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The Role of Nucleic Acid Sensing in Controlling Microbial and Autoimmune Disorders

Keesha M. Matz[*,2], **R. Marena Guzman**[*,2], and **Alan G. Goodman**[*,†,1]

[*]School of Molecular Biosciences, College of Veterinary Medicine, Washington State University, Pullman, WA, United States

[†]Paul G. Allen School for Global Animal Health, College of Veterinary Medicine, Washington State University, Pullman, WA, United States

Abstract

Innate immunity, the first line of defense against invading pathogens, is an ancient form of host defense found in all animals, from sponges to humans. During infection, innate immune receptors recognize conserved molecular patterns, such as microbial surface molecules, metabolites produces during infection, or nucleic acids of the microbe's genome. When initiated, the innate immune response activates a host defense program that leads to the synthesis proteins capable of pathogen killing. In mammals, the induction of cytokines during the innate immune response leads to the recruitment of professional immune cells to the site of infection, leading to an adaptive immune response. While a fully functional innate immune response is crucial for a proper host response and curbing microbial infection, if the innate immune response is dysfunctional and is activated in the absence of infection, autoinflammation and autoimmune disorders can develop. Therefore, it follows that the innate immune response must be tightly controlled to avoid an autoimmune response from host-derived molecules, yet still unencumbered to respond to infection. In this review, we will focus on the innate immune response activated from cytosolic nucleic acids, derived from the microbe or host itself. We will depict how viruses and bacteria activate these nucleic acid sensing pathways and their mechanisms to inhibit the pathways. We will also describe the autoinflammatory and autoimmune disorders that develop when these pathways are hyperactive. Finally, we will discuss gaps in knowledge with regard to innate immune response failure and identify where further research is needed.

1. INTRODUCTION

Several nucleic sensing pathways have been identified over the last few decades that have increased our understanding of diseases that occur when these pathways are dysfunctional. The last decade has experienced an upsurge of new discoveries regarding nucleic acid sensing, many due to advances in technology. Nevertheless, intricacies of how the failure of nucleic acid-sensing mechanisms leads to autoinflammation and autoimmunity remain unsolved. In this review, we explore what is known about how the failure of nucleic acid-

[1]Corresponding author: alan.goodman@wsu.edu.
[2]These authors contributed equally to this work.

sensing mechanisms leads to autoimmunity and autoinflammation as well as highlight questions that remain to be solved.

Autoinflammation and autoimmunity are often mistakenly used interchangeably but refer to the origin of disease. Namely, while autoinflammatory diseases are driven primarily by dysregulation of the innate immune system and do not rely on T cells or B cells for disease to progress, autoimmune diseases are driven primarily by T-cell and B–cell mediation (Arakelyan et al., 2017). Several autoimmune diseases originate from the innate immune system but then require lymphocytes for progression, indicating that disease is often a result of more than one component of immunity. Details that differentiate autoimmunity and autoinflammation remain controversial, but our current understanding of these pathologies is based on our ample understanding of innate immune recognition.

Central to the autoinflammatory and autoimmune disorders discussed in this review are the sensors that detect cytosolic nucleic acids to stimulate an innate immune response. The primary role of the innate immune system is to be the first line of defense against foreign microbes. The recognition of microbes and nucleic acid depends on pattern recognition receptors (PRRs) that recognize a variety of pathogen-derived molecules called pathogen-associated molecular patterns (PAMPs). While many types of PAMPs are encountered only during microbial infection, nucleic acid-mediated PRR activation can be microbe-or host-derived. That is, the innate immune response can be activated by the presence of self-nucleic acids that escape the nucleus, a major etiological cause of the autoinflammatory and autoimmune disorders discussed here. As such, in this review, we will describe the receptors of RNA and DNA nucleic acids and the signaling pathways that each stimulate. Then, for both the RNA and DNA sensing pathways, we will identify the specific types of microbial infections that activate innate immune responses and how each microbe has evolved mechanisms to inhibit these pathways. Finally, we will discuss the autoinflammatory and autoimmune disorders that develop when these nucleic acid signaling pathways are dysfunctional.

2. RNA NUCLEIC ACID SENSING IN VIRAL IMMUNOLOGY AND AUTOIMMUNITY

2.1 Detection of Intracellular RNA

2.1.1 Protein Kinase R—Protein kinase R (PKR) is encoded by the *EIF2AK2* gene, and it is an interferon (IFN)-induced, double-stranded RNA (dsRNA)-dependent protein kinase that phosphorylates the alpha subunit of eukaryotic initiation factor 2 (eIF2α), resulting in the inhibition of mRNA translation initiation (Kitajewski et al., 1986). PKR has also been shown to be a component of IFN activation to facilitate a robust innate immune response (Balachandran et al., 2000). PKR itself is induced by IFN, resulting in a positive feed-forward loop that further amplifies the innate immune response (Li et al., 2011). Double-stranded RNA activation of PKR results in its dimerization and autophosphorylation (Dever, 2002). Downstream IFN gene induction is induced primarily by the NF-κB transcription factor following PKR-mediated phosphorylation of IκB (Kumar et al., 1994), but not IRF3 activation (Smith et al., 2001). A number of viruses have encoded mechanisms to block PKR

activation to allow for enhanced virus replication, such as adenovirus, reovirus, influenza virus, and hepatitis C virus (Gale et al., 1997; Katze et al., 1987; Lloyd and Shatkin, 1992; Lu et al., 1995).

The activation of PKR is also inhibited by other cellular factors, such as the gene encoded by *DNAJC3*, namely $P58^{IPK}$ (Lee et al., 1992). Specifically, $P58^{IPK}$ interacts with PKR at the site that promotes its dimerization and autophosphorylation (Gale et al., 1996). Importantly, $P58^{IPK}$ is activated during influenza virus infection and $P58^{IPK}$ dysfunction results in late onset type 1 diabetes, which will be discussed in a following section (Ladiges et al., 2005; Melville et al., 1999).

2.1.2 Toll-Like Receptors—Toll-like receptors (TLRs) are integral membrane glycoproteins, have a tri-modular structure, and contain 16–28 leucine-rich repeats (LRRs), which are necessary for interaction and recruitment of several adaptor proteins (Kawasaki et al., 2011; Matsushima et al., 2007). TLRs are a subset of PRRs expressed on the cell membrane of professional immune cells like monocytes, macrophages, dendritic cells, B cells, and non-immune cells like keratinocytes and epithelial cells (Kawasaki et al., 2011; Novak et al., 2010). TLRs are classified by their ectodomain for ligand binding (Kawai and Akira, 2009; Kumar et al., 2009). Thirteen TLRs have been identified in mammals but only TLR3, TLR7/8, and TLR9 recognize microbial nucleic acids in endolysosomal compartments while the others bind to bacterial or parasitic PAMPs such as triacyl lipopeptides, peptidoglycan, or lipopolysaccharide on the cell surface (Kawai and Akira, 2009; Kawasaki et al., 2011).

TLR3 recognizes dsRNA, a product of RNA virus replication lifecycles, in endolysosomal compartments. Recognition of dsRNA by TLR3 leads to signaling through NF−κB and subsequent activation of IFNs (Alexopoulou et al., 2001). This IFN–β promoter activation is uniquely mediated by the adaptor protein, Toll-interleukin 1 receptor domain (TIR)-containing adaptor inducing IFN-β (TRIF or TICAM-1) (Oshiumi et al., 2003). This recognition process by TLR3 must be tightly regulated to ensure IFN activation only in the presence of non-self nucleic acid. The structural composition of the dsRNA is important in efficient recognition by TLR3. For example, the 2′-OH group in cytidylic acid is necessary for the dsRNA to be recognized by TLR3 (Okahira et al., 2005). More recently, work has been done to examine the functional structure of TLR3 that has the ability to recognize dsRNA. Glycosylation and cathepsin cleavage of TLR3 occur as it is transported from the endoplasmic reticulum through the Golgi apparatus and into an endolysosome (Toscano et al., 2013). The TLR3 C terminal and N terminal cleavage product complex that results is necessary for the recognition of dsRNA (Garcia-Cattaneo et al., 2012; Murakami et al., 2014). This mature TLR3 is fully functional in the endolysosome and ready to accurately recognize non-self dsRNA (Toscano et al., 2013). An interesting exception has also been discovered whereby poliovirus-derived single-stranded RNA segments that have loop structures resembling dsRNA can also activate TLR3 when they come from damaged or inflamed cells (Tatematsu et al., 2013). As we will discuss below, TLR3 plays a key role in controlling viral infections that involve dsRNA structures and it is also involved in the manifestation of autoimmune disorders such as type 1 diabetes.

TLR7/8 resides in endolysosomal compartments and recognizes ssRNA as the ligand of activation. Signaling occurs through the adaptor molecule MyD88 and IRF7 (Diebold et al., 2004; Heil et al., 2004; Kawai et al., 2004). For example, TLR7 and TLR8 have been shown to aid in host defense against the paramyxovirus, Sendai virus (Melchjorsen et al., 2005). HIV is also an antagonist for TLR7/8 mediated antiviral responses robust sensing by these TLRs leads to recruitment of effector cells to the site of viral infection (Schlaepfer and Speck, 2008). Mechanistically, TLR7/8 sensing of ssRNA occurs in a sequence-independent manner. The uridine and ribose molecules of RNA are known antagonists of TLR7 (Diebold et al., 2006). TLR7/8 activation induces a robust IFN response alongside the production of other cytokines such as: interleukin (IL)-1β, IL-6 and IL-12. IL-1β in particular is produced when non-self ssRNA and TLR7/8 activation results in activation caspase-1 (Nicholas et al., 2011). More recently, researchers also determined that the RNA editing phenomenon of adenosine-to-inosine conversion enhances TLR7/8 activation. In this experiment, TLR7 sensing of ssRNA was enhanced in inosine-modified viral RNA (Sarvestani et al., 2014). The cooperative role between TLR7 and TLR8 is also an important part of the mechanism that results in an IFN response to ssRNA. Influenza virus infection was effectively controlled in a rat study where the dual administration of TLR7/8 was administered and effectively suppressed viral load (Hammerbeck et al., 2007). Additionally, during Japanese encephalitis virus infection, TLR8 can compensate for a lack of TLR7 by activating an effective response alone (Awais et al., 2017). TLR7/8 is a necessary component of the antiviral response that responds to foreign ssRNA in endolysosomal compartments and activates an IFN response.

2.1.3. RIG-I-Like Receptors—RIG-I-like receptors (RLRs) recognize viral RNA and initiate innate immune response signaling (Loo and Gale, 2011). RLRs are characterized by their central DExD/H box RNA helicase domain that senses cytosolic dsRNA (Gack, 2014). There are three known RLRs with unique functions: retinoic acid-inducible gene I (RIG-I) (Yoneyama et al., 2004), melanoma differentiation-associated gene 5 (MDA5) (Kang et al., 2004), and laboratory of genetics and physiology 2 (LGP2) (Cui et al., 2001). RLRs are expressed in most human tissues to allow for widespread type I IFN induction upon viral infection. RLRs are expressed at low levels in resting cells, and then the expression is increased in response to viral infection. RIG-I and MDA5 have similar functions such that they initiate antiviral signals to induce IFN gene activation (Kang et al., 2004; Yoneyama et al., 2004). LGP2 functions as a regulator of RIG-I and MDA5 (Yoneyama et al., 2005). Therefore, the antiviral response is a balanced system where the outcome of a viral infection is determined by the level of viral replication as compared to the level of antiviral response activation.

RIG-I and MDA5 are structurally similar with two caspase-recruitment domains (CARDs) at the N-terminus region, a central DExD/H domain, and C-terminal domain (CTD) (Kang et al., 2004, Yoneyama et al., 2004). Once the RIG-I and MDA5 central DExD/H domain and CTD bind viral RNA, the CARD domains interact with the mitochondrial antiviral signaling (MAVS) adaptor protein. MAVS is composed of an N-terminal CARD-like domain and C-terminal transmembrane domain, both of which are necessary for protein function and signaling (Seth et al., 2005). The activation signal is then transmitted through Fas-associated

protein with the death domain (FADD)/receptor-interacting protein 1 (RIP1) that leads to the translocation of the NF-κB transcription factor into the nucleus (Honda et al., 2006). Signaling through MAVS can also activate IKKε and TANK-binding kinase 1 (TBK1) that phosphorylate IRF3 and allows for translocation to the nucleus (Sharma et al., 2003). NF-κB and IRF3 are transcription factors that lead to the production of proinflammatory cytokines, namely IFN-β for type I IFN response to viral infection (Yoneyama et al., 2005).

Mitochondrial antiviral-signaling protein (MAVS, also known as IPS-1, VISA, and Cardif) is an adaptor molecule that also induces IFN from RIG-I and MDA5 signaling (Kawai et al., 2005). The MAVS molecule has a CARD domain that interacts with the CARD domains of RIG-I and MDA5. MAVS signaling requires TBK1 and IKKε protein kinases and activates transcription factors NF-κB and IRF3, leading to IFN induction (Kawai et al., 2005). Autoamplification of IFN signaling ensues because RIG-I and MDA5 are IFN-inducible (Honda et al., 2006). The abundance of IFNs induces up-regulation of IFN-stimulated genes (ISGs) (Pine et al., 1990). This can occur through the Jak/STAT (signal transducer and activator of transcription) upon binding by IFN-β (Darnell et al., 1994). The antiviral signals are then spread to surrounding infected and uninfected cells. Cells enter into antiviral states that control the infection by resisting viral replication. ISGs are responsible for amplifying the antiviral response and encoding proteins that have direct antiviral activity (Yoneyama et al., 1996). The production of innate immune cytokines and chemokines recruits professional immune cells to the site of infection and initiate the adaptive immune response (Kadowaki et al., 2000). Activation of RIG-I and MDA5 by dsRNA leads to activation of a signaling cascade and subsequent IFN induction during antiviral innate immune responses (Fig. 1).

Since an effective IFN response requires equilibrium within the system, regulators such as LGP2 are key in modulating activation signals. LGP2 has a different structure as compared to RIG-I and MDA5 because it lacks the two CARD domains (Murali et al., 2008). The ATPase domain of LGP2 functions upstream of RIG-I and MDA5 to facilitate recognition of cytosolic viral RNA (Satoh et al., 2010). Studies have shown that LGP2 binds dsRNA and negatively regulates RIG-I and MDA5 activation. These studies observed negative feedback regulation during Sendai virus and Newcastle disease virus infection (Rothenfusser et al., 2005; Yoneyama et al., 2005). However, a recent study has suggested that LGP2 might also have a positive enhancement regulation mechanism for MDA5 and RIG-I. Structural analysis of LGP2 revealed that RNA-dependent binding of dsRNA by LGP2 enhanced MDA5 antiviral signaling (Uchikawa et al., 2016). LGP2 has also been described as a necessary component of an effective IFN response during positive-sense picornavirus infection (Satoh et al., 2010). However, other studies have shown that LGP2 negatively regulates RIG-I function by sequestering viral RNA or competing with IKKε for interaction with MAVS (Komuro and Horvath, 2006; Rothenfusser et al., 2005; Saito et al., 2007). To clarify these seemingly disparate roles for LGP2, it was shown that in mice lacking LGP2, there was increased resistance during negative-sense vesicular stomatitis virus (VSV) infection while IFN signaling was defective during Cardiovirus A, a member of the *Picornaviridae* family, infection, causing the mice to be more susceptible to infection (Venkataraman et al., 2007). Taken together, LGP2 has an important regulatory role in IFN signaling, but the response is variable among different RNA viruses.

RIG-I and MDA5 have variable recognition abilities for foreign cytosolic RNA (Kato et al., 2006). The varying abilities for RIG-I and MDA5 to discriminate between self and non-self allows for specification in the antiviral innate immune response. RIG-I and MDA5 both have the ability to recognize dsRNA. However, RIG-I is known to recognize *Orthomyxoviridae*, *Flaviviridae*, and *Paramyxoviridae* family viruses while MDA5 specifically recognizes picornavirus infections (Kato et al., 2006; Loo et al., 2008). RIG-I and MDA5 activation together can also be essential to induce strong IFN responses during viral infections, such as West Nile virus (Errett et al., 2013). The length of the dsRNA plays a key role in activation of RIG-I or MDA5. RIG-I recognizes short dsRNA (up to 1 kb) while MDA5 recognizes long dsRNA molecules (more than 2 kb) (Kato et al., 2008). For example, the replicative form of the picornavirus genome is a 7.5 kb dsRNA intermediate that has been shown to robustly activate MDA5 in infected cells (Feng et al., 2012). RIG-I has additional abilities to discriminate between self and non-self by recognition of single-stranded RNA with a 5′-triphosphate (5′-PPP) or with a 5′-diphosphate (5′-PP) (Goubau et al., 2014; Hornung et al., 2006; Pichlmair et al., 2006). This was determined because influenza virus infection activates RIG-I in the absence of a dsRNA intermediate during the replication life-cycle (Pichlmair et al., 2006). Host ssRNA exists in the cytosol with a 5′-guanosine cap because it has undergone post-transcriptional modifications. Therefore, the 5′-PPP is an important feature in discrimination because self and non-self because it is unique to viral cytosolic ssRNA. The 5′-PPP is a component of the RNA molecule after viral polymerase replication has taken place (Hornung et al., 2006). It was also described that RIG-I can recognize ssRNA with 5′-PP, a special feature of mammalian reoviruses (Goubau et al., 2014). Recently, it was shown that a conserved residue (H830) of RIG-I is essential to prevent sensing of self RNA that bears a N_1-2′-*O*-methyl group. Additionally, yellow fever virus encodes a methyl transferase to allow escape of viral RNA recognition (Schuberth-Wagner et al., 2015). Together, RIG-I and MDA5 recognize different features of foreign RNA molecules that lead to unique activation of these RLRs during different viral infections. The length of the viral dsRNA along with 5′-PPP, 5′-PP, or cap methylation features on ssRNA dictates the activation of either RIG-I or MDA5 in antiviral innate immune responses.

RNA binding to RIG-I and MDA5 requires specific molecular mechanisms to facilitate controlled and effective activation of the RLRs. Positive and negative regulatory mechanisms of RIG-I and MDA5 are necessary to tightly control IFN signaling. It has been shown that RIG-I retains an inactive configuration until RNA binding occurs and the ATPase activity increases to induce signal transduction of the antiviral response (Gee et al., 2008). Exposure of the RIG-I and MDA5 CARD domains leads to structural changes, such as ubiquitination and phosphorylation, that vary levels of activation. The RNF125 ubiquitin E3 ligase suppresses RIG-I and MDA5 activity by causing ubiquitination of their CARD domains and subsequent proteasomal degradation (Arimoto et al., 2007). Further, RNF125 enhancement by IFN creates a negative feedback loop that controls RIG-I and MDA5 activation during infection (Arimoto et al., 2007). In contrast, strong activation of RIG-I is facilitated by K63-polyubiquitin chains binding to RIG-I at the CARD domains (Zeng et al., 2010). RIG-I and MDA5 are also regulated by phosphorylation and dephosphorylation of its CARD domains through PP1α and PP1γ phosphatases. The function of PP1α and PP1γ to dephosphorylate the CARD domains of RIG-I and MDA5 is needed to facilitate strong

induction of an IFN response (Wies et al., 2013). This positive and negative regulation of RIG-I and MDA5 is important in maintaining appropriate control of IFN induction and serving as a first line of defense against viral infections. There are many regulatory mechanisms for RIG-I-and MDA5-mediated IFN induction that help in effective viral control. However, dysfunctions in recognition and signaling can lead to increased viral susceptibility and even autoimmunity.

