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Conserved strategies for pathogen evasion of cGAS–STING immunity
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The cyclic GMP–AMP synthase (cGAS)–Stimulator of Interferon Genes (STING) pathway of cytosolic DNA sensing allows mammalian cells to detect and respond to infection with diverse pathogens. Pathogens in turn encode numerous factors that inhibit nearly all steps of cGAS–STING signal transduction. From masking of cytosolic DNA ligands, to post-translational modification of cGAS and STING, and degradation of the nucleotide second messenger 2′,3′-cGAMP, pathogens have evolved convergent mechanisms to evade cGAS–STING sensing. Here we examine pathogen inhibitors of innate immunity in the context of newly discovered regulatory features controlling cellular cGAS–STING activation. Comparative analysis of these strategies provides insight into mechanisms of action and suggests aspects of cGAS–STING regulation and immune evasion that remain to be discovered.

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Introduction
The cGAS–STING pathway detects cytosolic DNA and triggers a robust immune response that restricts replication of diverse pathogens. The enzyme cyclic GMP–AMP synthase (cGAS) directly senses cytosolic DNA and catalyzes synthesis of the nucleotide second messenger 2′,3′-cGAMP [1–5]. 2′,3′-cGAMP diffuses throughout the cell and binds to Stimulator of Interferon Genes (STING), a signaling adapter which oligomerizes and traffics from the endoplasmic reticulum (ER) to the ER-Golgi intermediate compartment (ERGIC), where it drives downstream innate immune responses through the type I interferon and NF-kB pathways to inhibit pathogen infection [6–10].

Activation of type I interferon and inflammatory signaling by cGAS–STING during infection places diverse bacterial and viral pathogens under selective pressure to disable this pathway. While the genomes of DNA viruses and bacteria may serve to directly activate cGAS, damage to the mitochondria during infection with RNA viruses can also trigger cGAS activation through exposure of mitochondrial DNA [11]. Therefore, pathogens from divergent groups encode proteins targeting cGAS, 2′,3′-cGAMP, and STING to disrupt signaling. Despite the great diversity of these pathogens and the effectors they employ to restrict cGAS–STING activation, shared strategies can be identified which allow escape from the innate immune response (Figure 1).

Within the past two years, major advances have expanded our understanding of the mechanism of cGAS–STING signal transduction, providing new insight into how different viral and bacterial factors restrict signaling. In particular, formation of higher-order phase-separated droplets has emerged as a checkpoint for regulating cGAS activation [12], new structures of STING in complex with TBK1 have provided a mechanism for assembly of the STING signalosome and activation of downstream signaling [13,14], and extracellular 2′,3′-cGAMP signaling has emerged as an entirely new facet of cGAS–STING biology [15,16]. While other recent reviews provide in-depth analysis of these new discoveries [17,18], here we focus on conserved strategies utilized by different pathogens for evasion of cGAS–STING immunity. Study of these strategies has provided important insight into cellular regulation of cGAS–STING signaling, and likewise these pathogen immune escape factors will continue to serve as useful tools to gain mechanistic insight into pathway function and regulation. In turn, our deepening understanding of the cGAS–STING pathway creates new questions regarding the mechanisms of different groups of viral and bacterial factors which inhibit signaling and indicates new strategies which may be exploited by pathogens for immune evasion.

Pathogens target cGAS to evade cytosolic DNA sensing
In order to productively infect a target cell, viruses and intracellular bacteria utilize diverse techniques to prevent activation of cGAS before they initiate replication (Figure 2).
Summary of the cGAS–STING pathway and potential pathogen evasion strategies. Recognition of cytosolic double-stranded DNA triggers assembly of cGAS into DNA ladder structures, and liquid droplets. Oligomerization into a minimal 2:2 cGAS:DNA complex is required for activation to produce the second messenger 2′3′-cGAMP from ATP and GTP. 2′3′-cGAMP is subsequently recognized by STING which oligomerizes to form a signalosome complex and traffics to the ERGIC and perinuclear regions. This leads to recruitment of the downstream kinase TBK1 to promote innate immune signaling. Points in the pathway which are known (checked box) or potential (red open box) pathogen targets for restriction of cGAS–STING signaling are summarized on the right in the viral escape checklist.

