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Balancing STING in antimicrobial defense and autoinflammation

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ABSTRACT

Rapid detection of microbes is crucial for eliciting an effective immune response. Innate immune receptors survey the intracellular and extracellular environment for signs of a microbial infection. When they detect a pathogen-associated molecular pattern (PAMP), such as viral DNA, they alarm the cell about the ongoing infection. The central signaling hub in sensing of viral DNA is the stimulator of interferon genes (STING). Upon activation, STING induces downstream signaling events that ultimately result in the production of type I interferons (IFN I), important cytokines in antimicrobial defense, in particular towards viruses. In this review, we describe the molecular features of STING, including its upstream sensors and ligands, its sequence and structural conservation, common polymorphisms, and its localization. We further highlight how STING activation requires a careful balance: its activity is essential for antiviral defense, but unwanted activation through mutations or accidental recognition of self-derived DNA causes autoinflammatory diseases. Several mechanisms, such as post-translational modifications, ensure this balance by fine-tuning STING activation. Finally, we discuss how viruses evade detection of their genomes by either exploiting cells that lack a functional DNA sensing pathway as a niche or by interfering with STING activation through viral evasion molecules. Insight into STING's exact mechanisms in health and disease will guide the development of novel clinical interventions for microbial infections, autoinflammatory diseases, and beyond.

1. Introduction

The innate immune system provides the first line of host defense against microbial infection and is essential to initiate adaptive immune responses. Pattern recognition receptors (PRRs) sense pathogen-associated molecular patterns (PAMPs) of invading microbes [1]. Amongst these PRRs are DNA and RNA sensors, which detect foreign nucleic acids and activate downstream signaling pathways, leading to the production and secretion of pro-inflammatory cytokines, chemokines, and type I interferons (IFN I: 13 IFNα subtypes, IFNβ, -ε, -κ, and -ω) [2]. Secreted IFN I engages the IFN I receptor (*in cis* or *in trans*), activating the JAK/STAT pathway and thereby inducing the transcription of interferon-stimulated genes (ISGs) [3] (Fig. 1). The protein products of ISGs establish an antiviral state in host cells, stimulate adaptive immunity, and aid the elimination of the pathogen. Many components of the nucleic acid sensing machinery are ISGs themselves, ensuring a positive feedback loop [4]. Most PAMPs are exclusive to (groups of) pathogens, yet nucleic acids can originate from host cells as well. For example, DNA localized outside the nucleus or mitochondria can trigger strong innate immune responses [5]. This creates a paradox: undesired recognition of nucleic acids by PRRs can cause autoinflammatory and autoimmune disorders [6], yet detection of nucleic acids forms an indispensable mechanism of host defense against pathogens. Hence, there is a need to carefully balance activation and inactivation of innate immune responses following sensing of PAMPs or their host-derived equivalents.

Key DNA and RNA sensors survey various cellular compartments and induce different downstream responses. The recognition of viral or host RNA by the RNA sensing machinery has been expertly reviewed elsewhere and will not be discussed here [7,8]. Of the known DNA sensors, Toll-like receptor (TLR) 9 is localized to endosomal compartments where it detects DNA that contains unmethylated CpG motifs originating from pathogens and dying cells and triggers IFN I production [9]. Absent in melanoma 2 (AIM2) and interferon-γ inducible protein 16 (IFI16) detect cytosolic and nuclear DNA and activate the inflammasome, leading to the maturation and secretion of interleukin (IL)-1β and/or IL-18, and pyroptosis [10]. How cytosolic DNA triggers IFN I production was unknown until 2008 when the groups of Barber

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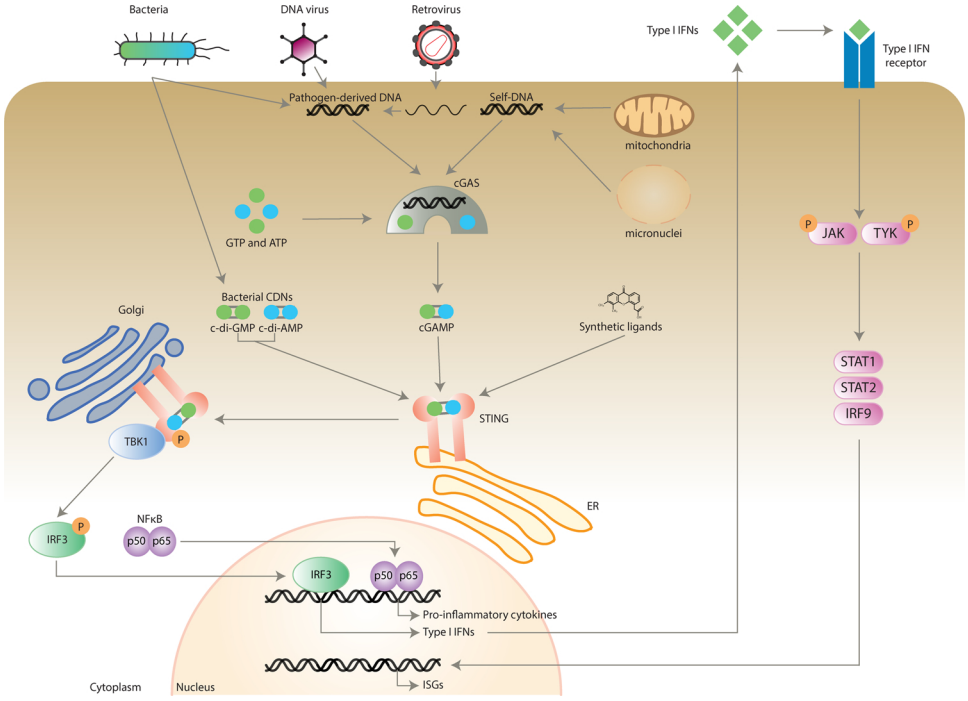

Fig. 1. cGAS/STING-dependent innate immune signaling. Microbial infections introduce pathogen-derived DNA in the cytosol. Self-DNA can also be sensed by cytosolic DNA sensors following leakage from mitochondria or the cell nucleus or localization in micronuclei. Upon encountering stimulatory DNA, cGAS utilizes GTP and ATP to produce the second messenger cGAMP. This cellular CDN as well as bacterial CDNs, such as c-di-AMP/GMP, or synthetic STING ligands bind and activate STING, inducing trafficking of STING from the ER towards the Golgi compartments. As a next step, TBK1 associates with and phosphorylates STING, allowing recruitment of IRF3. The activated transcription factors IRF3 (and NFκB) are translocated into the nucleus as dimers, where they initiate the production of IFN I (and pro-inflammatory cytokines). In turn, secreted IFN I binds to the IFNAR and activates the JAK/STAT pathway in an autocrine or paracrine fashion, inducing the transcription of ISGs.

and Zhong discovered it to rely primarily on the adaptor stimulator of interferon genes (STING; also termed MITA, ERIS, MPYS, TMEM173) [11–13]. The discovery of STING led to the challenging search for upstream sensor(s) and numerous candidates have been proposed over the years (Supplementary Table 1) [14–31]. In 2013, Chen and colleagues identified cyclic GMP-AMP synthase (cGAS) as the main cytosolic sensor for double stranded (ds) DNA upstream of STING [14]. IFI16 cooperates with cGAS in this pathway in keratinocytes and macrophages [29,30]. How other candidate DNA sensors (Supplementary Table 1) contribute to STING-dependent IFN I signaling requires further investigation. Perhaps they function as co-sensors for cGAS that fine-tune the magnitude and duration of IFN I production following detection of cytosolic DNA.

