chemodynamic therapy, and photothermal therapy to enhance the therapeutic effects on tumors. Moreover, cancer vaccines synthesized from metal nanomaterials can be used to enhance tumor immunity in some "cold tumors" with low immunogenicity.

efficacy of chemodynamic therapy. This approach significantly improves overall therapeutic efficiency, offering an optimized treatment strategy for solid tumors, particularly those with low oxidative stress levels.[166] Chemodynamic therapy (CDT) combined with multifunctional nanocarriers and immune pathway activation not only enhances the oxidative stress-mediated cytotoxic effects within the tumor microenvironment but also achieves long-term suppression of both primary and metastatic tumors through immune activation and memory effects.

**4.4. Photothermal Therapy and Immunotherapy.** Photothermal therapy (PTT) leverages the photothermal conversion effect of nanomaterials under near-infrared (NIR) irradiation to locally heat tumor tissues, thereby inducing apoptosis or necrosis in tumor cells. This process releases tumor-associated antigens, which subsequently activate an antitumor immune response.[167−169] Metal-based nanomaterials, with their excellent photothermal conversion efficiency and immune-activating capabilities, demonstrate unique advantages in combination therapies.[170] Gold nanoparticles exhibit remarkable photothermal effects under NIR laser irradiation. By increasing the local temperature, they not only directly induce apoptosis in tumor cells but also promote immunogenic cell death, further stimulating an immune response.[171] Similarly, manganese-integrated Prussian blue nanoparticles, with high photothermal conversion efficiency, damage cells through photothermal stimulation while simultaneously leveraging the manganese ions to activate the STING signaling pathway.[172] This activation induces a specific immune response and enhances the immune cell infiltration at the tumor site. The combination of this immune activation process with photothermal effects enables more durable antitumor outcomes and strengthens the synergy with immune checkpoint blockade (ICB) therapies.[173,174] Furthermore, substituting iron in Prussian blue with metal elements such as $Zn^{2+}$, $Co^{3+}$, $Ni^{3+}$, and $Gd^{2+}$ yields Prussian blue analogues suitable for magnetic resonance imaging, energy storage, and chemical catalysis.[175] These analogues show promising potential in photothermal therapy and other combination treatment approaches. Furthermore, photothermal therapy can be combined with other treatment modalities. Tungsten oxide ($WO_3$) and bismuth-based nanomaterials not only efficiently generate heat under NIR light to directly kill tumor cells but also regulate redox activity to produce reactive oxygen species (ROS) and other reactive molecules, supporting synergistic anticancer effects with photodynamic therapy (PDT) and CDT.[176,177] In certain studies, the localized heating effect of photothermal therapy enhances drug delivery by increasing vascular permeability, thereby improving the efficacy of immunotherapy.[178−180] Photothermal therapy using metal-based nanomaterials holds substantial potential for activating the STING pathway and modulating the tumor immune microenvironment, demonstrating exceptional promise, especially in combination with immunotherapy. Future research should focus on optimizing the photothermal conversion efficiency and biocompatibility of these nanomaterials to reduce potential toxicity and enhance the feasibility for clinical applications.


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**4.5. Cancer Vaccines.** Cancer vaccines have garnered significant attention in tumor immunotherapy for their ability to induce tumor-specific immune responses.[181] Nanovaccines significantly enhance the immune efficacy of vaccines by improving stability, optimizing antigen recognition, and delivering with precision.[182] Nanostructures offer significant advantages in enhancing antigen immunogenicity. By integrating antigens and adjuvants onto nanostructures, the specificity and efficacy of antigen delivery are markedly improved, further optimizing dendritic cell activation.[183] This approach is crucial for inducing long-lasting antitumor immune responses. Metal-based nanovaccines demonstrate significant advantages in antigen stability and controlled release. Their high porosity and surface modification capabilities enhance antigen recognition and enable targeted delivery to immune cells.[184,185] In a manganese-containing metal nanovaccine, manganese ions not only facilitate antigen loading and promote its release into the cytoplasm but also act as an immune adjuvant to activate the STING pathway, further enhancing the immune response. This dual functionality enables the vaccine to exhibit strong efficacy in antitumor activity and suppression of tumor metastasis.[186] Metal ions with redox-regulating functions, such as $Mn^{2+}$ and $Fe^{3+}$, not only activate the STING signaling pathway but also induce pyroptosis in tumor cells, thereby releasing additional immunogenic signals.[98] Metal-based nanovaccines incorporating adjuvants like iron and zinc optimize antigen presentation and enhance the durability of antitumor immunity through these mechanisms. Metal-based nanovaccines, with their high porosity, flexible surface modification, and stable controlled antigen release, offer a novel strategy for achieving more efficient and targeted tumor immunotherapy. They hold great promise as a key platform for the design of next-generation vaccines.