For example, viruses with a DNA genome or genome intermediate (e.g. herpesviruses, and retroviruses), must prevent exposure of DNA to the cytosol, or risk activation of cGAS. These viruses shield DNA from sensing within the viral capsid until it reaches the nucleus, and mutations altering capsid stability regulate cytosolic DNA sensing [19,20].

Another strategy to prevent or restrict cGAS activation is to target cGAS for degradation, reducing levels of this sensor, and impairing 2′3′-cGAMP synthesis. This is accomplished in different ways by both DNA and RNA viruses. For example, the dengue virus (DENV) protease complex NS2B3 cleaves cGAS to prevent its activation by mitochondrial DNA during infection [11]. The related flavivirus Zika virus (ZIKV) utilizes an indirect strategy: its NS1 protein stabilizes caspase-1 leading to cGAS cleavage [21**]. Another indirect strategy is utilized by DNA viruses in the *Poxviridae* family, where the vaccinia virus (VACV) F17 protein dysregulates mTOR, leading to enhanced cGAS degradation and impaired cytosolic DNA sensing late in infection [22**].

In the event that viral DNA is exposed in the cytosol before replication and gene expression, the nuclear-replicating herpesviruses carry immune antagonists directly within the viral particle to disable DNA sensing after infection. Herpes simplex virus 1 (HSV-1) VP22 and human cytomegalovirus (HCMV) UL83 are both tegument proteins which bind cGAS and block downstream signaling [23,24]. Another member of the *Herpesviridae*, Kaposi’s sarcoma-associated herpesvirus (KSHV), also encodes a tegument protein that inhibits cGAS, ORF52 (also named KicGAS) [25]. ORF52 blocks cGAS activation through a mechanism which requires both cGAS and DNA binding by ORF52. While these proteins from diverse herpesviruses seemingly vary in their requirement for DNA binding activity, they share striking
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Pathogen factors block cGAS activation. Upon DNA binding, cGAS undergoes a conformational change activating 2′3′-cGAMP synthesis. Assembly into a minimal 2:2 complex is required for catalytic activity, but further assembly into long DNA ladder structures and larger oligomers bridged by interactions with the unstructured N-terminus results in formation of phase-separated liquid droplets. ATP and GTP are converted in a two-step process to 2′3′-cGAMP within the cGAS active site, which is released into the cytosol and diffuses throughout the cell. Red text and arrows indicate steps in this process at which different viral and bacterial factors prevent or interfere with signaling. The box at the bottom indicates indirect viral strategies which trigger cGAS degradation.

Pathogens also target cGAS through post-translational modification, resulting in impaired 2′3′-cGAMP synthesis. A second HSV-1 tegument protein, UL37, was recently demonstrated to inhibit cGAS by deamidating a critical residue in the cGAS activation loop [29**]. The activation loop is repositioned in a switch-like fashion after DNA binding, enabling 2′3′-cGAMP synthesis [2,30–32]. Deamidation of a single asparagine residue in this loop by UL37 results in significantly impaired 2′3′-cGAMP production, perhaps by blocking this switch-like conformational change.

Many open questions remain in the field regarding how cGAS senses pathogen infection. The nature of the cGAS ligand during infection with different pathogens remains unclear — whether it is always the viral or bacterial genome, or to what extent oxidative stress and exposure of mitochondrial DNA or cellular genomic DNA may play a role in cGAS activation during infection remains a topic of debate. Further, a striking number of viral cGAS antagonists serve as virion structural components, including several herpesvirus tegument proteins, and VACV F17. Given that virion stability and efficiency of viral DNA packaging may influence cytosolic DNA sensing during infection, further work to establish the exact mechanisms by which these proteins antagonize cGAS-STING signaling will provide important insight to help unite our understanding of their structural and immune antagonist roles.

Pathogens degrade 2′3′-cGAMP to block STING activation

The nucleotide second messenger 2′3′-cGAMP is highly stable in the mammalian cytosol [33**]. This RNA signal can be disseminated through gap junctions to activate STING signaling in adjacent uninfected bystander cells, bypassing pathogen factors targeting STING in the infected cell [34]. Similarly, 2′3′-cGAMP can be packaged within nascent virions, driving a rapid immune response upon infection of a new target cell [35,36]. These aspects of 2′3′-cGAMP biology make it a critical target for elimination by viral and bacterial pathogens (Figure 3).

