

Tumor-responsive covalent organic polymeric nanoparticles enhancing STING activation for cancer immunotherapy

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ABSTRACT

The cyclic guanosine monophosphate-adenosine monophosphate synthase and the stimulator of interferon genes (cGAS-STING) has emerged as a promising target for cancer immunotherapy. However, the development of natural STING agonists is impeded by several challenges, including limited biostability, poor pharmacokinetics, and inefficient cytosolic delivery. Herein, we meticulously designed a double-layer polyethylenimine (PEI) modified nanoscale covalent organic polymer (CPGP) for efficient delivery of 2'3' cyclic guanosine monophosphate-adenosine monophosphate (cGAMP), a natural STING agonist. The double-layer PEI structured CPGP enhanced both the loading capacity and stability of cGAMP. Furthermore, CPGP improved the intracellular delivery efficiency and amplified the activation of STING pathway for the secretion of type-I interferon and pro-inflammatory cytokines. In contrast, single-layered nanoparticles failed to permit stable loading and intracellular delivery of cGAMP for immune response. The nano-STING agonist also mitigated the immunosuppressive tumor microenvironment (TME) by reducing regulatory T cells and polarizing M2 macrophages to the M1 phenotype, thereby creating an immune-supportive TME to enhance adaptive immune responses. The combination of CPGP and immune checkpoint blockers showed synergistic effect, further enhancing the inhibition effect on tumor growth. This double-layer PEI modified CPGP may offer a generalizable platform for other natural dinucleotide STING agonists to overcome the cascade delivery barriers, augmenting immune activation for tumor immunotherapy.

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Immunotherapy has revolutionized cancer treatment and become a clinically validated strategy for multiple types of cancer. Among immunotherapy, the cyclic guanosine monophosphate-adenosine monophosphate synthase and the stimulator of interferon genes (cGAS-STING) pathway has emerged as a promising target for cancer immunotherapy [1–3]. As a cytosolic sensor for double-stranded DNA (dsDNA), cGAS binds to dsDNA, leading to conformational changes and subsequent activation of the cGAS [4–6]. Upon activation, cGAS facilitates the conversion of adenosine triphosphate and guanosine triphosphate into 2'3' cyclic guanosine monophosphate-adenosine monophosphate (cGAMP), a cyclic

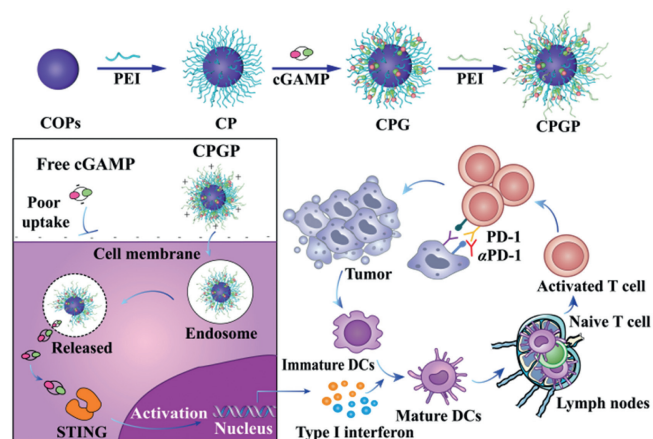
dinucleotide [7,8]. Functioning as STING agonists, cGAMP stimulates STING protein on the endoplasmic reticulum surface for the induction of type I interferon (IFN-I) and other proinflammatory cytokines. These immune responses promote dendritic cell (DC) maturation and prime T cells, orchestrating host innate and adaptive immunity against cancer [9,10]. The critical role of cGAMP in STING-mediated immune surveillance renders it an appealing agonist for cancer immunotherapy.

Although promising, the therapeutic efficacy of exogenous cGAMP is greatly limited by multiple barriers, such as limited biostability, poor pharmacokinetics, and inefficient tumor accumulation and cytosolic delivery [11–13]. In addition, the potential risk of non-specific STING activation often leads to off-target inflammation or autoimmunity [8,14]. Therefore, addressing these challenges confronted by cGAMP is critical to realize its full therapeutic potential and advance clinical translation.

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Scheme 1. Schematic overview of the fabrication of CPGP and its mechanism for STING activation and immune responses.

