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CHAPTER ONE

Discrimination Between Self and Non-Self-Nucleic Acids by the Innate Immune System

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Contents

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Abstract

During viral and bacterial infections, the innate immune system recognizes various types of pathogen-associated molecular patterns (PAMPs), such as nucleic acids, via a series of membrane-bound or cytosolic pattern-recognition receptors. These include Toll-like receptors (TLRs), RIG-I-like receptors (RLRs), AIM2-like receptors (ALRs), and cytosolic DNA sensors. The binding of PAMPs to these receptors triggers the production of type I interferon (IFN) and inflammatory cytokines. Type I IFN induces the expression of interferon stimulated genes (ISGs), which protect surrounding cells from infection. Some ISGs are nucleic acids-binding proteins that bind viral nucleic acids and suppress their replication. As nucleic acids are essential components that store and transmit genetic information in every species, infectious pathogens have developed systems to escape from the host nucleic acid recognition system. Host cells also have their own nucleic acids that are frequently released to the extracellular milieu or the cytoplasm during cell death or stress responses, which, if able to bind pattern-recognition receptors, would induce autoimmunity and inflammation. Therefore, host cells have acquired mechanisms to protect themselves from contact with their own nucleic acids. In this review, we describe recent research progress into the nucleic acid recognition mechanism and the molecular bases of discrimination between self and non-self-nucleic acids.

1. INTRODUCTION

Invading microbes are initially recognized by the host cell's innate immune system via germ line-encoded pattern-recognition receptors (PRRs). PRRs recognize conserved pathogen-specific molecular signatures such as viral nucleic acids and fungal and bacterial cell-wall components, which are termed pathogen-associated molecular patterns (PAMPs). Because activation of the innate immune system triggered by PRR recognition is a critical host defense mechanism, many infectious pathogens have developed the ability to suppress PRR-mediated responses in order to escape detection. The binding of PAMPs to PRRs initiates a signal transduction cascade culminating in the induction of innate immune responses through the production of inflammatory cytokines, type I interferon (IFN), and other mediators. Cytokines transmit a signal to neighboring cells that induce the expression of an array of antiviral and antibacterial genes. These factors prevent pathogen replication by binding viral or bacterial components or by impairing host cell protein synthesis. In addition to triggering immediate host defensive responses, cytokines also prime and orchestrate antigen-specific adaptive immune responses (Kawai and Akira, 2011; Rathinam and Fitzgerald, 2011; Wu and Chen, 2014).

Nucleic acids, such as RNA and DNA, are also PAMPs. Mammals have several distinct classes of nucleic acid-recognizing PRRs, including Toll-like receptors (TLRs), RIG-I (retinoic-acid inducible gene I)-like receptors (RLRs), AIM2 (absent in melanoma 2)-like receptors (ALRs), and intracellular DNA sensors such as cyclic GMP-AMP synthase (cGAS). These receptors are classified according to their cellular localizations, the types of nucleic acids they recognize, and the specific signaling pathways that they activate. For instance, TLRs localize on plasma membrane or endocytic membrane and recognize extracellular nucleic acids, whereas other nucleic acid-recognizing PRRs are cytosolic DNA and RNA sensors; TLR3, TLR7, TLR8, TLR13, and RLRs recognize RNA, and TLR9 and DNA sensors recognize DNA; TLRs, RLRs, and DNA sensors induce the production of type I IFN and inflammatory cytokines, whereas ALRs induce the activation of the inflammasome and produce IL-1β and IL-18. Other than PRRs, several interferon stimulatory genes (ISGs) also bind to pathogen-derived nucleic acids to restrict viral and bacterial replication and prevent the spread of infection to other cells.

Endogenous nucleic acids, such as mRNA, tRNA, mitochondrial DNA, and genomic DNA, that are released during stress responses or cell death can also engage with PRRs to trigger inflammatory cytokines and type I IFN, leading to the initiation and perpetuation of chronic inflammation. Inappropriate or prolonged detection of endogenous nucleic acids underlies many autoimmune diseases. Therefore, host cells have innate mechanisms to protect them from unwanted contact with endogenous (self) nucleic acids. These mechanisms can be largely subdivided into three categories: the cellular localization of PRRs, nucleic acid modifications, and the degradation of unnecessary nucleic acids.

In this review, we describe the most recent research progress into the innate immune system's nucleic acid recognition mechanism and the molecular bases of its discrimination between self and non-self (pathogen) nucleic acids (Fig. 1).

2. INTRACELLULAR NUCLEIC ACID SENSORS

2.1 RLRs

The RLR family is composed of the proteins RIG-I and MDA5, which have similar multi-domain architectures: tandem N-terminal caspase activation and recruitment domains (CARDs) that propagate downstream signaling, a DExD/H box RNA helicase domain, and a C-terminal domain

