Received: 8 August 2022 | Accepted: 11 October 2022

DOI: 10.1002/jmv.28220

REVIEW

JOURNAL OF MEDICAL VIROLOGY WILEY

SARS-CoV-2, HIV, and HPV: Convergent evolution of selective regulation of cGAS–STING signaling

Si Shen[1,2] | Yajuan Rui[1,2] | Yanpu Wang[1,2] | Jiaming Su[1,2] | Xiao-Fang Yu[1,2]

[1]Cancer Institute (Key Laboratory of Cancer Prevention and Intervention, China National Ministry of Education), The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China

[2]Cancer Center, Zhejiang University, Hangzhou, Zhejiang, China

Correspondence

Jiaming Su and Xiao-Fang Yu, Cancer Institute (Key Laboratory of Cancer Prevention and Intervention, China National Ministry of Education), The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, 310000 Zhejiang, China.
Email: xiaosuyoc@zju.edu.cn and xfyu1@zju.edu.cn

Funding information

Leading Innovative and Entrepreneur Team Introduction Program of Zhejiang; National Natural Science Foundation of Zhejiang Province; National Natural Science Foundation of China

Abstract

Recognizing aberrant cytoplasmic double-stranded DNA and stimulating innate immunity is essential for the host's defense against viruses and tumors. Cyclic GMP–AMP (cGAMP) synthase (cGAS) is a cytosolic DNA sensor that synthesizes the second messenger 2′3′-cGAMP and subsequently activates stimulator of interferon genes (STING)-mediated activation of TANK-binding kinase 1 (TBK1)/interferon regulatory factor 3 (IRF3) and the production of type I interferon (IFN-I). Both the cGAS–STING-mediated IFN-I antiviral defense and the countermeasures developed by diverse viruses have been extensively studied. However, recent studies have revealed a convergent evolutionary feature of severe acute respiratory syndrome coronavirus 2 and human immunodeficiency virus (HIV) viral proteins in terms of the selective regulation of cGAS–STING-mediated nuclear factor-κB (NF-κB) signaling without any effect on cGAS–STING-mediated TBK1/IRF3 activation and IFN production. The potential beneficial effect of this cGAS–STING-mediated, NF-κB-dependent antiviral effect, and the possible detrimental effect of IFN-I in the pathogenesis of coronavirus disease 2019 and HIV infection deserve more attention and future investigation.

KEYWORDS

cGAS–STING signaling, convergent evolution, viruses

1 | INTRODUCTION

Innate immunity is the host's main barrier for restricting viral replication. Recognition of pathogen-associated molecular patterns (PAMPs) via a vast array of pattern recognition receptors (PRRs) that stimulate innate immune responses is essential for the host's ability to combat viral infection.[1] Virus-sensing PRRs that are well studied include Toll-like receptors,[2] RIG-I-like receptors,[3] the nucleotide oligomerization domain-like receptors,[4] C-type lectin receptors,[5] and cytosolic DNA sensors (cyclic GMP–AMP (cGAMP) synthase [cGAS],[6] IFI16,[7] DDX41,[8] LRRFIP1,[9] and AIM2[10–13]). These sensors are widely expressed in various cellular compartments and constitute a continuous surveillance system against viral infection. Following the recognition and binding of PAMPs, these PRRs activate associated signaling pathways and evoke innate immune responses.[14] Innate immune activation manifests as a robust induction of IRF-dependent expression of interferons (IFNs) and a nuclear factor-κB (NF-κB)-dependent expression of proinflammatory cytokines or chemokines, which are critical for the host's ability to identify and withstand "nonself" pathogens.[15,16]

Cytosolic double-stranded DNA (dsDNA) is a potent activator of innate immunity. As part of this activation, the cytosolic DNA-sensing

pathway known as cGAS–stimulator of interferon genes (cGAS–STING) signaling has been shown to recognize a broad spectrum of viruses, including DNA viruses, RNA viruses, and retroviruses.[17–19] STING (also known as MITA, ERIS, MPYS, or TMEM173), an important adaptor in the cell, mediates multiple signaling pathways and plays an important role in antiviral innate immunity.[20–23]

The activator of STING, 2′3′-cGAMP, is produced by the cGAS, which recognizes DNA fragments in the cytoplasm.[6,24,25] STING can also be activated by the bacterial cyclic dinucleotides (CDNs), c-di-AMP, and c-di-GMP.[26,27] In addition to being directly produced in the cytoplasm, CDNs can also enter into the cytoplasm through the viral carriage,[28,29] cell–cell gap junctions,[30] and cell membrane transporters (solute carrier family 19 member 1 [SLC19A1], leucine-rich repeat containing 8 [LRRC8], and purinergic receptor P2X 7 [P2X7R]).[31–35] Once cGAMP and CDNs bind to STING, STING undergoes a conformational switch, leaves the endoplasmic reticulum (ER) with the assistance of Rhomboid 5 homolog 2 (iRhom2),[36] STING ER exit protein (STEEP),[37] translocon-associated protein beta (TRAPβ),[21] transmembrane p24 trafficking protein 2 (TMED2),[38] Yip1 domain family member 5 (YIPF5),[39] and other proteins, and moves to the Golgi apparatus through coated protein complex (COPII)-coated vesicles. Golgi-localized glycosaminoglycans interact with STING to initiate its oligomerization in the Golgi,[40] where STING recruits TANK-binding kinase 1 (TBK1) and IκB kinase (IKK) to trigger interferon regulatory factor 3 (IRF3) and NF-κB activation, respectively (Figure 1). In addition, it has been reported that a novel transcript isoform of STING without transmembrane domains, designated STING-β, sequesters cGAMP and impairs signal transduction.[41] cGAS–STING-mediated IRF3 and NF-κB signaling then triggers the stimulation of type I interferon (IFN-I), interferon-stimulated genes, and proinflammatory cytokines that orchestrate countermeasures against viral infection.[42]

For many years, IRF3-triggered IFN-I production has been considered the major antiviral immunity-related effect of cGAS–STING signaling. However, recent studies have demonstrated that STING mutants deficient in IRF3–IFN-I activation can protect the host against viral infection, suggesting that IFN-I-independent activities of cGAS–STING also elicit potent antiviral immunity.[43,44] As we mentioned above, in addition to IRF3, cGAS–STING activation simultaneously stimulates NF-κB cascades, which activate the transcription and expression of a variety of antiviral factors, induce dendritic cell (DC) maturation, and promote antigen presentation, indicating a prominent role for this NF-κB-dependent activity during viral pathogenesis.[45–47]