Promoted by the advancements in nanotechnology, nanomaterials-based drug delivery systems have been extensively studied and exploited for cancer treatment due to biocompatibility, reduced toxicity, stability, enhanced permeability and retention effect for targeting. Nanoparticles can targeted deliver therapeutic agents to tumor in a controlled manner, allowing to effectively overcome the limitations associated with the use of cGAMP [15–18]. Among them, positively charged inorganic or organic nanoparticles have been developed for the targeted delivery of cGAMP [19–21]. Nevertheless, the highly hydrophilic and negative-charged nature of cGAMP raises concerns about unstable loading and premature leakage during *in vivo* delivery, thereby impeding its efficacy [12]. Furthermore, even with the assistance of nanomaterials, the efficient delivery cGAMP into cytosol still faces significant challenges. Consequently, there is an urgent need to rationally design nanocarriers to facilitate the cascade delivery of cGAMP into the cytoplasm.

Herein, we rationally designed a tumor microenvironment (TME)-responsive nanoparticles (CPGP) for efficient cGAMP delivery to address above issues (Scheme 1). A nanoscale covalent organic polymer (COP) was firstly prepared and modified with polyethyleneimine (PEI) for cGAMP loading. To protect cGAMP from premature release during *in vivo* delivery and enhance intracellular delivery efficiency, we encapsulated additional layer of PEI molecules on the outer surface of nanoparticles. The double-layer PEI structured CPGP enhanced both the loading capacity and stability of cGAMP. Furthermore, CPGP improved the intracellular delivery efficiency and promoted endosomal escape. Accordingly, it amplified the activation of the STING pathway, initiating an innate immune response driven by IFN-I that primes T cells. Furthermore, CPGP mitigated the immunosuppressive TME by reducing regulatory T cells (Tregs) and polarizing M2 macrophages to the M1 phenotype, creating an immune-supportive TME to facilitate adaptive immune responses. Moreover, when combined with anti-programmed cell death protein 1 antibody (α PD-1), the tumor inhibition of CPGP was further enhanced. Overall, our study demonstrates that tumor-responsive CPGP, as a nano-STING agonist, effectively activates STING pathway for tumor immunotherapy, providing a general platform for other natural dinucleotide STING agonists to overcome cascade delivery barriers.

Uniform nanoscale COPs composed of 4,4'-dithiodianiline and 1,3,5-benzenetricarboxaldehyde were synthesized through Schiff-base reaction with ferric trichloride as the catalyst. The spherical COPs exhibited an average diameter of 200 nm, as observed in the scanning electron microscopy (SEM) and transmission electron microscopy (TEM) images (Figs. 1A and B). To load negatively charged

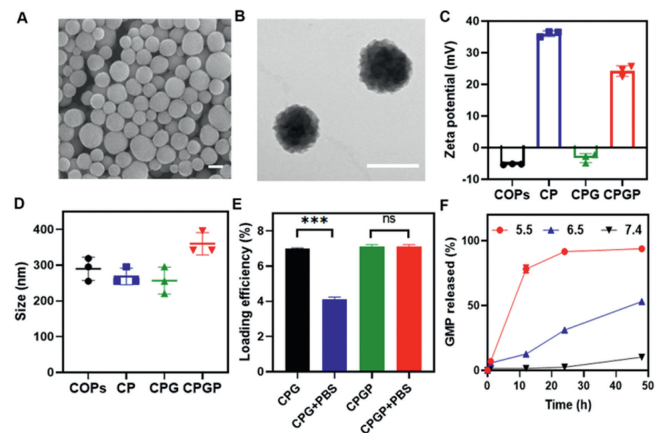


Fig. 1. (A) SEM image of CPGP. Scale bar: 200 nm. (B) TEM image of CPGP. Scale bar: 200 nm. (C) Zeta potential of COPs, CP, CPG, and CPGP. (D) The diameter of COPs, CP, CPG, CPGP determined by dynamic light scattering. (E) Loading efficiency of cGAMP with CPG or CPGP in PBS buffer. (F) The release curve of GMP at different time points. Data represent means $\pm$ SD ($n=3$). *** $P < 0.001$. ns: no significant difference.