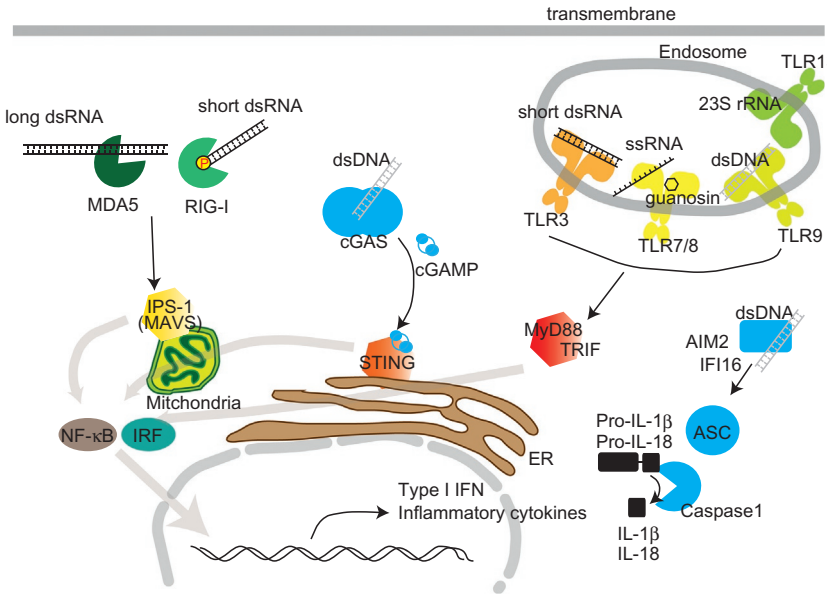

Fig. 1 Recognition of nucleic acids by PRRs. TLR3, 7/8, 9 and 13 are localized in endosomes. TLR3 recognizes dsRNAs, TLR7/8 recognizes ssRNAs and guanosine derivatives such as R837 and R848, TLR9 recognizes dsDNAs, and TLR13 recognizes 23S rRNAs. Ligand binding TLRs associate with MyD88 and/or TRIF in the cytosol. Intracellular RNA is recognized by RIG-I and MDA5, which bind to short dsRNAs and long dsRNAs, respectively. The binding of RIG-I and MDA5 to nucleic acids induces the formation of filaments that bind to mitochondria-localizing IPS-1 (MAVS). Intracellular dsDNAs bind to cGAS and produce cGAMP. cGAMP binds to STING which localizes in the endoplasmic reticulum (ER). Activation of the MyD88/TRIF, IPS-1 and STING adaptor proteins induces translocation of the transcription factors NF-κB and IRF to the nucleus following the production of type I IFN and inflammatory cytokines. AIM2 and IFI16 bind to dsDNAs and form an inflammasome with ASC and caspase-1. Activation of caspase-1 cleaves pro-IL-1β or pro-IL-18 to the mature forms of IL-1β and IL-18, respectively.

(CTD) (Yoneyama and Fujita, 2008). RIG-I binds to blunt ends of dsRNA displaying 5′-diphosphate and 5′-triphosphate moieties and to at least 10–19 bp of the adjacent dsRNA (Hornung et al., 2006; Schlee et al., 2009). RIG-I binds to the 5′ terminus of dsRNA as a monomer in the absence of ATP and forms filamentous oligomers near the dsRNA end in a ATP-dependent manner (Peisley et al., 2013; Wu et al., 2014). In contrast, individual molecules of MDA5 bind dsRNA internally in a highly cooperative manner and form long filaments around dsRNA in the absence of ATP (Berke et al., 2012; Wu et al., 2013). These data support the theory that RIG-I recognizes short dsRNAs whereas MDA5 preferentially binds longer dsRNAs. In the absence of dsRNAs, the CARDs of RIG-I and MDA5

interact with their helicase domain, forming an inhibitory complex (Kowalinski et al., 2011). Upon dsRNA recognition, RIG-I and MDA5 form filaments along dsRNA and their CARDs bind to the CARD of the adaptor protein interferon-β promoter stimulator 1 (IPS-1, also known as mitochondrial antiviral signaling (MAVS) protein). IPS-1 oligomerizes upon RIG-I and MDA5 binding and activates the downstream type I IFN pathway (Hou et al., 2011).

Genetic studies revealed that specific viruses were recognized by RIG-I and MDA5: Newcastle disease virus (NDV), Sendai virus (SeV), vesicular stomatitis virus (VSV), influenza virus, and Japanese encephalitis virus are specifically recognized by RIG-I. In contrast, picornaviruses, including encephalomyocarditis virus (EMCV), Mengo virus, and Theiler's virus, are recognized by MDA5. Dengue virus and West Nile viruses (WNV) are recognized by both RIG-I and MDA5 (Fredericksen et al., 2008; Gitlin et al., 2006; Loo et al., 2008; Rehwinkel et al., 2010). In addition to RNA viruses, RIG-I is involved in the recognition of DNA viruses including herpes simplex virus (HSV) and adenovirus (Chiu et al., 2009; Rasmussen et al., 2009). Furthermore, RIG-I binds short dsRNA intermediates containing a 5′-triphosphate group transcribed by DNA-dependent RNA polymerase III (Pol III) to induce IFNβ (Ablasser et al., 2009; Chiu et al., 2009). Recently, 5S ribosomal RNA pseudogene 141 (RNA5SP141) was found to bind to RIG-I during HSV-1 and influenza A virus (IAV) infections to enhance the expression of type I IFNs (Chiang et al., 2018).

2.2 ALRs

ALRs belong to the PYHIN protein family that typically consist of an N-terminal pyrin domain and one or two C-terminal hematopoietic IFN-inducible nuclear protein with 200 amino acids (HIN-200) domains. The HIN-200 domain contains a oligonucleotide/oligosaccharide-binding fold (OB fold), which is a common DNA-binding motif. Although only 4 *PYHIN* genes are present in humans, 13 are encoded in mice. AIM2 is the only ALR that is conserved between humans and mice. The AIM2 ALR acts as a cytosolic dsDNA sensor that oligomerizes on cytosolic foreign dsDNA and nucleates the polymerization of ASC (adaptor protein apoptosis-associated speck-like protein) to form a caspase-1 activating inflammasome, a filamentous supramolecular signaling platform that is required to instigate innate immune responses. Activated caspase-1 then cleaves pro-IL-1β or pro-IL-18 enabling the release of the mature active cytokines IL-1β and IL-18 (Fernandes-Alnemri et al., 2009;

Hornung et al., 2009; Roberts et al., 2009). AIM2 also has a crucial role in the development of the innate immune response against pathogen infections that include *Francisella tularensis* (Fernandes-Alnemri et al., 2010), HSV-1 (Maruzuru et al., 2018) and human papillomavirus (Reinholz et al., 2013). IFI16 is also a member of the ALR family. It is able to sense pathogenic DNA in both the cytoplasm and the nucleus, and recognizes DNA from viruses including human immunodeficiency virus 1 (HIV-1) (Monroe et al., 2014) and Kaposi sarcoma-associated herpesvirus (KSHV) (Kerur et al., 2011).