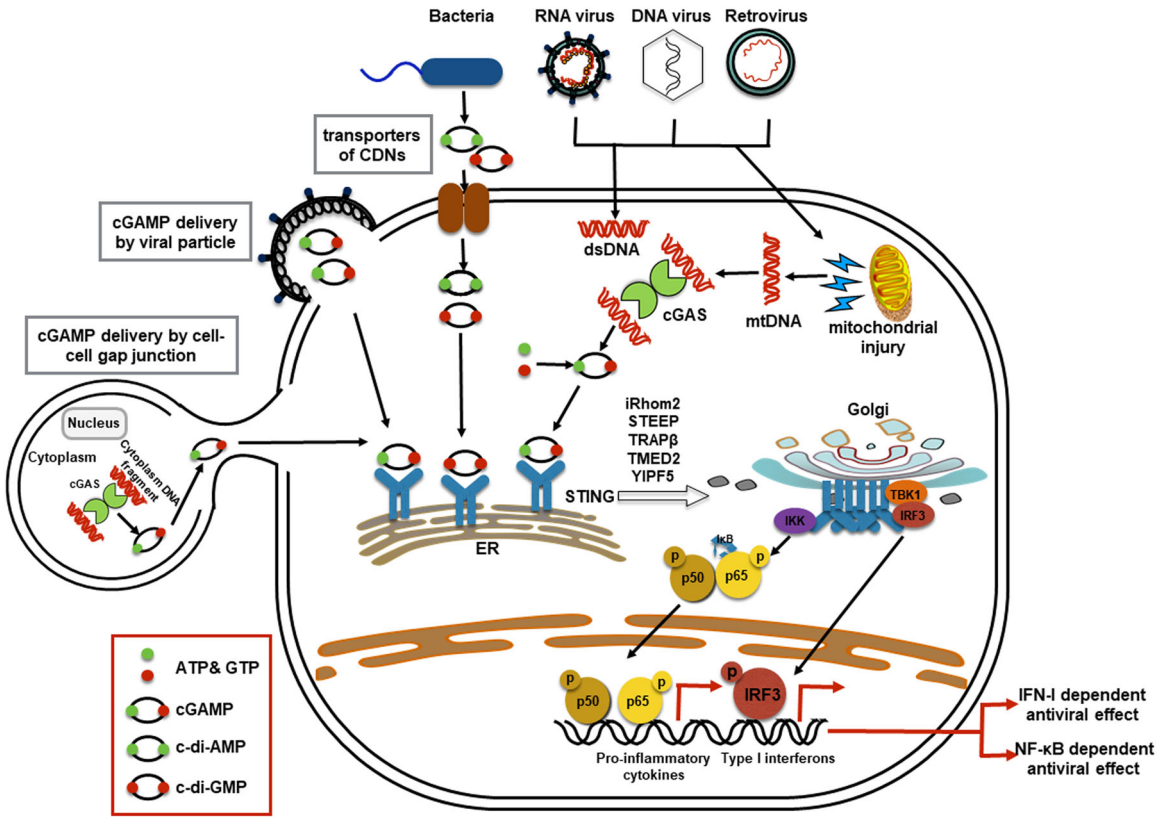

FIGURE 1 Overview of cGAS–STING signaling activation during pathogen infection. CDN, cyclic dinucleotide; cGAS, cyclic GMP–AMP (cGAMP) synthase; ER, endoplasmic reticulum; IRF3, interferon regulatory factor 3; iRhom2, rhomboid 5 homolog 2; mtDNA, mitochondrial DNA; NF-κB, nuclear factor-κB; STEEP, STING ER exit protein; STING, stimulator of interferon genes; TMED2, transmembrane p24 trafficking protein 2; TRAPβ, translocon-associated protein beta; YIPF5, Yip1 domain family member 5.

Of note, cGAS–STING signaling in the host can sense and respond to infection with a multitude of viruses, inducing a robust antiviral immunity. It has been widely reported that cGAS, a cytoplasmic DNA sensor, detects dsDNA derived from DNA viruses such as herpes simplex virus 1 (HSV-1) and human papillomavirus (HPV),[24,48] as well as reverse-transcribed DNA from retroviruses such as human immunodeficiency virus (HIV).[49,50] Also, HIV commonly replicates in the gut, which houses a vast microbiota that produces CDNs to activate STING signaling.[51,52] What is intriguing to us is that many studies have established that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the positive-sense RNA virus responsible for the coronavirus disease 2019 (COVID-19) pandemic, is also recognized by cGAS–STING signaling via mitochondrial DNA (mtDNA) leakage and cytoplasmic chromatin DNA induced during syncytia formation.[53–55] Since cGAS–STING-mediated IFN-I- and NF-κB-dependent immunity both threaten viral survival, viruses have evolved multiple immune evasion strategies. Understanding the immune evasion tricks used by a virus is frequently important for understanding the pathogenesis of that virus. Recently, we have discovered an interesting convergent evolutionary process that is responsible for selective antagonism to cGAS–STING–NF-κB signaling in diverse viruses, including SARS-CoV-2, HIV, and HPV.

2 | SARS-COV-2-TRIGGERED cGAS–STING ACTIVATION AND VIRAL EVASION

As we mentioned above, SARS-CoV-2 infection can activate the cGAS–STING pathway in two different ways. Viral infection triggers mitochondrial stress, which causes mitochondrial dysfunction as well as the shuttling of mtDNA from the host's mitochondria directly to the cytoplasm of its cells. Mass spectrometry (MS) analysis of the SARS-CoV-2-infected lung-on-chip model has revealed an enrichment of mitochondrial proteins in virally infected cells.[53] Moreover, after SARS-CoV-2 infection, the mitochondrial surface becomes swollen, and the cristae appear to be disrupted, indicating that SARS-CoV-2 infection disturbs mitochondrial homeostasis and induces mtDNA release.[53]

In addition to mtDNA leakage, syncytia formation is another major cause of cGAS–STING activation during SARS-CoV-2 infection.[56,57] Syncytia, large multinucleated cells produced by cell–cell fusion, are commonly seen in viral infection.[58] In the syncytia, cytoskeletal elements such as actin filaments (F-actin) appear diminished and collapsed during cell fusion, resulting in the disruption of the actin cytoskeleton and a cascading reduction in the levels of nuclear envelope lamin A and C proteins.[54] These proteins are important for maintaining laminar integrity and nuclear morphology.[59] The lamin A/C deficiency leads to genomic instability, DNA damage, and nuclear blebbing, which generate cytoplasmic chromatin leakage and micronuclei formation.[60–62] Subsequently, this chromosomal DNA and micronuclei in the cytoplasm are recognized by cGAS and activate cGAS–STING-mediated innate immunity.

Thus, cGAS–STING activation challenges the survival of SARS-CoV-2. Now, through extensive screening of agonists targeting PRR-sensing pathways, it has been found that the STING activators, CDNs, and a diamidobenzimidazole compound, diABZI-4, strongly antagonize viral infection in vitro.[63,64] Also, Liu et al.[65] have identified a novel STING agonist, CF501, that shows an excellent adjuvant effect with COVID-19 vaccines. Given that cGAS–STING triggers potent antiviral immunity, it is not surprising that SARS-CoV-2 has begun to evolve countermeasures to evade immune surveillance. However, recent fundamental studies have revealed that SARS-CoV-2 infection triggers a prolonged cGAS–STING-mediated IFN-I immune response that leads to immunopathology,[53] indicating that SARS-CoV-2 is defective in suppressing IFN-I and is selectively antagonizing IFN-I-independent antiviral immunity.