**4.6. Other Metal-Based Materials.** Metal materials play a crucial role in enzyme-catalyzed therapy. There is a novel copper-doped polypyrrole enzyme (CuP) with triple enzyme-like activities, mimicking catalase (CAT), glutathione peroxidase (GPx), and peroxidase (POD).[187] CuP alleviates tumor hypoxia and repolarizes macrophages from M2 to M1, enhancing immunity. PEG-modified CuP (CuPP) amplifies these effects under heat and, combined with αPD-L1, achieves near-complete tumor suppression. In recent years, beyond copper-based materials, other metal-based materials have also demonstrated significant potential in nanozyme-catalyzed therapy. Iron oxide-based nanoparticles, due to their peroxidase-like activity and Fenton reaction capabilities, can generate a large amount of reactive oxygen species (ROS) within the tumor microenvironment. This directly induces tumor cell death and enhances immune cell infiltration.[188] Additionally, molybdenum-based nanozymes possess unique sulfur−nitrogen metabolic functions and can activate the STING pathway through oxidation reactions under specific conditions, thereby promoting antitumor immune responses.[189]

In summary, metal-based platforms can induce various synergistic therapeutic strategies to further enhance immune responses. These platforms can be combined with other treatment strategies such as chemotherapy, chemodynamic therapy (CDT), and photothermal therapy (PTT) (Figure 3). For "cold tumors" with low immunogenicity, the efficacy of single-agent immunotherapy may be significantly weaker compared to "hot tumors." Therefore, combination therapies based on metal platforms are more effective than monotherapies in reducing drug-related toxicity, preventing drug resistance, and enhancing antitumor efficacy.[190,191]

## 5. ADVANTAGES OF METAL NANOMATERIAL-MEDIATED TUMOR IMMUNOTHERAPY

Due to the immunosuppressive nature of the tumor microenvironment, the efficacy of single therapeutic approaches is often limited.[192] Metal nanomaterials, with their high targeting capability and diverse bioactivity, exhibit unique advantages in multimodal cancer therapy. First, nanomaterials exhibit excellent targeting ability in drug delivery, primarily due to the enhanced permeability and retention (EPR) effect.[193,194] This effect, attributed to the high permeability and poor lymphatic drainage of the tumor vasculature, allows passive accumulation of nanomaterials within the tumor stroma.[195] The EPR effect can also further promote the recruitment of immune cells by inducing oxidative stress and increasing vascular permeability.[196] Additionally, by controlling the particle size and shape of metal nanomaterials, their distribution and cellular uptake at tumor sites can be optimized, thus improving the synergy of immunotherapy.[197] A Cu-MOF is engineered with spiked structures to enhance tumor penetration and distribution, thereby synergistically activating copper-induced cell death and the STING pathway, ultimately improving the efficacy of tumor immune responses.[198] Alongside that, metal nanoparticles can be further functionalized with antibodies, liposomes, transferrin, folic acid, and carbohydrates, enhancing their targeting specificity within tumor cells.[199] For instance, oxygen-carrying platinum-loaded nanovesicles effectively suppressed postoperative recurrence of triple-negative breast cancer after targeting the tumor site.[200] Second, metal nanomaterials can modulate the tumor immune microenvironment by activating the STING pathway.[154,201−203] Activation of this pathway converts immune-resistant tumors into immune-active ones, significantly improving the efficacy of immunotherapy. $Mn^{2+}$ promotes dendritic cell maturation and enhances immune memory, effectively inhibiting tumor recurrence.[202] The combination of COX-2 inhibitors and zinc-based nanomaterials activates the STING pathway, enhancing the efficacy of combination therapies.[204] Manganese−zinc bimetallic-regulated nanomaterials significantly enhance tumor immune responses and improve therapeutic outcomes by augmenting STING pathway activation and synergizing with PD-L1 blockade therapy.[126] Finally, metal nanomaterials can serve as drug carriers, inducers of ICD, and immunomodulators, integrating various therapeutic modalities to enhance antitumor efficacy.[205] By surface-modifying nanomaterials, multiple antigens can be copresented to further enhance the specificity of T cell responses to tumor antigens.[206]