Activation of STING (Fig. 1) is induced upon binding of cyclic dinucleotides (CDNs), such as the non-canonical second messenger cyclic [G(2′-5′)pA(3′-5′)p] (2′3′cGAMP, here referred to as cGAMP), produced by cGAS [14,32]. Subsequent conformational changes in the STING homodimers permit their relocation from the endoplasmic reticulum (ER) to perinuclear Golgi compartments. Subsequently, Tank-binding kinase 1 (TBK1) associates with STING and recruits interferon regulatory factor 3 (IRF3) [33–35]. Various phosphorylation events culminate in the translocation of IRF3 dimers into the nucleus to stimulate IFN I transcription. In addition, the transcription factors nuclear factor-κB (NF-κB) and STAT6 are also activated downstream of STING, inducing pro-inflammatory cytokine and chemokine production [36,37]. Besides innate immune responses, other processes regulated by STING include autophagy, senescence, and cell death pathways, reviewed elsewhere [38].

Here, we will zoom in on the characteristics, activation, and regulation of STING signaling in the IFN I response. Where relevant, we will discuss aspects of cGAS in relation to STING's function. We will consider how STING-deficient cells provide a niche for viruses that would otherwise activate the cGAS-STING pathway and how viruses evade activation of STING in STING-expressing cells. In addition, we review how erroneous STING activation leads to autoinflammatory disorders and how cells ensure STING activation remains balanced. The role of STING in tumor biology and anti-tumor immunity will not be covered here, in light of recent reviews on this topic [39,40].

2. STING, a central hub in cytosolic DNA sensing

2.1. Importance of STING

Evidence from knock-out models has highlighted STING's importance during microbial infection *in vitro* and *in vivo*. Fibroblasts and myeloid cells from STING knockout mice were greatly affected in their ability to produce IFN I following infection with the DNA viruses herpes simplex virus 1 (HSV-1), vaccinia virus (VACV), cytomegalovirus (HCMV), and baculovirus [12,33]. These cells were also deficient in their protection against other microbes, including *Listeria monocytogenes* [33]. *In vivo*, STING-deficient mice are more susceptible to lethal infection by HSV-1, but not the RNA virus Encephalomyocarditis virus (EMCV) [33]. Surprisingly, STING-deficient mice also demonstrated increased susceptibility to the negative-stranded RNA virus vesicular stomatitis virus (VSV) [33]. Although not formally tested, this may result from decreased tonic IFN I signaling in the absence of STING and hence reduced expression of ISGs, including the RNA sensing machinery. Through IFN I induction, STING also promotes adaptive immune responses, e.g. STING-deficient mice show diminished cytotoxic T-cell activation upon plasmid DNA vaccination, indicating that STING facilitates the adjuvant activity of DNA-based vaccines [33]. Besides targeted STING knockout mice, the mutagen-induced mouse strain 'Goldenticket' has a T596A substitution in STING resulting in a loss-of-function phenotype [41]. These mice also succumb more readily to lethal infection by HSV-1 and fail to produce IFN I upon infection with *Listeria* [41,42]. *In vitro* studies have also implicated STING in the detection of adenovirus (AdV), human immunodeficiency virus (HIV), the RNA viruses Dengue virus (DENV) and Zika virus (ZIKV), many bacterial species such as *Mycobacteria tuberculosis*, *Legionella pneumophila*, *Streptococcus pneumonia*, *Chlamydia*, *Neisseria*, and *Francisella,* and the malaria parasite *Plasmodium falciparum* [43–53]. With regard to these examples, it is not clear to what extent STING is essential for host survival, although STING clearly impacts on IFN I production and pathogen burden. For instance, while Goldenticket mice are more permissive to mycobacterial infection, their overall survival upon chronic mycobacterial infection is unaltered [46].

Loss-of-function mutations in STING have not been reported in humans. Nonetheless, various human STING variants are associated