2.2. RNA Sensing During Viral Infections

Mutations within the genes coding for RNA sensors have been shown to increase susceptibility to a variety of viral infections. Additionally, viruses have mechanisms to antagonize specific aspects of the antiviral innate immune response. Decreasing IFN induction during viral infection is advantageous for the virus because it increases its infectivity potential. Several RNA viruses that exhibit these characteristics include: hepatitis C virus, Dengue virus, West Nile virus, Zika virus, respiratory syncytial virus, Nipah virus, Ebola virus, and Rotavirus (Table 1).

2.2.1. Hepatitis C Virus—Hepatitis C virus (HCV) is a positive-sense ssRNA virus within the *Flaviviridae* family that activates RIG-I during infection (Sumpter et al., 2005). HCV uses viral proteases and viral proteins to target specific components of IFN signaling and decrease antiviral responses. The HCV-NS3/4A viral protease is involved in many mechanisms of antiviral suppression. HCV-NS3/4A is known to cleave MAVS and decrease IFN signaling. A point mutation in MAVS at Cys-508 renders it resistant to NS3/4A cleavage (Li et al., 2005). HCV-NS3/4A are also known to induce expression of the translocase of outer mitochondrial membrane 70 (TOM70) and induce IFN signaling in hepatocytes (Kasama et al., 2012). However, the HCV nonstructural (NS) protein 3 (HCV-NS3) then suppresses TOM70 induction of IRF3 mediated immunity by cleaving MAVS upstream of TOM70. Also, HCV-NS3/4A viral protease has also been shown to inhibit IL-28 induction. IL-28 contains NF-κB and IRF3 binding sites, meaning it can be induced by these transcription factors (Ding et al., 2012). Thus, the actions of HCV-NS3/4A aid in viral persistence within the host. The HCV-NS4B viral protein is also involved in antiviral suppression. HCV-NS4B interferes with TBK1 interactions, inhibiting these proteins from properly relaying IFN signaling (Ding et al., 2013). Finally, the HCV core protein was shown to inhibit TLR7-mediated IFN induction as well as IRF7 and STAT1 expression in plasmacytoid dendritic cells (Stone et al., 2014), and polymorphisms in genes encoding TLR3/7/8 result in increased susceptibility to HCV infection (El-Bendary et al., 2018). Together, HCV-NS3/4A, HCV-NS4B, and HCV-Core are viral components that suppress IFN induction and evade innate immune responses.

2.2.2. Dengue Virus and West Nile Virus—Dengue virus (DENV) and West Nile virus (WNV) are both mosquitoborne viruses within the *Flaviviridae* family (Ahlers and Goodman, 2018; Fredericksen et al., 2008; Loo et al., 2008; Nasirudeen et al., 2011). DENV and WNV both activate the IFN-mediated innate immune response through RIG-I and MDA5. Knockdown of RIG-I and MDA5 resulted in increased susceptibility to DENV infection (Nasirudeen et al., 2011). This highlights the importance of RIG-I and MDA5 in controlling DENV infection. Innate immune responses to WNV infection occur in two major

phases, with RIG-I and MDA5 being important sensors at both phases. The initial response to WNV leads to IRF3 activation and ISG induction. Later stages in WNV infection are dominated by IFN-dependent antiviral gene expression. In response to WNV infection, RIG-I and MDA5 act through MAVS as they work together to stimulate a strong IFN response and subsequent signal amplification (Fredericksen et al., 2008). DENV and WNV both have antiviral evasion mechanisms that antagonize IFN induction after RIG-I and MDA5 sensing.

DENV has many mechanisms of innate immune suppression at different stages of infection. During early antiviral responses, before IFN induction, DENV induces the production of autophagic proteins, and autophagy activation suppresses the antiviral response (Huang et al., 2016). As the infection progresses, DENV also suppresses IFN induction by keeping viral dsRNA within intracellular membranes to hide the dsRNA from recognition by RLR receptors (Uchida et al., 2014). Virus induced double-membrane vesicles form early in infection and contain the dsRNA along with viral nonstructural proteins and replication machinery (Junjhon et al., 2014; Mackenzie et al., 1996). Therefore, viral replication can be occur within these vesicles in the first 48 h of infection with little dsRNA exposure in the cytosol (Uchida et al., 2014). However, other studies have shown that DENV NS4A is part of the membrane-bound replication complex that is also associated with viral RNA (Miller et al., 2007), also similar to the flavivirus Kunjin virus (Roosendaal et al., 2006). Additionally, DENV viral RNA was shown to associate with the rough ER (Grief et al., 1997). Therefore, it remains to be fully clarified if DENV viral RNA is fully incorporated within virus-induced membrane structures to avoid RLR recognition or if they are on the surface of cytosolic membrane structures. To evade host immune responses, DENV also uses nonstructural viral proteins direct suppression IFN signaling. Three nonstructural proteins of DENV are known to down-regulate IFN-β expression. The presence of DENV-NS4B caused the most significant decrease in IFN activity while DENV-NS2A and DENV-NS4A also antagonized IFN, but to a lesser extent than DENV-NS4B (Muñoz-Jordán et al., 2003). Additional research following this study described the mechanism by which the nonstructural proteins decreased innate immune responses during DENV infection. A viral nonstructural protein complex (DENV-NS2B/NS3) interacts with IKKε to inhibit kinase activity and ultimately decrease IFN induction (Angleró-Rodríguez et al., 2014). Also, DENV-NS2A/NS4B inhibits TBK1 phosphorylation in a dose dependent manner (Dalrymple et al., 2015). Experiments also indicated that DENV infection caused a reduction in STAT2 expression suggesting the virus antagonized this innate immune response gene (Ashour et al., 2009). DENV-NS5 is the viral polymerase and it has a role in inhibiting STAT2 function. Mature DENV-NS5 is the product of a polyprotein and this was important for STAT2 binding and subsequent inhibition. Precursor DENV-NS5 in the form of a polyprotein had a single role in inducing degradation of STAT2 while the proteolytically processed, mature DENV-NS5 protein had a single role in binding STAT2 (Ashour et al., 2009). DENV-NS5-mediated degradation of STAT2 is facilitated by the host E3 ubiquitin ligase, UBR4 (Morrison et al., 2013). Finally, the DENV protease complex (NS2B/NS3) has been shown to inhibit TLR3-mediated IFN induction (Rodriguez-Madoz et al., 2010). Together these studies highlight that many DENV nonstructural proteins function in suppressing IFN induction during innate immune antiviral responses.

WNV also encodes mechanisms of innate immune suppression. IFN responses in myeloid cells are necessary for control of WNV infection. Mice lacking MAVS and the type I IFN receptor had extremely low cytokine production coupled with high WNV replication. These findings highlight the importance of IFN signaling through MAVS to control WNV infection in myeloid cells (Pinto et al., 2014). Due to the neuroinvasive nature of WNV, IFN responses to control WNV infection in the central nervous system have been studied (Ramos et al., 2012). *In vivo* experiments showed a significant upregulation of IL-1β during acute WNV infection. IL-1β showed a synergistic role with IFN signaling to control WNV infection in neurons (Pinto et al., 2014). WNV susceptibility has also been linked to gene expression changes in peripheral blood cells. Individuals with resistance to WNV infection had higher IL-4 levels in serum as compared to individuals who developed severe symptoms. These IL-4 levels altered expression of many genes and correlated with disease outcome (Qian et al., 2014). Neuroinvasive human cases from WNV infection were also linked to mutations in *RFC1* gene through a screen of common genetic polymorphisms. *RFC1* aids in proper activation of DNA polymerase (Loeb et al., 2011). Additionally, experiments in mice revealed that during WNV infection, MAVS is essential for RLR signaling. Mice that lacked MAVS exhibited uncontrolled infection and a lack of regulatory T-cell expansions that is normally a characteristic of acute WNV infection. These findings highlight the importance of MAVS mediated RLR signaling to control WNV infection (Suthar et al., 2010). WNV NS1 inhibited K63-linked ubiquitination of RIG-I and blocked IRF3 signaling upon WNV recognition. It was specifically determined that WNV-NS1 interaction with MDA5 and RIG-I induced proteasome degradation of these intracellular receptors (Zhang et al., 2017b). Lastly, an attenuated WNV strain containing a mutant NS4B protein (P38G), exhibited increased T-cell priming via a TLR7-mediated mechanism (Xie et al., 2013), and TLR3 is important in blocking WNV replication and spread into the brain (Szretter et al., 2010; Wang et al., 2004). Together, there are a variety of antiviral mechanisms in different cell types employed by WNV to antagonize the IFN response.

Interestingly, type 2 diabetes has been shown to increase susceptibility of severe DENV and WNV infection. One study showed that DENV infected patients with type 2 diabetes were at a higher risk of developing dengue hemorrhagic fever as compared to DENV infected patients without type 2 diabetes. This was quantified by an increase in IL-4 and IL-10 cytokine production in patients with DENV and type 2 diabetes because these cytokines are an important immunopathogenesis marker for dengue hemorrhagic fever (Lee et al., 2013). Another study described an increase in WNV titer in serum, peripheral tissue, and the brain of the diabetic mouse model. Type 2 diabetes caused a non-specific WNV response that increased susceptibility of neuroinvasive WNV infection (Kumar et al., 2012). These studies highlight the important balance in innate immune signaling that must be present to efficiently clear a viral infection.

2.2.3. Zika Virus—Similar to DENV and WNV, Zika virus (ZIKV) is part of the *Flaviviridae* family and is transmitted by mosquitoes. A robust IFN response is also needed to control ZIKV infection. ZIKV infection induced RLR signaling in human skin fibroblasts to control infection. Human skin fibroblasts infected with ZIKV showed upregulation of TLR3, RIG-I, MDA5, and ISGs. There was also sequential activation observed where TLR3

was activated 6 h post-infection and RIG-I and MDA5 were activated later in infection (Hamel et al., 2015). Other mosquito-borne flaviviruses have been known to infect dendritic cells, and this was consistent with ZIKV. Researchers observed that RIG-I response to ZIKV in human dendritic cells was activated during infection. However, there was observable inhibition of IFN protein translation. Mechanistically, ZIKV was also able to control IFN signaling by blocking STAT1 and STAT2 phosphorylation (Bowen et al., 2017). These studies show that ZIKV infection leads to the activation of RIG-I and MDA5 but that ZIKV also has mechanisms to antagonize down-stream IFN signaling.

There are specific IFN adaptor molecules that increase ZIKV susceptibility and some nonstructural proteins of the virus antagonize IFN signaling, as shown for DENV and WNV. The MAVS adaptor protein within the IFN signaling cascade is important in the early IFN response because mice lacking MAVS had higher viremia than control mice (Piret et al., 2018). During the development of a ZIKV mouse model, experiments revealed that a triple knockout of IRF3, IRF5, and IRF7 increased susceptibility to ZIKV infection through decreased IFN signaling. Also, mice lacking the IFN receptor had higher viral load in the brain and spinal cord that could not be controlled, which correlates with the neuroinvasive nature of the virus (Lazear et al., 2016). On the other hand, increased IFN induction and placental inflammation can lead to brain damage in newborns, and inhibition of TLR3 and TLR8 led to decreased pro-inflammatory cytokine responses in trophoblasts (Luo et al., 2018). Many ZIKV nonstructural proteins have been shown to facilitate the inhibition of IFN signaling observed during infection. For example, ZIKV-NS5 binds STAT2 and its expression correlates with subsequent proteasome degradation of STAT2 (Kumar et al., 2016). The IFN inhibitory role of ZIKV-NS5 in other flaviviruses is consistent for that of ZIKV. DENV-NS5 acts on STAT2 but the mechanism is slightly different than that of ZIKV because it involves the E3 ubiquitin ligase UBR4 to induce degradation (Grant et al., 2016). ZIKV-NS1 has also been shown to inhibit IFN signaling induction through binding of TBK1. This inhibitory role of the ZIKV-NS1 was observed only in ZIKV strains that caused epidemics after 2012. This highlights the importance of a fixed mutation in viral evolution because the ZIKV-NS1 fixed mutation helped the virus increase infectivity by decreasing IFN-β induction (Xia et al., 2018). Therefore, adaptor molecules are important for regulating an efficient antiviral response and without them IFN signaling may be uncontrolled. Additionally, ZIKV-NS5 and ZIKV-NS1 have IFN inhibitory roles during viral infection.

2.2.4. Respiratory Syncytial Virus—Respiratory syncytial virus (RSV) disproportionately causes more severe symptoms in infants as compared to older populations. RSV has a negativesense non-segmented RNA genome and it is part of the *Pneumovirus* genus of the *Paramyxoviridae* family. RSV dsRNA is sensed by RLRs and TLRs (reviewed in Klein Klouwenberg et al., 2009; Mukherjee and Lukacs, 2013), and host immune responses play a major role in the differences in viral susceptibility (Loo et al., 2008; van Drunen Littel-van den Hurk and Watkiss, 2012). RSV infection is known to specifically cause severe lower respiratory tract infection in newborn infants (Marr et al., 2014). Differences in the innate immune response to RSV determine the disease severity in a child. One study found polymorphisms in immune-related genes of pre-term babies that correlated with increased disease susceptibility as compared to babies carried to term

(Siezen et al., 2009). Another study found a consistent association in 22 single-nucleotide polymorphisms (SNPs) within 21 innate immune genes and the development of severe RSV bronchiolitis. These SNPs were identified in a cohort of children hospitalized for severe RSV bronchiolitis as compared to the control population. One SNP identified in this study with a highly significant association with bronchiolitis was the vitamin D receptor (Janssen et al., 2007). Vitamin D is known to mediate NF-κB and STAT1 expression (Stoppelenburg et al., 2014). Vitamin D deficiencies have been correlated with increased risk and severity of RSV (Hansdottir et al., 2010). Specifically, the *FokI* vitamin D receptor polymorphism abrogated vitamin D's control of the STAT1-mediated antiviral response (Stoppelenburg et al., 2014). Together, these findings illustrate the importance of vitamin D in controlling the induction of STAT1 during antiviral responses and the importance of this regulation in RSV infection. Many SNPs have been linked to RSV susceptibility and loss-of-function SNPs in the vitamin D receptor have a strong association with the development of severe RSV bronchiolitis.

Increased susceptibility to RSV has also been linked to dysfunctions in IFN signaling from loss-of-function in plasmacytoid dendritic cells (pDCs) and direct inhibition of IFN signaling by RSV nonstructural proteins. Researchers have determined that pDCs are important in activating IFN responses in lungs during RSV infection. This epidemiological study found that newborn infants had increased susceptibility to RSV because they did not have fully functioning pDCs and therefore there was low IFN induction by RIG-I (Marr et al., 2014). Respiratory macrophages and pDCs are critical in combating RSV infection, not only through RLR signaling, but also through TLR3-and TLR7-mediated mechanisms (Qi et al., 2015). Using mouse pneumonia virus, the rodent-specific form of RSV, it was shown that TLR7 was critical for the host defense response and IFN induction during infection (Davidson et al., 2011). These results were corroborated through analysis of RSV-infected human pDCs (Schijf et al., 2013). RSV is also known to decrease IFN signaling in airway epithelial cells through degradation of STAT2 (Ramaswamy et al., 2004) and through an RSV-NS1-dependent but TLR3-independent mechanism (Xu et al., 2014b). Additionally, RSV-NS2 was identified as inducing these inhibitory effects on the IFN response (Ramaswamy et al., 2006). This innate immune response inhibition by RSV aids in viral replication specifically within airway epithelial cells. The control of RSV is complex, and it requires fully functioning proteins within the IFN pathway. As seen for other viruses, the RSV nonstructural proteins have individual roles in antagonizing the antiviral response.

2.2.5. Nipah Virus—Nipah virus (NiV) is another virus in the *Paramyxoviridae* family, but unlike RSV, it is part of the *Henipavirus* genus (Ciancanelli et al., 2009). NiV is a deadly zoonotic virus, and there is a 40–90% case mortality rate in human infected with NiV in Southeast Asia (Bharaj et al., 2016). NiV dsRNA is sensed by RIG-I, but not MDA5, to initiate IFN induction (Habjan et al., 2008). Research has shown that many of the NiV proteins contribute the deadly symptoms of NiV by antagonizing IFN stimulated antiviral responses (Bharaj et al., 2016). First, the NiV phosphoprotein (P) gene encodes the NiV-P, NiV-V, and NiV-W proteins that all antagonize IFN signaling (Ciancanelli et al., 2009). The NiV-V protein, mainly found in the cytoplasm, binds STAT1 and STAT2 proteins to prevent dimerization and nuclear transport (Rodriguez et al., 2004). The NiV-W protein has a very

similar role to the NiV-V protein except it sequesters STAT1 in the nucleus to inhibit subsequent ISG activation. Therefore, the NiV-V and NiV-W proteins have dual roles but are located in either the nucleus or cytoplasm to block STAT1 and induce antiviral functions. The NiV-P protein can also bind STAT1 to sequester the inactive protein in the nucleus, but to a lesser extent than NiV-V and NiV-W (Ciancanelli et al., 2009; Shaw et al., 2004). In comparison, Cedar virus is a henipavirus that is not pathogenic to humans and the Cedar virus P gene products do not antagonize STAT proteins as seen in NiV infection. This suggests that the antagonizing properties of NiV-P gene protein products greatly contribute to the highly lethal nature of the virus (Lieu et al., 2015). Second, the NiV nucleoprotein also decreased IFN responses in a dose dependent manner. The specific mechanism of inhibition is through targeting of STAT1 and STAT2 complex formation in the cytoplasm. NiV nucleoprotein decreases STAT1/STAT2 nuclear transport and subsequently down-regulates ISG expression (Sugai et al., 2017). Third, the NiV matrix protein has been shown to inhibit IKKε kinase activity that is involved in IFN signaling. The NiV matrix protein acts by degrading TRIM6, an E3-ubiquitin ligase that generates unanchored polyubiquitin chains for IKKε activation. Therefore, this degradation by the NiV matrix protein results in decreased activity of IKKε activity and decreases IFN signaling (Bharaj et al., 2016). Finally, the nonstructural C protein of paramyxoviruses inhibits IFN signaling (Gotoh et al., 2003; Mathieu et al., 2012), via inhibition of TLR7 in pDCs (Yamaguchi et al., 2014). Together, the gene products from NiV phosphoprotein, nucleoprotein, and matrix protein have been shown to antagonize IFN induction at different steps in its signaling pathway. This likely contributes to the high virulence of NiV in humans.

