Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
CHAPTER THIRTEEN

Intracellular Antiviral Immunity

Maria Bottermann, Leo C. James

MRC Laboratory of Molecular Biology, Cambridge, United Kingdom

Corresponding author: e-mail address: lcj@mrc-lmb.cam.ac.uk

Contents

1. Pattern Recognition Receptors in Antiviral Defense 312
   1.1 Toll-Like Receptors 312
   1.2 C-Type Lectin Receptors 314
   1.3 NOD-Like Receptors 315
   1.4 RIG-I-Like Receptors 316
   1.5 AIM-Like Receptors 318
   1.6 OAS-Like Receptors 319

2. TRIM Proteins in Innate Immunity 320
   2.1 Structure of TRIM Proteins 321
   2.2 Functions of TRIM Proteins in Viral Restriction 322
   2.3 Functions of TRIM Proteins in Innate Immune Regulation 323
   2.4 The Role of TRIM21 in Innate Immunity 326
   2.5 TRIM21 Effector Mechanism 336
   2.6 The Role of TRIM21 in Innate Immune Regulation and Autoimmunity 339

Acknowledgments 341
References 341

Abstract

Innate immunity is traditionally thought of as the first line of defense against pathogens that enter the body. It is typically characterized as a rather weak defense mechanism, designed to restrict pathogen replication until the adaptive immune response generates a tailored response and eliminates the infectious agent. However, intensive research in recent years has resulted in better understanding of innate immunity as well as the discovery of many effector proteins, revealing its numerous powerful mechanisms to defend the host. Furthermore, this research has demonstrated that it is simplistic to strictly separate adaptive and innate immune functions since these two systems often work synergistically rather than sequentially.

Here, we provide a broad overview of innate pattern recognition receptors in antiviral defense, with a focus on the TRIM family, and discuss their signaling pathways and mechanisms of action with special emphasis on the intracellular antibody receptor TRIM21.
ABBREVIATIONS

AIM2  absent in melanoma 2
ALR   AIM-like receptor
AP-1  activator protein 1
ARF   ADP-ribosylation like
ASC   apoptosis-associated speck-like protein
BIR   baculoviral inhibitory repeat-like domain
BVDV  bovine viral diarrhea virus
CARD  caspase activation and recruitment domain
CDR   complementarity-determining region
cGAMP cyclic guanosine monophosphate–adenosine monophosphate
cGas  cyclic GMP–AMP synthase
CIITA class II major histocompatibility complex transactivator
CLR   C-type lectin receptors
CpG   deoxycytidylate-phosphate–deoxyguanylate
CypA  cyclophilin A
DAI   DNA-dependent activator of IFN-regulatory factors
DAMP  damage-associated molecular patterns
DAXX  death domain-associated protein
DC    dendritic cell
DC-SIGN DC-Specific Intercellular adhesion molecule-3-Grabbing Nonintegrin
DDX   DEAD box helicase
DENV  Dengue virus
DExD/H-box DEAD/DEAH box helicases
DHX   DEAH box helicase
DRP1  dynamin-related protein 1
DUB   deubiquitinase
EBV   Epstein–Barr virus
EIAV  equine infectious anemia virus
EMCV  encephalomyocarditis virus
Fc    fragment crystallizable
FcR   Fc receptor
FcRn  neonatal Fc receptor
FCV   feline calcivirus
FMDV  foot-and-mouth disease virus
FMF   familial Mediterranean fever
FN3   fibronectin type 3
GSK3  glycogen synthase kinase 3
hAdV  human adenovirus
HCMV  human cytomegalovirus
hCoV  human coronavirus
HCV   hepatitis C virus
HIV   human immunodeficiency virus
HRV   human rhinovirus
HSV   herpes simplex virus
HTLV  human T-lymphotropic virus
IAV   influenza A virus
| Abbreviation | Full Form |
|--------------|-----------|
| IBV          | influenza B virus |
| IFI16        | interferon-γ-inducible protein 16 |
| IFN          | interferon |
| IRF          | interferon regulatory factor |
| ISG          | interferon-stimulated gene |
| IkB          | inhibitor of kappa B |
| JEV          | Japanese encephalitis virus |
| JNK          | c-Jun N-terminal kinases |
| LGP2         | laboratory of genetics and physiology 2 |
| LPS          | lipopolysaccharide |
| LRR          | leucine-rich repeat |
| LRRFIP1      | leucine-rich repeat flightless-interacting protein 1 |
| MATH         | meprin and TRAF homology |
| MAV-1        | mouse adenovirus 1 |
| MAVS         | mitochondrial antiviral signaling |
| MCMV         | mouse cytomegalovirus |
| MDA5         | melanoma differentiation-associated gene 5 |
| MEF          | mouse embryonic fibroblast |
| MLV          | murine leukemia virus |
| MMTV         | mouse mammary tumor virus |
| MNDA         | myeloid cell nuclear differentiation antigen |
| MV           | measles virus |
| Myd88        | myeloid differentiation primary response gene 88 |
| NAP-1        | NF-κB-activating kinase-associated protein |
| NDV          | Newcastle disease virus |
| NF-κB        | nuclear factor κB |
| NLR          | NOD-like receptor |
| N-MLV        | N-tropic murine leukemia virus |
| NOD          | nucleotide-binding and oligomerization domain |
| OAS          | oligoadenylate synthetase |
| OLR          | OAS-like receptor |
| PAMP         | pathogen-associated molecular pattern |
| PHD          | plant homeodomains |
| PML          | promyelocytic leukemia protein |
| PRR          | pattern recognition receptor |
| PYD          | pyrin domain |
| PYHIN1       | pyrin and HIN domain-containing protein 1 |
| RGNNV        | red-spotted grouper nervous necrosis virus |
| RIG-I        | retinoic acid-inducible gene I |
| RING         | really interesting new gene |
| RIP          | receptor-interacting serine/threonine protein |
| RIPK         | RIP kinase |
| RLR          | RIG-I-like receptor |
| ROS          | reactive oxygen species |
| RT           | reverse transcription |
| SeV          | Sendai virus |
| SGIV         | Singapore grouper iridovirus |
PATTERN RECOGNITION RECEPTORS IN ANTIVIRAL DEFENSE