cyclic dinucleotide cGAMP, we coated the surface of the COPs with branched PEI, resulting in a modified COP named as CP. The successful coating of PEI was confirmed by the change in zeta potential (Fig. 1C). After the incorporation of cGAMP, the obtained CPG exhibited a reduced zeta potential to a negative value, demonstrating its successful loading. To enhance loading stability and cytosolic delivery of cGAMP, an additional layer of PEI was added to the outer surface of CPG, leading to the formation of CPGP. The reversal of surface charge confirmed the successful construction of double-layer PEI coated CPGP. These surface modification affects the hydrodynamic size of the COPs (Fig. 1D). Whereafter, we examined the stability of CPGP by monitoring changes in the hydrodynamic size. The data showed that CPGP could maintain good dispersion in water, phosphate buffered saline (PBS), normal saline, and serum within 5 days (Fig. S1 in Supporting information). Stable loading is the first prerequisite to promote immune activation *in vivo*, where the insufficient stability and premature leakage largely restrain the development of STING agonists. CPGP achieved a loading efficiency of 7.2% for cGAMP according the liquid-phase analysis (Fig. 1E). We thus investigated the loading stability of cGAMP in PBS, which often decrease the affinity between cGAMP and the carrier, causing the premature leakage of cargoes. As shown in Fig. 1E, there is neglectable effect on the loading efficiency after the incubation of CPGP in PBS, indicating the loading stability of cGAMP. In contrast, a significant leakage of cGAMP was shown in CPG group with 42.7% of cGAMP leaked. Besides, CPGP exhibited a pH-dependent release behavior of cGAMP, which had minimal release at pH 7.4 (Fig. 1F). A promoted release was achieved when the acidity increasing, with 78.7% release in medium with pH 5.5 at 12 h. These results demonstrate that the nanoparticles remain stable during blood circulation but efficiently release the cargoes upon exposure to tumor tissue for STING activation.

Given the robust loading and tumor-responsive drug release, we next assessed the intracellular delivery of cGAMP by incubating DC2.4 cells with fluorescently labeled CPGP. Fluorescence microscopy images and flow cytometry analysis revealed that Cy5-labeled CPGP underwent extensive cellular internalization after being treated for 24 h (Fig. 2A, Fig. S2 in Supporting information). Notably, the cellular uptake of CPGP was 5.9-fold over that of CPG, indicating the additional PEI layer enhanced the efficiency of intracellular delivery (Fig. S3 in Supporting information). As the additional PEI layer turned the surface charge to positive (24.6 mV), this uptake enhancement probably due to the positive-charged CPGP interacted with cells more efficiently than the negative CPG. To