The genome of SARS-CoV-2 is approximately 30 kb in size, containing 14 open-reading frames (ORFs) and encoding 29 viral proteins.[66] Rui and colleagues[67] have screened the structural proteins, accessory proteins, and the main viral protease of SARS-CoV-2 and have identified ORF3a and 3CLpro as potent inhibitors of the cGAS–STING pathway (Figure 2). Interestingly, viral ORF3a and 3CLpro specifically inhibit cGAS–STING-mediated NF-κB signaling but not IRF3 signaling. Mechanically, ORF3a binds to the C-terminus

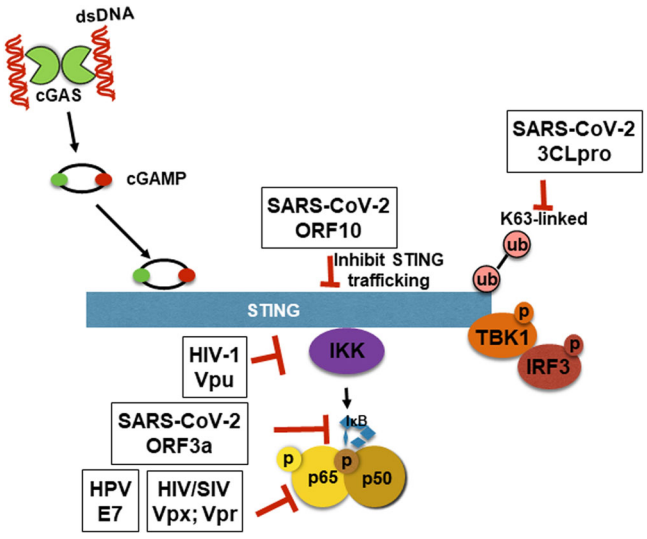

FIGURE 2 Schematic of multiple viral proteins involved in the convergent antagonism of cGAS–STING–NF-κB signaling. SARS-CoV-2 ORF3a interacts with STING and inhibits the degradation of IκBα to suppress p65 nuclear translocation. SARS-CoV-2 3CLpro inhibits K63-linked ubiquitination of STING to inhibit NF-κB signaling. HIV/SIV Vpx, Vpr, and HPV E7 selectively suppress NF-κB signaling and p65 nuclear translocation. HIV-1 Vpu binds to STING and specifically antagonizes STING-IKKβ signalosome assembly. SARS-CoV-2 ORF10 obstructs STING trafficking and impedes NF-κB activation. cGAS, cyclic GMP–AMP (cGAMP) synthase; dsDNA, double-stranded DNA; HIV, human immunodeficiency virus; HPV, human papillomavirus; IκBα, NF-κB inhibitor alpha; IKK, IκB kinase; IRF3, interferon regulatory factor 3; NF-κB, nuclear factor-κB; STING, stimulator of interferon genes; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TBK1, TANK-binding kinase 1.

and N-terminus of STING in a unique manner and prevents the degradation of NF-κB inhibitor alpha (IκBα), stabilizing the p65/p50 heterodimer. The stabilization of IκBα blocks the nuclear accumulation of p65 and ultimately suppression NF-κB signaling.[68] Moreover, ORF3a is present in the genomes of the pathogenic coronaviruses SARS and SARS-CoV-2 but is missing from the less-pathogenic β-coronaviruses HKU1 and OC43. ORF3a from SARS-CoV shares a homologous sequence and similar inhibitory ability with SARS-CoV-2. The evolution of ORF3a strengthens the immune evasion capacity of viruses and may explain the pathogenicity discrepancy among the various coronaviruses.

ORF3a has a Cys-rich region that has the potential to bind zinc, and a lipid-soluble zinc metal chelator, N, N, N′, N′-tetrakis (2-pyridylmethyl)-ethylenediamine, has been shown to block ORF3a function, making this inhibition a promising pharmacological intervention against SARS-CoV-2. In addition to ORF3a, 3CLpro complementarily suppresses STING-mediated NF-κB activation by disrupting the K63-linked ubiquitin modification of STING, which is pivotal for assembling the STING functional complex and downstream cascades.[69] Meanwhile, SARS-CoV-2 ORF9b and ORF10 are also reported to suppress cGAS–STING signaling. Han et al.[70] have demonstrated that ORF10 restrains cGAS–STING-induced IRF3/IFN-I signaling by interacting with STING to attenuate the STING–TBK1 assembly and impair STING oligomerization. Given that ORF10 also prevents the ER-to-Golgi trafficking of STING, it is likely that ORF10 also inhibits cGAS–STING-mediated NF-κB signaling since the NF-κB activation also relies on STING trafficking.[71] However, it has been established that ORF9b impedes the phosphorylation and nuclear translocation of IRF3,[72] rather than NF-κB signaling,[67] to suppress cGAS–STING-induced IFN-I. Taken together, these findings indicate that the cGAS–STING pathway recognizes SARS-CoV-2 infection and induces robust and broad antiviral immunity to thwart viral replication, but this virus also encodes at least three viral proteins that oppose NF-κB signaling, increasing the ability of viruses to evade the host's defense against it.

3 | HIV-MEDIATED cGAS–STING ACTIVATION AND VIRAL SUPPRESSION

HIV infection-mediated activation of cGAS–STING is a controversial and complex topic. Several studies have deemed HIV-1 a poor inducer of innate immunity. Cingöz and Goff[73] have demonstrated that infection with an HIV-1 strain lacking the *env*, *nef*, and *vpr* genes is barely able to activate measurable innate immune responses. Three prime repair exonuclease 1 (TREX1), a cytosolic exonuclease,[74] is reported to account for this poor immune activation. TREX1 binds to cytosolic HIV DNA and digests excess HIV DNA, which can be recognized by cGAS and activate antiviral innate immunity. However, in *Trex1*−/− human $CD4^+$ T cells and macrophages, cytosolic HIV DNA accumulates and stimulates cGAS–STING signaling.[75] Remarkably, HIV-1 is incapable of infecting DCs and inducing innate immune responses in them, a situation that increases the pathogenicity of HIV-1. When HIV-1 is complemented by the effect of Vpx, which overcomes sterile alpha motif and HD domain-containing protein-1 (SAMHD1) restriction,[76,77] DCs are effectively infected with HIV-1 and immune activation is augmented.[78] Meanwhile, Lahaye et al.[78] have found that the HIV-1 capsid cloaks the viral DNA, preventing innate immune sensing and activation. When the HIV-1 capsid is mutated to a sequence analogous to that of HIV-2, the cytosolic viral complementary DNA becomes exposed and then can be sensed by cGAS. Another reason that can explain the silencing of immunity in the case of HIV-1 is the fact that this triggering of cGAS–STING activation of viruses may depend on the viral load. Khan et al.[79] have reported that only a productive HIV-1 infection can evoke cGAS–STING-mediated innate immunity.

Nevertheless, several studies have asserted that infection with HIV-1 triggers cGAS–STING activation.[49,80] Since in this case the abundance of the cytoplasmic HIV DNA is below the detection limit, and an intact core physically hides the viral DNA from cGAS,[81] the host has developed alternate strategies to broaden its immune surveillance. Lahaye et al.[50] have demonstrated that the non-POU domain-containing octamer-binding protein (NONO) detects the nuclear viral core and promotes the recognition of HIV dsDNA by cGAS, thereby eliciting an antiviral immune response. Polyglutamine binding protein 1 (PQBP1) is another extensively confirmed coactivator of the recognition of HIV DNA by cGAS. Yoh et al.[82] have shown that PQBP1 directly binds to immunogenic reverse-transcribed HIV-1 DNA and interacts with cGAS, initiating downstream cascades. Furthermore, Yoh et al.[83] have discovered a two-step authentication immune-activation system in the host to fight retroviral infection: After HIV-1 infection occurs, PQBP1 recognizes the HIV-1 capsid before replication begins. PQBP1 then wraps around and decorates the viral core, serving as an alarm signal to summon cGAS. Then once the viral core disassembly and DNA synthesis are initiated, cGAS activates potent antiviral immunity. In addition to direct activation of cGAS–STING in virally infected cells, HIV-1's commonly commensal relationship with bacteria and DNA viruses can also lead to a stimulation of STING activation.[51,52,84] Thus, it is necessary for HIV to evade cGAS–STING-mediated antiviral activity for survival.