AIM2 is potentially able to bind to small DNA fragments below 20 bp in length; however, binding and oligomerization of AIM2 on long DNA fragments are required to initiate filament formation and mediate a robust innate immune response. In contrast, a transient association between the IFI16 HIN-200 domains and dsDNA larger than 60 bp permits at least four IFI16 molecules to cluster, initiating filament assembly (Morrone et al., 2014).

2.3 cGAS

cGAS is a cytosolic DNA sensor that recognizes DNA derived from pathogens or host cells (Gao et al., 2013; Sun et al., 2013; Zhang et al., 2013). It is involved in the immune recognition of HSV-1; retroviruses such as HIV-1, murine leukemia virus, and simian immunodeficiency virus; and reverse transcribed (+) ssDNA (Reinert et al., 2016; Sun et al., 2013). It is currently unclear how cGAS recognizes retroviruses, but cGAS-deficient mice exhibit reduced type I IFN expression following retrovirus infection (Gao et al., 2013). cGAS also plays an important role in eliciting anti-mycobacterial immunity by recognizing DNA released by *Mycobacterium tuberculosis* (Collins et al., 2015; Wassermann et al., 2015; Watson et al., 2015).

Biochemical and structural analysis of cGAS showed that it is able to bind to dsDNAs smaller than 20 bp in length (Civril et al., 2013; Li et al., 2013); however, 20 bp dsDNAs are unable to activate cGAS *in vivo*. Another study demonstrated that effective activation of cGAS occurs in the presence of dsDNA over 40 bp in length (Herzner et al., 2015). Recent work revealed that cGAS is activated in a length-dependent manner and that cGAS dimers form a ladder-like networks with DNA over 45 bp in length, which is sufficient for activation of innate immune responses *in vitro* and *in vivo* (Andreeva et al., 2017).

cGAS is a cytoplasmic nucleotidyltransferase, which, upon dsDNA binding, catalyzes the synthesis of cGAMP from GMP and AMP. In turn,

cGAMP binds to and activates the STING adaptor protein, which initiates signaling to induce type I IFN production (Sun et al., 2013). cGAMP also functions as a second messenger for transducing alarm signals to surrounding cells: it is delivered from producing cells to neighboring cells through gap junctions, where it promotes STING activation and antiviral immunity independent of type I IFN signaling (Ablasser et al., 2013). During virus infection and expansion, cGAS-synthesized cGAMP can be packaged into viral particles and extracellular vesicles. The viral particles then deliver cGAMP to target cells such as macrophages and dendritic cells (DCs). This triggers innate immunity and antiviral defenses (Gentili et al., 2015; Xu et al., 2016).

2.4 ISGs

Type I IFNs produced upon pathogen infection protect host cells by inducing the expression of ISGs. Some ISGs mediate antibacterial responses, while others mediate antiviral responses. As already discussed, RIG-I and MDA5 are well-known RNA sensors; however, these factors are also key ISGs that stimulate antiviral responses against hepatitis C virus (HCV), WNV, and Venezuelan equine encephalitis virus (VEEV). It has been proposed that RIG-1 and MDA5 inhibit viral replication by binding to the viral RNA genome (Schoggins et al., 2011). In addition, the RNA-activated protein kinase R (PKR), the tetratricopeptide repeats (IFITs) family protein, oligoadenylate synthase (OAS), and the Moloney leukemia virus 10 (MOV10) protein are also known to bind to pathogenic or endogenous RNA. PKR is activated by RNA having bulges and internal loops. Upon activation, PKR phosphorylates eukaryotic initiation factor 2α (eIF2α), which induces the inhibition of translation and leads to apoptosis (Zhang et al., 2001).

OAS has been identified as an enzyme that senses viral dsRNA. OAS is activated upon viral dsRNA binding and catalyzes the generation of the second messenger, 2′-5′-oligoadenylate (2′-5′A). 2′-5′A activates endoribonuclease L (RNase L), which degrades host and viral RNA (Chebath et al., 1987). Another OAS family member is OASL (oligoadenylate synthetase-like), which promotes antiviral activity by enhancing the sensitivity of RLR activation (Lee et al., 2013; Zhu et al., 2014). MOV10 is a member of the RNA helicase superfamily-1, and is also associated with Argonaute 2 (AGO2), a component of the RNA-induced silencing complex. MOV10 was originally identified as a protein that prevents production of the endogenous Moloney murine leukemia virus infection

in mice (Goodier et al., 2012; Schnieke et al., 1983). Later studies determined that MOV10 is able to reduce the infectivity of HIV-1, simian immunodeficiency virus, and murine leukemia virus (Wang et al., 2010). MOV10 is thought to multifunctional protein that MOV10 binds to polymerase basic protein 2 (PB2) in nucleoprotein (NP) of IAV and inhibits IAV replication which is unnecessary for RNA helicase activity (Zhang et al., 2016a).