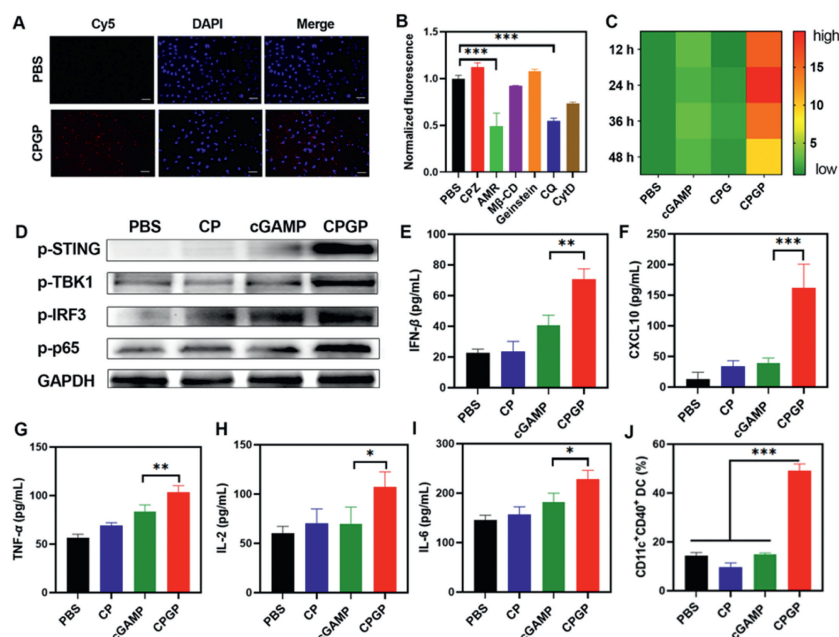


Fig. 2. (A) Intracellular uptake of CPGP in DC2.4 cells after 24 h incubation. Red: Cy5; Blue: 4',6-diamidino-2-phenylindole (DAPI). Scale bar: 50 μ m. (B) Flow cytometry analysis of endocytosis mechanism of CPGP. (C) STING pathway activation of CPGP in RAW-LuciaTM ISG cells. (D) Detection of p-IRF3, p-TBK1, p-p65, and p-STING protein in BMDCs by Western blot analysis. (E–I) Secretion of IFN- β (E), CXCL10 (F), TNF- α (G), IL-2 (H), and IL-6 (I) in medium after co-incubation CPGP with BMDCs for 24 h. (J) The maturation of BMDCs (CD40⁺) with various treatments. Data represent means $\pm$ SD ($n = 5$). * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

further elucidate the internalization pathway of CPGP, DC2.4 cells were pre-treated with various inhibitors that targeting distinct endocytic pathways, followed by co-incubation with Cy5-labeled CPGP. As depicted in Fig. 2B, the cellular uptake of nanoparticle was markedly decreased to 49.1% in the amiloride (AMR)-treated group in comparison to the control group. A comparable reduction (55.0%) was also observed in the chloroquine (CQ)-treated group. These results suggested that CPGP was effectively internalized through macropinocytosis and clathrin-mediated endocytosis [22,23]. It is noting that no significant cytotoxic effects were observed when incubated DC2.4 cells with different concentrations of CPGP for 24 h, even at a high concentration of 140 μ g/mL (Fig. S4 in Supporting information), indicating the excellent biosafety of CPGP.

The double-layer PEI structured CPGP enhanced both the loading capacity and stability of cGAMP, and robust STING activation was thus expected. We initially assessed the capability of CPGP to stimulate IFN-I responses in RAW 264.7 cells with IFN-stimulated gene (RAW-LuciaTM ISG). The results revealed both free cGAMP and CPG only elicited a minimal response, whereas CPGP induced the most robust activating effect. The production of IFN-I by CPGP was 15.6- and 7.6-fold over that of PBS and CPG at 24 h, respectively (Fig. 2C). Meanwhile, the dynamic STING activation was clearly observed, which reached the maximal level at 24 h and started to decrease after that. We next investigated the STING activation of CPGP in bone marrow-derived dendritic cells (BMDCs). The expression of downstream proteins following STING activation was assessed using Western blot analysis with glyceraldehyde-3-phosphate dehydrogenase (GAPDH) as internal reference. Fig. 2D displayed that the increased phosphorylation of STING and the downstream phosphorylated interferon regulatory factor 3 (p-IRF3) protein expression in BMDCs after CPGP treatment. Moreover, STING activation prompted the translocation of p65 subunit of nuclear factor κ B into the nucleus, where it interacted with p-IRF3, simultaneously inducing the expression of interferon- β (IFN- β) and other inflammatory cytokines [24]. We then evaluated the secretion of cytokines under different treatments. Notably, CPGP

significantly enhanced the secretion of IFN- β , which induced 1.8-fold higher than that of free cGAMP (Fig. 2E). Meanwhile, as a downstream product of the STING signaling pathway, the secretion of CXCL10 was also significantly upregulated by CPGP, 4.1-fold higher than that induced by free cGAMP (Fig. 2F), indicating the superior delivery efficiency of CPGP. Furthermore, the secretion of inflammatory cytokines after nanoparticles incubation were also evaluated. As shown in Figs. 2G–I, CPGP potently promoted the secretion of proinflammatory cytokines including tumor necrosis factor- α (TNF- α), interleukin-2 (IL-2), and IL-6, which were significantly higher than free cGAMP and CP, respectively. The production of IFN-I and other cytokines are critical for DC maturation and activation as well as triggering subsequent immune response. For this, we co-cultured BMDCs with CPGP for 48 h and assessed their maturation by flow cytometry. The CD40 induced by CPGP was 5.2- and 3.3-fold higher than that induced by free cGAMP and CP (Fig. 2J), respectively, demonstrating the robust BMDC activation. Collectively, these results demonstrate that CPGP exerts a potent and sustained activation of the STING innate pathway, resulting in the enhanced secretion of IFN-I and inflammatory cytokines for subsequent DCs maturation.