By means of various assay systems, Su et al.[85] have demonstrated that HIV-2/SIV Vpx can specifically limit cGAS–STING-triggered NF-κB activity, but not that of IRF3, to evade cGAS–STING activation (Figure 2). In particular, the functional domain in STING that is critical only for NF-κB activation is indispensable for Vpx binding. As one of the core pathways of the host's innate immune response, NF-κB signaling can activate the transcription and expression of a variety of antiviral factors, including a variety of interleukins and proinflammatory cytokines, and induce DC maturation to promote antigen presentation.[86] The maturation of DCs is fundamental to the host defense against viral infection, and it steers pathogen-specific adaptive immune responses.[87] It has been shown that Vpx clearly suppresses the cGAS–STING-triggered maturation of DCs as part of its defense mechanisms to escape immune surveillance. In addition, Vpr has been found to possess a synergistic

ability to act with Vpx to inhibit cGAS–STING-triggered NF-κB signaling. Another study has demonstrated that Vpr inhibits NF-κB by interfering with the degradation of IκBα.[88]

Although Vpx is an accessory protein that is found in HIV-2/SIV but is missing from the HIV-1 genome, it is unclear which viral protein encoded by HIV-1 is the source of the evolutionary convergence in selective STING inhibition. Most of the structural and nonstructural proteins in the HIV-1 and HIV-2 genomes are the same; only Vpu is specifically encoded by HIV-1. Several studies have indicated that Vpu is a potent suppressor of NF-κB-mediated antiviral immunity. Via comparative gene set enrichment and cytokine array analyses in infected $CD4^+$ T cells, infection with *vpu*-deficient HIV-1 strains has been shown to induce stronger NF-κB-triggered immune responses than those of wild-type viruses, suggesting that Vpu suppresses the expression of NF-κB-targeted restriction factors.[89] Furthermore, Bour et al.[90] have discovered that the expression of Vpu in HIV-infected T cells suppresses tumor necrosis factor-α-induced degradation of IκBα by recruiting the E3 ubiquitin ligase complex, β-transducin repeat-containing E3 ubiquitin-protein ligase (β-TrCP). In addition, Sauter et al.[91] have proposed an interesting concept that different viral proteins show distinct regulation of NF-κB signaling. NF-κB not only plays an important role in antiviral immunity but also assists viruses in the efficient transcription of their genes.[92] There are NF-κB-binding sites in the long terminal repeats (LTRs) of HIV-1. The binding of NF-κB p50/p65 heterodimers increases the accessibility of the LTRs to cellular RNA polymerase II.[93] Thus, HIV-1 utilizes the early protein Nef to boost NF-κB activation and the late protein Vpu to inhibit it.[91] Collectively, numerous studies have clearly demonstrated immunosuppression of Vpu and indicated that Vpu may selectively inhibit cGAS–STING-mediated NF-κB signaling, but the mechanism of this inhibition is still unclear. In-depth research has revealed that Vpu is a STING antagonist that selectively suppresses NF-κB signaling but not IRF3 (Figure 2). Mechanically, Vpu interacts with STING to disrupt STING's recruitment of IκB kinase-β, the critical component of NF-κB signaling, and obstruct the nuclear translocation of p65. HIV-1 viruses containing a Vpu mutant defective in STING inhibition have an improved replicative and infective ability. Thus, suppression of cGAS–STING-mediated NF-κB activation is pivotal for viral survival and spread, and interfering with this immune evasion strategy is a promising strategy for anti-HIV therapy.

4 | OTHER VIRAL INHIBITION OF cGAS–STING–NF-κB SIGNALING

A range of DNA viruses is among the most common activators of cGAS–STING signaling, including members of the *Herpesviridae*, *Hepadnaviridae*, *Papillomaviridae*, and *Adenoviridae*. DNA viruses must encode dedicated viral proteins to thwart the host defense.[94,95] HPV is a ubiquitous DNA tumor virus, and Lau et al.[96] have demonstrated that the HPV oncoprotein E7 is an antagonist of the cGAS–STING pathway. E7 interacts with STING to suppress IFN-β production, and the E7 LXCXE motif that is involved in binding to Rb is also necessary for counteracting cGAS–STING activation. Further studies have demonstrated that the HPV E7-mediated IFN-β inhibition is the result of suppression of the NF-κB element rather than that of IRF3 (Figure 2) (unpublished data). The finding that E7 convergently antagonizes NF-κB signaling further substantiates the commonality of selective regulation of cGAS–STING signaling by RNA viruses, DNA viruses, and retroviruses.

5 | NF-κB DEPENDENT ANTIVIRAL FUNCTION INDUCED BY THE cGAS–STING PATHWAY

Ever since the discovery of STING in 2008[21] and cGAS in 2013,[6] cGAS–STING pathway-mediated IRF3 activation and subsequent IFN-I production have been widely considered to be the major contributors to antiviral activity.[97,98] However, IFN-I production can also contribute to impaired host immunity and viral persistence. Many studies have shown that the blockade of chronic IFN-I signaling controls persistent lymphocytic choriomeningitis virus infection and reduces HIV-1 reservoirs by enhancing immune recovery.[99–101] Meanwhile, the aberrant and persistent activation of IFN-I has also been detected in critically ill COVID-19 patients; excessive IFN-I disturbs and exhausts the immune system and is associated with poor clinical outcomes in these patients.[53,102,103] Recently, an IFN-I-independent antiviral function of STING has come to the attention of scientists. Wu, Yamashiro, and colleagues have generated a STING mutant mouse model that features precise ablation of IFN-I activation while preserving the IFN-I-independent activity of the STING molecule. Interestingly, a STING mutant mouse model lacking STING-mediated IFN-I responses shows a restriction of HSV-1 infection that is comparable to that of mice with wild-type STING, indicating that the IFN-I-independent responses possess potent antiviral activity.[43,44] As we have described above, in addition to stimulating IRF3–IFN-I signaling, STING activation also augments NF-κB transcriptional activity. NF-κB activation is a hallmark of many viral infections, and it coordinates innate and adaptive immunity to accomplish the overall goal of resisting viral replication.[104,105] Thus, STING-mediated NF-κB signaling is a strong candidate for IFN-I-independent antiviral activity. To escape this immune surveillance, viruses must make use of the evasive tricks we have described to facilitate infection and replication.

6 | CONCLUSION

Numerous studies in recent years have shed light on the range and importance of cGAS–STING-mediated innate immunity in combating viruses. The cGAS–STING-mediated IFN-I antiviral defense and the counter-response by diverse viruses have been extensively studied in infectious diseases.[94] Nevertheless, recent studies have certified the existence of an NF-κB-dependent antiviral mechanism.[43] Our review

summarizes and discusses the NF-κB-dependent antiviral activity mediated by cGAS–STING signaling. To counteract immune surveillance, various viruses have developed evolutionarily convergent strategies to escape the cGAS–STING-triggered NF-κB pathway (Figure 2). This convergent evolutionary inhibition by multiple viruses demonstrates the importance of the cGAS–STING–NF-κB system for controlling viral infection. In addition, there are redundant and complementary STING antagonists that have evolved in SARS-CoV-2,[67] further indicating the significance of cGAS–STING–NF-κB signaling in the host defense against virus infection.