3. EXTRACELLULAR NUCLEIC ACID RECOGNITION

3.1 TLRs

TLRs recognize many types of PAMPs, including lipids, lipoproteins, proteins, and nucleotides. The TLR family comprises 10 members (TLR1–TLR10) in humans and 12 (TLR1–TLR9, TLR11–TLR13) in mice. TLRs are composed of an extracellular domain with leucine-rich repeats (LRRs) that mediates the recognition of PAMPs, a transmembrane domain, and a cytoplasmic Toll/IL-1 receptor (TIR) domain that initiates downstream signaling. The TLR family can be divided into two subgroups: TLRs that localize to the cell surface and TLRs that reside in intracellular compartments such as endosomes, lysosomes, and endolysosomes. Each subgroup recognizes distinct PAMPs. For example, the nucleic acid-sensing TLRs exclusively localize intracellularly; TLR3, TLR7, TLR8 and TLR13 recognize RNA, whereas TLR9 recognizes DNA. Binding of TLR to pathogenic nucleic acids induces an association with a specific set of TIR domain-containing adaptors, such as MyD88 and TRIF, which activates the transcription factors NF-κB and the interferon regulatory factor family (IRFs). Transcription factor activation then induces the production of type I IFN and inflammatory cytokines. Although different TLRs bind to distinct synthetic ligands, their sensitivity to microbial components overlaps. TLRs are highly expressed on innate immune cells such as macrophages and DCs, which are professional antigen presenting cells that produce inflammatory cytokines and type I IFN. One of these TLRs, TLR13, has recently been shown to recognize a 23S ribosomal rRNA sequence that is the binding site of macrolide, lincosamide, and streptogramin group antibiotics (including erythromycin) in bacteria (Oldenburg et al., 2012). However, other intracellular nucleic acid sensors, such as cGAS and RLRs, are expressed in a variety of cell types including epithelial cells, macrophages and DCs. Therefore, the cooperative recognition of invaded pathogens by distinct receptors is important in triggering a robust innate immune response.

3.2 TLR9

TLR9 was first identified as a DNA sensing receptor expressed in professional innate immune cells such as DCs and macrophages. TLR9 preferentially binds to hexamers containing unmethylated CpG (cytosine-phosphate-guanine dideoxynucleotide) motifs (Hemmi et al., 2000). Studies on TLR9-deficient mice have shown that TLR9 acts as a sensor for DNA viruses such as cytomegalovirus (MCMV), HSV-1 (Hochrein et al., 2004), HSV-2 (Lund et al., 2003), and adenovirus (Zhu et al., 2007) in DCs. However, innate immune recognition of these viruses in non-DCs is dependent on cytosolic DNA sensing of viral DNA and is TLR-independent.

Structural analysis of the TLR9 extracellular domain bound to a CpG-DNA 12-mer indicated that TLR9 and CpG-DNA form a symmetric complex with 2:2 stoichiometry, and CpG-DNA was found to bind to both protomers in the TLR9 dimer (Ohto et al., 2015). Investigation of the optimal DNA sequence motifs for TLR9 binding and activation suggested that TLR9 has an additional DNA-binding site to enhance its activation (Pohar et al., 2015a,b). A recent structural study confirmed that TLR9 has a second DNA-binding site that binds to DNA containing cytosine at the second position from the 5′ end (5′-xCx DNA), which cooperatively promotes the dimerization and activation of TLR9 (Ohto et al., 2018).

3.3 TLR3

TLR3 detects double-stranded RNA (dsRNA) and its synthetic analogue, polyinosinic-polycytidylic acid (poly I:C) (Alexopoulou et al., 2001). TLR3-deficient mice are susceptible to ssRNA viruses, such as WNV (Daffis et al., 2008), Semliki Forest virus (Schulz et al., 2005), and EMCV (Hardarson et al., 2007) as well as DNA viruses, such as MCMV (Tabeta et al., 2004) and HSV-1 (Zhang et al., 2007). TLR3 deficiency in humans also causes an increase in HSV-1 infection rates (Zhang et al., 2007).

Structural analysis of the mouse TLR3 ectodomain in complex with dsRNA indicated that TLR3 forms a homodimer with a flat horseshoe-like shape, and positively charged residues in the ectodomains of the two TLR3 protomers each bind the sugar-phosphate backbone of one dsRNA ligand (Liu et al., 2008). The positively charged residues of the ligand binding sites in TLR3 are in two discrete regions near the N- and C-termini of the horseshoe. The ligand binding sites of TLR3 are separated by approximately 120 Å, which is equivalent to dsRNA of approximately 45 bp in length, the minimal length that has been determined for stable binding of TLR3 to dsRNA.

3.4 TLR7 and TLR8

TLR7 and TLR8 recognize single-stranded RNA molecules (ssRNAs) (Diebold et al., 2004; Heil et al., 2004; Lund et al., 2004). Human TLR7, TLR8, and mouse TLR7 also recognize imidazoquinoline derivatives such as imiquimod (R837), resiquimod (R848), and guanine analogues, whereas mouse TLR8 does not. Cells derived from TLR7-deficient mice are unable to induce cytokine production in response to ssRNA viruses such as IAV, VSV, and HIV-1 (Hemmi et al., 2002; Lund et al., 2004). In addition, TLR7 detects bacterial ssRNAs from strains such as Group B *Streptococci*. However, it is not able to sense ssRNAs from other bacteria such as *Listeria monocytogenes* and Group A *Streptococci* (Mancuso et al., 2009). TLR7 is predominantly expressed in plasmacytoid DCs (pDCs) and is involved in the robust expression of IFNα in both humans and mice.

Structural analysis of TLR7 indicated that it forms an m-shaped dimer with two binding sites, which act as a dual receptor for ssRNA and guanosine. Binding of ssRNA to TLR7 enhances the affinity of the guanosine binding site for its ligand. The specific binding of both ligands to TLR7 is crucial for its dimerization and activation (Zhang et al., 2016b). Conversely, synthetic agonists for TLR7 (R837 and R848) and TLR8 (CL097, CL075 and R848) can, in isolation, directly bind and induce dimer formation of their respective receptors (Tanji et al., 2013; Zhang et al., 2016b) (Fig. 1).