2.2.6. Ebola Virus—Ebola virus is negative-sense RNA virus with a non-segmented genome similar to that of RSV and NiV. Ebola virus is a hemorrhagic fever virus in the *Filoviridae* family. *Zaire ebolavirus* (EBOV) has a fatality rate of up to 90% in humans and the viral dsRNA is sensed by RIG-I to activate innate immune responses (Habjan et al., 2008; Kash et al., 2006). Early studies on EBOV were performed in human liver cells. In this study, researchers determined that IFN signaling was suppressed during infection. Through genomic analysis of gene expression, many antiviral genes were suppressed during infection. Researchers hypothesized a global IFN suppression model and also identified specific antiviral genes, such as IRF3, as being suppressed during EBOV infection (Kash et al., 2006). Further research revealed that the EBOV viral protein 35 (EBOV-VP35) had a specific inhibitor mechanism for IRF3. This was a highly specific suppression model because a point mutation in EBOV-VP35 altered its inhibitor function. EBOV-VP35 also had a role in enhancing viral replication (Hartman et al., 2008). Furthermore, EBOV-VP35 binds dsRNA, inhibiting RIG-I-mediated detection of viral dsRNA (Cardenas et al., 2006), and EBOV-VP35 is an important cofactor in the viral polymerase complex (Prins et al., 2010). Together, EBOV-VP35 plays an important role in EBOV pathogenesis both for spread of the virus within the host as well as IFN specific suppression. Further research on EBOV-VP35 enhanced the understanding of its inhibition mechanism. PACT (PKR activator) is a dsRNA binding protein that is known to induce activation of RIG-I. Experiments showed that EBOV-VP35 was able to inhibit PACT from activating RIG-I through direct binding. This was observed in a dose-dependent manner where increased presence of EBOV-VP35 increased PACT inhibition. EBOV-VP35 can also bind viral dsRNA and decrease activation

of RIG-I during EBOV infection (Luthra et al., 2013). Finally, EBOV-VP35 can inhibit TLR3-mediated signaling, but this occurs in a dsRNA-independent manner suggesting that the TLRs can circumvent VP35-mediated IFN inhibition (Leung et al., 2011; Yen et al., 2014). Taken together, EBOV-VP35 is a key antagonist of IFN induction during EBOV infection.

Further *in vivo* experiments have shown a more complex picture of EBOV infection than just the antagonizing properties of EBOV-VP35 (Caballero et al., 2016). Transcriptomics analysis of peripheral blood mononuclear cells from cynomolgus macaques infected with EBOV showed strong innate immune activation during viral infection. Many ISGs were upregulated in response to viral infection via an intramuscular injection. These findings were contrasting to previous studies that had shown the EBOV-VP35 protein targeted the IFN response for suppression. The authors of this study proposed a model of infection where EBOV-VP35 inhibits IRF3 activation in the single infected cell. Then, in neighboring cells, EBOV-VP35 might be inducing IRF3 nuclear translocation to facilitate induction of IFN signaling through an unknown mechanism. This hypothesis aims to explain why in isolated EBOV-VP35 experiments, the protein appears to decrease IFN signaling but then during *in vivo* EBOV infection, ISGs are upregulated (Caballero et al., 2016). This elevated pro-inflammatory response to EBOV has been described in other studies. Rhesus macaques were infected with EBOV and monitored daily throughout the infection (Ebihara et al., 2011). Blood samples described the cytokine and chemokine profile throughout the course of infection. IL-1β and IL-6 pro-inflammatory cytokines were upregulated during infection. Interestingly, anti-inflammatory cytokines such as IL-10 and IL-13 were also increased in fatal EBOV cases. This shows that the cytokine balance during infection might be an important indicator of disease outcome. This study also showed anti-coagulation induced by the virus and ultimately contributed to overall pathogenesis (Ebihara et al., 2011). These findings were also evident in samples for fatal human cases of Ebola virus disease, symptoms of which include hemorrhagic fever. Many cytokines and chemokines were upregulated in fatal human cases. When looking at the disease progression *in vivo*, uncontrolled pro-inflammatory responses are a characteristic of fatal EBOV cases. Biomarkers of infection were identified as IL-1β and IL-6 along with IL-8 at late stages of infection (McElroy et al., 2014). These EBOV studies highlight the important balance of the innate immune response in determining disease outcome. EBOV viral proteins have been identified to inhibit IFN signaling during infection.

2.2.7. Rotavirus—Rotavirus (RV) is a segmented dsRNA virus within the *Reoviridae* family. It causes severe diarrhea in young children and is known to infect epithelial cells of the small intestine (Barro and Patton, 2005). RV dsRNA has been shown to activate RIG-I like receptors within intestinal epithelial cells. This virus is unique in that it is sensed by both RIG-I and MDA5 either together or separately. When MAVS, RIG-I, or MDA5 were silenced, RV titer increased and IFN-β production decreased. These findings suggested that RV induced IFN-β production through MAVS signaling after RIG-I and MDA5 activation (Broquet et al., 2011). Researchers have looked further into the specific RV RNA transcripts that activate IFN signaling. Nascent single-stranded RNA transcripts produced during viral replication were a strong inducer of IFN signaling (Uzri and Greenberg, 2013). Also, large

RNA transcripts produced 6 h after cells were infected with RV activated IFN signaling. This finding was only observed 6 h after infection but not 1 h after infection. Both the single-stranded RNA transcripts and large RNA produced 6 h after infection had uncapped RNA at the 5′ end. RNA lacking 2′-*O*-methylated 5′ cap was detected in the large RNA as well. The viral protein 3 enzyme of RV is known to encode guanylyltransferase and methyltransferase. Therefore, inaccuracy in this enzyme would result in a lack of a 5′ cap or 2′-*O*-methyl group on the 5′ cap structure of viral RNA. Then, RNA lacking these structural components would activate RIG-I-like receptors and subsequent IFN-β production (Uzri and Greenberg, 2013). In conclusion, RNA sensing by RIG-I or MDA5 is important for controlled IFN induction during RV infection. Variations in RNA transcripts and processing are also an important indicator of IFN-β production levels. Regarding TLR signaling and RV, interestingly, TLR3 and TLR7 were required to protect the gut from inflammatory-inducing conditions through proper recognition of the gut virome, which includes RV (Yang et al., 2016).

RV nonstructural proteins are also known to antagonize innate immune responses. Specifically, RV-NS1 (or NSP1) is an antagonist of IRF3 through a common mechanism found in other viruses where it induces proteasome-dependent degradation of IRF3 to decrease IFN signaling (Barro and Patton, 2005). RV-NS1 also has a novel mechanism of decreasing NF-κB activation. This viral protein induces proteasome-dependent degradation of β-transducin repeat containing protein, a cellular protein that functions within the multi-subunit complex responsible for NF-κB activation (Graff et al., 2009). Another study also demonstrated that RV-NS1 decreased IFN-β production through a mechanism independent of IRF3 degradation as previously reported. RV-NS1 directly bound to RIG-I to decrease activation and IFN-β production. This direct interaction was confirmed with immunoprecipitation and RV-NS1 interacted with RIG-I outside the IRF3 binding domain (Qin et al., 2011). Therefore, RV is sensed by RLRs and this sensing is enhanced with inefficiency of viral enzymes that make RNA products of replication more noticeable to the RLR sensing domain. However, the virus also has ways to combat this innate immune activation and RV-NS1 is a main driver that decreased IFN-β production through antagonizing of RIG-I, NF-κB, and IRF3 activation.

2.3 Defects in RNA Sensing and Autoimmunity

Hyperactive or non-functional mutations within the genes coding for RNA sensors or their interacting proteins have been show to lead to autoimmune-like phenotypes, such as type 1 diabetes, Aicardi–Goutières syndrome, Crohn's disease, Singleton–Merten syndrome, and systemic lupus erythematosus. As described below, many of these phenotypes are the result of imbalanced IFN or insulin signaling, autophagy, or responses to pathogens (Table 2).

2.3.1. The Role of MDA5 in Type 1 Diabetes and Aicardi–Goutières Syndrome

—Type 1 diabetes (T1D) is characterized by the development of autoantibodies that target beta cells of the human pancreas. These autoantibodies and auto-reactive immune cells then trigger the destruction of insulin-producing pancreatic beta cells and lead to T1D. Researchers have found that there is a genetic component to disease susceptibility along with viral infection and environmental variables. Environmental factors are known to be

associated with disease manifestation, and one example is vitamin D deficiency. Also, Caucasians living in Europe have a high disease incidence that highlights the exogenous factors of T1D. Cohort studies linked enterovirus or coxsackie B virus infection with increased susceptibility to the development of T1D (Knip et al., 2005). Enterovirus is known to target beta cells in the human pancreas. Autopsied pancreases of T1D patients revealed a tropism of enterovirus for human pancreatic islet cells (Ylipaasto et al., 2004). A Finnish Diabetes Prediction and Prevention Study indicated a positive association between the development of autoantibodies for human pancreatic beta cells and enterovirus infection. Autoantibodies were more likely to be present in children infected with enterovirus as compared to the control groups (Lönnrot et al., 2000). In Europe there is a high prevalence of T1D and a low prevalence of enterovirus as compared to other regions of the world, such as Cuba. Therefore, another study observed the relationship between enterovirus and T1D in Cuba, where T1D incidence is low and enterovirus prevalence is high. The researchers found a direct correlation between enterovirus infection and the development of preclinical and clinical stages of T1D (Sarmiento et al., 2013). Molecular mimicry is a proposed mechanism for this correlation because antibodies made against enterovirus could also target beta cells (Jang et al., 2015). Acute cytolytic damage from enterovirus was also a proposed mechanism for the association of enterovirus infection with T1D (Sarmiento et al., 2013). A population-based cohort study in Taiwan of age-and sex-matched children also showed that T1D incidence was higher in the enterovirus-infected cohort as compared to non-enterovirus-infected cohort (Jang et al., 2015). A similar correlation is also evident for coxsackie B virus. Data collected throughout many countries in Europe concluded that diabetic children were more likely to have antibodies against coxsackie B virus 1 than the control group of children without diabetes (Oikarinen et al., 2014). Therefore, infections with enterovirus or coxsackie B virus increase susceptibility to T1D. This highlights the connection between innate immune signaling dysfunction in response to viral infection and the development of autoimmunity.

Dysfunctions in MDA5 have also been linked to the development of T1D. Genetic analysis through a genome-wide association study (GWAS) revealed genetic components of T1D susceptibility. SNPs have been associated with the development of T1D. Four SNPs with a strong association to disease susceptibility were located within the *IFIH1* gene that codes for MDA5. High *IFIH1* gene expression in peripheral blood mononuclear cells also correlated with susceptible genotypes. This study highlights an interesting genetic association and gene expression importance for *IFIH1* in the development of T1D (Liu et al., 2009). Another GWAS further linked T1D and *IFIH1*. It identified four rare variants of *IFIH1* that strongly correlated with a decreased risk of developing T1D (Nejentsev et al., 2009). Two of these *IFIH1* variants were correlated with a loss-of-function to MDA5 (Shigemoto et al., 2009). This resistance to T1D was evident when mice heterozygous for *IFIH1* ($MDA5^{+/-}$) on a NOD/Ltj background, a known mouse model of T1D, had decreased levels of MDA5 protein as compared to wild-type mice. Mice heterozygous for MDA5 drove a regulatory T-cell response that was protective against T1D during coxsackievirus infection. Mice homozygous for MDA5 on the NOD/Ltj background had high MDA5 protein levels that resulted in a strong effector T-cells response and beta cell destruction during T1D during coxsackievirus infection (Lincez et al., 2015). These findings show how MDA5 function correlates with

T1D susceptibility. Reduced MDA5 expression has also been linked to increased susceptibility to encephalomyocarditis virus strain D (EMCV-D) and diabetes. EMCV-D infects insulin-producing beta cells in the pancreas similar to enterovirus or coxsackie B virus. Therefore, a lack of viral infection control is likely to lead to the production of beta cell antigens that can cause destruction of the pancreas and increase susceptibility of T1D. Mouse experiments revealed that MDA5 along with TLR3 were essential in initiating a controlled IFN response against EMCV-D. Also, mice with knockouts in MDA5 and/or TLR3 had increased susceptibility to T1D (McCartney et al., 2011). Taken together, loss-of-function in MDA5 due to genetic polymorphisms or viral infection can lead to autoimmune disorders, namely T1D.

Over activation of MDA5 can also lead to autoimmune disorders. Researchers found that mice with a missense mutation in *IFIH1* quickly developed lupus-like autoimmune symptoms without the presence of a viral infection (Funabiki et al., 2014). This means that MDA5 not only has a role in controlling viral infections, but can also control autoimmune disorders. The *IFIH1* missense mutation leads to a gain-of-function in MDA5 and IFN induction spread throughout multiple organs. The cytokine production was directly correlative to MAVS activity, and without MAVS, the mice with the *IFIH1* missense mutation did not develop autoimmune symptoms. This clarified the importance of MDA5 signaling through MAVS in the development of autoimmune disorders (Funabiki et al., 2014). A regulator of IFN signaling, ubiquitin-specific peptidase (USP18), has an important cross talk function with MDA5. USP18 controls IFN-stimulated gene 15 protease during IFN signaling through MAVS. A lack of USP18 resulted in over activation of MDA5 and an uncontrolled pro-inflammatory response in pancreatic beta cells. The authors suggested that USP18 was a major regulator of IFN responses and clarified a mechanism by which MDA5 expression might influence the development of T1D (Santin et al., 2012). Therefore, MDA5 gain-of-function also causes unregulated IFN signaling that can lead uncontrolled beta cell destruction and the development of T1D.

Dysfunctions in the tight control of MDA5-mediated signaling have also been implicated in another autoimmune disease, Aicardi–Goutiéres syndrome (AGS) (Crow et al., 2015). AGS is an autoinflammatory, neurodevelopmental disorder that affects the brain, skin, and immune system. Characteristics range from chilblains (skin lesions) to cerebral calcifications and atrophy that may be present before birth but ultimately result in slow neurological decline due to the excess production of IFN-α (Rice et al., 2007). Analysis of AGS patient genomes revealed seven gene mutations linked associated with the disease. With regards to RNA sensing pathways, candidate genes of particular interest were *ADAR1*, encoding for an RNA-editing enzyme, and *IFIH1*, encoding for MDA5. Mutations in these genes led to an increase in IFN signaling in cerebrospinal fluid and serum that correlated with disease symptoms (Crow et al., 2015). *ADAR1* is a RNA-editing enzyme known to inhibit MDA5 signaling through MAVS (Pestal et al., 2015). Therefore, a loss-of-function mutation in *ADAR1* contributed to uncontrolled MDA5 antiviral response (Mannion et al., 2014; Pestal et al., 2015). More specifically, mice with a knock-in mutation in *ADAR1* that inhibited its RNA-editing ability exhibited embryonic lethality at embryonic day 13.5 due to MDA5 hyperactivity (Liddicoat et al., 2015). A study has also shown that the loss of *ADAR1* in human cells results in PKR hyperactivation and translational shutdown (Chung et

al., 2018). A gain-of-function mutation in *IFIH1* led to over expression of MDA5 and contributed to an over-reactive IFN response (Crow et al., 2015). It is important to note that clinical studies have shown that these gene mutations do not always lead to the same clinical symptoms in patients. One clinical study observed two siblings both with the loss-of-function mutation in *ADAR1*. Even though they both had the same mutation, their symptoms presented at different ages in childhood and symptoms were also variable. This is important information because early diagnosis and treatment of AGS can help with early administration of IFN suppression therapy to minimize brain damage induced by inflammation (Schmelzer et al., 2018). These disease phenotypes in relationship to uncontrolled IFN signaling show the functional importance of MDA5 and other genes involved in facilitating a controlled IFN response (Crow et al., 2015). Moreover, mutations in *IFIH1* in AGS patients reduce the tolerance of MDA5 to Alu retroelements, and that these retroelements can also activate MDA5 during the loss of *ADAR1* function. A gain-of-function mutation in MDA5 (G495R) also retains the minimal Alu duplex length to 30–40 bp (Ahmad et al., 2018). In conclusion, mutations in genes related to MDA5 signaling have been linked to the development of AGS.

2.3.2. P58^{IPK}, PERK, TLRs, and Type 1 Diabetes—The dynamic balance between the eIF2α kinases, such as PKR, with P58^{IPK} is important in determining the outcome of viral infection and the development of diabetes. As discussed previously, PKR is involved in amplifying the IFN response, and P58^{IPK} is a known inhibitor of PKR. P58^{IPK} is important for innate immune responses to viral infection along with the development of autoimmune disorders. P58^{IPK} was originally discovered and purified from influenza virus-infected cells (Lee et al., 1990). During influenza virus infection, P58^{IPK} inhibits PKR's ability to phosphorylate eIF2α, thus facilitating efficient translation of influenza virus mRNAs. In influenza virus infected cells lacking P58^{IPK}, there was a notable decrease in influenza mRNA translation and increase in eIF2α phosphorylation. In cells lacking the inhibitory target of P58^{IPK}, PKR, the results were reversed, and influenza virus mRNA translation increased while eIF2α phosphorylation decreased. This suggests efficient influenza virus replication if facilitated by P58^{IPK} inhibition of PKR and this has downstream ramifications on eIF2α phosphorylation. These results were also observed during VSV infection (Goodman et al., 2007). *In vivo* experiments enhanced our understanding of P58^{IPK} and identified it as a cellular inhibitor of the host defense (CIHD). Observation of P58$^{IPK–/–}$ mice infected with influenza virus showed the P58^{IPK} helps in host survival. P58$^{IPK–/–}$ mice had increased mortality but similar viral load as compared to the wild-type control mice. Additionally, in P58$^{IPK–/–}$ mice, there was an observed increase in eIF2α and PKR phosphorylation during influenza virus infection. These findings suggested that P58^{IPK} activation during viral infection actually enhanced host survival while also prolonging viral replication (Goodman et al., 2009). Through computational modeling, it was shown that during influenza virus infection there was a significant increase in P58^{IPK} while PKR and eIF2α phosphorylation were decreased. The infectious dose of virus also influenced this relationship. These findings were confirmed with vaccinia virus infection where rapid activation of P58^{IPK} was also observed (Goodman et al., 2011). Proviral roles of P58^{IPK} were further demonstrated during coxsackievirus B3 infection where P58^{IPK} suppressed virally induced apoptosis (Zhang Huifang et al., 2013). P58^{IPK} is an important regulatory in

influenza virus and vesicular stomatitis virus infection within the antiviral innate immune response signaling cascade. The tight regulation of PKR by P58^{IPK} is an important indicator of viral infection outcome.

P58^{IPK} also inhibits PERK, pancreatic ER-localized eIF2α kinase, which is encoded by *EIF2AK3*. Similar to that of PKR, PERK has a kinase binding domain very similar to that found in PKR where P58^{IPK} interacts to inhibit function. During ER stress, defined as the continued presence of unfolded proteins, P58^{IPK} is activated. P58^{IPK} then interacts with PERK and inhibits its activity through decreased phosphorylation. PERK functions during ER stress to decrease protein production in the ER. However, it is important to have regulatory proteins, such as P58^{IPK}, to prevent excess protein loss during stress. These findings show that P58^{IPK} is an important regulator of PERK in maintaining a controlled ER-stress response (Yan et al., 2002). P58^{IPK} and PERK are known to be expressed in pancreatic cells, hinting at an important connection between these proteins and the development of diabetes (Shi et al., 1999). In mice lacking PERK, progressive diabetes mellitus and exocrine pancreatic insufficiency develop (Harding et al., 2001). PERK has a high importance in controlling protein synthesis during the ER stress response. The important inhibitory role of P58^{IPK} on PERK was confirmed in *in vivo* experiments where adult mice lacking P58^{IPK} developed glucosuria, hyperglycemia, and hypoinsulinemia (Ladiges et al., 2005). These mice had greater levels of insulin producing beta cell destruction in the pancreas. The gene expression profiles in these mice were significantly altered to favor apoptosis of pancreatic islets. These findings suggest an important regulatory role of P58^{IPK} in preventing uncontrolled cell destruction during stress. In the absence of P58^{IPK}, these mice developed insulin deficiency phenotypes that are very similar to what is seen in type 1 and late stage type 2 diabetes (Ladiges et al., 2005). When PERK or P58^{IPK} were dysfunctional, ER stress homeostasis was disrupted leading to uncontrolled pancreatic beta cell apoptosis and severe diabetic phenotypes. The importance of the *DNAJC3* gene has also been shown recently in humans to be linked to autoimmunity. A large screen of individuals with diabetes revealed a loss-of-function mutation in *DNAJC3* that correlated with juvenile-onset diabetes and multisystemic neurodegenerative disorders. The identified homozygous stop mutation in *Dnajc3* in humans leads to a monogenic recessive form of diabetes mellitus (Synofzik et al., 2014). Taken together, P58^{IPK} is a key regulator in viral infection and autoimmune diseases through its interactions with PKR and PERK.