However, the current research still has some limitations. There are key questions and notions that are still not discussed in the literature (Box 1). Antagonistic mechanisms still need to be further elucidated, and this information may prove invaluable in helping us to block viral immune evasion strategies. The question of whether other types of viruses also encode viral proteins that specifically antagonize cGAS–STING–NF-κB signaling should also be thoroughly investigated. Given that various viruses selectively antagonize cGAS–STING downstream signaling, we hypothesize that cGAS–STING-mediated IRF3–IFN-I signaling may be relatively beneficial for viral survival, whereas NF-κB signaling is detrimental to viruses in the context of viral pathogenesis. It is true that chronic immune activation and sustained IFN-I induction are associated with the generation of viral reservoirs during latency in HIV infection.[106,107] In chronic infection, persistently low levels of IFN-I also contribute to the loss of $CD4^+$ T cells and immune exhaustion.[101,108] Meanwhile, it is widely recognized that aberrant activation of IFN-I is commonly detected in critical COVID-19 patients; this aberrant activation leads to immune dysfunction and predicts a poor clinical outcome.[53,102,103] Given that delayed, sustained IFN-I activation is beneficial to viral survival, and various viruses have evolved a selective suppression ability, we propose that NF-κB promotes the transcription and expression of one or more robust but currently unknown antiviral factor(s) that threaten the survival of multiple viruses. Therefore, identifying and characterizing the antiviral factor(s) transcribed by NF-κB is a worthy goal as part of the effort to develop "pan-antiviral" drugs.

BOX 1 Key questions to address

1. Is the selective inhibition of cGAS–STING-mediated NF-κB activity conserved among ORF3a and 3CLpro homologs across *Coronaviridae*?
2. NF-κB promotes HIV/SIV LTR activity. What is the effect of Vpr, Vpx, and Vpu on LTR activity during cGAS–STING activation?
3. Are there other types of viruses that have evolved the ability to specifically antagonize cGAS–STING-triggered NF-κB signaling?
4. Why have diverse viruses developed a convergent countermeasure to suppress cGAS–STING–NF-κB signaling?
5. Given the importance of cGAS–STING–NF-κB-mediated antiviral activity, can relevant broad-spectrum antiviral compounds be developed?

AUTHOR CONTRIBUTIONS

All authors read and approved the final manuscript. Si Shen wrote the preliminary version of the manuscript. Yajuan Rui and Yanpu Wang provided advice and suggestion for improving the manuscript. Jiaming Su and Xiao-Fang Yu edited and revised the manuscript.

ACKNOWLEDGMENTS

This study was supported by the National Natural Science Foundation of China (numbers 82102384, 82172239, 92169203, 31900133, 31970151, and 82271778), National Natural Science Foundation of Zhejiang Province (LY22C080002 and LQ21C010001), and Leading Innovative and Entrepreneur Team Introduction Program of Zhejiang (2019R01007). We also thank Dr. Deborah McClellan for her editorial assistance.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

All data are included in the article.

REFERENCES

1. Takeuchi O, Akira S. Pattern recognition receptors and inflammation. *Cell*. 2010;140:805-820. doi:10.1016/j.cell.2010.01.022
2. Kawai T, Akira S. The role of pattern-recognition receptors in innate immunity: update on Toll-like receptors. *Nat Immunol*. 2010;11:373-384. doi:10.1038/ni.1863
3. Rehwinkel J, Gack MU. RIG-I-like receptors: their regulation and roles in RNA sensing. *Nat Rev Immunol*. 2020;20:537-551. doi:10.1038/s41577-020-0288-3
4. Motta V, Soares F, Sun T, Philpott DJ. NOD-like receptors: versatile cytosolic sentinels. *Physiol Rev*. 2015;95:149-178. doi:10.1152/physrev.00009.2014
5. Dambuza IM, Brown GD. C-type lectins in immunity: recent developments. *Curr Opin Immunol*. 2015;32:21-27. doi:10.1016/j.coi.2014.12.002
6. Sun L, Wu J, Du F, Chen X, Chen Zhijian J. Cyclic GMP-AMP synthase is a cytosolic DNA sensor that activates the type I interferon pathway. *Science*. 2013;339:786-791. doi:10.1126/science.1232458
7. Unterholzner L, Keating SE, Baran M, et al. IFI16 is an innate immune sensor for intracellular DNA. *Nat Immunol*. 2010;11:997-1004. doi:10.1038/ni.1932
8. Zhang Z, Yuan B, Bao M, Lu N, Kim T, Liu YJ. The helicase DDX41 senses intracellular DNA mediated by the adaptor STING in dendritic cells. *Nat Immunol*. 2011;12:959-965. doi:10.1038/ni.2091
9. Yang P, An H, Liu X, et al. The cytosolic nucleic acid sensor LRRFIP1 mediates the production of type I interferon via a beta-catenin-dependent pathway. *Nat Immunol*. 2010;11:487-494. doi:10.1038/ni.1876
10. Hornung V, Ablasser A, Charrel-Dennis M, et al. AIM2 recognizes cytosolic dsDNA and forms a caspase-1-activating inflammasome with ASC. *Nature*. 2009;458:514-518. doi:10.1038/nature07725