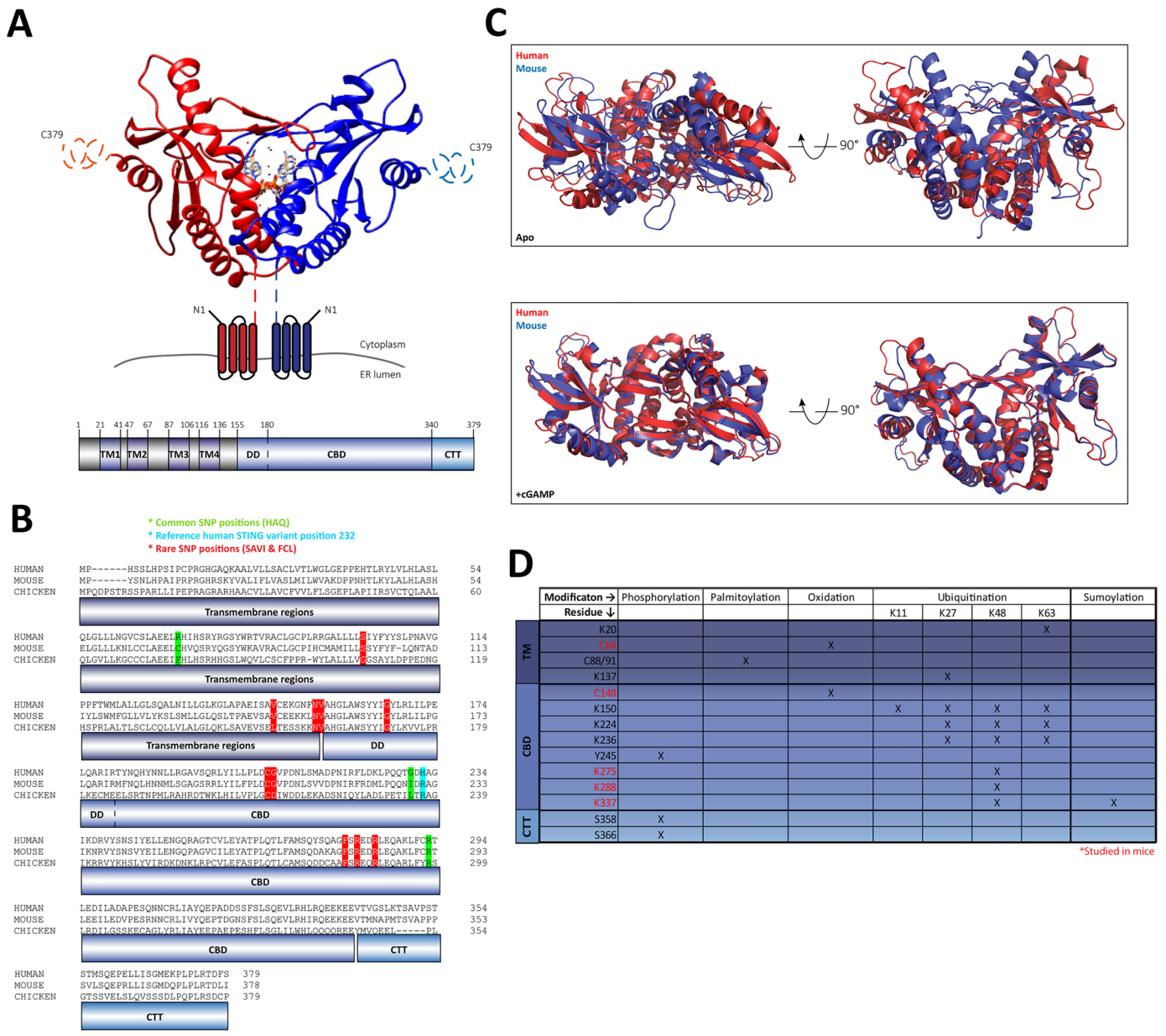

Fig. 2. STING structure and sequence information. (A) Structure of a human STING dimer in complex with cGAMP (PDB: 4loh) and schematic representation of the functional domains in hSTING (TM1-4, DD, CBD, and CTT). Domains not included in the crystal structure are added schematically. The STING monomers are indicated in red and blue. (B) Alignment of human (NP_938023.1), murine (NP_082537.1), and chicken (XP_001232171.2) STING protein sequences (Clustal Omega, multiple sequence alignment). Positions of amino acid substitutions arising from common or rare - disease-associated - SNPs are indicated in green or red, respectively. Of the common STING variants, reference STING has an R232H substitution compared to wild-type STING (R231 in murine and R237 in chicken STING), indicated in blue. (C) Top (left) and side (right) views illustrate overlap of the crystal structures of human (red) and murine (blue) STING molecules, when inactive (upper panel; apo human (PDB: 4 emu) and murine (PDB: 4kc0) STING) or active (lower panel; cGAMP-bound human (PDB: 4loh) and murine (PDB: 4loj) STING). (D) Overview of STING residues for which PTMs have been described. The STING domains in which the relevant residues are located are indicated on the left. Information from mouse studies is indicated in red. PDB: protein data bank.

with susceptibility to infection or autoinflammatory diseases (discussed below) [41,54–57]. Also in human cancers, STING signaling is frequently suppressed [58–62] pointing to a prominent role in antitumor immunity (reviewed elsewhere [39,40]). Finally, the identification of immune evasion molecules targeting the cGAS-STING pathway encoded by pathogens, e.g. HSV-1 and DENV, further underscores the importance of this pathway in antimicrobial defense (see below and [63,64]).

2.2. Activation of STING

Signals that lead to activation of STING can be divided into three groups: cellular cGAMP, bacterial CDNs, and synthetic STING ligands (Fig. 1).

The second messenger cGAMP is produced by the upstream sensor cGAS upon recognition of non-self (microbial) DNA or self DNA [44]. The length of DNA, rather than its sequence, determines its immunostimulatory properties: DNA sequences of at least 45bp enable multiple cGAS dimers to bind alongside each other [65,66]. The resulting phase transition (or liquid condensation) of DNA-cGAS complexes effectuates cGAS' enzymatic activity [65]. As endogenous DNA fragments are short in size (< 100 nt) and viral and bacterial DNA genomes are generally longer (> 100 kb), the length of microbial-derived DNA may thus permit discrimination between self and non-self

DNA by cGAS. Self-derived danger signals that activate cGAS frequently result from mislocalization of DNA outside the nucleus or mitochondria. cGAS gains access to self-DNA when localized to micronuclei, which are small nuclear vesicles containing (damaged) chromosomal DNA that has not been properly incorporated into daughter nuclei during mitosis due to errors in chromosome segregation, induction of DNA damage through radiotherapy, or senescence [67–72]. For example, cGAS associates with micronuclei in human cancer cells and in irradiated mouse embryonic fibroblasts, resulting in ISG production [73]. During senescence, cGAS activation induces a proinflammatory response, known as the senescence-associated secretory phenotype [72]. More detailed information on the role of DNA sensing in cancer and senescence can be found elsewhere [74,75]. Besides direct STING activation, cGAMP can also be transmitted to neighboring cells via gap junctions [76] and volume regulated anion channels [77] or through incorporation into viral particles during encapsidation [78,79], to accelerate STING activation in neighboring cells.

CDNs similar to cGAMP are produced by bacteria such as *Listeria* and bypass cGAS to directly bind and activate STING [80]. Bacterial CDNs include cyclic [G(3′-5′)pA(3′-5′)p] (3′3′cGAMP), cyclic diguanylate monophosphate (c-di-GMP), and cyclic diadenylate monophosphate (c-di-AMP) [81]. They are synthesized in bacterially infected cells or, when secreted by extracellular bacteria, enter the host cell cytoplasm through the reduced folate carrier SLC19A1 in the plasma membrane [82,83]. Besides canonical activation of STING through CDNs, Influenza A virus (IAV) infection may activate STING directly by a non-canonical mechanism involving lipid membrane alterations [84]. It is unclear how widespread such alternative routes of STING activation are.

Given the importance of STING in innate immunity, efforts to develop synthetic ligands of STING have rapidly increased [85], for instance to be used as (cancer) vaccine adjuvants. Intratumoral injection of STING agonists induced tumor regression in mice and the nucleotidic STING agonist MK-1454 (Merck) and ADU-S100 (Aduro Biotech) are currently under evaluation in phase I clinical trials, administered to patients with advanced/metastatic solid tumors or lymphomas, either alone or as a combination therapy with checkpoint inhibitors *(ClinicalTrials.gov)* [85,86]. The first non-nucleotidic compound tested as a clinical STING agonist was dimethyloxoxanthenyl acetic acid (DMXAA), but it failed in phase III clinical trials, despite promising results in mouse models [85,87,88]. Species-dependent differences in STING responsiveness were also observed for the chemical STING agonist carboxymethyl-acridanone: it induced murine (m)STING signaling, but did not efficiently activate human (h)STING [89,90]. This finding was later explained by differences in amino acid sequence and protein structure between murine and human STING (discussed below) [57,91,92].

2.3. Molecular characteristics of STING

Human STING is a 379-amino acid (aa) protein (encoded by the 8-exon *TMEM173* gene) and has several functional domains (Fig. 2A). Its N-terminal region (aa 1–139) contains four transmembrane (TM) domains responsible for membrane anchoring [11–13,93]. The C-terminal region of STING (aa 139–379) protrudes into the cytosol and harbors the CDN-binding domain (CBD, aa 155–340). Within this CBD, residues 155–180 form a dimerization domain (DD) involved in the formation of STING homodimers [94] and aa 163, 167, and 238–267 contribute to the CDN binding pocket located at the center of the homodimers [93] (Fig. 2A). Finally, residues 340–379 form STING's C-terminal tail (CTT), which functions as a platform for interaction with TBK1 and IRF3 [95].