4. MODIFICATIONS ENABLING DNA DISCRIMINATION

DNA methylation is utilized by bacterial restriction and modification systems to allow bacteria to distinguish between self and non-self-DNA. The mammalian genome contains cytosine (C) and guanosine (G) enriched regions, where the C and G bases are separated by a single phosphate group. This structural feature is known as a CpG motif, which is shorthand for 5′-C-phosphate-G-3′. Cytosine nucleotides in CpGs are commonly methylated by methyltransferases, and 70–80% of CpG sites in mammals are methylated. In contrast, the methylation levels of CpG sites in bacterial and viral genomes are significantly lower. Unmethylated CpG nucleotides are recognized by TLR9; therefore, methylation-based DNA modification is a well-established system that allows distinction between self and non-self-nucleic acids (Hemmi et al., 2000).

The oxidized base 8-hydroxyguanosine (8-OHG), a marker of DNA oxidative damage, promotes cytosolic immune recognition by decreasing

its susceptibility to 3′ repair exonuclease 1 (TREX1)-mediated degradation. Reactive oxygen species (ROS) or UV exposure are responsible for the generation of 8-OHG, which stimulates the production of UV-exposed skin lesions in lupus-prone mice and is abundant in lupus-induced skin lesions in humans (Gehrke et al., 2013).

In addition to DNA modifications, host cells have also evolved DNA-modulating proteins that directly or indirectly regulate their defense against viruses and suppress non-coding endogenous retrotransposons and retrovirus elements (Fig. 2).

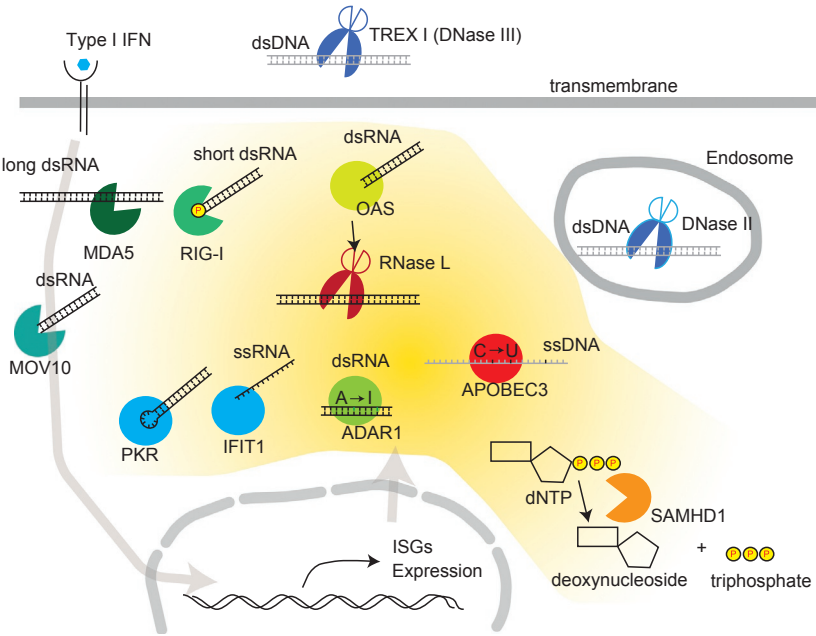

Fig. 2 Regulation of nucleic acid-related restriction by ISGs. Released type I IFNs induce various types of ISGs expression in surrounding cells. ISG expression protects cells from viral and bacterial infections. RIG-I and MDA5 work as a receptor and a viral restriction factor by binding to short dsRNAs and long dsRNAs, respectively. PKR binds to RNAs that have bulges and internal loops, MOV10 binds to dsRNAs, and IFIT1 binds to ssRNAs. OAS binds to dsRNAs and generates 2′-5′A to activate RNase L. APOBEC3 catalyzes the deamination of cytidine (C) to uridine (U) in ssDNA substrates. ADAR catalyzes the conversion of adenosine (A) to inosine (I) in dsRNA substrates. SAMHD1 is a triphosphohydrolase that converts deoxynucleoside triphosphates to deoxynucleoside and triphosphate, which reduces cellular dNTP levels. TREX1 (DNase III) degrades dsDNAs in extracellular spaces, and DNase II degrades endosomal dsDNAs derived from the macrophage engulfment of dead cells.

4.1 APOBEC3

Apolipoprotein B editing complex 3 (APOBEC3) family members are cytidine deaminases that catalyze the removal of an amino group from cytidine (C), forming uridine (U) in single-stranded DNA substrates. The human genome encodes seven APOBEC3 (A3) proteins. APOBEC3G (A3G) was initially identified as a suppressor of HIV-1 infectivity (Doyle et al., 2015). During synthesis of the first (minus) retroviral DNA strand, APOBEC-catalyzed deamination of cytosine (C) residues results in the accumulation of excessive levels of uracil (U). Subsequently, Uracil (U) is recognized as thymine (T) by the viral reverse transcriptase and adenine (A) is incorporated into the newly synthesized second (plus) DNA strand rather than guanine (G). Therefore, mutation levels in HIV-1 genomes are increased following replication; the consequential augmentation of mutant functional proteins results in a decrease in viral infectivity (Doyle et al., 2015).

Regions of non-coding endogenous retrotransposons and retrovirus elements in the human genome are remnants of ancestral retroviral germ line infections. The expansion and transposition of endogenous retroviruses are believed to induce cancers, autoimmune diseases, and other disorders in the host. Most retroelements have lost their ability to replicate because of the accumulation of inactivating mutations, but several, including some murine intracisternal A-particles (IAP) and MusD sequences, are still mobile. A3G plays a crucial role in restricting their retrotransposition (Esnault et al., 2005). The accumulation of endogenous viruses upon A3G suppression has been shown to induce type I IFN expression though a STING-mediated DNA sensing pathway (Stavrou et al., 2015).