11. Fernandes-Alnemri T, Yu JW, Datta P, Wu J, Alnemri ES. AIM2 activates the inflammasome and cell death in response to cytoplasmic DNA. *Nature*. 2009;458:509-513. doi:10.1038/nature07710
12. Roberts TL, Idris A, Dunn JA, et al. HIN-200 proteins regulate caspase activation in response to foreign cytoplasmic DNA. *Science*. 2009;323:1057-1060. doi:10.1126/science.1169841
13. Bürckstümmer T, Baumann C, Blüml S, et al. An orthogonal proteomic–genomic screen identifies AIM2 as a cytoplasmic DNA sensor for the inflammasome. *Nat Immunol*. 2009;10:266-272. doi:10.1038/ni.1702
14. Li D, Wu M. Pattern recognition receptors in health and diseases. *Signal Transduct Target Ther*. 2021;6:291. doi:10.1038/s41392-021-00687-0
15. Carty M, Guy C, Bowie AG. Detection of viral infections by innate immunity. *Biochem Pharmacol*. 2021;183:114316. doi:10.1016/j.bcp.2020.114316
16. Liu J, Qian C, Cao X. Post-translational modification control of innate immunity. *Immunity*. 2016;45:15-30. doi:10.1016/j.immuni.2016.06.020
17. Barber GN. STING: infection, inflammation and cancer. *Nat Rev Immunol*. 2015;15:760-770. doi:10.1038/nri3921
18. Anwar S, Ul Islam K, Azmi MI, Iqbal J. cGAS–STING-mediated sensing pathways in DNA and RNA virus infections: crosstalk with other sensing pathways. *Arch Virol*. 2021;166:3255-3268. doi:10.1007/s00705-021-05211-x
19. Huérfano S, Šroller V, Bruštíková K, Horníková L, Forstová J. The interplay between viruses and host DNA sensors. *Viruses*. 2022;14:666. doi:10.3390/v14040666
20. Abe T, Harashima A, Xia T, et al. STING recognition of cytoplasmic DNA instigates cellular defense. *Mol Cell*. 2013;50:5-15. doi:10.1016/j.molcel.2013.01.039
21. Ishikawa H, Barber GN. STING is an endoplasmic reticulum adaptor that facilitates innate immune signalling. *Nature*. 2008;455:674-678. doi:10.1038/nature07317
22. Sun W, Li Y, Chen L, et al. ERIS, an endoplasmic reticulum IFN stimulator, activates innate immune signaling through dimerization. *Proc Natl Acad Sci USA*. 2009;106:8653-8658. doi:10.1073/pnas.0900850106
23. Zhong B, Yang Y, Li S, et al. The adaptor protein MITA links virus-sensing receptors to IRF3 transcription factor activation. *Immunity*. 2008;29:538-550. doi:10.1016/j.immuni.2008.09.003
24. Wu J, Sun L, Chen X, et al. Cyclic GMP-AMP is an endogenous second messenger in innate immune signaling by cytosolic DNA. *Science*. 2013;339:826-830. doi:10.1126/science.1229963
25. Ablasser A, Goldeck M, Cavlar T, et al. cGAS produces a 2'-5'-linked cyclic dinucleotide second messenger that activates STING. *Nature*. 2013;498:380-384. doi:10.1038/nature12306
26. Cohen D, Melamed S, Millman A, et al. Cyclic GMP-AMP signalling protects bacteria against viral infection. *Nature*. 2019;574:691-695. doi:10.1038/s41586-019-1605-5
27. Woodward JJ, Iavarone AT, Portnoy DA. c-di-AMP secreted by intracellular *Listeria monocytogenes* activates a host type I interferon response. *Science*. 2010;328:1703-1705. doi:10.1126/science.1189801
28. Bridgeman A, Maelfait J, Davenne T, et al. Viruses transfer the antiviral second messenger cGAMP between cells. *Science*. 2015;349:1228-1232. doi:10.1126/science.aab3632
29. Gentili M, Kowal J, Tkach M, et al. Transmission of innate immune signaling by packaging of cGAMP in viral particles. *Science*. 2015;349:1232-1236. doi:10.1126/science.aab3628
30. Ablasser A, Schmid-Burgk JL, Hemmerling I, et al. Cell intrinsic immunity spreads to bystander cells via the intercellular transfer of cGAMP. *Nature*. 2013;503:530-534. doi:10.1038/nature12640
31. Luteijn RD, Zaver SA, Gowen BG, et al. SLC19A1 transports immunoreactive cyclic dinucleotides. *Nature*. 2019;573:434-438. doi:10.1038/s41586-019-1553-0
32. Lahey LJ, Mardjuki RE, Wen X, et al. LRRC8A:C/E heteromeric channels are ubiquitous transporters of cGAMP. *Mol Cell*. 2020;80:578-591.e575. doi:10.1016/j.molcel.2020.10.021
33. Zhou C, Chen X, Planells-Cases R, et al. Transfer of cGAMP into bystander cells via LRRC8 volume-regulated anion channels augments STING-Mediated interferon responses and anti-viral immunity. *Immunity*. 2020;52:767-781.e766. doi:10.1016/j.immuni.2020.03.016
34. Zhou Y, Fei M, Zhang G, et al. Blockade of the phagocytic receptor MerTK on tumor-associated macrophages enhances P2X7R-dependent STING activation by Tumor-derived cGAMP. *Immunity*. 2020;52:357-373.e359. doi:10.1016/j.immuni.2020.01.014
35. Ritchie C, Cordova AF, Hess GT, Bassik MC, Li L. SLC19A1 is an importer of the immunotransmitter cGAMP. *Mol Cell*. 2019;75:372-381.e375. doi:10.1016/j.molcel.2019.05.006
36. Luo WW, Li S, Li C, et al. iRhom2 is essential for innate immunity to DNA viruses by mediating trafficking and stability of the adaptor STING. *Nat Immunol*. 2016;17:1057-1066. doi:10.1038/ni.3510
37. Zhang BC, Nandakumar R, Reinert LS, et al. STEEP mediates STING ER exit and activation of signaling. *Nat Immunol*. 2020;21:868-879. doi:10.1038/s41590-020-0730-5
38. Sun MS, Zhang J, Jiang LQ, et al. TMED2 potentiates cellular IFN responses to DNA viruses by reinforcing MITA dimerization and facilitating its trafficking. *Cell Rep*. 2018;25:3086-3098.e3083. doi:10.1016/j.celrep.2018.11.048
39. Ran Y, Xiong MG, Xu ZS, Luo WW, Wang SY, Wang YY. YIPF5 is essential for innate immunity to DNA virus and facilitates COPII-dependent STING trafficking. *J Immunol*. 2019;203:1560-1570. doi:10.4049/jimmunol.1900387
40. Fang R, Jiang Q, Guan Y, et al. Golgi apparatus-synthesized sulfated glycosaminoglycans mediate polymerization and activation of the cGAMP sensor STING. *Immunity*. 2021;54:962-975.e968. doi:10.1016/j.immuni.2021.03.011
41. Wang PH, Fung SY, Gao WW, et al. A novel transcript isoform of STING that sequesters cGAMP and dominantly inhibits innate nucleic acid sensing. *Nucleic Acids Res*. 2018;46:4054-4071. doi:10.1093/nar/gky186
42. Yum S, Li M, Fang Y, Chen ZJ. TBK1 recruitment to STING activates both IRF3 and NF-κB that mediate immune defense against tumors and viral infections. *Proc Natl Acad Sci USA*. 2021;118:e2100225118. doi:10.1073/pnas.2100225118
43. Wu J, Dobbs N, Yang K, Yan N. Interferon-independent activities of mammalian STING mediate antiviral response and tumor immune evasion. *Immunity*. 2020;53:115-126.e115. doi:10.1016/j.immuni.2020.06.009
44. Yamashiro LH, Wilson SC, Morrison HM, et al. Interferon-independent STING signaling promotes resistance to HSV-1 in vivo. *Nat Commun*. 2020;11:3382. doi:10.1038/s41467-020-17156-x
45. Deng L, Zeng Q, Wang M, et al. Suppression of NF-κB activity: a viral immune evasion mechanism. *Viruses*. 2018;10:409. doi:10.3390/v10080409
46. Song K, Li S. The role of ubiquitination in NF-κB signaling during virus infection. *Viruses*. 2021;13:145. doi:10.3390/v13020145
47. Liu T, Zhang L, Joo D, Sun SC. NF-κB signaling in inflammation. *Signal Transduct Target Ther*. 2017;2:17023. doi:10.1038/sigtrans.2017.23
48. Sun L, Wu J, Du F, Chen X, Chen ZJ. Cyclic GMP-AMP synthase is a cytosolic DNA sensor that activates the type I interferon pathway. *Science*. 2013;339:786-791. doi:10.1126/science.1232458