Having verified the potent STING activation of CPGP *in vitro*, we sought to evaluate its anti-tumor efficacy. Since the accumulation of CPGP in tumor tissues is essential for therapeutic effect, the *in vivo* tumor targeted delivery ability of CPGP was firstly estimated using an *in vivo* imaging system. The tumor accumulation of Cy5-labeled CPGP was clearly shown at 12 and 24 h after intravenous injection. *Ex vivo* fluorescence imaging of tumors and major organs further validated the remarkable tumor targeting of CPGP (Fig. S5 in Supporting information).

Encouraged by the potent STING activation *in vitro* and tumor targeted delivery of CPGP, we proceeded to investigate the anti-tumor efficacy in CT26 tumor model. All mice were treated in accordance with the approved protocol of the Institutional Animal Care and Use Committee of Peking Union Medical College. Once the tumor volume reached approximately 50 mm³, the mice were randomly divided into six groups ($n = 5$ per group) and

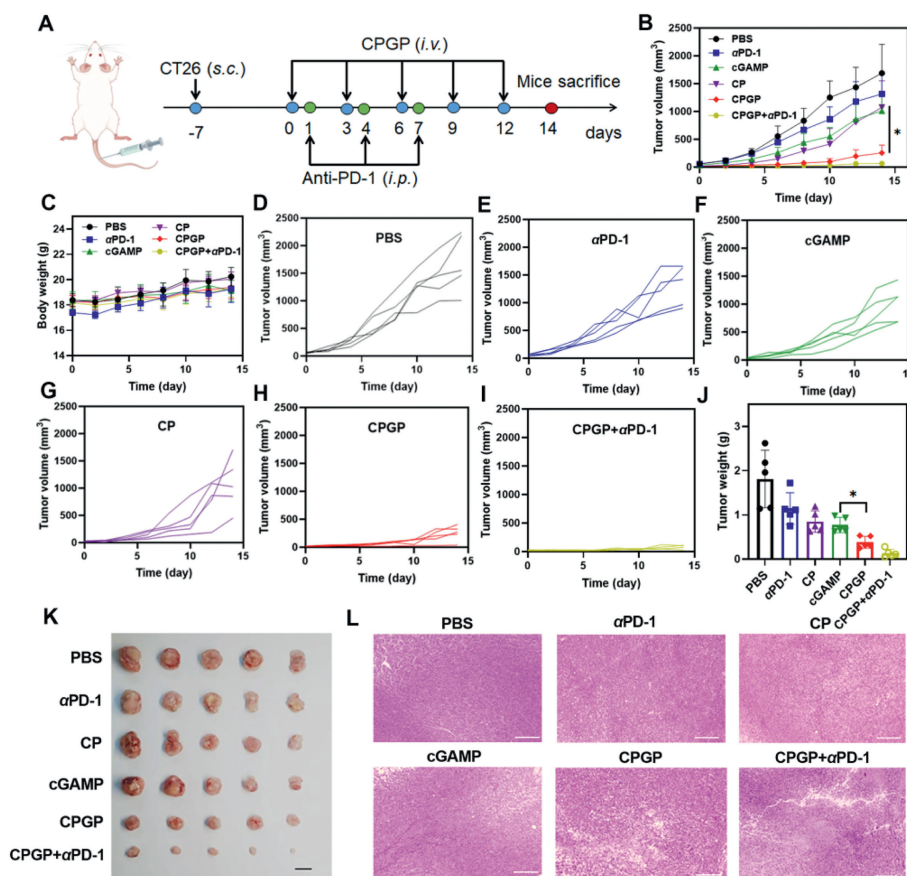


Fig. 3. (A) The establishment of subcutaneous CT26 tumors and therapeutic scheme by different formulations. (B, C) Overall tumor growth (B) and body weight (C) of the mice during the treatment period. (D–I) Tumor growth curves of the mice at different groups, respectively. (J) Tumor weight after different treatments. (K) Tumor image of the mice at the end of the treatments. Scale bar: 1 cm. (L) H&E staining of tumor tissues treated by various formulations. Scale bar: 50 μ m. Data represent means $\pm$ SD ($n = 5$). * $P < 0.05$.