In addition to the importance of translational control pathways, TLR signaling has also been implicated in regulating T1D. Pancreatic beta cells respond to dsRNA treatment via a TLR3 and TRIF dependent manner, leading to type I IFN induction. Additional treatment with IFN-γ leads to beta cell apoptosis (Rasschaert et al., 2005). Furthermore, beta cells that were knocked out for TLR3 or the type I IFN receptor were protected from apoptosis during dsRNA treatment (Dogusan et al., 2008). The presence of reactive oxygen species was also required for TLR3-mediated NF-κB activation and the induction of IFN-β and TNF-α (Seleme et al., 2012). In patients that died from fulminant T1D, a subtype of diabetes mellitus, TLR3 expression was detected in 85% of T cells that had infiltrated the pancreas and in 63% of infiltrated macrophages, leading to beta cell death (Shibasaki et al., 2010). Considering the important role of TLR3 in T1D pathogenesis, it follows that polymorphisms in *TLR3* were shown to be associated with increased risk for T1D (Assmann et al., 2014).

Finally, in insulitic islets isolated by laser capture microdissection from patients with recent onset T1D, there was increased ISG expression. Specifically, *TLR3* and *EIF2AK2* were of the significantly overexpressed ISGs, which further bolsters the link between translational control and innate immune signaling in T1D (Lundberg et al., 2016). In addition to TLR3, TLR7 also plays an important role in T1D autoimmune diabetes, since treating non-obese diabetic mice with TLR7 agonists accelerated the onset of autoimmune diabetes (Lee et al., 2011). In patients that are genetically susceptible to T1D who display increased levels of autoanti-bodies, there were increased levels of IL-1β, and treating peripheral blood mononuclear cells with TLR3 or TLR7 agonists led to increased percentages of IL-1β dendritic cells (Alkanani et al., 2012). As such, it has been shown that in TLR7 deficient mice, there was attenuated diabetic retinopathy (Liao et al., 2017). Taken together, targeting the TLR pathway may provide an opportunity for therapy in patients that may be susceptible to the onset of T1D.

2.3.3. Implication of RIG-I in Crohn's Disease—RIG-I has also been linked to autoimmune diseases such as inflammatory bowel disease (IBD) that encompasses Crohn's disease (CD) and ulcerative colitis (UC). Dysfunctions in innate immune response signaling, specifically through RIG-I, have been associated with the development of IBD symptoms. In RIG-I knockout mice, colitis-like phenotypes developed. In these mice, there was a noticeable decrease in the size of Peyer's patches that are an essential component of immunity as they defend against pathogens in the intestine. Therefore, the observed cellular apoptosis and decreased size of Peyer's patches in RIG-I deficient mice may increase susceptibility to the colitis-like phenotypes observed. These deficient mice also showed down-regulation of G protein αi2 subunit (Gαi2) in many tissues and negatively regulated T-cell responses (Wang et al., 2007). Gαi2 is necessary for many cellular processes and is a candidate gene associated with the development of human IBD (Hampe et al., 2001b). IBD developed in $G\alpha i2^{-/-}$ mice and increases in lymphocyte apoptosis lead to a decrease in the size of Peyer's patches (Ohman et al., 2002). The importance of RIG-I in the development of CD was confirmed in a global gene expression analysis. Gut tissue samples of CD and UC diagnosed patients were obtained. A decrease in transcription of RIG-I in epithelial layer of the ileum was associated with CD patients specifically. These results show that RIG-I is not only important in controlling viral infection, but it is also important in controlling the development of CD (Funke et al., 2011). Lack of tight regulation in RIG-I can lead to changes in Peyer's patches that increase susceptibility to autoimmune diseases, such as IBD.

An emerging correlation between autophagy regulation and RLR signaling in innate immune responses is important in autoimmune disease pathology of CD. Autophagy and IFN-mediated immunity are meticulously balanced in healthy individuals. Dysfunction in this balance can lead to auto-immune disorders, such as CD (reviewed in Deretic, 2016; Plantinga et al., 2012; Takahama et al., 2018). Autophagy is a degradation process that has been tied to antiviral innate immune responses. Atg5–Atg12 conjugation is a known regulator of autophagy and directly interacted with the CARD domain of RIG-I and MAVS individually. This binding decreases IFN pathway signaling and production. In this study, VSV replication was enhanced by Atg5–Atg12 activity because IFN production was suppressed. Therefore, autophagic regulation is an important indicator for infection

outcome. Importantly, Atg5–Atg12 can interact with MAVS even in the absence of viral infection. This means that Atg5–Atg12 has an important role in cellular homeostasis that negatively regulates the IFN response through RIG-I and MAVS signaling in healthy individuals (Jounai et al., 2007). In autophagic deficient cells lacking Atg5, RLR signaling and IFN secretion increase to resist VSV replication. This deficiency also results in increased dysfunctional mitochondrial function and the mitochondrial associated protein, MAVS. Dysfunctional mitochondria enhance reactive oxygen species present in the cell and this further enhances RLR signaling to further amplify IFN signals. Therefore, autophagic signaling is an important regulator of RLR signaling and these data show the important balance between autophagy and IFN-mediated immunity (Tal et al., 2009). NOD2, which is a member of the NOD-like receptor (NLR) family, is a PRR for bacterial lipopolysaccharides (Inohara et al., 2001; Ogura et al., 2001b), and mutations in NOD2 have been associated with the onset of CD (Hampe et al., 2001a; Hugot et al., 2001; Ogura et al., 2001a). NOD2-mediated autophagy has also been proposed as a component of CD onset. NOD2 directly interacts with RIG-I to negatively regulate IFN induction. Three specific NOD2 mutations associated with CD enhance the capacity of NOD2 and RIG-I to negatively signal IFN as compared to wild-type NOD2, while mutations in NOD2 exhibit impaired autophagosome formation. Together, RIG-I signaling with NOD2 not only functions in response to pathogens, but it also influences the onset of CD (Morosky et al., 2011). Negative regulation of IFN via autophagy through RIG-I with MAVS or NOD2 protects healthy individuals from developing autoimmune disorders such as CD, highlighting the interactions among NLRs, RLRs, autophagy and CD (further reviewed in Coutermarsh-Ott et al., 2016; de Bruyn and Vermeire, 2017).

In CD individuals, the balance of autophagy negative regulation and IFN signaling is disrupted. The loss of autophagy regulation has been proposed as a key pathogenesis mechanism in CD. One study found that an important autophagic response pathway is suppressed in CD inflamed epithelial tissue. The EIF2AK4-EIF2A-ATF4 pathway was identified as being important in controlling intracellular replication of adherent-invasive *Escherichia coli* in leading to robust autophagic gene expression. *EIF2AK4* encodes the GCN2 eIF2α kinase, which is activated during amino acid starvation. GCN2 then activates ATF4 and subsequently autophagy (B'Chir et al., 2013). This autophagic pathway is suppressed in inflamed CD tissue and there is not sufficient autophagic induction to control the intracellular *E. coli* replication. The adherent-invasive *E. coli* that colonize intestinal mucosa are in high abundance because autophagy is not properly activated thereby leading to increased inflammation in previously inflamed CD epithelial cells. This study highlights the relationships among translational control, autophagy, and inflammatory autoimmunity (Bretin et al., 2016). Autophagy can also be increased when the NF-κB transcription factor is inhibited. Porcine follicle development experiments showed that the follicle stimulating hormone inhibits NF-κB and subsequent IFN induction. This inhibition of NF-κB then led to enhanced autophagic activity through Jun N-terminal kinase signaling (Gao et al., 2016). Meta-analysis of individuals with and without CD linked two gene polymorphisms with disease susceptibility. Polymorphisms in *ATG16L1* that limit interaction with Atg12p–Atg5p to induce autophagy signaling were correlated with an increase in an individual's susceptibility to CD. Mutations in *IRGM* were also strongly associated with the

development of CD and this gene encodes the GTP-binding protein that induces autophagy signaling through RIG-I Polymorphisms in *ATG16L1* and *IRGM* were also documented as being risk factors for UC disease (Palomino-Morales et al., 2009). One of the CD-risk mutations in *ATG16L1*, T300A, was shown to improve overall survival in colorectal cancer patients. While this mutation was not associated with a change in autophagy, there was increased type I IFN production and sensitivity to dsRNA treatment via MAVS (Grimm et al., 2016). The mechanism behind the control that IRGM has on autophagy was shown to be through the interaction between IRGM and NOD2. In fact, IRGM, NOD2, and ATG16L1 form a complex that regulates the autophagic response to microbes (Chauhan et al., 2015). Together, IRGM confers antimicrobial and anti-inflammatory states that are important in regulating CD.

2.3.4. Singleton–Merten Syndrome, Systemic Lupus Erythematosus, and Prolidase Disorder—Dysfunction in IFN induction through MDA5 and RIG-I has also been linked to Singleton–Merten Syndrome (SMS) (Jang et al., 2015; Rutsch et al., 2015). SMS is a rare autoimmune disorder and classical SMS manifests in many ways such as dental dysplasmia, aortic calcification, glaucoma, and osteopenia. The disorder is known to have autosomal-dominant inheritance but clues about the genetic profile contributing to disease susceptibility have only recently been reported. Mutations in *IFIH1* and *DDX58*, the gene that encodes RIG-I, led to increased induction of IFN-β production and contributed to disease symptoms. The missense mutation in *IFIH1* enhanced MDA5 function and contributed to the enhanced IFN-β production in blood and dental tissue (Rutsch et al., 2015). Researchers also identified an atypical SMS phenotype in patients that exhibited variations in the clinical manifestations listed above. Two different variants of *DDX58* led to constitutively active functionality of RIG-I that led to uncontrolled IFN induction. The Glu373Ala variant of *DDX58* correlated with classical SMS symptoms except there were no dental abnormalities observed in these patients. The patients with the Cys268Phe variant of *DDX58* had glaucoma and skeletal abnormalities without dental dysplasmia or aortic calcification (Jang et al., 2015). These genetic analyses show the importance of regulated RIG-I and MDA5 induction because overproduction of IFN-β can lead to the characteristic clinical manifestations of SMS. Another rare autosomal disorder, prolidase disorder (PD), is associated with dysfunction in regulated in IFN induction. Mutations in the gene that encodes prolidase, *PEPD*, cause PD in newborns that present with dermatological symptoms, that range from rashes to lower extremity ulcers, due to increased immunoglobulin levels and decreased complement factor C1q. (Falik-Zaccai et al., 2010; Kurien et al., 2013; Pandit et al., 2013). Prolidase deficiency is also associated with systemic lupus erythematosus (SLE), an autoinflammatory disorder characterized by the production of antibodies against self-DNA and RNA (Arbuckle et al., 2003; Dubois and Tuffanelli, 1964; Lisnevskaia et al., 2014; Tan et al., 1966), which helps explain the phenotypic similarities between PD and SLE (Butbul Aviel et al., 2012; Kurien et al., 2013). Interestingly, during flaviviral infection, viral NS5 binds PEPD, resulting in decreased expression of the type I IFN receptor. Additionally, PD patients also exhibit decreased type I IFN receptor expression, further linking PD with defects in innate immunity (Lubick et al., 2015).

TLR-mediated detection of nucleic acids has been shown to exacerbate pathogenesis of SLE (Deane et al., 2007). Furthermore, lupus-prone TLR7-deficient mice do not generate antibodies to RNA-containing antigens, thus displaying less severe symptoms and prolonged survival (Christensen et al., 2006). Since the production of autoantibodies against self-nucleic acids is a major driving force behind SLE pathogenesis, it follows that B cells play a major role in the development of SLE (Fan et al., 2018). Indeed, galectin-9, an s-type lectin that induces apoptosis in activated T_H1 and T_H17 cells while promoting T_{reg} cell differentiation (Wu et al., 2014), inhibits maturation of pDCs and B cells, thereby decreasing cytokine and antibody production in response to TLR7 ligands (Panda et al., 2018). A recent study also showed that polymorphisms in the promoter of *TLR7* were associated with SLE (Skonieczna et al., 2018). Finally, while pDCs secrete increased levels of type I IFN in a TLR7-mediated manner in SLE patients (Murayama et al., 2017), lupus nephritis was recently shown to be independent of type I IFN yet remained dependent on TLR7 signaling (Wolf et al., 2018).

Taken together, diabetes, Aicardi–Goutières syndrome, inflammatory bowel diseases, lupus, and Singleton–Merten syndrome have all been linked to dysfunctions in RLR-and TLR-mediated initiation of IFN signaling. These autoimmune disorders demonstrate the important balance of the innate immune response needed to prevent the development of disorders.

3. INTRACELLULAR RECOGNITION OF DNA

Since 2000, multiple research groups have identified at least 15 different DNA binding proteins that induce an innate immune response, referred to as DNA sensors. For example, the DNA-dependent activator of IFN-regulatory factors (DAI) was the first cytosolic DNA sensor identified to bind directly to the Z and B forms of DNA as well as detect herpes simplex virus infection (Furr et al., 2011; Takaoka et al., 2007). When activated, DAI, also known as Z-DNA binding protein 1 (ZBP1), induces receptor-interacting protein kinase 3 (RIPK3)-mediated necroptosis that is inhibited by RIPK1 (Lin et al., 2016; Newton et al., 2016). However, in addition to DAI signaling, two discoveries in the last 10 years have exposed the complexity of DNA-sensing mechanisms as well as highlight the conserved function of different sensors to protect the host from exogenous DNA. The first discovery was the identification of STING (also known as MYPS/ERIS/MITA), encoded by the *TMEM173* gene, as a central adaptor protein for immunity to cytosolic nucleic acids and a PRR for cyclic dinucleotides (CDN) (Burdette et al., 2011; Ishikawa and Barber, 2008; Jin et al., 2008; Sun et al., 2009; Zhong et al., 2008). The second discovery came when cGAS was shown to be a direct DNA sensor that synthesizes cGAMP for STING activation (Gao et al., 2013b; Sun et al., 2013; Wu et al., 2013). Several other DNA sensors have been shown to interact with STING signaling such as DDX41, LSm14A, and MRE11 (Kondo et al., 2013; Li et al., 2012b; Zhang et al., 2011c). Other DNA sensors induce an innate immune response independent of STING, such as RNA polymerase III, LRRFIP1, Sox2, Rad50, DHX9/36, and AIM2 (Bürckstümmer et al., 2009; Chiu et al., 2009; Fernandes-Alnemri et al., 2009; Kim et al., 2010b; Roth et al., 2014; Xia et al., 2015; Yang et al., 2010). Additionally, the DNA sensors Ku70 and IFI16 have been shown to activate STING in cell-and pathogen-specific manners (Sui et al., 2017; Unterholzner et al., 2010). It is possible that other DNA sensors will be identified or that previously identified proteins will be shown to serve as

DNA sensors whether dependent or independent of STING. Importantly, the existence of diverse DNA sensors, including synthases, DNA repair proteins, helicases, and inflammasomes, indicates that recognition of endogenous and exogenous DNA is a critical component of the host immune response. Below we describe the centrality of the cGAS/STING signaling pathway, the pathways induced by STING-dependent sensors, and lastly the pathways induced by STING-independent sensors (Fig. 2).

3.1 A Central DNA-Sensing Pathway via cGAS and STING

The presence of host-or pathogen-derived dsDNA in the cytosol can be recognized by cyclic guanosine monophosphate (GMP)-adenosine monophosphate (AMP) synthase (cGAS), an enzyme that was recently identified as a critical DNA sensor (Gao et al., 2013b; Li et al., 2013). cGAS is encoded by the *MB21D1* gene and single-molecule assays have shown that the N terminus of human cGAS plays an important role in its own activation upon binding nonspecific DNA inducing downstream signaling through STING (Tao et al., 2017). Unlike some DNA sensors that recognize dsDNA in a sequence-specific manner, cGAS activation is independent of the DNA sequence because binding depends on electrostatic and hydrogen bonding interactions between the negative sugar-phosphate backbone of DNA and positive-charged surfaces of cGAS (Civril et al., 2013). Indeed, the crystallization of human cGAS revealed its unique zinc-ribbon motif insertion which provides DNA-binding specificity (Kranzusch et al., 2013). In this manner, cGAS is a general DNA sensor for its unique ability to bind sequence-independent B form dsDNA. In addition, cGAS is unique for its synthase function which catalyzes the production of $2'-3'$-cyclic GMP-AMP (cGAMP), the noncanonical CDN after binding DNA (Gao et al., 2013b). cGAMP has been shown to bind to STING to induce an innate immune response that results in the production of type I IFN (Ablasser et al., 2013; Diner et al., 2013; Shang et al., 2012; Sun et al., 2013). Several biochemical studies have also shown that cGAMP contains mixed phosphodiester linkages, a unique distinction from bacterial CDNs, and that the strength of IFN response depends on the phosphodiester link-age. That is, $2'-3'$-cGAMP has the strongest affinity for human STING. Nonetheless, the versatility of STING in recognizing CDNs continues to be an area of intense investigation and suggests that some regulation of this pathway depends on binding affinity (Ablasser et al., 2013; Gao et al., 2013c; Opoku-Temeng et al., 2016; Sun et al., 2013; Wu et al., 2013).

Upon binding of cGAMP, STING dimerizes and translocates in autophagosomes to a perinuclear region which is necessary for downstream signaling (Barker et al., 2013; Diner et al., 2013; Ishikawa et al., 2009; Moretti et al., 2017; Sun et al., 2009, 2013). STING is an ER-resident host protein that contains four transmembrane domains and globular carboxy-terminal domain (CTD) that enable the binding of STING to TBK1 (Bhat and Fitzgerald, 2014; Burdette and Vance, 2013). The binding of STING and TBK1 causes autophosphorylation of TBK1 at Serine-172, which then facilitates the direct phosphorylation of STING at its Serine-366 and Leucine-374 residues by TBK1. Consequently, phosphorylation of STING by TBK1 recruits IRF3 to also be phosphorylated by TBK1 (Li et al., 2017c; Liu et al., 2015a; Tanaka and Chen, 2012). The association of TBK1 with STING facilitates the dsDNA-mediated activation of the NF-κB and IRF3 transcription factors. Specifically, TBK1 controls the activation of STING-mediated NF-κB

signaling through its IKKαβ activation loop while the kinase domain of the ribosomal protein S6 kinase 1 (S6K1) binds to STING to facilitate the formation of a S6K1-STING-TBK1 complex that is necessary for the phosphorylation of IRF3 (Abe and Barber, 2014; Wang et al., 2016). Additionally, the activation of NF-κB by IKK depends on the phosphorylation of IκBα, which induces its degradation and activates NF-κB (Baeuerle and Baltimore, 1988; Beg and Baldwin, 1993; Israel, 2010; Mathes et al., 2008). Once activated in a cGAS/STING-dependent manner, IRF3 and NF-κB translocate to the nucleus and induce the expression of type I IFN, IL-6, IL-1β, and the production of proinflammatory cytokines like TNF-α (Paludan and Bowie, 2013). Additionally, STING translocation from the ER to an ER-Golgi intermediate compartment and the Golgi apparatus is an important rate-limiting event in signal transduction even in the absence of cGAMP (Chen et al., 2016; Dobbs et al., 2015). A recent study has demonstrated that STING senses bacterial c-di-AMP as a *vita*-PAMP, a sub-class of PAMPs derived only form living microbes, to induce ER stress and produce IFN (Moretti et al., 2017). This study and others indicate that ER-phagy and autophagy pathways play an important role in STING regulation during bacterial infections (Watson et al., 2015).

