Cyclic guanosine monophosphate–adenosine monophosphate (cyclic GMP-AMP, cGAMP) is the first cyclic di-nucleotide found in metazoa.

In mammalian cells, cGAMP is synthesized by cyclic GMP-AMP synthase (cGAS) from ATP and GTP upon cytosolic DNA stimulation.

cGAMP produced by cGAS contains mixed phosphodiester linkages, with one between 2'-OH of GMP and 5'-phosphate of AMP and the other between 3'-OH of AMP and 5'-phosphate of GMP.

This molecule, referred to as 2′3′-cGAMP (cyclic [G(2′,5′)pA(3′,5′)p]) (it was mistakenly assigned as 3′3′-cGAMP (cyclic [G(3′,5′)pA(3′,5′)p]) in its discovery paper in 2012),functions as an endogenous second messenger inducing STING-dependent type I interferon response.

cGAMP has also been shown to be an effective adjuvant that boosts the production of antigen-specific antibodies and T cell responses in mice.

cGAMP exercises antiviral functions in the cell where it is produced, but can also cross cell membranes by passive diffusion to exert effects on neighboring cells.

It may even be packaged into lentivirus (such as HIV-1), poxvirus and herpes virus, and under cell culture conditions has been found to transmit an antiviral signal to the cells infected with these viruses; however, there is reason to think that at least HIV is capable of evading this mechanism by some means.

Human and mouse breast and lung cancer cells express protocadherin 7 (PCDH7), which promotes the assembly of carcinoma-astrocyte gap junctions composed of connexin 43 (Cx43). Once engaged with the astrocyte gap-junctional network, brain metastatic cancer cells use these channels to transfer the second messenger cGAMP to astrocytes, activating the STING pathway and production of inflammatory cytokines such as interferon-α (IFNα) and tumor necrosis factor (TNF). As paracrine signals, these factors activate the STAT1 and NF-κB pathways in brain metastatic cells, thereby supporting tumour growth and chemoresistance. The orally bioavailable modulators of gap junctions meclofenamate and tonabersat break this paracrine loop, and we provide proof-of-principle that these drugs could be used to treat established brain metastasis [1)].

1)
Chen Q, Boire A, Jin X, Valiente M, Er EE, Lopez-Soto A, Jacob LS, Patwa R, Shah H, Xu K, Cross JR, Massagué J. Carcinoma-astrocyte gap junctions promote brain metastasis by cGAMP transfer. Nature. 2016 May 18;533(7604):493-8. doi: 10.1038/nature18268. PubMed PMID: 27225120; PubMed Central PMCID: PMC5021195.