administered with PBS, CP, α PD-1, cGAMP, CPGP, and CPGP plus α PD-1, respectively. Typically, the formulations were injected intravenously every 3 days. α PD-1 was co-administered 24 h post the intravenous injection to evaluate the synergistic effect (Fig. 3A). The tumor size and body weight were recorded every 2 days. As shown in Fig. 3B, in comparison to PBS group, free cGAMP and CP only demonstrated a modest tumor suppression effect. In contrast, CPGP significantly inhibited tumor growth with a tumor inhibition rate up to 84.9%, which was 2.1- and 2.3-fold over that of free cGAMP and CP, respectively. The strongest tumor growth inhibition was observed in CPGP combined with α PD-1 group (tumor suppression rate at 96.3%), demonstrating a synergistic therapeutic effect (Figs. 3D–I). Notably, no significant changes of mice weight across all treatment groups were observed, signifying the safety profiles of CPGP (Fig. 3C).

On the 14th day, tumors were collected and weighted. As depicted in Figs. 3J and K, the tumor weight of mice treated by CPGP was significantly lower than that treated by free cGAMP and CP, demonstrating the targeted delivery enabled superior anti-tumor efficacy. The lowest tumor weight was found in the treatment of CPGP + α PD-1 group, with an average tumor weight nearly 13.8-fold lower than that of the PBS group and 5.8-fold lower than that of the free cGAMP group. To further investigate the therapeutic effect of CPGP *in vivo*, the hematoxylin-eosin (H&E) staining of tumors was assessed (Fig. 3L). In line with the above results, the CPGP group displayed more pronounced histological damage compared to the other groups. Particularly, the combinational group exhibited the highest level of tumor cell necrosis and apoptosis. In addition, no noticeable damage was occurred in major or-

gans within each treatment group (Fig. S6 in Supporting information). Taken together, these results demonstrate the efficient immunotherapeutic effect of CPGP with excellent safety profile, and its combination with immune checkpoint blocker further enhances the anti-tumor response.

To explore the detailed mechanism of immune response induced by CPGP, we analyzed the population of infiltrated immune cells and cytokine induction in lymph nodes, spleens, and tumor tissues. Given that antigen-presenting cells serve as the primary targets of STING within the immune system, we initially investigated the maturation of DCs. Briefly, lymph nodes near the tumors were collected to isolate single cells for subsequent flow cytometry analysis. Compared with the control group, the CPGP-treated group showed a significant enhancement in the expression of the DC marker CD80, CD86, and CD40, (Figs. 4A and B; Fig. S7 in Supporting information), which was 1.4- and 2.5-fold higher than that of free cGAMP and CP, respectively, and it increased to 1.7- and 3.1-fold in combination with α PD-1. Additionally, the cytokines released in the tumor following various treatments were quantified to evaluate the activation of the STING pathway. As expected, the induction of IFN- β , CXCL10, TNF- α , IFN- γ , IL-2, and IL-6 was obviously observed after CPGP treatment (Figs. 4C–H), with levels being 1.9-, 2.1-, 2.1-, 2.3-, 2.2-, and 1.5-fold higher than that of free cGAMP group, respectively. The combination of α PD-1 further increased cytokine levels to 5.3-, 6.1-, 6.5-, 8.0-, 8.3-, and 2.7-fold over that of CP group, respectively. These results indicate that CPGP possesses the ability to activate STING pathway and induce cytokine production for DC maturation.