Pattern recognition receptors (PRRs) are upstream factors that initiate innate immune signaling in response to viral infection and induce an antiviral state. Rather than recognizing residue-specific epitopes of pathogens, as demonstrated by the adaptive immune response, PRRs bind to conserved patterns uniquely associated with pathogens, termed pathogen-associated molecular patterns (PAMPs) (Odendall and Kagan, 2017). PRRs are currently classified into six families according to structural and domain features: Toll-like receptors (TLRs), NOD-like receptors (NLRs), C-type lectin receptors (CLRs), RIG-I-like receptors (RLRs), OAS-like receptors (OLRs), and AIM-like receptors (ALRs) (Kagan and Barton, 2016). PRRs provide comprehensive immune surveillance as they not only recognize a large number of varied PAMPs but are also widely expressed and localize to the diverse cellular spaces that come into contact with viruses during infection. TLRs can recognize viral envelope constituents at the cell surface and viral genomes in endolysosomes, whereas in the cytosol, the viral genome is detected by NLRs, RLRs, ALRs, and OLRs.
1.1 Toll-Like Receptors

Toll-like receptors were the first PRRs discovered and are thus well studied. We will only give a brief overview as they have been extensively reviewed before (Akira and Takeda, 2004; Kawai and Akira, 2010; Kawasaki and Kawai, 2014; Lester and Li, 2014; Odendall and Kagan, 2017; Takeda and Akira, 2005; Thompson et al., 2011). The TLR family has 10 members in humans, TLR1–10, of which TLR1, TLR2, TLR4, TLR5, and TLR6 are expressed at the plasma membrane, while TLR3, TLR7, TLR8, and TLR9 are located in endosomes (Thompson et al., 2011). Although they can be found in diverse tissues (for instance, in intestinal epithelium) and a variety of immune cells, TLRs are mainly expressed in professional antigen-presenting cells (B cells, DCs, and macrophages). Why they display restricted tissue expression is unclear but may reflect that their role is in immune surveillance rather than the detection of infection per se. As professional cell sensors they are well placed to both activate the innate cellular response and promote adaptive immunity. Many TLRs were first discovered as receptors for bacterial PAMPs. For instance, TLR4 is the primary receptor for bacterial lipopolysaccharide (LPS) (Lu et al., 2008), while TLR2 is activated by bacterial lipoproteins such as lipoteichoic acid (Hashimoto et al., 2006; Oliveira-Nascimento et al., 2012). Signal transduction through TLR2 also requires heterodimerization with either TLR1 or TLR6 and helps broaden ligand specificity (Farhat et al., 2007; Kang et al., 2009; Schenk et al., 2009). TLR5 is largely responsible for the innate immune response to flagellin (Hayashi et al., 2001). This pattern suggests that plasma membrane-associated TLRs are mainly responsible for the detection of invading bacteria. However, more recently, it has been shown that TLR4 and TLR2 can produce a signaling response upon infection with RSV (Murawski et al., 2009; Rallabhandi et al., 2012), and TLR2 with mouse mammary tumor virus (MMTV) and murine leukemia virus (MLV) (Villano et al., 2014), measles virus (MV) (Bieback et al., 2002), and human cytomegalovirus (HCMV) (Compton et al., 2003). These studies demonstrate that plasma membrane-bound TLRs can also sense cell-bound viruses. However, although direct binding is suggested, it is unclear how such diverse ligands are detected and what the mechanism of activation is. Of the endosomal TLRs, TLR3 has been shown to recognize dsRNA and mediate a protective response against poliovirus, coxsackievirus, and herpes simplex virus 1 (HSV1), all of which use dsRNA intermediates in their life cycle (Tatematsu et al., 2014). Additionally, TLR3 is capable of recognizing stem loop structures in ssRNA (Tatematsu et al., 2013).