The cGAS/STING signaling pathway is induced by a variety of pathogens including DNA viruses, RNA viruses, retroviruses, and bacteria, all of which have evolved mechanisms to avoid detection by this pathway. Through a variety of mechanisms, several DNA viruses such as adenovirus, herpes simplex virus (HSV)-1, and human papilloma virus (HPV) have been shown to induce or actively inhibit a STING-dependent type I IFN response (Anghelina et al., 2016; Ishikawa et al., 2009; Lam and Falck-Pedersen, 2014; Lam et al., 2014; Liang et al., 2015; Sunthamala et al., 2014). For example, over a dozen proteins of HSV-1 have been found to actively suppress cytosolic-DNA recognition by the cGAS/STING pathway (Christensen et al., 2016; Horan et al., 2013; Ishikawa et al., 2009; Kalamvoki and Roizman, 2014; Su and Zheng, 2017; Xu et al., 2017; Ye et al., 2017; Zhang et al., 2016; Zheng, 2018). Similarly, the E2 proteins of HPV16 inhibit the transcription of different ISGs by targeting STING (Sunthamala et al., 2014). Another study has shown that both human and mouse cytomegalovirus (CMV) induce a cGAS/STING-dependent type I IFN response or actively inhibit STING through its UL82 tegument protein or US9 glycoprotein (Choi et al., 2018; Fu et al., 2017; Lio et al., 2016). Several studies have shown that some retroviruses including HIV, murine leukemia virus, and simian immunodeficiency virus can induce a type I IFN response due to recognition of reverse-transcribed DNA by cGAS and subsequent production of cGAMP (Gao et al., 2013a; Lahaye et al., 2013; Rasaiyaah et al., 2013). DENV can antagonize STING signaling by utilizing viral NS2B3 proteases to bind and cleave human STING although this cleavage does not occur in mouse or nonhuman primate STING (Aguirre and Fernandez-Sesma, 2017; Aguirre et al., 2012; Stabell et al., 2018; Yu et al., 2012). HCV has also been shown to antagonize STING signaling, highlighting the multifaceted role of STING in pathogen evasion beyond direct DNA sensing through cGAS (Ding et al., 2013; Maringer and Fernandez-Sesma, 2014; Moriyama et al., 2007; Nitta et al., 2013).

The fact that STING potentiates a type I IFN response in response to bacterial CDNs introduced a role for STING in regulating bacterial infection. First, it was found that synthetic c-di-GMP could induce a type I IFN response (McWhirter et al., 2009). Then, it

was found that *Listeria monocytogenes* secretes c-di-AMP that also induced a type I IFN response (Woodward et al., 2010). Further, a mutant mouse strain called Gold-enticket (Gt) had a null mutation in its STING allele ($Sting^{Gt/Gt}$) that rendered it unable to detect c-di-GMP and c-di-AMP from *Listeria* infection (Sauer et al., 2011). Finally, STING was shown to be a direct sensor of c-di-GMP (Burdette et al., 2011). Since then, studies have shown that STING mediates a type I IFN response specifically in response to CDNs such as those produced by *Staphylococcus aureus* and *Chlamydia trachomatis* (Barker et al., 2013; Gries et al., 2016; Zhang et al., 2014). Undoubtedly, the role of STING in detecting CDN-mediated type I IFN response was authenticated by the discovery that cGAS produces cGAMP in a DNA-dependent manner (Sun et al., 2013). Further studies since the discovery of cGAS and STING have further connected the CDN and DNA-mediated activation of this central pathway. In 2013, Chen's group showed that $cGAS^{-/-}$ macrophages, fibroblasts, and dendritic cells as well as $cGAS^{-/-}$ mice could not produce type I IFNs or cytokines in response to DNA treatment or infection with HSV-1 or vaccinia virus, but infection with Sendai virus, an RNA virus, did induce type I IFN (Li et al., 2013). These infections were further tested in $Sting^{Gt/Gt}$ mice and cells. Notably, the production of IFN-β in $cGAS^{-/-}$ cells was rescued by the delivery of cGAMP, but not in $Sting^{Gt/Gt}$ cells, further supporting the role of STING in binding to CDNs. Importantly, this was the first study to use cGAMP as a potential adjuvant in the context of STING. They found that injection of the protein antigen ovalbumin (OVA) in the presence or absence of cGAMP in wild-type or $Sting^{Gt/Gt}$ mice could boost the development of OVA-specific antibodies in wild-type mice only (Desmet and Ishii, 2012; Li et al., 2013). Clinical trials using STING agonists have followed. For example, a current Phase I clinical study is using the synthetic, STING-activating CDN agonist MIW815 (ADU-S100) to study its safety and efficacy in treating patients with advanced/metastatic solid tumors or lymphomas via intratumoral injections (ClinicalTrials.gov Identifier: NCT02675439). Another study has shown that c-di-GMP can be complexed with simple cell-penetrating peptides that enhance cellular delivery and biological activity in murine splenocytes but also that the bacterial 3′–3′-cGAMP is a superior stimulator of IFN genes ligand than c-di-GMP in human peripheral blood mononuclear cells (Yildiz et al., 2015). A more recent study has shown that expression of an inducible c-di-GMP-producing diguanylate cyclase in *Klebsiella pneumonia* increased endogenous concentrations of c-di-GMP which attenuated its virulence in the lung of mice (Rosen et al., 2017). Importantly, the attenuation of virulence was independent of STING, supporting the idea that CDNs can be used to influence pathogen virulence (Karaolis et al., 2007a,b; Rosen et al., 2017). Indeed, the use of CDNs as adjuvants has increased in the last few years and will likely continue to expand as more pathogens and diseases are studied under this framework (Dubensky et al., 2013; Junkins et al., 2018; Karaolis et al., 2007a; Miyabe et al., 2014; Škrnjug et al., 2014).

As seen by the diversity of pathogens that cGAS and STING signaling are able to regulate, the centrality of this pathway is evident. Many DNA sensors had been identified before cGAS, but our understanding of host defense mechanisms has greatly increased due to the unique synthase function of cGAS in producing cGAMP in response to the presence of viral DNA, thus acting as an amplifier of cGAS-mediated DNA sensing. In addition, the centrality of STING is highlighted by its ability to use host-derived CDN, 2′–3′-cGAMP, or bacterial

CDNs like 3′−3′-cGAMP, c-di-GMP, and c-di-AMP to an innate immune response. Indeed, several groups are investigating the potential use of CDNs as adjuvants in treating human diseases but also in controlling bacterial factors like virulence. Other groups are investigating novels ways, such as ER-phagy, that STING induces an innate immune response. All of these ongoing studies reflect the centrality of STING in the innate immune response to cytosolic nucleic acids (Table 3).

3.2. STING-Dependent Sensors: DDX41, Ku70, MRE11, and LSm14A

3.2.1. DDX41—DDX41 is a member of the DEXDc helicase family that was recently identified as a DNA sensor in myeloid dendritic cells (mDCs). Knockdown of DDX41 by short-hairpin RNA prevents induction of type I IFN response via IRF3 and NF-κB activation after treatment with DNA or viral DNA infection but not RNA (Fullam and Schroöder, 2013; Jiang et al., 2017; Zhang et al., 2011c). DDX41 can also bind directly to bacterial CDNs after which downstream signaling occurs via the recruitment of STING and TBK1 to activate IRF3 (Omura et al., 2016; Parvatiyar et al., 2012). Two residues of DDX41 (Tyr364 and Tyr414) are necessary for its recognition of DNA, and activation of DDX41 depends on phosphorylation of its Tyr414 residue by BTK (Bruton's tyrosine kinase), which then facilitates binding to STING (Lee et al., 2015). It is also known that the E3 ligase TRIM21 interacts with the DEAD domain of DDX41 and that DDX41 is subsequently degraded via ubiquitination of its Lys9 and Lys115 residues. These results were corroborated by the observation that knockdown of TRIM21 results in over-induction of type I IFN and overexpression of TRIM21 results in reduced IFN-β production (Zhang et al., 2012). One study showed that TBK1, NF-κB, and IRF3 activation are mediated by direct interaction of DDX41 with STING in dendritic cells, bone marrow-derived DCs, and human monocytes after infection with HSV-1 or adenovirus (Zhang et al., 2011c). This study found that knockdown of DDX41 or STING in THP-1 cells resulted in lower IFN-β production after DNA treatment or infection with HSV-1. Another study identified chicken DDX41 as a DNA sensor which results in the production of IFN-β in a STING-dependent manner after DNA treatment or infection with Newcastle disease virus (Cheng et al., 2017). This study used a ssRNA virus to show the role of DDX41 in mediating an innate immune response; however, it lacked experiments investigating the role of DDX41 in the context of DNA viruses and bacterial infection (Jiang et al., 2017). Nonetheless, it is important to note that DDX41 can bind to CDNs such as those produced by *L. monocytogenes* (Parvatiyar et al., 2012). Both DNA-and CDN-sensing roles of DDX41 indicate that it may detect a variety of intracellular viruses and bacteria.

3.2.2 Ku70—Ku70 is a DNA repair subunit protein that binds to DNA double-strand break ends and helps repair DNA via the non-homologous end-joining (NHEJ) pathway (Mimori et al., 1986). Recently, Ku70 was identified as a cytosolic DNA sensor that induces the production of IFN-λ1, a type III IFN, in primary human cell lines after viral infection after translocating from nucleus to cytosol to interact with STING (Sui et al., 2017; Zhang et al., 2011a). IRF1, IRF3, and IRF7 are implicated in this Ku70/STING pathway. One study has found that the Ku70/80 complex can directly sense hepatitis B virus (HBV) DNA which results in recruitment of PARP1, activation and translocation of IRF1 to the nucleus, and upregulation of chemokine secretion (Li et al., 2016). The relevance of this study is that it

shows the role of Ku70 in mediating an innate immune response of a DNA virus. Similarly, another study has found that Ku70 can sense the DNA of human T lymphotropic virus type 1 (HTLV-1). Specifically, this study also found that knockdown of Ku70 led to decreased IRF3 phos-phorylation and induction of IFN-β, TNF-α, and IFN-stimulated gene 56 (ISG56) (Wang et al., 2017). Importantly, Ku70 was shown to associate directly with STING to produce IFN-β. While HTLV-1 is a retrovirus, the involvement of Ku70 in detecting viral DNA indicates that Ku70 is an important DNA sensor that may act as reverse transcription intermediate and its role in inducing an innate immune response awaits further investigation. Other studies have shown that Ku70 induces a type III IFN response after HSV-2 infection independently of STING (Zhang et al., 2011a). Nonetheless, the binding of Ku70 to STING as well as mediating an IFN-λ1 response to cytosolic DNA and DNA viruses highlights ability of Ku70 to function both independently and dependently of STING.

3.2.3. MRE11—Meiotic recombination 11 homolog A (MRE11) is an exonuclease better known for its role in microhomology-mediated end-joining (MMEJ). Over-expression of MRE11 has been shown to cause mutations that lead to breast cancer (Sharma et al., 2015; Spehalski et al., 2017; Yuan et al., 2012). One study has shown that MRE11 can physically interact with cytosolic DNA, trigger STING translocation, and subsequently activate IRF3 via interaction with Rad50, another DNA repair protein. However, this response was not observed during infection with *Listeria* or HSV-1, suggesting that MRE11 may induce a type I IFN response specifically to DNA damage instead of pathogen defense (Kondo et al., 2013). The MRE11/Rad50/NBS1 (MRN) complex is known for its conserved role in DNA repair (Maser et al., 1997), yet in Kondo et al., NBS1 was shown to be dispensable for inducing STING trafficking upon treatment with exogenous DNA. An important function of the MRN complex is to induce a DNA damage response (DDR) from stimuli that results in DNA damage (Chapman and Jackson, 2008; He et al., 2012; Paull and Deshpande, 2014). How viruses persist despite active DDR remains an unanswered question. For example, how is HPV able to establish infection despite inducing a DDR, presumably when it causes double-stranded breaks during its replication cycle (Bristol et al., 2017; Kadaja et al., 2009). Therefore, a survey of the MRE11-STING pathway with multiple pathogens would help clarify the role of MRE11 in inducing an innate immune response via STING.

3.2.4. LSm14A—LSm14A is a processing body-associated sensor of viral RNA and DNA that was recently shown to induce a specific type I IFN response via induction of IFN-α, IFN-β, and IL-6 through regulation of STING activation in mouse dendritic cells but not mouse embryonic fibroblasts or macrophages. This indicates that LSm14A is a cell-specific sensor of DNA that functions through nuclear mRNA processing. Further investigation into this DNA sensor will clarify its role in DNA-sensing and how it may function. Currently, only HSV-1 has been shown to induce an innate immune response through LSm14A and STING (Li et al., 2012b; Liu et al., 2016).

3.2. STING-Independent DNA Sensors: TLR9, RNA Polymerase III, DHX9/DHX36, AIM2, IFI16, Sox2, LRRFIP1, and Rad50

3.3.1. TLR9—TLR9 was first identified by its ability to recognize unmethylated 2′-deoxyribo(cytidine-phosphate-guanosine) (CpG) DNA from bacteria, and viral DNA is also

recognized by TLR9 (Bauer et al., 2001; Hemmi et al., 2000; Hochrein et al., 2004; Tabeta et al., 2004). Additionally, TLR9 detects ssDNA of at least 21 nucleotides, and methylated ssDNA or dsDNA only weakly activate TLR9 (Pohar et al., 2015a,b). However, the addition of oligonucleotides as short as two nucleotides augments TLR activation (Pohar et al., 2017). In support of this, it has been shown that the endonuclease DNaseII is also required for a robust TLR9-mediated response (Chan et al., 2015). Preference for microbial DNA rather than self-DNA is due to TLR9's location in the endolysosomes (Li et al., 2012a). TLR9 is localized in intracellular vesicles of the ER, lysosomes, and endosomes of resting cells. DNA recognition by TLR9 occurs after transport to endolysosomes, which is mediated by the multi-spanning protein UNC93B (Kawasaki et al., 2011; Latz et al., 2007; Tabeta et al., 2004, 2006). UNC93B physically interacts with TLR9 through its transmembrane domain 2 where the ectodomain of TLR9 is processed by cathepsins to become active (Ewald et al., 2011; Latz et al., 2007; Park et al., 2008; Sepulveda et al., 2009; Tabeta et al., 2006). TLR9 contains a large nonconserved Z-loop between LRR14 and LRR15 that is susceptible to cathepsin-mediated proteolysis. While processing of the Z-loop is required for subsequent TLR9 oligomerization, DNA binding to TLR9 is independent of the Z-loop (Ewald et al., 2011; Li et al., 2012a; Ohto et al., 2015). The chromatin protein HMGB1 (high mobility group box 1) enhances DNA recognition by TLR9 by bending it and bringing it closer to the RAGE (receptor for advanced glycation endproducts) receptor and delivering the HMGB1-DNA complex to early endosomes (Li et al., 2012a; Murugesapillai et al., 2017; Tian et al., 2007). Additionally, it has been recently shown that TLR9 has two DNA-binding sites, namely CpG and 5′-TCG binding sites, both of which contribute to the dimerization of TLR9 (Ohto et al., 2018). Additional activation of TLR9 is enhanced by endosome maturation and acidification (Latz et al., 2004; Wagner, 2004; Yasuda et al., 2005). After DNA binds to TLR9, there is subsequent induction of an innate immune response via two mechanisms. The first is through activation of NF-κB-dependent proinflammatory cytokines, and the second is through IRF7-dependent type I IFN induction. While both pathways are mediated by the adapter protein MyD88 (myeloid differentiation primary response 88) and the TNFR-associated factor TRAF6, IRF7-dependent IFN-α production requires TLR9 trafficking from endosomes to endolysosomes which is mediated by adaptor protein 3 (AP3) (Gohda et al., 2004; Medzhitov et al., 1998; Sasai et al., 2010). In contrast, TLR9 that is transported by UNC93B to the early endosome is cleaved and signals through NF-κB to induce proinflammatory cytokine genes that encode TNF-α, IL-6, and IL-12 (Sasai et al., 2010).

Pathogen-specific studies investigating the mechanism by which TLR9 induces an innate immune response were driven by the discovery that TLR9 recognizes unmethylated CpGs and that human CpGs are methylated and therefore immunologically inert. For example, the genome of HSV-1/2 is heavily unmethylated and CpG-rich, and thus induces a TLR9-dependent immune response in murine bone marrow-derived macrophages (BMDMs) (Lundberg et al., 2003). Bacteria are also capable of activating a TLR9-dependent innate immune response. For example, bacterial species such as *Campylobacter jejuni*, *K. pneumonia*, and *S. aureus* were shown to activate TLR9 based on the abundance of [CG] content. That is, higher CG base content resulted in increased activation of TLR9 and IL-8 production (Dalpke et al., 2006). One study has demonstrated that *TLR9*$^{-/-}$ mice infected

with *K. pneumonia* had impaired activation and maturation of dendritic cells, reduced TNF-α induction, and lower production of TNF-α and IL-12. Interestingly, when dendritic cells from wild-type mice were intratracheally transferred into *TLR9*$^{-/-}$ mice, bacterial load was significantly reduced and TNF-α and IL-12 cytokine production increased (Bhan et al., 2007). Of note, human TLR9 is predominantly expressed in plasmacytoid dendritic cells and B cells, resulting in a strong type I IFN response via MyD88/IRF7 signaling. Conversely, murine TLR9 is expressed abundantly in myeloid immune cells and can also result in IFN-γ production and the recruitment of NK, αβ-, and γδ-T cells (Hartmann, 2017; Hornung et al., 2002; Krug et al., 2004; Walker et al., 2010). For example, it has been shown that CMV infection in mice activates a TLR9/MyD88 response that occurs selectively in CD11^{+} dendritic cells (Krug et al., 2004; Puttur et al., 2016). Other DNA viruses that have been implicated in activating an innate immune response through TLR9 are Varicella zoster virus (VZV), Epstein-Barr virus (EBV), Kaposi sarcoma-associated herpesvirus (KSHV), vaccinia virus (VV), adenovirus (AdV), and human CMV (Appledorn et al., 2008; Basner-Tschakarjan et al., 2006; Fiola et al., 2010; Lim et al., 2006; Samuelsson et al., 2008; Varani et al., 2007; West et al., 2011; Yu et al., 2011). However, the majority of viruses will result in the activation of lymphocytes that can then initiate adaptive responses that differ between mouse and human models of infection. These species-specific differences highlight the importance of understanding how evolution of host defense mechanisms relates to TLR9-mediated immune responses.