4.2 SAMHD1

The sterile alpha-motif (SAM) and histidine-aspartate (HD) domain-containing protein 1 (SAMHD1) was identified as a factor that inhibits HIV-1 infection in myeloid cells (Laguette et al., 2011). SAMHD1 is a potent dNTP triphosphohydrolase that converts deoxynucleoside triphosphates (dNTPs) into their corresponding deoxynucleoside and inorganic tripolyphosphate moieties (Goldstone et al., 2011). SAMHD1 decreases the concentration of intracellular dNTPs in myeloid cells to a level that is unable to support reverse transcription, establishing a cellular state that is not permissive to HIV-1 infections (Lahouassa et al., 2012). Since DNA viruses also utilize cellular dNTPs, SAMHD1 additionally limits the

replication of DNA viruses such as vaccinia virus and HSV-1 in myeloid target cells (Hollenbaugh et al., 2013).

As well as suppressing HIV-1 propagation, SAMHD1 was originally identified as a binding protein for the HIV-1 accessory protein, virion-associated protein (Vpr). HIV-2 genomes also express the accessory protein Vpx, which augments the ability of HIV-2 to infect myeloid cells and was initially proposed to counteract SAMHD1 (Sharova et al., 2008). Later studies showed that Vpx binds to SAMHD1 and induces its degradation (Hrecka et al., 2011; Laguette et al., 2011).

5. MODIFICATIONS ALLOWING RNA DISCRIMINATION

RNA classes include transfer RNA (tRNA), messenger RNA (mRNA), and non-coding RNA (ncRNA). Although over 100 different types of RNA modifications have been identified across all living organisms, little is known about their resultant functions. The more abundant host RNA modifications have been elucidated, which include pseudouridine (ψ) and 2′-*O*-methylation (2′OMe) in tRNA, and N^6-methyladenosine (m^6A) and 5-methyl-cytidine (m^5C) in mRNA. These modifications elicit various functional roles such as translation, localization, and stability. Among these, it is well known that discrimination of self and non-self-RNA is dependent upon naturally occurring modifications at the 5′ end of RNA. Mammalian cell mRNAs usually have a 5′ cap structure, called cap 0 (m7Gppp) that consists of a guanine nucleotide that is connected to mRNA via a reverse 5′–5′-triphosphate bridge. In addition, the guanosine is methylated at the N7 position. The methylated guanosine cap residues of mRNAs are recognized and bound by the eukaryotic translation initiation factor 4E (eIF4E) to recruit transcripts to the ribosome and initiate translation. In higher eukaryotes, the mRNA cap is further modified by ribose 2′-*O*-methylation on the first and sometimes second nucleotides adjacent to the cap, forming cap 1- or cap 2-mRNA (Werner et al., 2011).

5.1 2′-*O*-Methyltransferase

N7 methylation is important for various processes including transcriptional elongation, poly-adenylation, splicing, and nuclear export. Although the functional role of 2′-*O*-methylation in the cap 1 and cap 2 structures on mRNA is not generally understood, other studies have indicated that methylation serves as a molecular signature to distinguish self and non-self mRNA

(Daffis et al., 2010; Zust et al., 2011). Many viruses that replicate in the cytoplasm (for example, picornavirus, flavivirus, coronavirus, and poxvirus) encode their own RNA modification enzymes, including 2′-*O*-methyltransferase. The importance of viral RNA modifications in replication has been supported by studies that the infection of viruses lacking 2′-*O*-methyltransferase activity induces higher type I IFN expression, and unmodified genomic RNA was recognized by the host RNA sensor, MDA5 (Zust et al., 2011). The functional importance of 2′-*O*-methyltransferase activity for the infectivity of RNA viruses was also verified by studies on dengue virus (DENV) (Zust et al., 2018), Middle East respiratory syndrome coronavirus (MERS-CoV) (Aouadi et al., 2017), and ronivirus (Zeng et al., 2016). These viruses also encode 2′-*O*-methyltransferase and its disruption also causes type I IFN induction and virus elimination from the host following infection. Together, these results indicate that RNA viruses have evolved to encode their own methyltransferases that mimic host RNA methylation patterns to avoid recognition by the host's innate immune system.

5.2 ADAR

ADARs (adenosine deaminases acting on RNA) catalyze the conversion of adenosine (A) to inosine (I) in double-stranded RNA (dsRNA) substrates. Such "A-to-I editing" alters the coding of RNA, as inosine is read as guanosine (G) instead of adenosine by ribosomes during translation, leading to the production of non-functional proteins. In humans, two autoimmune disorders, Dyschromatosis Symmetrica Hereditaria (DSH) and Aicardi-Goutières Syndrome (AGS), are attributed to specific mutations that have been mapped to the *Adar1* gene (Rice et al., 2012). Furthermore, *Adar1* inducible knockout (KO) mice exhibit a high level of IFN production in neuronal tissues, a key characteristic of AGS. In healthy cells, ADAR1-mediated nucleotide conversions are believed to be important for the suppression of viral replication and, more importantly, endogenous RNA recognition by the RNA sensor, MDA5. Correspondingly, mutations in either MDA5 or MAVS rescue the embryonic lethal phenotype of *Adar1* KO mice (Liddicoat et al., 2015; Mannion et al., 2014; Pestal et al., 2015).