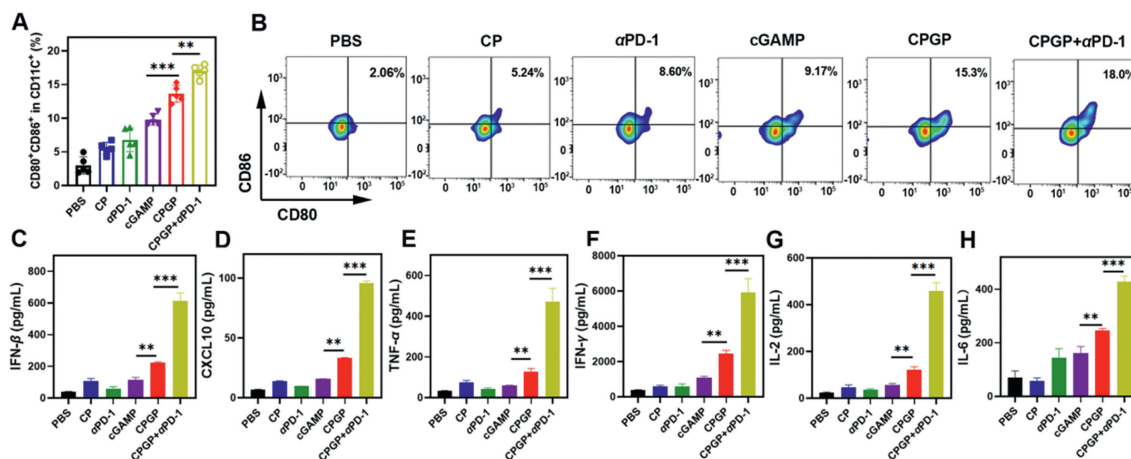


Fig. 4. (A, B) Representative fluorescence-activated cell sorting plots and quantitative analysis of CD80⁺CD86⁺ in tumor-draining lymph nodes. (C-H) The secretion of IFN-β (C), CXCL10 (D), TNF-α (E), IFN-γ (F), IL-2 (G), and IL-6 (H) intratumoral cytokines in mice treated with different formulations. Data represent means ± SD (n = 5). **P < 0.01, ***P < 0.001.

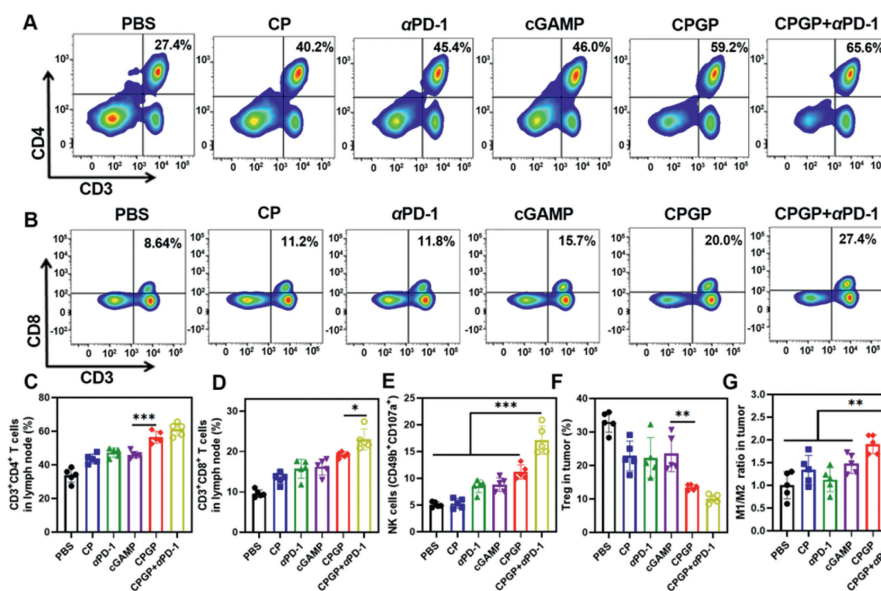


Fig. 5. (A–D) Representative fluorescence-activated cell sorting plots and quantitative analysis of CD4⁺ T cells and CD8⁺ cytotoxic T cells in tumor-draining lymph nodes. (E) Percentages of CD107a⁺ NK cells in tumor-draining lymph nodes. (F) Representative flow analyses and quantification of the ratio of Tregs (CD4⁺ Foxp3⁺ T cells) in tumor. (G) The ratio of M1/M2-type of macrophages in tumor. Data represent means ± SD (n = 5). *P < 0.05, **P < 0.01, ***P < 0.001.

STING activation is shown to link the innate and adaptive immunity. To investigate the impact of STING activation on the adaptive immune response, we quantified the population and activation of CD4⁺ and CD8⁺ T cells in the lymph nodes, tumor, and spleen, which were significant in regulating immune response. The results revealed that the ratio of CD4⁺ T cells with CPGP treatment was remarkably elevated compared to those treated with PBS, CP, and cGAMP, respectively (Figs. 5A and C; Figs. S8 and S9 in Supporting information). Additionally, there was an increase in the percentage of CD8⁺ T cells (Figs. 5B and D; Fig. S10 in Supporting information). The production of cytotoxic IFN-γ from CD8⁺ T cells, a crucial effector molecule employed by lymphocytes for direct tumor cell lysis, was also assessed. The CPGP treatment exhibited a 1.5-fold higher level of CD8⁺IFN-γ⁺ T cells in tumor-infiltrating lymphocytes compared to free cGAMP group (Fig. S11 in Supporting information). Notably, the combination of CPGP with αPD-1 further augmented the T cell response, suggesting a synergistic effect.