Cyclic dinucleotide phosphodiesterase (CdnP) proteins of Mycobacterium and Streptococcus species enzymatically cleave cyclic dinucleotide molecules. Initially, these proteins were reported to cleave bacterial cyclic dinucleotides like cyclic di-AMP to avoid host immune recognition, as these endogenous bacterial signaling molecules can also be sensed by STING as pathogen-associated molecular patterns [10,37,38]. However, the Mycobacterium tuberculosis CdnP enzyme exhibits activity toward host 2′3′-cGAMP as well as bacterial cyclic di-AMP, indicating that it may serve a dual function in infection to prevent host recognition of bacterial cyclic di-AMP as well as degradation of host 2′3′-cGAMP [39].

Similarly, VACV and other related poxviruses encode a nuclease called poxvirus immune nuclease (poxin) which
Viral and bacterial enzymes degrade 2′,3′-cGAMP. The second messenger 2′,3′-cGAMP is highly stable in the mammalian cytosol. 2′,3′-cGAMP can be packaged within budding virions to activate STING in newly infected cells, or spread cell-to-cell through gap junctions to activate bystander immunity in neighboring uninfected cells. Viral and bacterial enzymes degrade 2′,3′-cGAMP in order to prevent binding to STING, and activation of downstream immune signaling.

degradation of 2′,3′-cGAMP in order to prevent activation of the cGAS–STING pathway [33,44]. Poxin is highly specific for host 2′,3′-cGAMP, and deletion of poxin from the viral genome resulted in attenuation of VACV in a mouse model of infection. Functionally, poxin enzymes are also found in the genomes of insect viruses in the family Baculoviridae, and moths and butterflies, which serve as hosts to these viruses [33,44]. The emerging role for cGAS–STING signaling in insects is likely to enable discovery of additional insect pathogen inhibitors of pathway activation [40–42]. In mammals, no cytosolic enzymes have been discovered which degrade 2′,3′-cGAMP, but instead the extracellular enzyme ectonucleotide pyrophosphatase/phosphodiesterase family member 1 (ENPP1) has been shown to be the major source of 2′,3′-cGAMP-degrading activity in mammalian tissue and plasma [43]. Interestingly, avian poxviruses lack a homolog of poxin, but do encode a predicted homolog of ENPP1, indicating these viruses may have obtained alternative means of degrading 2′,3′-cGAMP during infection [44]. Together, these results indicate that 2′,3′-cGAMP degradation is a more widespread mechanism for control of innate immune signaling than previously understood.

Given that 2′,3′-cGAMP can be passed between cells through gap junctions, and infiltrate nascent virions [34–36], future study is required to understand if pathogens possess specific mechanisms for blocking these unique aspects of 2′,3′-cGAMP biology. Recent studies showed that 2′,3′-cGAMP can be exported from cells by an unknown transporter and imported into immune cells through the reduced folate transporter SLC19A1 to activate an immune response [15,16]. This indicates that 2′,3′-cGAMP import and export may also be important steps at which viruses and bacteria interfere with immune signaling during infection.

**Pathogens block STING signalosome assembly**

Several viruses employ strategies to degrade STING to prevent its activation by 2′,3′-cGAMP (Figure 4). Similar to degradation of cGAS, DENV and other related flaviviruses proteolytically cleave STING using the viral protease complex NS2B3, blocking induction of signaling [45,46]. In addition, the HCMV IE86 protein promotes STING degradation in the proteasome, restricting activation of downstream signaling [47].

Several processes, including oligomerization [13,48], palmitoylation [49,50], K63-linked ubiquitination [51,52], and ER to ERGIC trafficking [53,54] are reported to be