49. Gao D, Wu J, Wu YT, et al. Cyclic GMP-AMP synthase is an innate immune sensor of HIV and other retroviruses. *Science*. 2013;341:903-906. doi:10.1126/science.1240933
50. Lahaye X, Gentili M, Silvin A, et al. NONO detects the nuclear HIV capsid to promote cGAS-mediated innate immune activation. *Cell*. 2018;175:488-501.e422. doi:10.1016/j.cell.2018.08.062
51. Dillon SM, Frank DN, Wilson CC. The gut microbiome and HIV-1 pathogenesis: a two-way street. *AIDS*. 2016;30:2737-2751. doi:10.1097/qad.0000000000001289
52. Erttmann SF, Swacha P, Aung KM, et al. The gut microbiota prime systemic antiviral immunity via the cGAS–STING–IFN-I axis. *Immunity*. 2022;55:847-861.e810. doi:10.1016/j.immuni.2022.04.006
53. Domizio JD, Gulen MF, Saidoune F, et al. The cGAS–STING pathway drives type I IFN immunopathology in COVID-19. *Nature*. 2022;603:145-151. doi:10.1038/s41586-022-04421-w
54. Zhou Z, Zhang X, Lei X, et al. Sensing of cytoplasmic chromatin by cGAS activates innate immune response in SARS-CoV-2 infection. *Signal Transduct Target Ther*. 2021;6:382. doi:10.1038/s41392-021-00800-3
55. Liu X, Wei L, Xu F, et al. SARS-CoV-2 spike protein-induced cell fusion activates the cGAS–STING pathway and the interferon response. *Sci Signal*. 2022;15:eabg8744. doi:10.1126/scisignal.abg8744
56. Buchrieser J, Dufloo J, Hubert M, et al. Syncytia formation by SARS-CoV-2-infected cells. *EMBO J*. 2020;39:e106267. doi:10.15252/embj.2020106267
57. Rajah MM, Hubert M, Bishop E, et al. SARS-CoV-2 alpha, beta, and delta variants display enhanced spike-mediated syncytia formation. *EMBO J*. 2021;40:e108944. doi:10.15252/embj.2021108944
58. Leroy H, Han M, Woottum M, et al. Virus-mediated cell–cell fusion. *Int J Mol Sci*. 2020;21:9644. doi:10.3390/ijms21249644
59. Buxboim A, Swift J, Irianto J, et al. Matrix elasticity regulates lamin-A,C phosphorylation and turnover with feedback to actomyosin. *Curr Biol*. 2014;24:1909-1917. doi:10.1016/j.cub.2014.07.001
60. Sullivan T, Escalante-Alcalde D, Bhatt H, et al. Loss of A-type lamin expression compromises nuclear envelope integrity leading to muscular dystrophy. *J Cell Biol*. 1999;147:913-920. doi:10.1083/jcb.147.5.913
61. Goldman RD, Shumaker DK, Erdos MR, et al. Accumulation of mutant lamin A causes progressive changes in nuclear architecture in Hutchinson–Gilford progeria syndrome. *Proc Natl Acad Sci USA*. 2004;101:8963-8968. doi:10.1073/pnas.0402943101
62. Karoutas A, Szymanski W, Rausch T, et al. The NSL complex maintains nuclear architecture stability via lamin A/C acetylation. *Nat Cell Biol*. 2019;21:1248-1260. doi:10.1038/s41556-019-0397-z
63. Humphries F, et al. A diamidobenzimidazole STING agonist protects against SARS-CoV-2 infection. *Sci Immunol*. 2021;6:eabi9002. doi:10.1126/sciimmunol.abi9002
64. Li M, Ferretti M, Ying B, et al. Pharmacological activation of STING blocks SARS-CoV-2 infection. *Sci Immunol*. 2021;6:eabi9007. doi:10.1126/sciimmunol.abi9007
65. Liu Z, Zhou J, Xu W, et al. A novel STING agonist-adjuvanted pan-sarbecovirus vaccine elicits potent and durable neutralizing antibody and T cell responses in mice, rabbits and NHPs. *Cell Res*. 2022;32:269-287. doi:10.1038/s41422-022-00612-2
66. Yang H, Rao Z. Structural biology of SARS-CoV-2 and implications for therapeutic development. *Nat Rev Microbiol*. 2021;19:685-700. doi:10.1038/s41579-021-00630-8
67. Rui Y, Su J, Shen S, et al. Unique and complementary suppression of cGAS–STING and RNA sensing- triggered innate immune responses by SARS-CoV-2 proteins. *Signal Transduct Target Ther*. 2021;6:123. doi:10.1038/s41392-021-00515-5
68. Ghosh S, May MJ, Kopp EB. NF-kappa B and Rel proteins: evolutionarily conserved mediators of immune responses. *Annu Rev Immunol*. 1998;16:225-260. doi:10.1146/annurev.immunol.16.1.225
69. Zhang J, Hu MM, Wang YY, Shu HB. TRIM32 protein modulates type I interferon induction and cellular antiviral response by targeting MITA/STING protein for K63-linked ubiquitination. *J Biol Chem*. 2012;287:28646-28655. doi:10.1074/jbc.M112.362608
70. Han L, Zheng Y, Deng J, et al. SARS-CoV-2 ORF10 antagonizes STING-dependent interferon activation and autophagy. *J Med Virol*. 2022;94:5174-5188. doi:10.1002/jmv.27965
71. Balka KR, De Nardo D. Molecular and spatial mechanisms governing STING signalling. *FEBS J*. 2021;288:5504-5529. doi:10.1111/febs.15640
72. Han L, Zhuang MW, Deng J, et al. SARS-CoV-2 ORF9b antagonizes type I and III interferons by targeting multiple components of the RIG-I/MDA-5–MAVS, TLR3–TRIF, and cGAS–STING signaling pathways. *J Med Virol*. 2021;93:5376-5389. doi:10.1002/jmv.27050
73. Cingöz O, Goff SP. HIV-1 is a poor inducer of innate immune responses. *mBio*. 2019;10:e02834-18. doi:10.1128/mBio.02834-18
74. Mazur DJ, Perrino FW. Identification and expression of the TREX1 and TREX2 cDNA sequences encoding mammalian 3′-->5′ exonucleases. *J Biol Chem*. 1999;274:19655-19660. doi:10.1074/jbc.274.28.19655
75. Yan N, Regalado-Magdos AD, Stiggelbout B, Lee-Kirsch MA, Lieberman J. The cytosolic exonuclease TREX1 inhibits the innate immune response to human immunodeficiency virus type 1. *Nat Immunol*. 2010;11:1005-1013. doi:10.1038/ni.1941
76. Hrecka K, Hao C, Gierszewska M, et al. Vpx relieves inhibition of HIV-1 infection of macrophages mediated by the SAMHD1 protein. *Nature*. 2011;474:658-661. doi:10.1038/nature10195
77. Laguette N, Sobhian B, Casartelli N, et al. SAMHD1 is the dendritic- and myeloid-cell-specific HIV-1 restriction factor counteracted by Vpx. *Nature*. 2011;474:654-657. doi:10.1038/nature10117
78. Lahaye X, Satoh T, Gentili M, et al. The capsids of HIV-1 and HIV-2 determine immune detection of the viral cDNA by the innate sensor cGAS in dendritic cells. *Immunity*. 2013;39:1132-1142. doi:10.1016/j.immuni.2013.11.002
79. Khan H, Sumner RP, Rasaiyaah J, et al. HIV-1 Vpr antagonizes innate immune activation by targeting karyopherin-mediated NF-κB/IRF3 nuclear transport. *eLife*. 2020;9:e60821. doi:10.7554/eLife.60821
80. Vermeire J, Roesch F, Sauter D, et al. HIV triggers a cGAS-dependent, Vpu- and Vpr-regulated type I interferon response in CD4(+) T cells. *Cell Rep*. 2016;17:413-424. doi:10.1016/j.celrep.2016.09.023
81. Sumner RP, Harrison L, Touizer E, et al. Disrupting HIV-1 capsid formation causes cGAS sensing of viral DNA. *EMBO J*. 2020;39:e103958. doi:10.15252/embj.2019103958
82. Yoh SM, Schneider M, Seifried J, et al. PQBP1 is a proximal sensor of the cGAS-dependent innate response to HIV-1. *Cell*. 2015;161:1293-1305. doi:10.1016/j.cell.2015.04.050
83. Yoh SM, Mamede JI, Lau D, et al. Recognition of HIV-1 capsid by PQBP1 licenses an innate immune sensing of nascent HIV-1 DNA. *Mol Cell*. 2022;82:2871-2884. doi:10.1016/j.molcel.2022.06.010
84. Cheung AKL, Huang Y, Kwok HY, Chen M, Chen Z. Latent human cytomegalovirus enhances HIV-1 infection in CD34(+) progenitor cells. *Blood Adv*. 2017;1:306-318. doi:10.1182/bloodadvances.2016000638
85. Su J, Rui Y, Lou M, et al. HIV-2/SIV Vpx targets a novel functional domain of STING to selectively inhibit cGAS–STING-mediated NF-κB signalling. *Nat Microbiol*. 2019;4:2552-2564. doi:10.1038/s41564-019-0585-4