3.3.2. RNA Polymerase III—RNA polymerase III transcribes AT-rich dsDNA into an RNA-containing 5′-triosphate moiety which can then be recognized by RIG-I (retinoic acid-inducible gene I) and induce a type I IFN response through IRF3, IRF7, and NF-κB (Ablasser et al., 2009; Chiu et al., 2009). The observation that RNA polymerase III can sense cytosolic DNA has helped researchers investigate the complex ways that pathogens avoid recognition by the innate immune system (Bauernfeind et al., 2010). While Chen's group showed that inhibition of RNA polymerase III resulted in abrogated IFN-β production from *Legionella pneumophila* infection, Hornung's group found that inhibition of RNA polymerase III resulted in abrogated IFN-α production from EBV infection (Ablasser et al., 2009, Chiu et al., 2009). Another study demonstrated that during infection with invertebrate iridescent virus 6 (IIV-6), an insect DNA virus, the mammalian host requires RNA polymerase III to produce IFN-β (Ahlers et al., 2016). Through whole exome sequencing of 21 human patients, a recent study found that different mutations in the RNA polymerase III gene can explain why some patients suffer from severe acute VZV infection (Ogunjimi et al., 2017). In contrast, sequencing of 222 patients suffering from herpesviral encephalitis did not result in identification of RNA polymerase III mutations, which may be explained by the presence of high AT base content in several genome islands of VZV and overall lower cGAS expression in blood cells (Gram et al., 2017; Ogunjimi et al., 2017). Together, these studies indicate the important role of RNA polymerase III in mediating an innate immune response to DNA viruses.

3.3.3. DHX9/DHX36—DEAH box proteins 9 and 36 (DHX9 and DHX36) are cytosolic helicases that were found to bind to CpG viral DNAs but not RNAs in human primary dendritic cells (Kim et al., 2010b). Specifically, DHX9 and DHX36 sense CpG-

oligodeoxynucleotides, CpG-B and CpG-A, respectively, through the adaptor protein MyD88. DHX9 and DHX36 both bind directly to the TIR domain of MyD88 independent of TLR9 signaling (Hochrein et al., 2004; Hokeness-Antonelli et al., 2007; Kim et al., 2010b; Ohnishi et al., 2009). Cytosolic binding of DHX9/DHX36 to CpG-B/A is corroborated by fractionation experiments that showed DHX9/36 are not present in any endosomal structures (Kim et al., 2010b). After binding to MyD88, DHX9 activates NF-κB, which then induces TNF-α and IL-6 production while DHX36 activates IRF7 and induces high IFN-α production. Interestingly, DHX9 and DHX36 were first identified as RNA helicases as they are part of the DExD/H box family, including proteins that have critical roles in RNA metabolism. However, DHX9 and DHX36 have also been shown to act as DNA helicases (Linder, 2006; Zhou et al., 2003). The role of DHX9 as an RNA or DNA helicase has been studied in the context of cancer such as colorectal and lung cancer, where DHX9 regulation is cancer-specific (He et al., 2017; Mi et al., 2016; Rahman et al., 2017; Sun et al., 2014). It is also known that DHX9 binds to viral dsRNA in myeloid dendritic cells, leading to the activation of NF-κB and IRF3, along with the production of IFN-α/β (Zhang et al., 2011d). Similarly, DHX36 has been shown to form a complex with DDX1 and DDX21 to function as a dsRNA sensor that uses the TRIF adaptor molecule to activate NF-κB and a type I IFN response in dendritic cells (Zhang et al., 2011b). As DNA sensors, DHX9/36 proteins have shown to mediate an innate immune response to HSV but not influenza virus (Kim et al., 2010b). These and other studies evidence suggests that the function of RNA and DNA sensing in DHX proteins depends both on cell type and viral genome that highlights the need for more in-depth investigation in this family of proteins.

3.3.4. AIM2 and IFI16—Cytosolic DNA can also bind directly to the AIM2 (absent in melanoma 2) inflammasome protein and activate ASC (apoptosis-associated speck-like protein containing a CARD), a critical component of the inflammasome complex (Fernandes-Alnemri et al., 2007, 2009; Muruve et al., 2008). AIM2 is member of an IFN-inducible HIN-200 family of proteins that contains an N-terminal pyrin domain and a C-terminal oligonucleotide/oligosaccharide-binding domain (Ludlow et al., 2005). Recruitment and activation of caspase-1 by AIM2 depends on the pyrin domain and direct interaction with the adaptor protein ASC. Direct binding of cytoplasmic DNA to AIM2 results in oligomerization which results in the formation of the oligomeric ASC pyroptosome that is required for caspase-1-dependent inflammatory cell death known as pyroptosis (Fernandes-Alnemri et al., 2007, 2009). While other inflammasome proteins such as NALP3 belong to the NLR protein family, AIM2 is not an NLR due to its unique pyrin domain needed for binding of host and pathogen-derived DNA in the cytosol which was first found to directly activate the inflammasome complex independent of NALP3 (Buürckstuümmer et al., 2009; Fernandes-Alnemri et al., 2009; Halle et al., 2008; Pétrilli et al., 2007). Nevertheless, AIM2-dependent DNA binding also results in the maturation of proinflammatory cytokines like pro-IL-1β and pro-IL-18 into their active and secreted forms, IL-1β and IL-18 (Muruve et al., 2008; Pétrilli et al., 2007). A recent study has shown that AIM2-like receptor knockout mice respond differently to endogenous retroviral DNA which suggests that AIM2-like receptors might have a more important role in sensing endogenous DNA (Nakaya et al., 2017).

Several bacterial species activate the AIM2 receptor to induce an inflammasome-mediated immune response, such as *Francisella tularensis* and *L. monocytogenes* (Fernandes-Alnemri et al., 2010; Jones et al., 2010; Kim et al., 2010a). *Listeria* is known to activate several innate immune pathways, but in the context of a inflammasome-dependent caspase-1 activation response, AIM2 compensates for an inflammasome response in NLRC4-and NLRP3-deficient mouse macrophages (Kim et al., 2010a). Other bacterial species that have been shown to activate AIM2 include *Streptococcus pneumonia*, some *Mycobacterium* species, *L. pneumophila*, and *S. aureus* (Fang et al., 2011; Ge et al., 2012; Hanamsagar et al., 2014; Saiga et al., 2012). The disruption of bacterial vacuoles allows bacterial DNA to be recognized by AIM2. For example, *Francisella novicida* infection increases the expression of IRF1 which then induces the expression and activation of IFN-inducible GTPases called guanylate-binding proteins (GBPs) to disrupt the bacterial vacuole (Meunier et al., 2015). GBPs colocalize with the IFN-inducible protein IRGB10 to cause bacteriolysis and ultimate exposure of DNA that can be recognized by AIM2 (Man et al., 2015). Recently, *Chlamydia muridarum* and *trachomatis* have also been shown to employ GBPs to induce caspase-1 and caspase-11-mediated inflammasome responses via NLRP3 and AIM2 (Finethy et al., 2015). In contrast, the role of AIM2 in detecting viral DNA is much less explored. For example, mouse CMV and HPV have been shown to activate an AIM2-mediated inflammasome assembly but the mechanism whereby viral DNA is exposed in the cytosol remains unclear (Milutin Gašperov et al., 2014; Shi et al., 2015). Interestingly, recent studies have showed that influenza virus can induce lung damage that results in the release of host DNA and subsequent AIM2-mediated activation (Schattgen et al., 2016; Zhang et al., 2017a). However, Zhang et al. showed that AIM2-deficient human and mouse cells are still able to induce caspase-1 activation, which may be due to difference in viral dose, virus propagation source, or difference between cell culture and *in vivo* models. It will be interesting to see how further research into different host cell types, *in vivo* models and accessory proteins that mediate AIM2-dependent activation of caspase-1 will clarify pathogen and host-specific differences.

Another DNA sensor closely related to AIM2 is IFI16 (gamma-IFN-inducible protein Ifi-16 or IFN-inducible myeloid differentiation transcriptional activator), which is part of the pyrin and HIN-200 domain-containing protein family. In contrast to AIM2, which induces the assembly of an inflammasome complex, IFI16 is known to induce a type I IFN response upon binding to intracellular dsDNA (Trapani et al., 1994; Unterholzner et al., 2010). Knockdown of IFI16 has shown that it is required to maintain EBV latency in Akata cells, an EBV-producing cell line (Pisano et al., 2017). A more recent study has shown that IFI16-depleted human foreskin fibroblasts display increased replication of HSV-1 as well as expression of HSV-1 immediate-early, early, and late proteins, which confirms previous studies using siRNA to knockdown IFI16 (Johnson et al., 2014; Merkl et al., 2018). Although IFI16 is thought to induce a type I IFN response through STING, one study also links IFI16 to caspase-1 and ASC induction in response to KSHV, showing that the inflammasome also functions in the nucleus (Kerur et al., 2011). However, it has been shown that in primary fibroblasts, IFI16 is not required for an immune response to human CMV and that the AIM-like receptors are unnecessary for the response to immunostimulatory DNA (Gray et al., 2016). Further research into the specific pathway in which IFI16 mediates

an innate immune response to different pathogens might indeed show more similarities between AIM2 and IFI16 as inflammasome assemblers and their specific roles in a cytosolic DNA-mediated immune response.

3.3.5. Sox2, LRRFIP1, and Rad50—Sex determining region Y-box 2 (Sox2) is a transcription factor that is expressed in the cytosol of neutrophils and that was recently discovered to bind bacterial DNA in a sequence-specific manner (Xia et al., 2015). Specifically, upon bacterial DNA stimulation, Sox2 interacts with TAB2, which causes the TAB2/TAK1 kinase complex to dimerize and lead to the activation of NF-κB and AP-1 signaling. A recent study analyzed the long control regions, which are important sites of viral replication regulation for HPV16, and found that overexpression that Sox2 can repress the *E6* and *E7* oncogene expression of HPV16 (Martínez-Ramírez et al., 2017). Although this study did not investigate innate immune induction by Sox2, this study highlights the role of Sox2 in mediating a DNA virus infection and will need further investigation to clarify its mechanism. While further research is needed to understand the DNA sensing pathway by Sox2 in humans, the discovery of Sox2 as a DNA sensor also highlights the conserved sequence-specific recognition system of foreign DNA used by eubacteria and archaea (Jinek et al., 2012; Xia et al., 2016).

Leucine-rich repeat flightless-interacting protein 1 (LRRFIP1) is a transcriptional repressor that binds to a GC-rich consensus sequence (5-AGCCCCCGGCG-3) and is thought to control smooth cell proliferation via platelet-derived growth factor repression, and positively regulate TLR signaling (Choe et al., 2013; Dai et al., 2009; Labbé et al., 2017). One study showed that LRRFIP1 can mediate a type I IFN response to VSV and *Listeria* infection via a β-catenin-dependent pathway (Yang et al., 2010). Specifically, this study showed that LRRFIP1 interacts and promotes β-catenin activation, resulting in the binding of β-catenin to IRF3. The LRRFIP1-β-catenin interaction results in the recruitment of the acetyltransferase p300 to the IFN-β-enhanceosome through IRF3. Importantly, Yang et al. showed that knockdown of LRRFIP1 decreased the expression of IFN-β mRNA induced by bacterial DNA in the cytosol but not by extracellular LPS. Similarly, the presence of LRRFIP1 increased production of IFN-β following *Listeria* and VSV infection. While further studies have examined the role of LRRFIP1 in inducing a type I IFN response during RNA virus infection, additional studies investigating the role of LRRFIP1 in sensing cytosolic DNA would be beneficial (Bagashev et al., 2010; Liu et al., 2015b). For example, while the crystal structure of LRRFIP1 shows that it remains highly extended while bound to DNA but aggregates at high concentrations of DNA (Nguyen and Modis, 2013), further studies examining the conformational changes of LRRFI1P1 from different DNA pathogens will help elucidate how DNA-binding mediates signaling through LRRFIP1.

As described previously, Rad50 is an important DNA repair protein in the MRN complex. Recently, a study has shown that Rad50 directly interacts with DNA to form a complex with the adaptor protein CARD9 and induce an immune response resulting in the production of IL-1β (Roth et al., 2014; Zhong et al., 2018). These groups observed that delivery of dsDNA or infection with vaccinia virus resulted in recruitment of Rad50 binds which recruited CARD9 and then the B-cell lymphoma/leukemia 10 protein (Bcl10) is recruited through its CARD-binding domain, the entire complex being necessary to activate NF-κB, increased

transcription of pro-IL-1β, and IL-1β production. Importantly, this study also showed that activation of NF-κB and subsequent proinflammatory response was independent of an inflammasome-mediated immune response or type I IFN response via STING as seen by unaffected levels of caspase-1 and IRF3. The implications of this study highlight the importance of the MRN complex in sensing DNA and inducing an innate immune response through STING-dependent and independent mechanisms. Specifically, many viruses have developed strategies to avoid Rad50-mediated NF-κB activation and subsequent IL-1β production. For example, adenovirus is known to inhibit Rad50 signaling while several vaccinia virus strains produce a soluble IL-1 receptor that can bind the host-produce IL-1β and prevent fever (Alcamí and Smith, 1996; Stracker et al., 2002). A recent study has shown that even different serotypes of adenovirus have different effects in their mechanism of inhibiting MRN/ATM activation (Pancholi and Weitzman, 2018). Further investigation into the MRN proteins like MRE11 and Rad50 will help elucidate the pathogen-specific mechanisms by which host innate immune response is blocked by DNA viruses as well as create the possibility of viral targets.

In summary, a number of DNA-sensing proteins have been identified over the past decade: TLR9, DAI, AIM2, RNA polymerase III, LRRFIP1, DHX9/DHX36, IFI16, Ku70, DDX41, Sox2, and cGAS. Notably, DAI has recently been shown to recognize viral RNA in addition to its role in DNA sensing to induce necroptosis (Maelfait et al., 2017; Thapa et al., 2016). The ability of STING to potentiate signals from many of these DNA sensors and bind CDNs places it central to the DNA sensing pathway for viral and bacterial infections. Indeed, the wide diversity of proteins that can recognize DNA and induce an innate immune response shows that host defense mechanisms have a critical role in promoting protection and host survival. When these DNA-sensing mechanisms are dysfunctional, they can result in autoimmune and autoinflammatory disorders, a significant area of research driven by the need to discover new therapeutic targets. The next section will discuss autoimmune and autoinflammatory disorders in the context of DNA-sensing.

3.4. Autoimmune and Autoinflammatory Disorders Derived From Immune System Dysfunction

A critical application of innate and adaptive immunity in the context of human disease has been to dissect how autoimmune and autoinflammatory disorders occur as a result of immune system dysfunction. Autoinflammatory disorders are generally driven by innate immune components and do not actively rely on adaptive immune components. In contrast, autoimmunity generally refers to disorders that originate from defects in the innate immune system but require adaptive immune components such as lymphocyte influx or T and B-cell responses. A classic group of autoinflammatory disorders are the cryopyrin-associated periodic syndromes (CAPS), also known as familial cold autoinflammatory syndrome (FCAS), which result from gain-of-function mutations in the *NLRP3*/*CIAS1* gene (Cordero et al., 2018; Hoffman et al., 2001; Kanneganti et al., 2006; Li et al., 2017a). On the other hand, classic autoimmune disorders include Aicardi–Goutières syndrome (AGS), and although several mutations in AGS patients are rooted in innate immune dysfunction, AGS has both autoimmune and autoinflammatory components. Differences in disease progression have been observed between human and mouse models, illustrating species-specific

differences in these disease phenotypes. In characterizing autoimmune and autoinflammatory diseases, it is important to dissect the origins of disease. Our understanding of autoimmune disorders relies on our knowledge of innate immune recognition proteins such as the DNA sensors described above. While not all autoimmune/inflammatory disorders have a common DNA-sensing origin, this section will focus on disorders that originate in failures of DNA sensing pathways.

3.5. DNA-Sensing Molecular Mechanisms of Diseases and Nucleic Acid Accumulation

A group of disorders that result from errors in the innate immune system that result in constitutive activation of type I IFN signaling are collectively termed type I interferonopathies. While there are different causes of type I interferonopathies, two classes can summarize the majority of those derived from errors in DNA-sensing proteins with an end result of unregulated production of IFNs. The first derives from mutations in genes encoding enzymes that regulate accumulation of nucleic acids that ultimately feed into the cGAS/STING pathway. The second results from constitutive activation or hypersensitivity of the cGAS/STING and RLR pathways. In the next subsections we describe how nucleic acid accumulation through mutations or dysfunction of genes encoding the proteins TREX1, RNase H2, SAMHD1, and STING results in autoimmune/autoinflammatory diseases such as AGS, SLE, Sjögren's syndrome, STING-associated vasculopathy with onset in infancy (SAVI), and familial chilblain lupus (Table 4).

3.5.1. TLR9, TREX1, RNase H2, and SAMHD1—As introduced in the previous section, AGS is characterized as a heritable inflammatory disease that can lead to severe neurological disorders. In addition to the roles that *ADAR1* and MDA5 have in AGS, AGS has also been documented to be caused by genetic mutations encoding nucleic-acid-metabolizing proteins, such as TREX1, RNASEH2A-C (Ribonuclease H2), and SAMHD1 (Crow et al., 2006a,b; Rice et al., 2009, 2012, 2014). Mutations in three of these proteins, namely TREX1, RNase H2, and SAMHD1, result in the direct accumulation of nucleic acids and subsequent activation of the cGAS/STING signaling pathway. Dysfunctions in nucleic acid sensing are also found in SLE patients and include hyperactivity of TREX1 or TLR9 in B cells (Barrat et al., 2005; Christensen et al., 2005; Crispín et al., 2013; Lenert, 2010; Wu et al., 2009; Yu, 2006).

As described in the previous section focused on cytosolic RNA sensing, mice lacking TLR7 exhibited decreased SLE pathology, due to lower levels of autoantibodies and lymphocyte activation. In contrast, the loss of TLR9 results in increased SLE pathology, lymphocyte activation, type I IFN, and autoantibodies (Christensen et al., 2006). B cells from SLE patients display impaired TLR9 signaling and decreased levels of CD19 and CD21, while pDCs from SLE patients displayed normal TLR9 signaling. However, TLR7 signaling was normal in SLE B cells (Gies et al., 2018). Moreover, when lupus-prone *Sle1* mice were crossed with $TLR9^{-/-}$ mice, SLE pathology was exacerbated, and TLR7 expression was increased, leading to increased antigen presentation on DCs (Celhar et al., 2018). Similar results were also observed in $TLR9^{-/-}$ mice treated epicutaneously with imiquimod, which induces local inflammation, as compared to wild-type mice (Liu et al., 2018). Recently, a mechanism behind TLR9-mediated tolerance of SLE was shown to function through the

AhR transcription factor, which is activated in apoptotic cells via TLR9 and drives anti-inflammatory IL-10 production. The loss of AhR also resulted in a more severe SLE phenotype (Shinde et al., 2018). Together, these studies highlight the protective role TLR9 in TLR7-mediated SLE and the role of apoptotic-cell DNA in promoting B-cell tolerance.