## 6. SAFETY OF METAL NANOMATERIALS

The nonspecific distribution, excessive accumulation, and neurotoxicity of metal ions within the body present significant challenges that may limit their clinical translation.[207,208] The toxicity mechanisms of metal nanoparticles vary depending on the type of particles. For example, zinc oxide nanoparticles can induce oxidative stress in certain cellular environments, leading to apoptosis, whereas iron oxide nanoparticles exhibit a lower level of oxidative stress, providing better biocompatibility.[209] Once inside the body, metal nanoparticles (NPs) tend to


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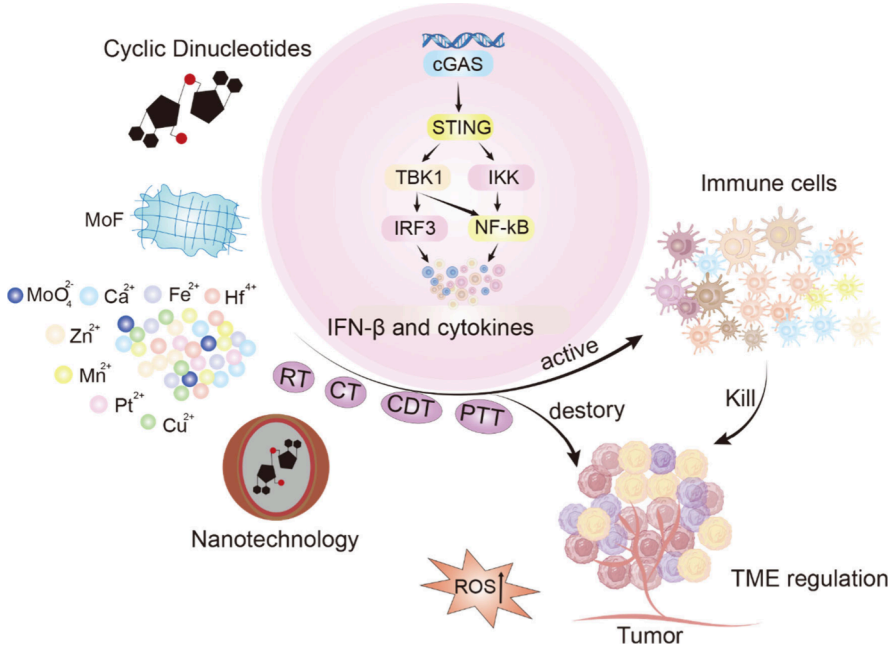


**Figure 4.** Applications of metal-based nanomaterials in tumor immunotherapy. Various metal-based nanomaterials activate the cGAS-STING signaling pathway to regulate the tumor immune microenvironment and induce tumor cell death. They also enhance immune activation and therapeutic efficacy through mechanisms such as oxidative stress, DNA damage, and boosting immune cell activity. These nanomaterials can be combined with radiotherapy, chemotherapy, and other therapeutic modalities for synergistic cancer treatment.