2.3.1. Isoforms of hSTING

Two alternative transcripts encode shorter isoforms of hSTING that differ in some of the above-described functional domains [96,97]: MITA-related protein (MRP; 283 aa) has a unique 30 aa C-terminal tail due to a frameshift resulting from aberrant splicing of exon 7 [97] and STING-β (231 aa) lacks STING's transmembrane domains due to transcription from an alternative start site in intron 5 [96]. MRP and STING-β transcripts were found in multiple human tissues and MRP protein expression was detected in the human hepatoma cell line Huh7 [96,97]. Overexpression of MRP or STING-β interfered with IFN I induction by full-length STING [96,97]. Thus, both variants inhibit STING signaling *in vitro*, but further studies need to determine their role *in vivo*.

2.3.2. Sequence conservation and structural features of STING

Many species encode STING homologs, yet its domain involved in IFN I induction is more recently acquired in evolution [98]. Sequence alignments show marked conservation in STING protein sequence across species (Fig. 2B: human, mouse, and chicken). Chicken STING has 39 % and 44 % aa sequence identity with murine and human STING, respectively. Human and murine STING display 69 % sequence identity (81 % homology). Particularly STING's CBDs are highly conserved amongst vertebrates [98]. The aa sequence of functional regions such as the TBK1 binding site and the STING dimerization domain are also almost identical (Fig. 2B) [99].

Structural models of the CBD of human, murine, and porcine STING (crystallography) and full-length human and chicken STING (cryo-electron microscopy) are currently available (Fig. 2C) [57,93,99–102]. In accordance with sequence homology, full-length structural models using cryo-EM (apo or in complex with CDNs or TBK1) show highly similar conformations between species and reveal the conformational changes in STING involved in ligand binding, multimerization, and TBK1-induced phosphorylation events [99,101]. Most notably the structure of cGAMP-bound STING is nearly identical between species, illustrating the evolutionary conservation of STING activation ([101]; and Fig. 2C, lower panel).

A few structural differences in apo-STING have been observed between species, causing differential sensitivity towards CDNs and chemical ligands. Crystal structures of several human CBDs in the absence or presence of cGAMP or bacterial c-di-GMP revealed a symmetrical ligand-binding pocket located deep in a cleft at the dimer interface of STING homodimers [57,94]. Unlike hSTING, the CBD of porcine STING has an asymmetrical ligand binding pocket, which – even stronger than its human and murine homologs – preferably accommodates the asymmetrical cellular CDN 2′3′ cGAMP over symmetrical 3′3′ CDNs of bacterial origin [100]. In addition, apo-hSTING has an open and inactive conformation, whereas mSTING prefers a closed and active conformation aided by the presence of an isoleucine at position 229 (G230 in hSTING) (Fig. 2C, upper panel) [92,103]. This difference likely creates a higher conformational energy barrier for CDNs and small molecules to overcome in hSTING compared to mSTING contributing to their differential response to CDNs and synthetic ligands, such as DMXAA [92]. Indeed, substitution of hSTING G230 for an isoleucine enables DMXAA to activate hSTING [103].

2.3.3. Polymorphisms in human STING

Several non-synonymous single nucleotide polymorphisms (SNPs) have been identified in the *TMEM173* coding sequence that affect STING's function (Fig. 2B). Some SNPs yield gain-of-function mutations rendering STING overactive and causing severe autoinflammatory diseases [54]. These SNPs are rare and usually not inherited due to severe health problems at young age; they are discussed below. Other - more common - SNPs lead to reduced STING function and a decreased sensitivity towards CDNs. These STING variants are more widely prevalent amongst humans, with regional distribution. Five common *TMEM173* alleles (each present in > 1 % of the human population) were identified from the 1000 Genome Project database [81]. These encode the most common, wild type, STING molecule (WT; R71-G230-R232-R293, found in 58 % of the allelic products analyzed) and four variants that harbor one or more substitutions: R71H-G230A-R293Q (abbreviated as HAQ, occurring in 20 % of humans), R232H (14 %), G230A-R293Q

(AQ, 5 %), and R293Q (1.5 %) (Fig. 2B, highlighted in green and blue) [81]. Please note that the NCBI reference sequence for hSTING represents the R232H variant, encoded by the first *TMEM173* gene cloned, rather than WT hSTING, encoded by the most frequent *TMEM173* allele.

When introduced into (STING-negative) HEK293T cells, WT hSTING was responsive to all CDNs tested (cGAMP, 3′3′cGAMP, c-di-AMP, and c-di-GMP) [81]. While STING variant HAQ is responsive to all CDNs and only slightly reduces IFN I induction compared to WT STING [81], fibroblasts and macrophages expressing the HAQ variant had strongly reduced IFNβ production upon *Listeria* infection [56]. *In vivo*, it remains to be resolved how HAQ/HAQ homozygosity affects susceptibility to (pathogen-induced) diseases. One study shows that individuals carrying the HAQ variant were more susceptible to infection with *Legionella pneumophila*, while others suggest that the HAQ variant may have a protective effect during HIV infection, as long-term non-progressors were more often HAQ/HAQ homozygous [104,105]. Such differences of course also relate to the role of IFN I in pathogen-specific pathology.

The R232H hSTING variant displays reduced responsiveness to c-di-GMP or cGAMP and fails to respond to c-di-AMP or 3′3′cGAMP [81]. This difference with WT hSTING is important to keep in mind given the use of the R232H variant in many (overexpression) studies. Like WT hSTING, murine and chicken STING carry an arginine (R) at the corresponding positions 231 and 237, respectively (NCBI reference sequences). WT mSTING responds to all CDNs [91], however, substitution of R231 by an alanine residue (R231A) abolishes responsiveness to bacterial CDNs, but not to cGAMP [32]. Carrying an arginine at position 232 (hSTING) could thus favor the induction of an innate immune response, in particular against bacterial infections when bacterial CDNs are a major route of STING activation.

3. What if STING fails?

3.1. STING signaling-deficient cells, a niche for viruses

Viral infection triggers a cGAS-STING-dependent antiviral immune response. During co-evolution, viruses have evolved sophisticated strategies to manipulate their hosts' immune responses, for instance by interfering with signal transduction ([64,106]; and see below). Myeloid cells express all components of the cGAS-STING pathway and in these cells many cellular restriction factors and viral immune evasion strategies have been delineated. Additionally, viruses appear to have adapted to infect cell types that do not respond to cytosolic DNA, potentially providing an immune-privileged niche for viruses to replicate and/or persist.