TLR7 and TLR8 can both sense long ssRNA, with TLR7 also capable of recognizing specific motifs in short dsRNA (Thompson et al., 2011). They have been implicated in the response to RNA viruses such as influenza (Diebold, 2004; Lund et al., 2004), coxsackie B virus (Triantafilou et al., 2005), vesicular stomatitis virus (VSV) (Lund et al., 2004), and hepatitis C virus (HCV) (Lee et al., 2015; Wang et al., 2011a). Finally, TLR9 is capable of recognizing unmethylated deoxycytidylate–phosphate–deoxyguanylate (CpG) motifs, which are common in viral and bacterial DNA, but do not occur in mammalian DNA (Hemmi et al., 2000). TLR9 is important in the defense against DNA viruses such as human adenovirus (hAdV) (Zhu et al., 2007), mouse cytomegalovirus (MCMV) (Krug et al., 2004), and Epstein–Barr virus (EBV) (Fiola et al., 2010). The role of TLR10 has not been elucidated yet; however, there is evidence that it functions as a negative regulator of TLR signaling and thus is an inhibitory TLR (Jiang et al., 2016; Oosting et al., 2014), while one study reported that it is involved in the immune response against influenza virus (Lee et al., 2014).

All activating TLRs, apart from TLR3, signal through the adapter molecule myeloid differentiation primary response gene 88 (MyD88), which results in the activation of NF-κB and AP-1 signaling pathways. Mice deficient in MyD88 primarily succumb to bacterial rather than viral infection, in common with other immunodeficiencies such as agammaglobulinemia (Villano et al., 2014). TLR3 and TLR4 have been shown to signal through a TIR-domain-containing adapter-inducing interferon-β (TRIF)-dependent pathway, which also results in the activation of IRF, NF-κB, and AP-1 signaling pathways (Kawasaki and Kawai, 2014).

1.2 C-Type Lectin Receptors

CLRs are mainly expressed on dendritic cells but also on other myeloid cells. They are characterized by a carbohydrate recognition domain which allows them to bind pathogen-associated carbohydrate motifs (Geijtenbeek and Gringhuis, 2009). This makes them especially important in the defense against bacteria and fungi (Drummond and Brown, 2013). A well-known CLR is DC–Specific Intercellular adhesion molecule–3–Grabbing Nonintegrin (DC-SIGN), which interacts with mannose and fucose residues on pathogen surfaces. It has since been shown that DC-SIGN can act as a receptor for numerous enveloped viruses including HIV (Geijtenbeek et al., 2000), dengue virus (DENV) (Tassaneentrithep et al., 2003), and MV (de Witte et al., 2006), through interactions with their envelope glycoproteins, exemplifying
how viruses can directly exploit the host’s defense mechanisms. Since CLR
are exclusively expressed on the cell surface, they will not be discussed further
here but have been excellently reviewed (Dambuza and Brown, 2015;
Drummond and Brown, 2013; Geijtenbeek and Gringhuis, 2009; Hoving
et al., 2014; Osorio and Reis e Sousa, 2011; Sancho and Reis e Sousa, 2012).