An important detector of cytosolic DNA is TREX1 (three prime pair exonuclease 1), whose major function is to digest ssDNA and dsDNA in the cytosol and prevent autoimmune activation (de Silva et al., 2007; Hoss, 1999; Lehtinen et al., 2008; Mazur and Perrino, 1999; Yang et al., 2007). Unlike other proofreading DNases, TREX1 is anchored to the ER by its C-terminal region (Chowdhury et al., 2006; Mazur and Perrino, 2001; Richards et al., 2007; Stetson et al., 2008; Wolf et al., 2016). Indeed, the role of TREX1 in AGS has been documented extensively by several groups which have identified different loss-of-function mutations in the *TREX1* gene in AGS (Abe et al., 2014; Bailey et al., 2012; Crow, 2011; Crow et al., 2006a; Grieves et al., 2015; Lindahl et al., 2009; Namjou et al., 2011; Olivieri et al., 2013; Orebaugh et al., 2011; Uyur Yalçın et al., 2015). Mouse models of TREX1 deficiency have demonstrated that $TREX1^{-/-}$ mice have increased type I IFN signaling, inflammation in multiple tissues, and increased mortality (Gall et al., 2012; Peschke et al., 2016; Stetson et al., 2008; Xu et al., 2014a). Importantly, disease progression in $TREX1^{-/-}$ mice depends significantly on cGAS, STING, and sub-sequent IRF3 activation, due in part by the accumulation of 2′–3′-cGAMP in $TREX1^{-/-}$ mice. Importantly, double knockout cGAS/TREX1 mice lack the autoinflammatory phenotype due to the loss of the cGAS DNA sensor (Ahn et al., 2012; Gao et al., 2015; Gray et al., 2015). The origin of cytosolic DNA that leads to overstimulation of cGAS and STING has also been studied extensively (Ablasser et al., 2014). Some groups have shown that TREX1 may function specifically to be a detector of viral retroelements which is supported by its role in metabolizing the of HIV-derived DNA and overall HIV pathogenesis (Booiman et al., 2014; Pontillo et al., 2013; Wheeler et al., 2016; Yan et al., 2010). Indeed, Beck-Engeser et al. suggest that the treatment of AGS patients with retroelement inhibitors may is a potential therapy, but Achleitner et al. has shown that these types of drugs do not improve disease (Achleitner et al., 2017; Beck-Engeser et al., 2011). Alternatively, it could be that TREX1 functions primarily to prevent DNA damage and serves a dual purpose in feeding into the cGAS/STING pathway when it detects cytosolic DNA. This hypothesis is supported in part from evidence showing that TREX1 metabolizes cytosolic DNA and contributes to the prevention of genome instability (Ahn et al., 2014; Domínguez-Sánchez et al., 2011; Yang et al., 2007). Indeed, a recent study has shown that TREX1 has a nuclease-independent function in preventing L1-mediated retrotransposon-induced DNA damage, thus maintaining genome integrity (Li et al., 2017b).

AGS is also caused by mutations in alleles in the trimeric protein RNase H2, whose two main functions are to degrade RNA/DNA hybrids resulting from misincorporation of ribonucleotides and to cleave dsDNA at a phosphodiester linkage adjacent to a single ribonucleotide (Crow et al., 2006b; Reijns et al., 2012). It is now well-documented that mutations in *RNASEH2A*, *RNASEH2B*, and *RNASEH2C* lead to the abnormal accumulation of nucleic acids which result in AGS (Chon et al., 2013; Coffin et al., 2011; Günther et al., 2015; Hiller et al., 2012; Kind et al., 2014; Pizzi et al., 2015; Pokatayev et al., 2016; Ramantani et al., 2010; Reijns et al., 2011). RNase H2-deficient mouse models show

that mutations in this complex are embryonic lethal, indicating a critical function of all subunits (Reijns et al., 2012). Nonetheless, mice expressing mutant *RNASEH2A* and *RNASEH2B* alleles show that these mutations result in the direct accumulation of nucleic acids that induce IFN through cGAS/STING signaling (Mackenzie et al., 2016; Pokatayev et al., 2016). Evidence suggests that the specific origin of nucleic acids that leads to RNase H2-mediated inflammatory disease may occur through DNA damage responses as well as recognition of retroelements (Bartsch et al., 2017, 2018; Günther et al., 2015; Zhao et al., 2018). Furthermore, two recent studies have also shown that DNA damage leading to the formation of micronuclei induces an IFN response through cGAS and that this occurs in frequently in the absence of *RNASEH2B* (Harding et al., 2017; Mackenzie et al., 2017).

A third and recently characterized protein that plays a role in AGS is SAMHD1 (SAM domain and HD domain-containing protein 1), which encodes an enzyme with phosphohydrolase activity as well as antiviral protection from HIV (Beloglazova et al., 2013; Goldstone et al., 2011; Powell et al., 2011; Rice et al., 2009). Specifically, SAMHD1 detects and cleaves deoxyribose adenine triphosphates (dNTPs) to prevent the reverse transcription of the HIV genome (Goldstone et al., 2011; Lahouassa et al., 2012). A recent study using SAMHD1-deficent mice showed these mice lack autoimmune phenotypes but are hyperactive in cGAS/STING signaling and induce the expression of type I IFN genes *Ifit1* and *Ifi44* (Behrendt et al., 2013; Maelfait et al., 2016). Additionally, SAMHD1 has also been implicated in DNA damage responses through its ability to maintain genome stability, digest ssDNA fragments at stalling replication forks, and inhibiting a cGAS/STING inflammatory response (Coquel et al., 2018; Kretschmer et al., 2015; Medeiros et al., 2018). A recent study has shown that SAMHD1 can suppress innate immune induction independently of its dNTPase activity. Specifically, SAMHD1 can mediate suppression of NF-κB through its interaction with NF-κB1/2 and preventing phosphorylation of IκBα, and also by interacting with IKKε to prevent IKKε-dependent phosphorylation of IRF7 (Chen et al., 2018). Importantly, this study suggests that because SAMHD1 negatively regulates an innate immune response, it may serve as a therapeutic target. Indeed, all of these recent findings highlight the need to continue studying the multiple mechanisms that TREX1, RNase H2, and SAMHD1 have in mediating an inflammatory response that can lead to AGS and other inflammatory diseases.

3.5.2. Sjögren's Syndrome—Sjögren's syndrome (SS) is an autoimmune disorder characterized by dry mouth and eyes due to reduced lacrimal and salivary gland secretion first described in 1933 by Henrik Sjögren (Mutlu and Scully, 1993). The molecular mechanisms behind SS are unclear as symptoms are similar to rheumatoid arthritis and many groups have grappled with defining indicators and causes (Baldini et al., 2018; Daniels and Fox, 1992; Wang et al., 2018; Yang et al., 2018). Studies have documented that the DNA sensor IFI16 is upregulated in SS patients and leads to increased antibodies against IFI16 (Alunno et al., 2015; Baer et al., 2016; Mondini et al., 2006). A recent study has implicated STING hyperactivation as a possible cause of SS, shown by the increase in circulating levels of the IFN-α, IFN-β, IL-6, and TNF-α proinflammatory cytokines in primary salivary gland cells of mice after DMXAA-mediated activation of STING. Notably, these mice developed antibodies to STING, and STING/TBK1/IRF3 signaling resulted in increased IFN-β

production in the salivary glands. In addition, transfection with cGAMP in salivary glands also resulted in robust production on IFN-β which suggests that a possible mechanisms for SS might be due to the presence of cytosolic DNA that leads to the activation of cGAS and subsequent STING signaling (Papinska et al., 2018). Importantly, this is the first study to associate SS with accumulation of nucleic acids that activate the cGAS/STING signaling pathway, but further dissection of the pathway in this disorder will be needed to clarify a mechanism.

In summary, it is evident that accumulation of nucleic acids leads to autoinflammatory and autoimmune diseases such as AGS, SLE, and SS. The proteins TREX1, RNase H2, and SAMHD1 all have important roles in protecting the cell from hyperactive cytosolic nucleic acid signaling via the cGAS/STING signaling pathway. Further studies connecting cytosolic DNA presence to AGS, SLE, and SS will clarify how DNA damage responses and innate immune responses like cGAS/STING lead to autoimmune and autoinflammatory disorders.

3.6. Hypersensitivity of cGAS/STING Signaling

In addition to accumulation of nucleic acids, another important cause of autoimmune and autoinflammatory disorders is hypersensitivity of the cGAS/STING pathway. This type of dysfunction is due to mutations that result in the constitutive activation of STING and type I IFN in the presence or absence of ligands, namely CDNs. Two examples of such disorders are SAVI and familial chilblain lupus where mutations in the *TMEM173* gene encoding the STING protein result in constitutive production of IFN and proinflammatory cytokines. Lastly, we describe an example of a therapeutic option in a mouse model of MS that indirectly connects it to the cGAS/STING signaling pathway.

3.6.1. SAVI and Familial Chilblain Lupus—De novo, gain-of-function mutations in the *TMEM173* gene were documented to cause SAVI (Liu et al., 2014). The disease begins in the first few months of life and autoinflammatory symptoms include rash, flares, nodules, blistering of fingers, toes, nose, cheeks, fever, and joint pain (de Jesus et al., 2015; Jeremiah et al., 2014; Munoz et al., 2015; Picard et al., 2016). Other characteristics of SAVI include ulcerating skin lesions that resemble chilblain lupus. Indeed, sequencing of *TMEM173* in chilblain lupus patients has also revealed gain-of-function mutations in STING which lead to disease (König et al., 2017). Previously, the identified gain-of-function mutations in patient samples had involved one of four amino acids in STING at positions 147, 154, 155, or 166 which sequester STING in the ER, simulate ligand binding, resulting in increased production of IFNs (Dobbs et al., 2015; Liu et al., 2014; Zhang et al., 2013). However, substitutions in the amino acid residues 206, 281, and 284 of STING implicated a ligand-independent mechanism of STING activation (Melki et al., 2017). Additionally, a recent study in which whole exome sequencing was performed from a 9-month-old Ecuadorian boy displaying fever and a severe neck abscess revealed he had a missense heterozygous mutation resulting in the STING variant R284S which constitutively activates STING in the absence of CDNs (Konno et al., 2018). Interestingly, the chilblain lupus mutations that result in activation of STING and production of IFN-β are also induced in the absence of CDNs, indicating that other STING-trafficking mechanisms need to be investigated. For example, the constitutive production of IFN-β in SAVI has been thought to occur by activation of

TBK1 and IRF3. However, a study generated STING N153S heterozygous knock-in mice and observed that these mutants develop disease symptoms independent of IRF3 which suggests that other type I IFN-independent mechanisms are involved causing diseased state or that species-specific differences exist molecularly (Warner et al., 2017).

As seen by the gain-of-function mutations in *TMEM173*, it is evident that overstimulation or activation of STING is enough to induce a diseased state. The use of JAK1/2 inhibitors is currently a growing therapeutic approach being used treat other inflammatory diseases such as rheumatoid arthritis and myelofibrosis that may also be used to treat SAVI. Indeed, a recent study showed that when the JAK inhibitor baricitinib was used to treat SAVI patients, resulting in amelioration of vasculitis (Sanchez et al., 2018). Nevertheless, many questions remain regarding JAK inhibitors such as their side effects which prevent FDA approval (Shreberk-Hassidim et al., 2017). Another therapeutic strategy lies in the development of STING-specific inhibitors to treat STING-mediated autoinflammatory diseases. In fact, covalent small-molecules have been developed that target a transmembrane domain of STING to block its palmitoylation and subsequent multimeric assembly at the Golgi (Haag et al., 2018). These molecules improve inflammatory disease in *TREX1*$^{-/-}$ mice and may soon be used for clinical trials in SAVI patients or other STING-mediated interferonopathies.

3.6.2. S6K1 and Multiple Sclerosis—One interesting therapeutic example for autoimmune disorders has been observed through the use of the mouse model of multiple sclerosis (MS), namely experimental autoimmune encephalitis (EAE). MS is an autoimmune disease that leaves scars, namely sclerosis, in the myelin sheath of multiple nerve fibers over time by the influx of T lymphocytes into the CNS (McFarland and Martin, 2007). Symptoms include muscle weakness, fatigue, difficulty balancing and walking, as well tremors, speech problems, and cognitive issues like cerebral and brainstem dysfunction (Landtblom et al., 2010; Minagar, 2014). There are varying degrees of MS ranging from subtle to severe that change over time as the disease progresses. Microarray analysis, large-and small-scale gene expression studies, and GWAS have been performed in patients and have revealed over 20 mutations that may lead to disease, some of which induce the production of cytokines by Th1 and Th17 cells (Munoz-Culla et al., 2013; Murugaiyan et al., 2011). There is no explicit evidence supporting DNA-sensing mechanisms involved in MS pathogenesis, however, there is one possible therapeutic option that indirectly connects to the cGAS/STING signaling pathway. Earlier, the ribosomal kinase S6K1 was described in the mechanism for cGAS/STING signaling where it forms a complex with STING and TBK1 to induce IRF3 activation in the context of cytosolic DNA sensing (Wang et al., 2016). Inhibition of S6K1 with a pan-ribosomal S6 kinase inhibitor BI-D1870 protected mice from EAE (Takada et al., 2016). Furthermore, when EAE mice were injected with DNA nanoparticles (DNPs) which led to selective activation of STING, subsequent IFN-α/β release, and overall suppression of EAE by reducing the recruitment of Th1 and Th17 cells into the CNS (Lemos et al., 2014). This therapeutic option mediated by DNPs suggests that other accessory proteins may indeed be able to serve as targets for other autoimmune or inflammatory diseases.

While type I interferonopathies are characterized by varying degrees of autoinflammation, autoimmunity, or immunodeficiency, only a few have been documented to be caused directly

or indirectly by dysregulation of DNA-sensing mechanisms. Specifically, the molecular dissection of autoinflammatory and autoimmune disorders like AGS, SS, SAVI, and familial chilblain lupus has all revealed a commonality in DNA-sensing errors. Namely, mutations in the proteins TREX1, RNase H2, and SAMHD1 lead to nucleic acid accumulation while mutations in *TMEM173* lead to overstimulation of STING and subsequent overproduction of IFN-β. On the other hand, SLE and SMS are indirectly connected to DNA-sensing mechanisms but nonetheless represent the complexity of the mechanisms behind these disorders.

4. PROSPECTIVE

Detailed mechanistic understanding of innate immunity is crucial for the development of novel therapies to combat microbial infection and provide relief to those suffering from certain autoimmune pathologies. Already, it has been shown that the STING pathway can be exploited to reduce infectious load of a number of viral (Guo et al., 2017; Skouboe et al., 2018) and bacterial (Barker et al., 2013; Karaolis et al., 2007b; Rosen et al., 2017) pathogens. Additionally, STING-specific adjuvants can boost vaccine efficiency (Junkins et al., 2018; S̆krnjug et al., 2014) and be used for cancer immunotherapy (Miyabe et al., 2014). Similarly, RIG-I agonists can be used to reduce viral burden (Bedard et al., 2012; Coch et al., 2017; Green et al., 2016; Nielsen et al., 2017; Pattabhi et al., 2015) and induce anti-tumor activity (Dassler-Plenker et al., 2016). Given these advances in developing small molecules and methods to activate innate immunity to reduce microbial burden, methods to inhibit hyperactive innate immune signaling may aid in the development of therapies for autoimmune disorders. Already, small molecules have been developed that target cGAS and reduce its activity (An et al., 2015; Hall et al., 2017; Vincent et al., 2017). Given the evolutionary arms race between pathogens and host, especially with respect to the co-evolution of DNA-and retro-viruses with humans (Elde and Malik, 2009), might it be possible to develop virally based strategies or molecules to inhibit hyperactive innate immunity? As the saying goes, “…keep your enemies closer.”

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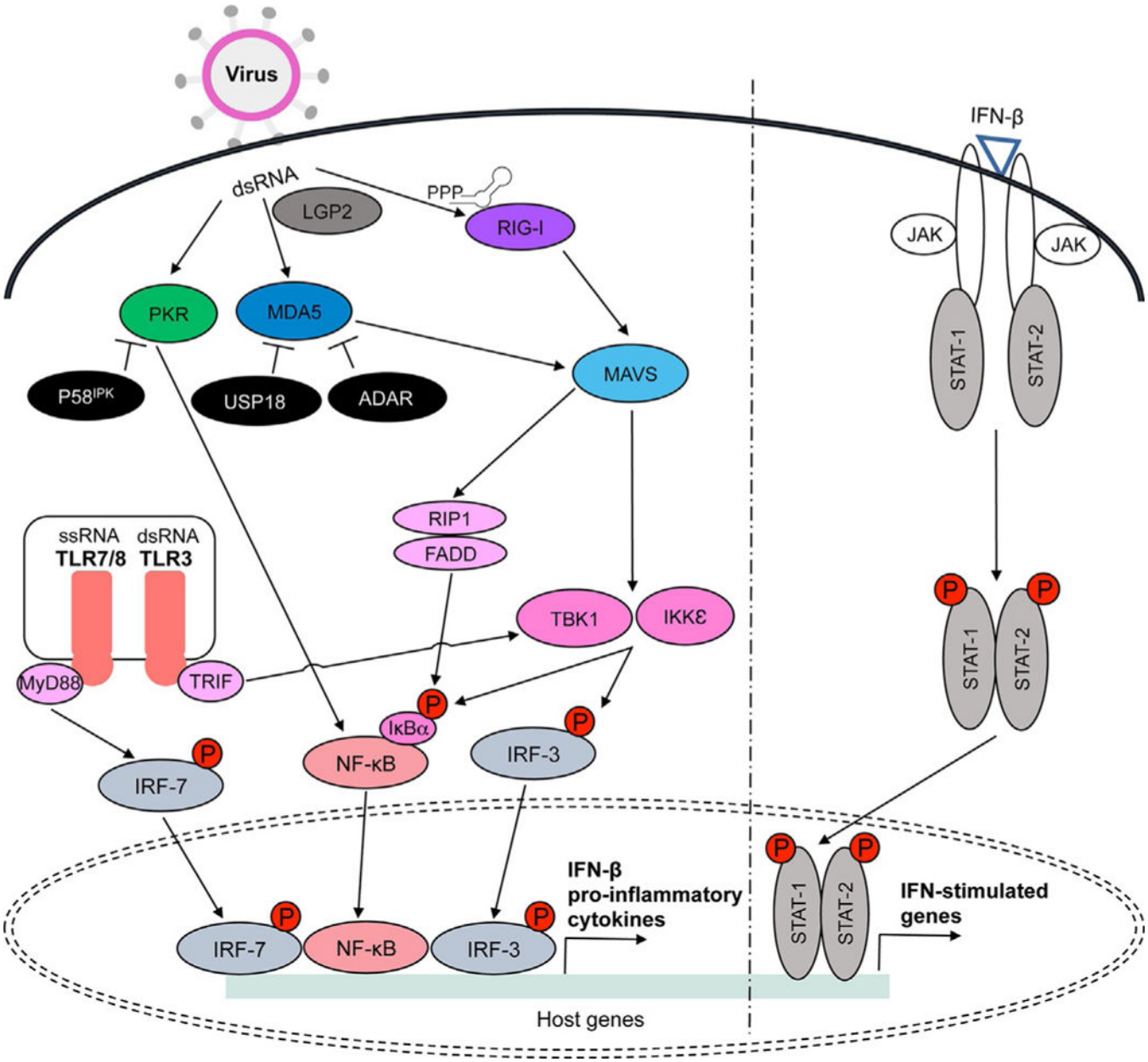

Fig. 1.