3.1.1. Human B lymphocytes and Epstein-Barr virus (EBV)

Human B cells are the primary site of persistence for Epstein-Barr virus (EBV). Although infections with this human herpesvirus generally remain asymptomatic due to effective host immunity, EBV-induced pathologies comprise infectious mononucleosis and EBV-associated lymphoid or epithelial malignancies [107]. EBV is an enveloped DNA virus and its life cycle consists of a lytic phase, supporting viral replication [107], and a latent phase, during which no progeny is produced and the viral genomes reside in memory B cells [108]. How does EBV hide in these immune cells without overtly activating (innate) immunity? We found that human B lymphocytes fail to produce IFN I in response to cytoplasmic DNA exposure [109]. This is likely explained by the absence of STING transcripts and proteins in primary human B cells and in EBV-negative B cell lines. Other DNA sensing and signaling proteins (cGAS, IFI16, TBK1, IRF3) were detected [109]. In contrast to human B cells, murine B cells appear to have intact STING signaling and express IFNα and IFNβ upon cytosolic DNA stimulation [110]. STING was in fact first identified in murine B cells, as a molecule inducing apoptosis [111].

Surprisingly, EBV transformation of human B cells is accompanied by substantial expression of STING protein [109]. Since STING itself is an ISG, a potential explanation is that STING levels are increased in these cells as a consequence of activation of the RNA sensing machinery upon exposure to EBV [112,113]. Despite this, EBV-transformed B cells do not secrete IFN I upon cytoplasmic DNA exposure [109]. These EBV-positive lymphoblastoid cells (LCL) are in latency stage III and produce 9 viral proteins, several viral miRNAs, and two viral long non-coding RNAs [114]. How these EBV gene product(s) contribute(s) to creating a cellular milieu, where the virus could benefit from STING expression while preventing the antiviral effects of IFN I induction, is unknown.

Thus, EBV has developed intricate mechanisms to exploit the human B cell niche. Other viruses that infect human B cells, such as KSHV, may similarly exploit STING dysfunction within these cells.

3.1.2. Human T lymphocytes and HIV

HIV is a retrovirus that infects human $CD4^+$ helper T cells, macrophages, and dendritic cells. When left untreated, it can cause acquired immunodeficiency syndrome [114]. Combined antiretroviral therapy is highly effective in reducing patient viral loads to undetectable levels – i.e. suppressing HIV replication – but latent virus persists for life in a reservoir of resting $CD4^+$ T cells [115]. These latently infected T cells contain HIV as stably integrated proviral DNA, generated upon reverse transcription of the RNA genome of incoming viruses [114]. Why would HIV exploit a critical immune cell for its replication and persistence? Defective cytosolic DNA sensing in human T cells would contribute to their permissiveness for HIV-1. Introduction of DNA into the cytosol of activated human T cells prior to or after HIV-1 infection did not reduce viral replication, in contrast to pretreatment of the cells with IFNβ [116]. Activated human $CD4^+$ T cells did not upregulate IFN I or ISG expression upon DNA transfection or HIV-1 infection [116]. The mechanistic details underlying this non-responsiveness are not completely clear. Key components of the DNA sensing machinery were expressed in activated T cells, including STING itself. Besides, the IFN I/IFNAR signaling pathway downstream of the RNA sensor RIG-I was functional in activated $CD4^+$ T cells, since infection with the RNA virus Sendai (SeV) induced an IFN I response [116]. Less is understood about human resting $CD4^+$ T cells. They do not mount an IFN I response upon DNA transfection or SeV infection, but mechanistic details were not explored. When cGAMP was used to complement HDAC inhibitors as a novel approach for reactivation and clearance of the latent HIV reservoir, the synergistic effect of cGAMP addition relied mostly on NF-κB-signaling [117]. This is consistent with resting $CD4^+$ T cells - of which part harbor HIV - being defective in STING-dependent IFN I production [116]. Of note, *in vivo*, cGAMP may also act on STING-proficient, neighboring cells and additionally induce an IFN I response to aid the clearance of virus-infected T cells.

Besides HIV, a defective STING pathway may similarly render human T cells vulnerable to other pathogens, including DNA viruses (e.g. varicella-zoster virus and human herpes virus 6) or retroviruses (e.g. human T-lymphotropic virus type 1), that replicate through a DNA intermediate. Novel anti-HIV approaches that rely on STING activation may thus also be applicable for the treatment of infections with other pathogens.

3.1.3. Hepatocytes and hepatitis B virus (HBV)

The double stranded DNA virus hepatitis B virus (HBV) causes chronic liver infections, which can lead to liver failure and hepatocellular carcinoma [118]. HBV has a tropism for human hepatocytes, which have undetectable levels of STING protein [119]. In line with this, human hepatocytes did not upregulate ISGs in response to DNA transfection and this coincided with permissiveness to HBV infection and replication [119]. Likewise, murine hepatocytes are STING deficient and have a dysfunctional DNA sensing pathway. *In vivo,* selective mSTING expression in hepatocytes of STING-deficient mice rescued the IFN I response to a DNA stimulus and enhanced control of HBV in a mouse-adapted AdV-HBV infection model [119]. Reconstitution of IFN I

signaling in cGAS-STING-defective cells may thus be of therapeutic value for viruses that exploit loopholes in DNA sensing to establish (persistent) infections.

In summary, these findings substantiate that certain cell types fail to mount a full-blown IFN I response downstream of cGAS-STING (Supplementary Table 2) and imply that not all (primary) cells possess a functional DNA sensing pathway. Different mechanisms underlie the unresponsiveness in hepatocytes, B cells, and T cells, ranging from loss of STING protein to diminished IFN I induction even when STING is present. The latter points to the existence of additional, unknown factor (s) important for regulation of cGAS-STING signaling. Future experiments should investigate the effects of STING deficiency in B and T lymphocytes upon exposure to DNA- or retroviruses, i.e. when multiple PRRs are activated and various evasive strategies are operative. Selective depletion of individual sensing/signaling molecules will allow dissection of their contributions to the antiviral response in various cell (sub)types and differentiation stages. EBV, HIV, or HBV persist in cells with a defective IFN I response to cytosolic DNA exposure suggesting that it provides a niche for viral replication and/or persistence. Many (tumor) cell lines also have defects in STING signaling, indicative of a selective advantage for survival and growth [120]. Why primary hepatocytes, B and T cells have dysfunctional STING responses is unknown at present, but may relate to the risks associated with excessive IFN I production or other functions of STING, such as NF-κB signaling and apoptotic cell death [121].

3.2. Uncontrolled STING activation in type I interferonopathies

While certain cell types fail to activate STING-dependent IFN I signaling, there are no patients known with homozygous loss-of-function hSTING variants (gnomAD:ENSG00000184584), suggesting that STING signaling is essential for human survival. Yet, STING knockout mice are viable, further emphasizing the species differences in STING signaling [12,41]. Human cases have been described with pathological overproduction of IFN I, termed type I interferonopathies [122], and these patients suffer from autoinflammatory and autoimmune disorders. Some of these can arise due to defects upstream of STING, for instance Aicardi-Goutières syndrome (AGS) [123].