86. O'Sullivan BJ, Thomas R. CD40 ligation conditions dendritic cell antigen-presenting function through sustained activation of NF-κB. *J Immunol*. 2002;168:5491-5498. doi:10.4049/jimmunol.168.11.5491
87. Hilligan KL, Ronchese F. Antigen presentation by dendritic cells and their instruction of CD4+ T helper cell responses. *Cell Mol Immunol*. 2020;17:587-599. doi:10.1038/s41423-020-0465-0
88. Kogan M, Deshmane S, Sawaya BE, Gracely EJ, Khalili K, Rappaport J. Inhibition of NF-κB activity by HIV-1 Vpr is dependent on Vpr binding protein. *J Cell Physiol*. 2013;228:781-790. doi:10.1002/jcp.24226
89. Langer S, Hammer C, Hopfensperger K, et al. HIV-1 Vpu is a potent transcriptional suppressor of NF-κB-elicited antiviral immune responses. *eLife*. 2019;8:e41930. doi:10.7554/eLife.41930
90. Bour S, Perrin C, Akari H, Strebel K. The human immunodeficiency virus type 1 vpu protein inhibits NF-κB activation by interfering with βTrCP-mediated degradation of IκB. *J Biol Chem*. 2001;276:15920-15928. doi:10.1074/jbc.M010533200
91. Sauter D, Hotter D, Van Driessche B, et al. Differential regulation of NF-κB-mediated proviral and antiviral host gene expression by primate lentiviral Nef and Vpu proteins. *Cell Rep*. 2015;10:586-599. doi:10.1016/j.celrep.2014.12.047
92. Chan JK, Greene WC. Dynamic roles for NF-κB in HTLV-I and HIV-1 retroviral pathogenesis. *Immunol Rev*. 2012;246:286-310. doi:10.1111/j.1600-065X.2012.01094.x
93. Williams SA, Chen LF, Kwon H, Ruiz-Jarabo CM, Verdin E, Greene WC. NF-kappaB p50 promotes HIV latency through HDAC recruitment and repression of transcriptional initiation. *EMBO J*. 2006;25:139-149. doi:10.1038/sj.emboj.7600900
94. Ma Z, Damania B. The cGAS–STING defense pathway and its counteraction by viruses. *Cell Host Microbe*. 2016;19:150-158. doi:10.1016/j.chom.2016.01.010
95. Phelan T, Little MA, Brady G. Targeting of the cGAS–STING system by DNA viruses. *Biochem Pharmacol*. 2020;174:113831. doi:10.1016/j.bcp.2020.113831
96. Lau L, Gray Elizabeth E, Brunette Rebecca L, Stetson Daniel B. DNA tumor virus oncogenes antagonize the cGAS–STING DNA-sensing pathway. *Science*. 2015;350:568-571. doi:10.1126/science.aab3291
97. Dobbs N, Burnaevskiy N, Chen D, Gonugunta VK, Alto NM, Yan N. STING activation by translocation from the ER is associated with infection and autoinflammatory disease. *Cell Host Microbe*. 2015;18:157-168. doi:10.1016/j.chom.2015.07.001
98. Schoggins JW, Wilson SJ, Panis M, et al. A diverse range of gene products are effectors of the type I interferon antiviral response. *Nature*. 2011;472:481-485. doi:10.1038/nature09907
99. Teijaro JR, Ng C, Lee AM, et al. Persistent LCMV infection is controlled by blockade of type I interferon signaling. *Science*. 2013;340:207-211. doi:10.1126/science.1235214
100. Wilson EB, Yamada DH, Elsaesser H, et al. Blockade of chronic type I interferon signaling to control persistent LCMV infection. *Science*. 2013;340:202-207. doi:10.1126/science.1235208
101. Cheng L, Ma J, Li J, et al. Blocking type I interferon signaling enhances T cell recovery and reduces HIV-1 reservoirs. *J Clin Invest*. 2017;127:269-279. doi:10.1172/jci90745
102. Lowery SA, Sariol A, Perlman S. Innate immune and inflammatory responses to SARS-CoV-2: implications for COVID-19. *Cell Host Microbe*. 2021;29:1052-1062. doi:10.1016/j.chom.2021.05.004
103. Zhou Z, Ren L, Zhang L, et al. Heightened innate immune responses in the respiratory tract of COVID-19 patients. *Cell Host Microbe*. 2020;27:883-890.e882. doi:10.1016/j.chom.2020.04.017
104. Gilmore TD. Introduction to NF-kappaB: players, pathways, perspectives. *Oncogene*. 2006;25:6680-6684. doi:10.1038/sj.onc.1209954
105. Santoro MG, Rossi A, Amici C. NF-kappaB and virus infection: who controls whom. *EMBO J*. 2003;22:2552-2560. doi:10.1093/emboj/cdg267
106. Dickey LL, Martins LJ, Planelles V, Hanley TM. HIV-1-induced type I IFNs promote viral latency in macrophages. *J Leukoc Biol*. 2022. doi:10.1002/jlb.4ma0422-616r
107. Rojas M, Luz-Crawford P, Soto-Rifo R, Reyes-Cerpa S, Toro-Ascuy D. The landscape of IFN/ISG signaling in HIV-1-infected macrophages and its possible role in the HIV-1 latency. *Cells*. 2021;10:2378. doi:10.3390/cells10092378
108. Bosinger SE, Utay NS. Type I interferon: understanding its role in HIV pathogenesis and therapy. *Curr HIV/AIDS Rep*. 2015;12:41-53. doi:10.1007/s11904-014-0244-6

How to cite this article: Shen S, Rui Y, Wang Y, Su J, Yu X-F. SARS-CoV-2, HIV, and HPV: convergent evolution of selective regulation of cGAS–STING signaling. *J Med Virol*. 2022;95:e28220. doi:10.1002/jmv.28220