Approximately half of the mammalian genome is composed of non-coding retrotransposons, such as SINEs (short interspersed nuclear elements) and Alu elements, which typically form dsRNA duplexes (Lander et al., 2001; Waterston et al., 2002). Retrotransposons are subjected to extensive

A-to-I RNA editing by ADAR (Ramaswami et al., 2012). It is possible that the location of repetitive elements determines their immunogenicity. Retrotransposons located within introns do not persist in the cytosol and therefore are unable to activate MDA5. Repetitive elements in 3′ UTRs, although rare, can be retained and form duplexes to activates MDA5. Editing of self-dsRNA by ADAR1 generates multiple I-U mismatches to avoid MDA5 recognition (Berke et al., 2012; Wu et al., 2013). In the absence of ADAR1 activity, long dsRNA stem loops can activate MDA5. However, A-to-I editing also alters the RNA secondary structure, which may lead to recognition by innate immune receptors (Liddicoat et al., 2015; Pestal et al., 2015). Recent data have shown that ADAR1 predominantly edits Alu elements in RNA polymerase II (pol II)-transcribed mRNAs, but not those transcribed by pol III in human cells (Chung et al., 2018), and A-to-I conversion in Alus suppresses MDA5 activation *in vitro* (Ahmad et al., 2018).

6. ENDOGENOUS NUCLEIC ACIDS AS DAMPs

Apoptosis is a process of programmed cell death that occurs in multicellular organisms, where cellular components, such as RNA and DNA, are completely degraded. However, during non-apoptotic cell death events, including necrosis, intracellular contents are released into the surrounding tissues. Released endogenous RNA and DNA are potent inducers for the activation of innate immune signaling as they can bind to both endogenous and exogenous nucleic acid receptors. Endogenous nucleic acids are also released as damage-associated molecular patterns (DAMPs) during stress conditions such as chemotherapy, UV, and radiation that also induce non-apoptotic cell death.

6.1 Stress-Induced Release of Nucleotides

Radiation damage elicits the production of dsRNA, which activates TLR3 and causes inflammatory diseases in various tissues such as the skin and small intestine (Bernard et al., 2012; Takemura et al., 2014, 2018). Intracellular DNA is also released upon cellular stress. Chemicals such as mutagenic 7,12-dimethylbenz(a)anthracene (DMBA), cisplatin, and etoposide induce cytosolic leakage of nuclear DNA, which intrinsically induces type I IFN expression through the cGAS-STING pathway (Ahn et al., 2014). Mitochondrial (mt) DNA released into the cytosol upon mitochondrial stress

is sensed by cGAS (West et al., 2015). In addition, DNA released by tumor chemotherapy and radiation therapy acts as an adjuvant that activates the cGAS-STING pathway by releasing type I IFN from DCs (Deng et al., 2014; Woo et al., 2014). Such inductions of the inflammatory response are further facilitated by nucleotide binding proteins that enhance DNA incorporation into immune cells and protect it from nucleases. Inflammatory diseases in mice and humans are induced when released intracellular DNA and RNA, including endogenous retroelements and non-coding RNA, cannot be adequately cleared.

6.2 The Role of Nucleotide Binding Proteins in Inflammation

Various nucleotide binding proteins have been identified as factors that exacerbate inflammation. Most nucleotide binding proteins are expected to protect DNA from degradation by DNase and RNase in the extracellular fluid and facilitate its incorporation into innate immune cells. High mobility group box 1 (HMGB1) is a nuclear protein that binds to DNA and participates in processes such as transcription and repair. However, when it is released in complex with DNA in response to cell damage or inflammation, it acts as a potent inflammatory cytokine. HMGB1/DNA complexes facilitate incorporation into innate immune cells by binding to RAGE (receptor for advanced glycosylation end) on the surface of B-cells and DCs, which leads to the recruitment of TLR9 and potentiates type I IFN expression (Yanai et al., 2009). Another report has demonstrated that HMGB1 and its related family members, HMGB2 and HMGB3, bind to DNA and these complexes activate TLRs. In addition, a recent finding indicated that HMGB1 is able to induce the formation of U-turns and bends in dsDNA that nucleate cGAS dimers, leading to the formation of cGAS ladder-like networks with DNA (Andreeva et al., 2017). Another factor that can convert self-DNA into a pathogenic ligand is LL37, which is the active form of cathelicidin, an endogenous anti-microbial peptide that is produced by keratinocytes and neutrophils. LL37 has been found to bind to self-DNA released from necrotic cells in psoriatic lesional skin. The LL37-DNA complex forms condensed structures that protect self-DNA from nuclease degradation. The LL37-DNA complex is then translocated into the endocytic compartments of pDCs, inducing TLR9 activation and resulting in a sustained type I IFN response (Lande et al., 2007, 2011). The production of LL37 is associated with the onset of inflammatory diseases such as Systemic Lupus Erythematosus (SLE).

Cells also secrete extracellular vesicles called exosomes. Exosomes are endosomal membrane vesicles with a diameter of ~40–150 nm and contain various molecular constituents, including proteins and nucleic acids, from their cells of origin. Nucleic acids in exosomes are also protected from nuclease degradation. Cancer cells release exosomes that contain DNA or RNA. These exosomes are captured by DCs which then induce type I IFN production (Kitai et al., 2017; Nabet et al., 2017).

7. ENDOGENOUS NUCLEOTIDES FACILITATE INFLAMMATION

Mutations in genes encoding SAMHD1, TREX1 (DNase III), DNase II, Ribonuclease (RNase) H2, and ADAR are associated with AGS and chilblain lupus, which are rare early-onset inflammatory diseases characterized by inappropriate immune activation and overproduction of type I IFN (Rice et al., 2009, 2012). In healthy cells, SAMHD1, TREX1, DNase II, RNase H2, and ADAR suppress the accumulation of endogenous extracellular DNA or intracellular RNA derived from non-coding retrotransposons such as SINEs, Alus, long-non coding RNAs (lncRNAs) and circular RNAs (circRNAs).

7.1 Self-DNA Accumulation and Inflammation

SAMHD1 deficient mice show reduced cellular dNTP concentrations and elevation of ISG expression in various cell types, which are similar characteristics exhibited by cells from AGS and SLE patients (Behrendt et al., 2013). However, one study unexpectedly found that SAMHD1 deficient mice show increases in ISG, but no SLE-like phenotype (Rehwinkel et al., 2013).