In 2014, six patients were reported with symptoms similar to AGS [54]. They failed to thrive, developed peripheral vascular inflammation with vascular and tissue damage, and suffered from pulmonary manifestations, such as interstitial lung disease, which were fatal for two patients. As all six patients had nonsynonymous SNPs in *TMEM173* leading to gain-of-function mutations in STING (V147L, V155M, and 4x N154S), the disease was termed STING-associated vasculopathy with onset in infancy (SAVI) [54]. Since then, additional SAVI-associated STING variants have been described (V147M, C206Y, G207E, R281Q, R284G/S, and S102P + 279L) [54,55,124–139]. Another STING variant (G166E) was found in patients with a related interferonopathy, familial chilblain lupus (FCL) [140]. These gain-of-function STING variants are encoded by rare SNPs, which have mostly arisen *de novo*. Exceptions include the inherited FCL mutation and SNPs in three families with multiple SAVI patients (2x V155M, G207E) [55,127,136,140]. Interestingly, between these family members the disease severity frequently differs, which implies that there are other genetic or environmental factors involved in disease progression. Indeed, within one family some members have a risk allele of the RNA sensor *IFIH1* (MDA5) [127]. Disease severity differs between SNPs, both in humans and in mouse models [127,129,138]. For example, patients with the C206Y or G207E SNPs develop less pulmonary complications than patients with other SNPs and FCL disease progression is in general less severe than SAVI [54,127,138,140]. Of note: mouse models show that some but not all immunopathology can be attributed to constitutive IFN I production, pointing to roles for STING beyond IFN I signaling [141–143].

How these SNPs cause hyperactivation of STING is not clear, but can be speculated about based on the structural models described above (Fig. 2). In WT STING, C148 is important for polymerization through the formation of disulfide bonds [144]. In view of its proximity to C148, SAVI mutations at position 147 could enhance or stabilize STING polymerization. Two STING residues that are substituted in SAVI, N154 and V155, are located next to the dimerization domain of STING (Fig. 2B). The V155M alteration stabilizes the binding of one monomer (involving aa M155, L268, M271, and F279) to another STING monomer (involving W161), thereby mimicking ligand binding [55]. The V147L, N154S, and V155M mutations in SAVI-associated STING variants result in reduced interaction with the Ca^{2+} sensor stromal interaction molecule 1 (STIM1), which ensures correct localization of STING at the ER [145]. As overexpression of STIM1 still suppressed the IFN I production downstream of these STING variants, their interaction with STIM1 is probably partially but not fully disturbed [145]. Located within the CBD (Fig. 2B), residue R284 plays a role in the binding of the CTT to the polymerization interface, which prevents untimely STING polymerization and activation [144]. This autoinhibition is lost in SAVI STING variants with SNPs at position 284 (and possibly 281), leading to unbalanced IFN I production and autoinflammation.

4. Regulation of STING

To prevent the damaging effects of constitutive STING activation, tight regulatory mechanisms are in place. For example, STING expression levels are regulated by microRNAs (miRNAs) like miR-576 − 3p, which suppresses STING translation [146]. When STING is activated by CDNs, miR-576 − 3p is upregulated to prevent overproduction of cytokines [146]. STING expression and/or activity is also carefully balanced post-translationally to maintain homeostasis. Here, we will discuss mechanisms that ensure balanced STING signaling and how viruses tip this balance in their favor.

4.1. Intracellular localization of cGAS and STING

To initiate IFN I induction, each component of the DNA sensing pathway must be localized properly. The localization of cGAS is much debated. While originally thought to be exclusively cytosolic, cGAS may also reside in the nucleus, where it is likely retained following mitosis and nuclear membrane remodeling, or at the plasma membrane [72,147–150]. The N-terminal region of cGAS retains cGAS in the cytosol, possibly through interaction with undefined proteins [148]. Conversely, interactions with nuclear proteins, e.g. NONO, may favor a nuclear localization of cGAS [151]. Whether the localization of cGAS has an effect on STING activation remains to be elucidated.

Inactive STING localizes exclusively to the ER membrane, where it is retained by the Ca^{2+} sensor STIM1 [145]. Of note, whether STING reciprocally impacts on calcium flux through its interaction with STIM1 has not been investigated [152]. Once activated, inactive rhomboid protein 2 (iRhom2) facilitates STING's translocation from the ER to the ER-Golgi intermediate compartment (ERGIC) and Golgi compartments [153]. Additional factors that are required for translocation of STING are the cytoplasmic coat protein complex II (COPII) and ADP-ribosylation factor (ARF) GTPases [154,155]. Together, these molecules regulate the signaling output of STING. At the Golgi complex, STING interacts with TBK1, which in turn recruits and phosphorylates IRF3. When STING is retained in the ER, it can no longer activate IRF3 signaling [156].

4.2. STING degradation

STING signaling can be terminated by protein degradation. At steady state, Toll-Interacting Protein (TOLLIP) (partially) prevents degradation of STING in mouse embryonic fibroblasts (MEFs) [157]. To ensure proper STING expression levels before, during, and after activation, the protein is degraded in different organelles (proteasomes, autophagosomes, lysosomes). Proteasomal degradation of STING occurs

either in a ubiquitin-dependent (see below under ubiquitination) or -independent manner [158]. Data are conflicting regarding the role of autophagy in STING regulation. MEFs lacking one of the proteins of the autophagy machinery (Atg3, Atg5, Atg7 Atg9, or p62/SQSTM1) show reduced STING degradation and enhanced phosphorylation of TBK1 when stimulated with DNA or cGAMP [34,159,160]. However, others have found that loss of Atg7 in MEFs has no effect or even a negative effect on STING expression and signaling [159,161]. A QEVLR motif is present in mSTING (aa 326–330) and hSTING (aa 327–331) that - when recognized by the heat shock cognate 71 kDa protein (Hsc70) - targets proteins for chaperone-mediated autophagy (CMA) [161]. Finally, the lysosomal inhibitors bafilomycin A1 and chloroquine were most effective at preventing STING proteolysis, when compared to 3-MA and MG132, which block autophagosomal and proteasomal degradation, respectively [157,159,162,163], suggesting that lysosomal degradation is the main route of STING degradation.

4.3. Post-translational modifications

Post-translational modifications (PTMs) on STING provide a powerful means for cells to quickly adapt cytosolic DNA responsiveness to altered needs. Multiple types of PTMs have been found for STING, as listed below and summarized in Fig. 2D.

4.3.1. Phosphorylation of serines and tyrosines

Two serines of STING, S358 and S366, are phosphorylated by TBK1, which is essential for the activation of both STING and IRF3 [11,164]. Phosphorylation of S358 enables TBK1 to bind STING. TBK1 then trans-phosphorylates S366 of neighboring STING complexes, allowing the recruitment, phosphorylation, and dimerization of IRF3 [99]. Alanine substitutions of STING S358 or S366 abolish IRF3 activation [11,164], even in the constitutively active SAVI-associated STING variants [138]. Paradoxically, introduction of the phospho-mimic S366D also strongly reduces IRF3 dimerization and IFN I production [163,164]. This may be due to clearance of phosphorylated STING through autophagy, resulting in low levels of remaining STING that can signal to IFN I [163]. Similarly, phosphorylation at S366 by the serine/threonine kinases ULK1 and ULK2 increases STING degradation, without IRF3 activation [163]. The phosphatase PPM1A dephosphorylates STING at S358, to reverse STING activation by TBK1 [165].