RIG-I, MDA5, LGP2, PKR, and TLRs3/7/8 are activated during viral infection in the presence of non-self dsRNA. RIG-I recognizes short dsRNA and non-self ssRNA with 5′-triphosphate or 5′-diphosphate, while MDA5 recognizes long dsRNA. LGP2 acts upstream to regulate RIG-I and MDA5 activation in the presence of dsRNA. RIG-I and MDA5 interact with MAVS adaptor protein located on the mitochondrial membrane. MAVS then activates FADD/RIP1 and TBK1/IKKε protein kinases that induce nuclear translocation of NF-κB and IRF3 following phosphorylation of IκBα or IRF3. PKR is also activated in the presence of dsRNA and it transmits activation signals through NF-κB. Endolysosomal TLRs3 and 7/8 lead to TBK1 and IRF7 activation via adaptors TRIF and MyD88, respectively. NF-κB, IRF3, and IRF7 are transcription factors that induce proinflammatory cytokine production,

including IFN-β. Autoamplification of IFN signaling occurs through activation of the Jak/STAT pathway upon IFN-β binding. While IFN-stimulated genes spread antiviral signals to surrounding cells, viral proteins inhibit multiple steps of these pathways (see Table 1). Inhibitors of these signaling pathway also work to control activation signals and dysfunctions in these molecules can contribute to various autoimmune disorders. For example, $P58^{IPK}$ inhibits PKR while USP18 and ADAR suppress MDA5 activity (see Table 2).

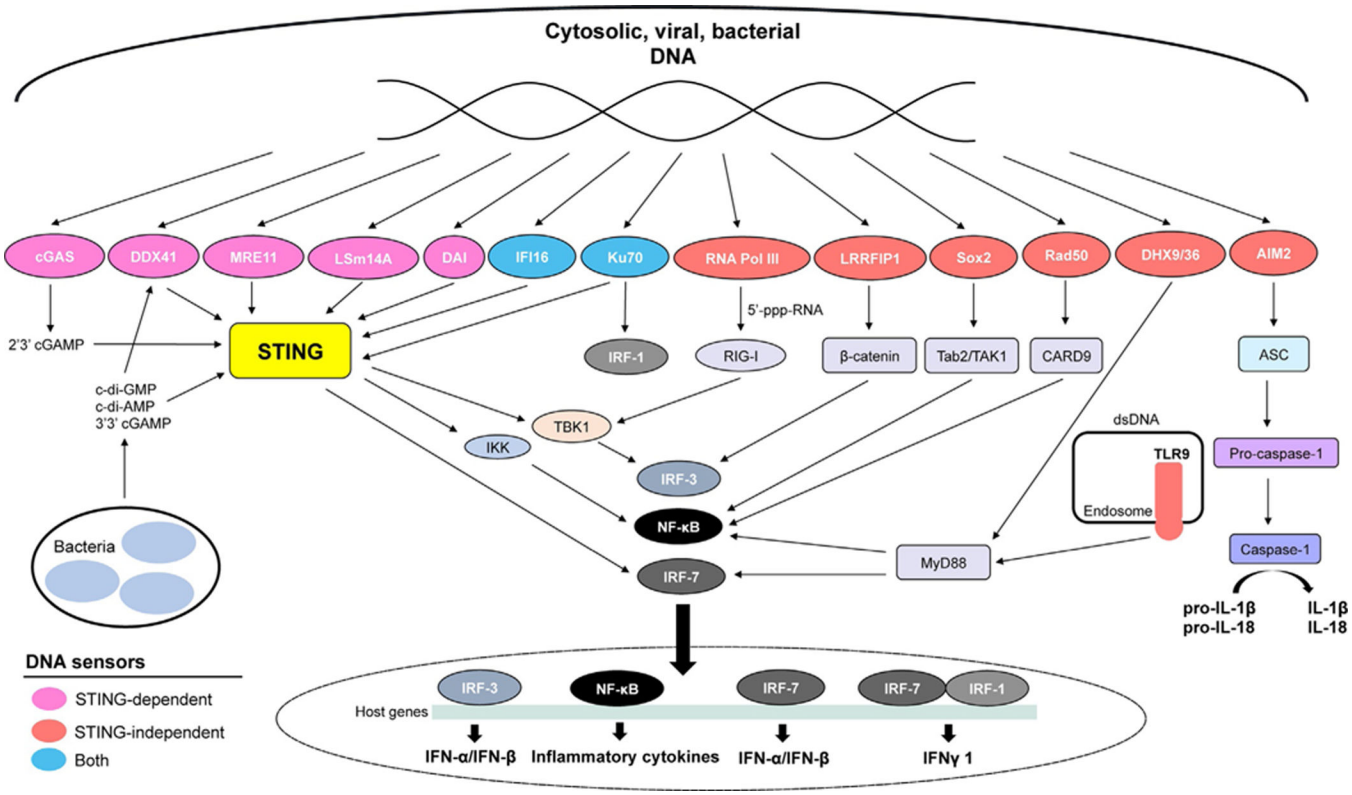

Fig. 2.

Sensing of cytosolic DNA or cyclic dinucleotides via multiple sensors leads through the induction of interferon and proinflammatory cytokines. Cytosolic DNA derived from viral or bacterial infection (see Table 3), as well as self-DNA, is sensed by receptors that signal through STING (pink), receptors that are independent of STING (red), and receptors that signal via STING-dependent or -independent mechanisms (blue). STING binds to cyclic dinucleotides, by-products of some bacterial infection and also metabolized by cGAS upon binding to dsDNA. While AIM2 leads to caspase and inflammasome activation, DNA-mediated activation of the other receptors leads to IRF or NF-κB transcription factor activation and the induction of IFN and proinflammatory cytokines. Dysfunction or hyperactivation of these DNA-sensing pathways can lead to autoimmunity (see Table 4).

Table 1

Summary of Host Proteins That Sense RNA Virus Infection, Viral Proteins That Inhibit Host Responses, and Polymorphisms That Affect Pathogenesis

Virus	Family	RLR Detection	Innate Immune Inhibition by Viral Components	Genetic Polymorphisms That Increase Susceptibility
Hepatitis C virus (HCV)	Flaviviridae (+) ssRNA	• RIG-I (Sumpter et al., 2005) • TLR7 (Stone et al., 2014)	• NS3/4A viral protease (Ding et al., 2012; Li et al., 2005) • NS3 (Kasama et al., 2012) • NS4B (Ding et al., 2013)	• Polymorphisms in TLRs3/7/8 result in increased HCV susceptibility (El-Bendary et al., 2018)
Dengue virus (DENV)	Flaviviridae (+) ssRNA	• RIG-I and MDA5 (Nasirudeen et al., 2011) • TLR3 (Rodriguez-Madoz et al., 2010)	• Virus induced double-membrane vesicles (Junjhon et al., 2014; Uchida et al., 2014) • NS4B, NS2A, NS4A (Muñoz-Jordán et al., 2003) • NS2B/NS3 (Angleró-Rodríguez et al., 2014; Rodriguez-Madoz et al., 2010) • NS2A/NS4B (Dalrymple et al., 2015) • NS5 (Ashour et al., 2009)	• Type 2 diabetes increases susceptibility to severe viral infection (Lee et al., 2013)
West Nile virus (WNV)	Flaviviridae (+) ssRNA	• RIG-I and MDA5 (Fredericksen et al., 2008) • TLR7 (Xie et al., 2013) • TLR3 (Szretter et al., 2010)	• NS1 (Zhang et al., 2017b)	• Lack of MAVS in myeloid cells (Pinto et al., 2014) • *RFC1*-DNA polymerase activator (Loeb et al., 2011) • Lack of MAVS (Suthar et al., 2010) • Type 2 diabetes (Kumar et al.,2012)
Zika virus (ZIKA)	Flaviviridae (+)ssRNA	• RIG-I, MDA5, and TLR3 (Hamel et al., 2015) • TLRs3/8 (Luo et al., 2018)	• NS5 (Grant et al., 2016; Kumar et al., 2016) • NS1 (Xia et al., 2018)	• MAVS (Piret et al., 2018) • IRF3, IRF5, IRF7 (Lazear et al., 2016)
Respiratory syncytial virus (RSV)	Paramyxoviridae (–)ssRNA	• RIG-I (Loo et al., 2008) • TLRs3/7 (Qi et al., 2015)	• NS2 (Ramaswamy et al., 2004, 2006) • NS1 (Xu et al., 2014b)	• *FokI*-vitamin D receptor (Hansdottir et al., 2010; Janssen et al., 2007; Stoppelenburg et al., 2014) • Plasmacytoid dendritic cells (Marr et al., 2014)
Nipah virus (NiV)	Paramyxoviridae (–)ssRNA	• RIG-I (Habjan et al., 2008)	• Phosphoprotein (Ciancanelli et al., 2009; Rodriguez et al., 2004; Shaw et al., 2004) •Nucleoprotein (Sugai et al., 2017) • Matrix protein (Bharaj et al., 2016) •Nonstructural C protein (Yamaguchi et al., 2014)	
Ebola virus (EBOV)	Filoviridae (–) ssRNA	• RIG-I (Habjan et al., 2008)	• VP35 (Caballero et al., 2016; Hartman et al., 2008; Luthra et al., 2013; Yen et al., 2014)	
Rotavirus (RV)	Reoviridae dsRNA-RT	• RIG-I and MDA5 (Broquet et al., 2011) • TLRs3/7 (Yang et al., 2016)	• NSP1 (Barro and Patton, 2005; Graff et al., 2009; Qin et al., 2011)	• Variable RNA transcripts (Uzri and Greenberg, 2013)

Table 2

Summary of Polymorphisms in RNA Sensors and Their Associated Syndromes

RNA Sensor	RNA Sensor Associated Protein	Genetic Polymorphisms That Causes Dysfunction	Associated Syndrome/Pathology
MDA5		1. Four loss-of-function variants *IFIH1*-gene that encodes MDA5 (Lincez et al., 2015; Liu et al., 2009; Nejentsev et al., 2009; Shigemoto et al., 2009) 2. Gain-of-function *IFIH1* mutations (Crow et al., 2015) 3. Missense mutation in *IFIH1* (Funabiki et al., 2014) 4. Missense mutation in *IFIH1* leading to overactive MDA5 (Rutsch et al., 2015)	1. Type 1 diabetes 2. Aicardi–Goutieres syndrome 3. Lupus-like symptoms 4. Singleton–Merten Syndrome
	USP18	1. Loss-of-function in USP18 induces overactivation of MDA5 (Santin et al., 2012)	1. Type 1 diabetes
	ADAR	1. Loss-of-function in ADAR induces overactivation of MDA5 (Crow et al., 2015; Pestal et al., 2015) 2. Gain-of-function mutation in *IFIH1* led to over expressed MDA5 (Crow et al., 2015; Schmelzer et al., 2018)	1–2. Aicardi–Goutieres syndrome
PKR			
	$P58^{IPK}$ interaction with PERK	1. Knockout of $P58^{IPK}$ (Ladiges et al., 2005) 2. Loss-of-function mutations in *Dnajc3* (Synofzik et al., 2014) 3. Homozygous stop mutation (Synofzik et al., 2014)	1. Symptoms associated with type 1 and late stage type 2 diabetes 2. Juvenile-onset diabetes and multisystemicneurodegenerative disorders 3. Monogenic recessive diabetes mellitus
RIG-I		1. Knockout of RIG-I (Wang et al., 2007) 2. Downregulation of G protein αi2 subunit (Hampe et al., 2001b) 3. Decreased expression of RIG-I (Funke et al., 2011) 4. Variants of *DDX58* causing overactive RIG-I (Jang et al., 2015)	1. Colitis-like phenotype associated with inflammatory bowel disease 2. Human inflammatory bowel disease 3. Crohn's disease 4. Singleton–Merten Syndrome
	NOD2	1. NOD2 mutations that imbalance IFN signaling through RIG-I (Morosky et al., 2011)	1. Crohn's disease
TLR3		1. Polymorphisms in *TLR3* (Assmann et al., 2014)	1. Type 1 diabetes
TLR7		1. Polymorphisms in *TLR7* promoter (Skonieczna et al., 2018)	1. Systemic lupus erythematosus

Table 3

Summary of Host Proteins That Sense DNA Virus or Bacterial Infections

DNA Sensor	DNA Sensor Associated Protein	Pathogens That Stimulate Sensor
cGAS	STING	• Adenovirus (AdV) (Anghelina et al., 2016; Ishikawa et al., 2009; Lam and Falck-Pedersen, 2014; Lam et al., 2014) • Herpes simplex virus 1 (HSV-1) (Christensen et al., 2016; Horan et al., 2013; Ishikawa et al., 2009; Kalamvoki and Roizman, 2014; Li et al., 2013; Su and Zheng, 2017; Xu et al., 2017; Ye et al., 2017; Zhang et al., 2016; Zheng, 2018) • Human papillomavirus (HPV) (Sunthamala et al., 2014) • Human and mouse cytomegalovirus (HCMV or MCMV) (Choi et al., 2018; Fu et al., 2017; Lio et al., 2016) • Human immunodeficiency (HIV) (Gao et al., 2013a; Lahaye et al., 2013; Rasaiyaah et al., 2013) • Dengue virus (DENV) (Aguirre and Fernandez-Sesma, 2017; Aguirre et al., 2012; Stabell et al., 2018; Yu et al., 2012) • Hepatitis C virus (HCV) (Ding et al., 2013; Maringer and Fernandez-Sesma, 2014; Moriyama et al., 2007; Nitta et al., 2013) • *Listeria monocytogenes* (Sauer et al., 2011; Woodward et al., 2010) • *Staphylococcus aureus* (Gries et al., 2016; Zhang et al., 2014) • *Chlamydia trachomatis* (Barker et al., 2013)
DDX41	STING	• HSV-1 (Zhang et al., 2011c) • AdV (Zhang et al., 2011c) • Newcastle disease virus (NDV) (Cheng et al., 2017) • *Listeria monocytogenes* (Parvatiyar et al., 2012)
DAI	STING	• HSV-1 (Furr et al., 2011)
IFI16	1. STING 2. ASC	• (1) Epstein-Barr virus (EBV) (Pisano et al., 2017) • (1) HSV-1 (Johnson et al., 2014; Merkl et al., 2018; Orzalli et al., 2012; Unterholzner et al., 2010) • (2) Kaposi's sarcoma-associated herpesvirus (KSHV) (Kerur et al., 2011)
Ku70	STING-dependent or independent	• Hepatitis B virus (HBV) (Li et al., 2016) • Human T lymphotropic virus type 1 (HTLV-1) (Wang et al., 2017) • HSV-2 (Zhang et al., 2011a)
MRE11	STING	• MRE11 is not required or induce a type I IFN response to HSV-1 or *Listeria monocytogenes* infection but plays a role in DNA damage recognition (Kondo et al., 2013)
LSm14A	STING	• HSV-1 (Li et al., 2012b)
RNA pol. III	RIG-I/MAVS	• *Legionella pneumophila* (Chiu et al., 2009) • EBV (Ablasser et al., 2009) • Invertebrate iridescent virus 6 (IIV-6) (Ahlers et al., 2016) • Varicella zoster virus (VZV) (Ogunjimi et al., 2017)
LRRFIP1	β-Catenin	• Vesicular stomatitis virus (VSV) (Yang et al., 2010) • *Listeria monocytogenes* (Yang et al., 2010)
Sox2	TAB2, TAK1	• HPV (Martınez-Ramırez et al., 2017)
DHX9/36	MyD88	• HSV-1 (Kim et al., 2010a)
Rad50	CARD9	• Vaccinia virus (VV) (Alcamí and Smith, 1996; Roth et al., 2014) • AdV (Pancholi and Weitzman, 2018; Stracker et al., 2002)
AIM2	ASC	• *Francisella tularensis* (Fernandes-Alnemri et al., 2010; Jones et al., 2010) • *Listeria monocytogenes* (Kim et al., 2010a,b) • *Streptococcus pneumonia*, *Mycobacterium tuberculosis*, *Legionella pneumophila*, *Staphylococcus aureus* (Fang et al., 2011; Ge et al., 2012; Hanamsagar et al., 2014; Saiga et al., 2012) • *Francisella novicida* (Meunier et al., 2015) • *Chlamydia muridarum*, *Chlamydia trachomatis* (Finethy et al., 2015) • MCMV (Shi et al., 2015) • HPV (Milutin Gasperov et al., 2014) • Influenza virus (Schattgen et al., 2016; Zhang et al., 2017a)
TLR9	MyD88	• HSV-1/2 (Krug et al., 2004; Lundberg et al., 2003) • *Campylobacter jejuni*, *Klebsiella pneumonia*, *Staphylococcus aureus* (Bhan et al., 2007; Dalpke et al., 2006) • VZV (Yu et al., 2011)

DNA Sensor	DNA Sensor Associated Protein	Pathogens That Stimulate Sensor
		• HCMV (Varani et al., 2007) • MCMV (Krug et al., 2004; Puttur et al., 2016) • EBV (Fiola et al., 2010; Lim et al., 2006) • KSHV (West et al., 2011) • VV and Ectromelia virus (Samuelsson et al., 2008) • AdV (Appledorn et al., 2008; Basner-Tschakarjan et al., 2006)

Table 4

Summary of Polymorphisms in DNA Sensors and Their Associated Syndromes

Protein	Genetic Polymorphisms That Lead to Autoimmunity/Autoinflammation	Associated Syndrome/Pathology
TLR9	1. Loss of TLR9 leads to increased lymphocyte activation, type I IFN, and autoantibodies (Christensen et al., 2006) 2. Impaired TLR9 signaling in B cells with decreased CD19/21 (Gies et al., 2018)	1–2. Systemic lupus erythematosus
TREX1	1. Loss-of-function mutations in *TREX1* of AGS patients (Abe et al., 2014; Bailey et al., 2012; Crow, 2011; Crow et al., 2006a; Grieves et al., 2015; Lindahl et al., 2009; Namjou et al., 2011; Olivieri et al., 2013; Orebaugh et al., 2011; Uyur Yalçın et al., 2015) 2. TREX1-deficient mice have cGAMP accumulation and produce high amounts of proinflammatory cytokines (Ahn et al., 2012, 2014; Gao et al., 2015; Gray et al., 2015) 3. Missense *TREX1* mutations present in systemic lupus erythematosus patients (Lee-Kirsch et al., 2007)	1–3. Aicardi–Goutières syndrome, familial chilblain lupus, systemic lupus erythematosus
RNase H2	1. Mutations in *RNASEH2A*, *RNASEH2B*, and *RNASH2C* lead to nucleic acid accumulation (Chon et al., 2013; Coffin et al., 2011; Günther et al., 2015; Kind et al., 2014; Pizzi et al., 2015; Ramantani et al., 2010; Reijns et al., 2011) 2. RNase H2-deficient mice are embryonic lethal; all subunits are necessary (Hiller et al., 2012; Reijns et al., 2012) 3. Mice that are RNASEH2A-and RNASEH2B-null have increased nucleic acid accumulation and increased ISG expression (Mackenzie et al., 2016; Pokatayev et al., 2016)	1–3. Aicardi–Goutières syndrome, lupus-like symptoms
SAMHD1	1. Over 16 missense, nonsense, and 12-nucleotide deletion mutations (e.g., AGS82, AGS92, and AGS91) have been identified in AGS patients and their families (Rice et al., 2009) 2. Mice deficient in *Samhd1* lack AGS symptoms but have increased ISG expression (Maelfait et al., 2016)	1. Aicardi–Goutières syndrome 2. Increased cGAS/STING signaling
STING	1. De novo gain-of-function mutations in *TMEM173* (Dobbs et al., 2015; Jeremiah et al., 2014; Konig et al., 2017; Konno et al., 2018; Liu et al., 2014, 2015a; Melki et al., 2017; Munoz et al., 2015; Picard et al., 2016; Warner et al., 2017) 2. Activation of STING via agonist leads to development of anti-STING antibodies, results in production of IFN-β in salivary gland cells (Papinska et al., 2018)	1. SAVI, familial chilblain lupus 2. Sjögren's syndrome