TREX1 is a 3′ repair exonuclease that digests cytosolic DNA. Mutations in TREX1 cause AGS and chilblain lupus (Crow et al., 2006, 2015; Stetson et al., 2008). The AGS-like symptoms in TREX1 deficient mice are rescued by genetic ablation of cGAS or STING (Gray et al., 2015).

Another major cellular nuclease is DNase II, which localizes in the lysosome and is largely responsible for the clearance of DNA from dead cells and expelled nuclei. *DNase II*$^{-/-}$ mice die in utero, and the embryos become severely anemic by embryonic day 17.5. However, these phenotypes were rescued by crossing with IRF3- or cGAS-deficient mice (Gao et al., 2015; Kawane et al., 2006). DNase II mutations have been found in human patients with inflammatory phenotypes (Rodero et al., 2017).

AGS is also caused by a mutation in RNase H2. Cells deficient in RNase H2 accumulate ribonucleotides within their genomic DNA, which results in single-stranded breaks. This DNA damage leads to activation of the cGAS-STING pathway (Mackenzie et al., 2016; Pokatayev et al., 2016).

7.2 Self-RNA Accumulation and Inflammation

Mutations in ADAR1 are also associated with AGS (Crow et al., 2015). ADAR1 deficiency in mice results in a lethal embryonic phenotype, which is accompanied by substantial expression of type I IFNs and hematopoietic failure (Wang et al., 2000). This embryonic lethality is partially rescued in *Adar1* and *Mavs* double mutants (Liddicoat et al., 2015; Mannion et al., 2014; Pestal et al., 2015). Cells deficient in ADAR1 induce type I IFN production, as self-dsRNA will not contain multiple I-U mismatches, enabling its recognition by MDA5 (Berke et al., 2012; Wu et al., 2013). A deficiency in IPS-1 (MAVS) prevents the recognition of long dsRNAs derived from 3′ UTRs or non-coding retrotransposons in ADAR1 deficient mice. In addition, treatment of cells with DNA methyltransferase inhibitors induces endogenous RNA virus transcription that enhances RLRs signaling; however, this response is decreased twofold in IPS-1 knockout cells (Chiappinelli et al., 2015; Roulois et al., 2015).

The microRNA let-7 is a highly abundant regulator of gene expression at the post-transcriptional level in the central nervous system. Extracellular let-7 activates the TLR7 RNA-sensor and induces neurodegeneration through neuronal TLR7 and is associated with progression of amyotrophic lateral sclerosis (ALS) (Lehmann et al., 2012). MicroRNA-21 is one of the most highly expressed members in various types of cells and has several functions such as cellular differentiation, cancer proliferation and cytokines production. MicroRNA-21 in macrophage reported to be induced by LPS and suppressed cytokines production in macrophages (Sheedy et al., 2010). Other microRNA such as microRNA-135-5p, microRNA-26b and microRNA-29a also reported to be contributed in inflammatory response after LPS stimulation (Li et al., 2016; Tang et al., 2017; Zhang et al., 2015), therefore increase or decrease of microRNA in macrophage and DC may causes the progression of inflammatory disease.

Over the past few years, thousands of lncRNA and circRNA have been identified in mammalian genome and shown to have various functions. Some of lncRNA and circRNA are proposed to regulate innate immune responses during TLR and RLR activation. Several lncRNAs, such as lncRNA-Cox2 and lncRNA-1992, are inducible expressed during innate immune activation and are suggested to regulate cytokines production by

inhibiting regulatory proteins expression (Carpenter et al., 2013; Li et al., 2014). A recent report showed that self-recognition of lncRNA-Lsm3b with RIG-I inhibits RIG-I activation to prevent overproduction of type I IFN for maintenance of immune homeostasis (Jiang et al., 2018). CircRNAs are generated through back splicing and have been postulated to function as microRNA sponges. A recent report indicated that circRNA generated from foreign introns potently stimulates innate immune signaling and inhibits viral infection (Chen et al., 2017), and circRNA biogenesis is directly involved in viral restriction (Li et al., 2017).

8. CONCLUSION

In this review, we have summarized the innate immune sensing mechanisms for nucleic acids as well as antiviral and antibacterial restriction factors that modulate the replication of nucleic acids. Host cells have mechanisms to protect endogenous nucleic acids from unwanted contact with host PRRs. These mechanisms can be subdivided into three categories: the cellular localization of PRRs, nucleic acid modifications, and the degradation of unnecessary nucleic acids. Although retroelements, such as SINE, LINE, Alus, and retrotransposons, are derived from host cells and could potentially initiate an innate immune response via MDA5 and RIG-I recognition, the activation of ADAR1 and SAMHD1 suppresses the recognition and accumulation of these retroelements. Protection against endogenous nucleic acid recognition is also achieved by nucleic acid degradation. TREX1 degrades dsDNA in the extracellular milieu derived from host cells. In addition, DNase II localizes in the lysosome and is largely responsible for the clearance of DNA from dead cells and expelled nuclei. Self-nucleic acids may be released into the extracellular space upon cell necrosis. These are degraded by DNases and RNases before they come into contact with nucleic acid-sensing TLRs in endosomes. In addition, RNA 2′-*O* methylation and CpG-DNA methylation in the host are other important signatures for self-nucleic acid discrimination.

In recent years, our understanding of self and non-self-nucleic acid recognition mechanisms has greatly increased because of advances in structural analyses, *in vitro* experiments, and DNA/RNA sequencing. However, the detailed molecular mechanisms of self-nucleic acid recognition during development, inflammatory diseases or stress conditions are still unclear. Nevertheless, the current accumulation of information regarding nucleic acid discriminatory systems will be applicable for the treatment and management of immunological disorders in the future.

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