Phosphorylation at tyrosine residues also contributes to the regulation of STING. SRC kinase-mediated phosphorylation at Y245 is upregulated during viral infection *in vitro* and prevents ubiquitin-independent 20S proteasomal degradation of STING [158,166]. This is balanced by the tyrosine-protein phosphatase nonreceptors (PTPN) types 1 and 2 [158].

4.3.2. Palmitoylation and oxidative modification of cysteines

Several cysteines in the transmembrane domain of STING (C64, C88, C91, C148, C292, and C309) are indispensable for IFN I induction [167]. STING is palmitoylated at C88 and C91 and mutating both residues or treating cells with the palmitoylation inhibitor 2-BP renders cells unable to induce an IFN I response upon stimulation with exogenous DNA [168]. In COS-1 cells stably expressing mSTING, palmitoylation of STING occurs after STING has been translocated from the ER to the Golgi [168]. Mechanistically, palmitoylation of STING at C88/91 may favor clustering of STING into lipid rafts through intermolecular disulfide bonds, which improves interactions with TBK1 and IRF3 [168]. Targeting of C91 with nitro-fatty acids or covalent small-molecule inhibitors might be a promising strategy to treat autoinflammatory diseases caused by excessive activation of IFN I through STING [90,169]. Cysteine residues C64 and C148 in STING are oxidized by reactive oxygen species upon chemically induced ER and mitochondrial stress and this causes STING to form intermolecular disulfide bonds, blocking IFN I induction [167]. C148 of STING may also form intermolecular disulfide bonds upon ligand binding [144]. It is unclear whether these amino acids reside in the cytosol or the ER/Golgi lumen [101,167].

4.3.3. Ubiquitination

Ubiquitin adduction by E3 ligases and removal by deubiquitinases (DUBs) provide powerful tools to regulate protein degradation, trafficking, and signaling. Ring Finger Protein (RNF) 5 and RNF90 target K150 in STING for K48-linked ubiquitination and proteasomal degradation, while RNF26 adds a K11-linked ubiquitin chain at the same lysine, presumably protecting STING from K48-dependent degradation [170–172]. Both RNF5 and RNF26 ubiquitinate K150 of STING early (6 h) after infection with HSV-1 or SeV. TRIM29 is upregulated upon cytoplasmic dsDNA accumulation and targets K288 and K337 of mSTING (equivalents of K289 and K338 in hSTING, respectively) for K48-dependent proteasomal degradation [173]. K275 in mSTING is ubiquitinated by TRIM30α leading to K48-dependent proteasomal degradation of the protein [174]; hSTING lacks a lysine at the corresponding position. The DUBs CYLD, USP20, and USP44 block proteasomal degradation of STING by removing K48-linked ubiquitin chains and mice lacking either of these genes display increased lethality upon challenge with HSV-1 [175–178]. USP18 acts as a platform for the interaction between STING and USP20, without the need of the catalytic domain of USP18 [176].

Ubiquitination of STING contributes to other regulatory processes, besides K48-dependent protein degradation. When overexpressed, TRIM56, Ubxn3b, MUL1, and TRIM32 each add K63-linked ubiquitin to STING at various sites (K20, K150, K224, and K236), thereby promoting TBK1 binding to STING and subsequent IRF3 phosphorylation and IFNβ gene activation [69,179–181]. USP49 removes K63-linked ubiquitin from STING, which halts the recruitment of TBK1 without affecting STING protein levels [182]. AMFR, an ER-associated E3 ubiquitin ligase, also binds STING and catalyzes K27-linked ubiquitination at multiple sites (K137, K150, K224, and K236), which facilitates the recruitment of TBK1 [183]. Binding of AMFR to STING is mediated by the insulin-induced gene 1 (INSIG1) product [183]. K27-linked ubiquitination of STING is reversed by the DUB USP13, which, like AMFR, interacts with STING at the ER membrane [184]. How these K27 ubiquitin modifications that facilitate recruitment of TBK1 are intertwined with localization of STING needs further study.

4.3.4. SUMOylation

Post-translational modification with the ubiquitin-like molecule SUMO stabilizes STING. Sumoylation of mSTING at K337 (K338 in hSTING) precludes recognition of the nearby QEVLR motif by Hsc70 and consequently blocks CMA-dependent degradation [161]. In line with this, during the early phase of HSV-1 infection, sumoylation of K337 by the E3 ligase TRIM38 prevents degradation of STING, resulting in enhanced STING activation and decreased viral titers [161]. During the late phase of HSV-1 infection (~12 h post-infection), however, STING is de-SUMOylated by Senp2, which binds to mSTING that is phosphorylated at S365 (equivalent to S366 in hSTING) [161].

In summary, STING is extensively regulated in a post-translational manner and likely even more PTMs of STING await identification. Analogous to cell-based regulation, viruses have evolved their own strategies to modulate STING signaling to promote their own survival and replication.

4.4. Viral regulation and evasion of STING by DNA viruses

Viruses acquired immune evasive gene products to counteract the cytosolic DNA sensing machinery and the antiviral effects of IFN I [64,106]. Here, we highlight how viral evasion molecules (de)regulate STING-dependent signaling (Fig. 3); viral evasion upstream or downstream of STING is reviewed elsewhere [63,185–188]. E1A from human AdV 5 and E7 from human papilloma virus 18 (HPV18) bind STING via their LXCXE motif and block downstream signaling [189]. Additionally,

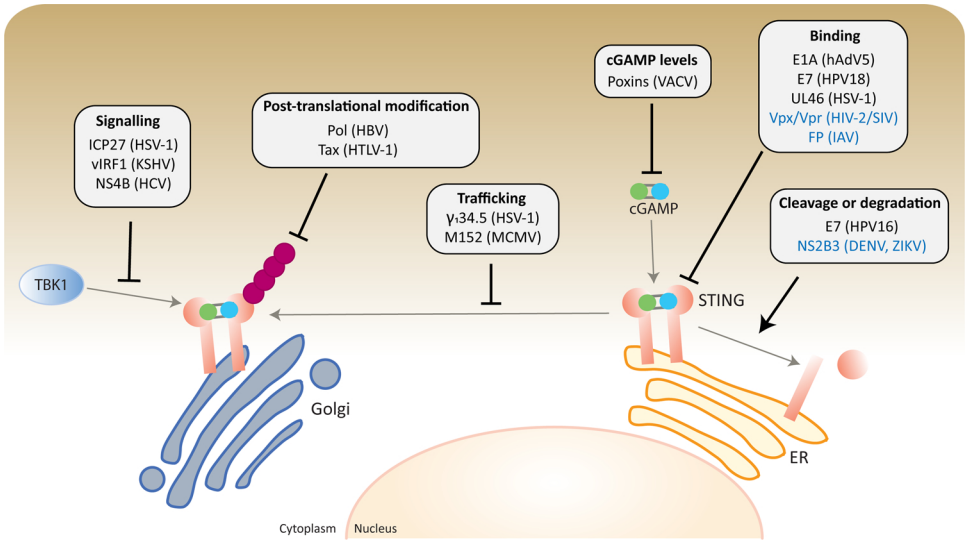

Fig. 3. Overview of viral evasion strategies that affect STING. Proteins encoded by viruses with DNA (black) or RNA (blue) genomes prevent antiviral IFN I responses at the level of STING activation, regulation, signaling, or degradation. Names of the viruses from which the evasion molecules arise are indicated in brackets.