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**Figure 3**

**Figure 4**
important for assembly of the STING signalosome and activation of downstream signaling. It remains unclear how these different processes may regulate one another, but interestingly, a number of pathogen factors interfere with one or more steps. Two RNA virus factors, Hepatitis C Virus NS4B, and the coronavirus HCoV-NL63 papain-like protease (PL-pro) both interfere with STING oligomerization [55,56]. Interestingly, it is the deubiquitinase activity rather than the protease activity of PL-pro that is required for antagonism of STING oligomer formation [56]. Several other pathogen factors have been discovered which appear to interfere specifically with STING ubiquitination, including the human T-lymphotropic virus I Tax protein [57], and Yersinia YopJ protein, which also functions as a deubiquitinase [58]. YopJ is additionally reported to block STING ER to ERGIC trafficking, perhaps implying a connection between these processes [58]. Several viral proteins directly target STING trafficking to the ERGIC, which requires the iRhom2/TRAPβ complex [54]. The HCMV tegument protein UL82 disrupts the complex between STING, iRhom2 and TRAPβ [59]. Similarly, HCMV UL42, along with its role in antagonizing cGAS oligomerization, is reported to stimulate degradation of TRAPβ in order to block STING trafficking [27]. Last, the bacterium Shigella flexneri encodes IpaJ which inhibits STING trafficking by an indirect mechanism, targeting ARF GTPases to block traffic out of the ER [60].

After assembly of STING oligomers in the ERGIC, downstream signaling factors associate in order to drive antiviral and inflammatory responses. The mechanism is best understood for the kinase TBK1 and transcription factor IRF3 which associate with the STING C-terminal tail and become activated by trans-phosphorylation driven by assembly of multiple molecules on adjacent STING monomers [13*,14*,61]. The KSHV vIRF1 protein blocks this process, preventing association of TBK1 [62]. Mareck’s disease virus is an avian oncovirucogenic herpesvirus, and its oncoprotein Meq functions in a similar way, blocking recruitment of TBK1 to STING in chicken cells [63**]. Interestingly, the oncoproteins E1A and E7 from adenovirus and human papillomavirus also bind and inhibit STING, however the mechanistic consequences of binding have not yet been elucidated [64]. HSV-1 ICP27 functions differently, associating with the active STING/TBK1 complex, and preventing IRF3 recruitment and phosphorylation to block the downstream type I interferon response [65].

Certain pathogens have adapted to benefit from STING activation during infection. The intracellular bacterium Listeria monocytogenes secretes cyclic di-AMP directly into the cytosol of an infected cell, which binds and drives activation of STING [66]. Activation of STING in this context appears to prevent the induction of protective immunity to Listeria. This indicates that Listeria, and potentially other pathogens, may strategically manipulate STING for their own benefit, embracing and dysregulating signaling, rather than evading it.

Viral factors targeting the activation of STING provide a platform to gain a greater and more mechanistic understanding of this process. The details of how STING becomes activated after binding to 2’5’-cGAMP in cells remain incomplete — it is unclear how oligomerization might regulate STING trafficking, and likewise at what step post-translation modifications are applied to STING and exactly how they regulate signaling. Many factors produced by pathogens interfere with these processes, and future systematic study of those acting at different points may provide increased insight into the cell biological processes underlying STING activation. Further, recent STING structures in complex with TBK1 now provide a framework for structural study of factors like KSHV vIRF1 and HSV-1 ICP27 which act on the STING/TBK1 signalosome to prevent downstream immune activation. The details of how STING recruits other downstream factors aside from TBK1 and IRF3 are still unclear, but recent work shows that the HIV-2 Vpx protein can selectively inhibit STING-mediated NF-κB activation [67**], providing an opportunity to better understand this process.

Open questions and future prospects

In the short time since the discovery of cGAS–STING signaling, viral and bacterial factors targeting nearly every step in this pathway have been identified. However, for most of these factors, the specific molecular details cGAS and STING inhibition have not been determined. How do pathogen factors recognize and interact with cGAS and STING on a molecular level, and how has pathogen evasion shaped the structure and regulation of this innate immune pathway? Could viral or bacterial cGAS–STING pathway inhibitors make useful therapeutics for treating autoimmune diseases? cGAS was recently identified as part of a large family of bacterial cGAS/DnCV-like nucleotidyltransferase (CD-NTase) enzymes, encompassing thousands of homologs which drive immunity to phage through the action of numerous distinct downstream effectors including STING-like proteins. [68,69**,70]. Could bacteriophages share strategies, or perhaps even conserved mechanisms of immune evasion with mammalian viruses? Phage are known to encode anti-CRISPR nucleases to degrade a cyclic oligoadenylate second-messenger for evasion of Type III CRISPR systems [71] raising the question of whether these viruses might also encode enzymes functionally similar to poxin for evasion of CD-NTase signaling. Intervention by pathogens has often provided important new insight into basic biological processes, and future studies of cGAS–STING signaling must continue to harness the power of viruses and bacteria to generate answers to these questions.
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