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# cGAMP transfer and delivery to myeloid cells: a systematic review of intercellular signaling, extracellular fate, and engineered strategies

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## ADMINISTRATIVE INFORMATION

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**Review Stage at time of this submission -** Completed but not published.

**Conflicts of interest -** None declared.

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**Amendments -** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 1 November 2026 and was last updated on 1 November 2026.

## INTRODUCTION

**Review question / Objective** What evidence supports the generation and release of cGAMP, its extracellular fate, and its transfer, uptake, or sensing by myeloid cells, and how do engineered delivery strategies affect cGAMP availability and STING-dependent responses?

**Rationale** cGAMP can act as an intercellular signal, but the evidence spans distinct processes, including its generation and release, survival in the extracellular space, uptake or surface sensing by recipient cells, and downstream STING responses. Engineered delivery systems add another evidence class and should not be assumed to reproduce natural transfer. This review synthesizes these processes across tumor and non-tumor settings, with particular attention to myeloid cells and the limits of cross-study inference.

**Condition being studied** Intercellular cGAMP signaling and transport; extracellular cGAMP metabolism and availability; myeloid-cell sensing; and cGAMP-associated STING activation.

## METHODS

**Search strategy** PubMed and Europe PMC were searched from database inception through 16 October 2026, without a language filter. Three complementary search branches were used:
(A) cGAMP terms combined with tumor/cancer or myeloid-cell terms and transport, transfer, uptake, export, extracellular fate, or transporter/enzyme terms;

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(B) cGAMP terms combined with transport, transfer, uptake, export, extracellular fate, connexin/gap-junction, ENPP, SMPDL3, CD38, LRRC8, SLC19A1, SLC46A2, ABCC1, or ABCC10 terms;
(C) cGAMP terms combined with engineered-delivery terms, including nanoparticles, carriers, liposomes, polymers, hydrogels, encapsulation, delivery, nanomedicine, or virus-like particles, and tumor/myeloid-cell terms.
Search terms included "cGAMP," "cyclic GMP-AMP," "2′3′-cGAMP," and "cyclic dinucleotide." Full database-specific search strings should be copied from Appendix A of the Supporting Information.

**Participant or population** No human participant population was required. Eligible evidence included relevant donor and recipient cell systems, myeloid cells and other antigen-presenting cells, primary cells, cell lines, ex vivo systems, and in vivo animal models.

**Intervention** Natural or experimentally manipulated cGAMP generation, release, transfer, extracellular degradation or stabilization, cellular uptake/import, and surface sensing; and engineered or exogenous delivery of cGAMP or a clearly defined cGAMP derivative to myeloid cells or other relevant antigen-presenting cells.

**Comparator** Comparators varied by study and included vehicle or untreated controls, free cGAMP, empty or control carriers, alternative formulations, control genotypes, and pathway or transporter perturbations. No single comparator was required.

**Study designs to be included** Original experimental in vitro, ex vivo, and in vivo studies, including full-text verifiable preprints. Reviews, protocols, commentaries, and other non-original reports were excluded.

**Eligibility criteria** Studies were eligible if they investigated at least one of the following:
1. tumor-derived cGAMP generation, release, intercellular transfer, extracellular availability, or host myeloid sensing;
2. natural intercellular cGAMP transfer in infection or tissue-injury settings involving myeloid recipients or a comparable transport mechanism;
3. extracellular cGAMP stability, degradation, binding, or export, including relevant enzyme or transporter mechanisms; or
4. engineered cGAMP generation or delivery, with assessment of uptake, intracellular availability, myeloid-cell responses, or STING-dependent function.

Studies focused solely on other STING agonists without cGAMP, non-original reports, and studies outside these mechanistic or delivery scopes were excluded.

**Information sources** PubMed and Europe PMC. The final search date was 16 October 2026.

**Main outcome(s)** Evidence of cGAMP generation or release, intercellular transfer, uptake/import or surface sensing by myeloid cells, and downstream cGAMP–STING pathway activation.

**Additional outcome(s)** Extracellular cGAMP integrity, degradation, binding, stability, and export; interferon or cytokine responses; antigen-presenting-cell function; and relevant antitumor, antiviral, inflammatory, or tissue-injury outcomes. For engineered delivery studies, formulation, target-cell uptake, and functional delivery outcomes were also recorded.

**Data management** Data were recorded using a structured extraction form covering publication status, study design and model, cGAMP source or cargo, release and delivery mechanisms, recipient cell type, interventions and comparators, experimental readouts, and reported findings. Page-level source locations were recorded where available. Information not reported or not sufficiently clear in the source was coded as "not reported" or "unclear."

**Quality assessment / Risk of bias analysis** For eligible live-animal intervention studies, risk of bias was assessed across the 10 SYRCLE domains, without calculating an overall score; insufficiently reported information was judged as unclear. For non-animal studies, a seven-domain methodological-reporting checklist developed for this review was used descriptively; it is not a validated risk-of-bias tool.

**Strategy of data synthesis** Because the included studies differed substantially in species, cell types, disease models, interventions, formulations, and outcomes, effect estimates were not pooled. Findings were synthesized narratively and organized by the stages of cGAMP generation/release, extracellular fate, recipient-cell contact and uptake or surface sensing, intracellular STING responses, and tissue-level outcomes. Each study was assigned one primary evidence theme for descriptive mapping; this classification was not interpreted as a measure of mechanism frequency or evidence certainty.

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**Subgroup analysis** No formal subgroup analyses were planned or conducted.

**Sensitivity analysis** No formal effect-estimate sensitivity analysis was conducted. A descriptive count excluding preprints was used only to check the distribution by publication status and was not interpreted as a mechanism-specific sensitivity analysis.

**Language restriction** No language restriction was applied in the database searches.

**Country(ies) involved** China.

**Other relevant information** This review was not prospectively registered, and no publicly accessible prospective protocol was available. This INPLASY submission is retrospective.

**Keywords** cGAMP; myeloid cells; intercellular transfer; extracellular availability; STING; engineered delivery; systematic review.

**Dissemination plans** The findings are being prepared for submission to a peer-reviewed journal.

**Contributions of each author**

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