naturally accumulate in the liver. While this characteristic may be beneficial for certain hepatic diseases, it also has the potential to exacerbate other conditions.[210] The toxicity and safety of metal nanomaterials are influenced by multiple factors, including synthesis methods, in vivo distribution and accumulation patterns, metabolic pathways, and excretion mechanisms.[211] While some metal nanomaterials exhibit potential advantages in activating immune responses, their accumulation within the immune system can lead to chronic inflammation and immunotoxic effects.[212,213] Currently, studies have integrated machine learning methods with high-throughput in vitro biological assays to develop models predicting the toxicity of metal oxide nanoparticles (MeONPs) in immune cells.[214] This approach provides a novel perspective for investigating the safety of metal nanomaterials. Additionally, inadequate targeting can cause nanoparticles to accumulate in nontarget tissues, increasing toxicity risks. Surface modification and coating techniques for metal nanomaterials enhance biocompatibility and, to some extent, improve targeting specificity. Surface modification of metal nanomaterials with polymers or biomolecules has been shown to effectively reduce toxicity while enhancing targeting specificity.[215] With advancements in green synthesis technologies, metal nanomaterials with favorable biocompatibility and safety profiles are now attainable,[216] and some metal nanomaterials have shown clinical potential.[217] Future research should focus on developing more precise, low-toxicity metal nanomaterials, particularly by optimizing their physicochemical properties, improving targeted delivery systems, and refining release mechanisms to minimize systemic toxicity and immunotoxicity to the greatest extent possible.

## 7. CONCLUSIONS AND FUTURE PROSPECTS

The activation of the STING pathway produces type I IFNs, which initiate an antitumor immune response and are considered to be a potential breakthrough in cancer immunotherapy. However, under certain conditions, activation of the intracellular cGAS-STING signaling pathway may inhibit the proliferation of NK cells, thereby weakening their antitumor effects. Therefore, the rational application of STING agonists is essential to enhancing the effectiveness of cancer immunotherapy. Current commercial agonists have several limitations, including rapid clearance, susceptibility to degradation by PDE enzymes, and a dependence on binding to cell membrane receptors.[218,219] Developing appropriate delivery systems may offer an effective strategy to overcome these challenges.

Metal-based nanomaterials, due to their multifaceted mechanisms, drug delivery capabilities, and ability to penetrate biological membranes, represent an ideal platform for STING pathway activation. Unlike other studies, this review focuses on the specific mechanisms by which metal-based nanomaterials activate the STING pathway, emphasizing their unique advantages in immunotherapy. Additionally, it explores the potential for combining STING pathway activation with other therapies, presenting a comprehensive view of a multimodal approach that fully leverages the antitumor potential of the cGAS-STING pathway (Figure 4).

Although metal-based nanomaterials hold great promise for applications in antitumor therapy, they face numerous challenges. Despite their effectiveness, the chronic toxicity resulting from nonspecific accumulation of metal-based nanomaterials cannot be overlooked. Additionally, their clearance efficiency and long-term safety in vivo remain critical concerns. The heterogeneity of the TME and the limited vascular permeability of many nanomaterials also pose significant obstacles to precise tumor targeting. To address these issues, surface modification has emerged as an effective strategy for improving the biocompatibility and targeting efficiency of metal nanomaterials. Coating metal nanoparticles


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with biopolymers can reduce systemic toxicity, enhance circulation times, and improve their biodistribution. Functionalizing these materials with ligands or antibodies further enhances their active targeting capability. Developing stimuli-responsive nanomaterials sensitive to specific TME conditions, such as pH, redox potential, or enzymatic activity, minimizes off-target effects and maximizes therapeutic efficacy. Moreover, designing multifunctional hybrid nanomaterials that integrate imaging, therapeutic, and targeting functions can streamline treatment processes, enhance therapeutic outcomes, and reduce systemic exposure to therapeutic agents. Computational modeling combined with high-throughput biological screening offers a powerful tool to predict and mitigate potential toxicity issues during the design phase of nanomaterials.

This research aims to provide a deeper understanding of metal-based nanomaterial mechanisms of action, optimize their antitumor activity, and improve their stability and feasibility in practical applications. Furthermore, it investigates strategies to refine the synthesis of these metal-based nanomaterials to ensure their stability and viability in clinical applications.

## ■ ASSOCIATED CONTENT

### Data Availability Statement

The data that supports the findings of this study are available from the corresponding author upon reasonable request.

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