E7 from the more prevalent HPV16 strain increases autophagy-mediated turnover of STING [190]. ICP27 from HSV-1 binds to TBK1 and STING in human macrophages and prevents activation of IRF3 [191]. Other HSV-1 gene products also associate with STING and block downstream responses (UL46) or interfere with STING trafficking ($\gamma_1$34.5) [192]. Similarly, M152 from murine cytomegalovirus (MCMV) delays the trafficking of STING from the ER to the Golgi, thereby interfering with IRF signaling and antiviral IFN I responses, but, interestingly, not with NF-κB responses [156]. Conversely, Vpx and the related Vpr gene products from HIV-2/SIV bind to a domain of STING that is important for the activation of NF-κB, but not IRF3, and thereby selectively suppress NF-κB signaling [193]. An alternative viral evasion strategy is employed by VACV strains, which encode nucleases (poxins) that cleave cGAMP and consequently prevent STING activation. Deletion of the poxin gene or expression of a catalytically inactive variant enhances the IFN I response and limits VACV replication [194]. Additionally, virulent, but not attenuated VACV strains block dimerization and phosphorylation of STING [195]. Several viral evasion strategies interfere with STING's function by preventing its proper post-translational modification. For example, vIRF1 of KSHV prevents binding of STING to TBK1 and thereby interferes with phosphorylation and activation of STING [196]. The viral polymerase of HBV prevents K63-linked polyubiquitination of STING, which blocks IFN-β induction and antiviral immunity in hepatocytes [197]. Finally, K63-linked ubiquitination of STING and consequently its interaction with TBK1 was decreased by the human T lymphotropic virus type 1 (HTLV-1) transactivator Tax [198,199]. As STING's stability and activity is heavily regulated by many PTMs, more viral proteins targeting these modifications to evade STING signaling are likely to be discovered.

4.5. Viral regulation and evasion of STING by RNA viruses

The increased susceptibility of STING-deficient mice to some RNA viruses (e.g. VSV) hints at an additional role for cGAS-STING signaling in combatting RNA virus infections [33]. This may be due to co-regulation of the expression of components of DNA and RNA sensing machinery, most of which are IFN-inducible themselves, by baseline IFN I levels. Hence, loss of one or the other pathway will indirectly reduce the expression and functionality of the other pathway [112]. However, the observation that multiple RNA viruses encode proteins that suppress the cGAS-STING pathway strongly suggests a direct contribution of this pathway in defense against RNA virus infection. Multiple Flaviviridae, including ZIKV, DENV, West Nile virus (WNV), Japanese encephalitis virus (JEV), and Hepatitis C virus (HCV) encode proteins that cleave STING (DENV, ZIKV, WNV, JEV) or cGAS (DENV), or interfere with the STING-TBK1 interaction (HCV) to inhibit IFN I induction [200–203]. For example, NS2B3 from DENV cleaves human (but not mouse) STING and mutation of the cleavage site yields higher IFN I levels upon DENV infection [200]. How cGAS-STING contributes to defense against RNA virus infection is unclear, but may involve the detection of host mitochondrial DNA that is released in the cytosol upon mitochondrial damage, as demonstrated in DENV-infected cells [203]. Finally, the hemagglutinin fusion peptide (FP) of IAV also directly binds STING and limits STING-dependent IFN I production upon membrane fusion [84].

5. Conclusions and outstanding questions

As a central signaling hub in innate immunity, STING is essential for mounting protective antimicrobial responses, with IFN I as a particularly powerful antiviral effector. However, its activity needs to be tightly controlled to prevent autoinflammatory diseases including type I interferonopathies. Much insight has been obtained into the structure and activation of STING, including the order of events and conformational changes that occur. This helps us understand how STING is regulated in space and time and how SNPs affect its function.

Regulation of STING activity takes place at many levels, such as trafficking, degradation, miRNA-mediated repression, and post-translational modifications. An outstanding question remains where and when DNA is sensed that, via cGAS or other DNA sensors, leads to STING activation and IFN I production. For instance, how is viral DNA exposed to cGAS when capsids protect the viral genome during its trafficking from the cytosol to the nucleus? Or does sensing occur inside the nucleus, as suggested by recent studies that find significant cGAS expression in the nucleus [148,151]? And what - apart from subcellular localization - determines whether cGAS-STING activation by host-derived DNA is desired or should be avoided (for example during cell division when compartmentalization within the cell is temporarily lost)?

Certain primary cells, such as human B and T lymphocytes and hepatocytes, display defects in DNA sensing. These loopholes in innate immunity can be exploited by persistent viruses, such as EBV, HIV-1, and HBV. It is not clear why these cell types lack an IFN I response downstream of STING. A parallel can be drawn with cancer cells, which frequently have lost STING expression and/or functionality to gain immune escape, proliferation, and survival [58–62]. Perhaps a fully functional DNA sensing pathway would lead to continuous IFN I production in such highly proliferative cells, due to accumulation of

replication-associated DNA by-products. Loss of STING signaling could thus represent a trade-off between attenuating the detrimental effects of IFN I and reduced antimicrobial potential. Alternatively, cells may avoid other STING-mediated processes. While beyond the scope of this review, it is clear that STING is involved in a plethora of processes within and beyond innate immunity, including NF-κB-mediated responses, autophagy, cell death, and senescence [204]. Additional functions of STING may be discovered soon. For example, its interaction with STIM1 may implicate STING in calcium homeostasis [152]. These processes jointly determine the overall outcome of STING signaling and the quality of the (antimicrobial) response. Future studies will reveal if the reported defects in DNA sensing in certain cell types are evolutionary conserved and extend to other cell types as well.

Aside from dysfunctional STING signaling, there is increasing evidence for cell type-specific regulation of STING-mediated responses. For optimal IFN I production, IFI16 cooperates with cGAS in human keratinocytes, fibroblasts, and macrophages [29,30,149], but not in human lung epithelial cells, which lack IFI16 expression [205]. The expression of co-sensors or regulators may also differ between differentiation states, in particular during embryonic development. For example, the regulatory protein NLRP14 is expressed by mammalian oocytes to suppress STING activation during fertilization, when sperm cell DNA reaches the oocyte cytosol [206]. The continuous identification of new factors that impact on STING function illustrates that not all elements in DNA sensing have been discovered yet.

In cells with a fully operative DNA sensing pathway, viruses may escape DNA sensing through immunomodulatory strategies to facilitate infection, persistence, and/or replication. A better understanding of the strategies used by microbes to manipulate, evade, and exploit the cell's innate immune defense will teach us how to (re-)activate STING signaling in infected cells and protect the host. All-in-all, these are intere STING times!

Declaration of Competing Interest

The authors whose names are listed immediately below certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cytogfr.2020.06.004.

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