As innate cytotoxic lymphocytes, natural killer (NK) cells play a crucial role in the anti-tumor immune response, either through the direct elimination of tumor cells or by augmenting adaptive anti-tumor immunity [25]. The percentage of NK cells after CPGP treatment was thus assessed. CPGP facilitated NK cell activation in the lymph nodes, exhibiting a 2.1-fold higher level over that of CP (Fig. 5E). Significantly, the concurrent administration of the αPD-1 further potentiated the activating effect.

The activation of STING pathway has been reported to reshape the immune-suppressive TME, thereby augmenting the efficacy of anti-tumor immunotherapy [26,27]. Tregs contribute to immunosuppression by inhibiting the function of effector T cells within the TME, facilitating tumor development and progression [28,29]. Additionally, a substantial population of tumor-associated macrophages (TAMs) undergoes polarization towards the M2 type, protecting tumor cells from immune surveillance and fostering tumor development [30]. To elucidate whether CPGP could reverse the immune-suppressive TME, we examined the expression

of Tregs and TAMs within the tumors and spleens (Fig. 5F and Fig. S12 in Supporting information). The results revealed that CPGP-treated group significantly reduced the percentage of Tregs compared to the control group, while free cGAMP failed to elicit this effect. In addition, the ratio of M1/M2 macrophages within the tumors were also evaluated. As illustrated in Fig. 5G, CPGP markedly upregulated the expression of CD86 while downregulating CD206 expression compared to other treatments, indicating that CPGP alleviated the immune-suppressive TME and supported effective immunotherapy.

Taken together, CPGP demonstrates multifaceted anti-tumor activity by effectively activating DCs and priming T cells, thereby enhancing the immune response. Furthermore, CPGP has the capability to overcome the immune-suppressive TME by decreasing the population of Tregs and increasing the ratio of M1/M2 macrophages. This augmentation of STING activation highlights the potential of CPGP as a potent immunomodulator for cancer immunotherapy.

In summary, the poor pharmacokinetics and inefficient cytosolic delivery are the major restrictions for the therapeutic efficacy of natural STING agonist cGAMP and further clinical translation. The developed CPGP nanoplatfrom here overcame the aforementioned limitations by a dual-layer PEI structure. CPGP significantly enhanced delivery stability, achieving efficient cytosolic delivery of cGAMP for the activation of the STING pathway. This, in turn, initiated an innate immune response driven by IFN-I, which primed T cells to kill tumor. Moreover, CPGP alleviated the immunosuppressive TME by reducing Tregs and polarizing M2 macrophages to the M1 phenotype, thus unleashing cascade adaptive immune response. The combination with α PD-1 further enhanced the immune sensitivity of tumor and achieved significant tumor suppression. Overall, the double-layer PEI structured nanoparticles offer a potential strategy for natural dinucleotide STING agonists to overcome cascade delivery barriers, augmenting STING pathway activation for tumor immunotherapy. It also sensitizes the immune response to immune checkpoint blockade therapy, offering a potential combinational strategy for the clinical cancer treatment.

Declaration of competing interest

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

CRediT authorship contribution statement

Shuang Liang: Data curation, Funding acquisition, Investigation, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review & editing, Conceptualization. **Jianjun**

Yao: Data curation, Formal analysis, Methodology, Software, Visualization, Writing – original draft. **Dan Liu:** Data curation, Formal analysis, Methodology, Software, Validation. **Mengli Zhou:** Data curation, Formal analysis, Software, Validation. **Yong Cui:** Conceptualization, Investigation, Resources, Supervision, Writing – review & editing. **Zhaohui Wang:** Conceptualization, Formal analysis, Funding acquisition, Investigation, Resources, Supervision, Validation, Writing – review & editing.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ccl.2024.109856.

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