1.3 NOD-Like Receptors

Nucleotide-binding and oligomerization domain (NOD)-like receptors
(NLRs) are cytosolic PPRs that mediate responses to a diverse range of PAMPs
such as LPS (Kayagaki et al., 2013), flagellin (Kayagaki et al., 2013), and viral
RNA (Allen et al., 2009; Li et al., 2015), but also host cell and environmental
factors such as cholesterol crystals (Duewell et al., 2010) and reactive oxygen
species (ROS) (Kanneganti, 2010). They are characterized by a central
NACHT domain as well as a C-terminal leucine-rich repeat (LRR) and can
be divided into five groups based on their N-terminal domain: NLRA (acidic
activation domain), NLRB (baculoviral inhibitory repeat-like domain (BIR)),
NLRC (caspase activation and recruitment domain (CARD)), NLRP (pyrin
domain (PYD)), and NLRX. Activation of NLRs can result in four different
effector functions: inflammasome activation, activation of innate immunity sig-
naling pathways, transcriptional regulation, and autophagy. Inflammasome for-
mation is mediated through members of NLRP and NLRC and results in
recruitment of Caspase-1 and the release of the inflammatory cytokines
IL-1β and IL-18, as well as pyroptosis. Members of NLRP lack a CARD
domain; they depend on the adaptor molecule apoptosis-associated speck-like
protein (ASC), which contains a C-terminal CARD domain, for recruitment
of Caspase-1. While members of the NLRC family, such as NLRC4, have a
CARD domain and thus do not require ASC for direct interaction with
Caspase-1, ASC is required for full activation and robust IL-1β release (Broz
et al., 2010; Lamkanфи and Dixit, 2014). Inflammasomes, especially NLRP3
inflammasomes, play an important role in the immune response to many
viruses, including influenza A virus (IAV) (Ichinohe et al., 2009, 2010), hAdV
(Barlan et al., 2011), encephalomyocarditis virus (EMCV), VSV (Rajan et al.,
2011), and rabies virus (Lawrence et al., 2013). Inflammasome activation by
hAdV can be caused by plasma membrane and endosomal damage (Barlan
et al., 2011), both of which occur during adenoviral infection (Luisoni
et al., 2015), and are known triggers for the NLRP3 inflammasome
(Hornung and Latz, 2010; Muñoz-Planillo et al., 2013). Viral RNA (Allen
et al., 2009) as well as RNA analogues such as polyI:C (Rajan et al., 2010)
can also activate the NLRP3 inflammasome; however, the mechanism is not yet fully elucidated. It has been suggested that recognition of viral RNA results in the activation of the RIPK1–RIPK3 complex which stimulates the mitochondria-associated GTPase DRP1, thus promoting mitochondrial damage and the production of ROS (Wang et al., 2014), another known trigger of the NLRP3 inflammasome (Abais et al., 2015; Heid et al., 2013). Other studies have identified DDX19A (Li et al., 2015) and DHX33 (Mitoma et al., 2013) as cytosolic RNA sensors that can interact with NLRP3, thus bridging viral RNA and the NLRP3 inflammasome. For a comprehensive overview of the role of inflammasomes in viral infection, see the following reviews: Franchi et al. (2008), Guo et al. (2015), Kanneganti (2010), Kim et al. (2016), Lamkanfi and Dixit (2014), and Thompson et al. (2011).

Members of NLRC are capable of activating immune signaling pathways in response to PAMP recognition. The most well known are NOD1 and NOD2 (NLRCs), which recognize bacterial peptidoglycans and activate both NF-κB and AP-1 signaling pathways (Franchi et al., 2009). NOD2 can also recognize viral ssRNA and mediate the production of IFNβ through MAVS (mitochondrial antiviral signaling)-dependent IRF3 activation (Sabbah et al., 2009). NLRC4 is predominately a potent inflammasome activator in response to bacterial ligands. Here, neural apoptosis inhibitory proteins (NAIPs, members of the NLRB family) act as receptors for bacterial PAMPs such as flagellin (NAIP5) or the type three secretion system (NAIP2), with NLRC4 being the adapter recruiting Caspase-1 to the NLRC4 inflammasome (Zhao and Shao, 2015; Zhao et al., 2011).

NLRA has only one member, CIITA, which is unique in that it can act as a transcription factor in the activation of MHC class II genes (Kim et al., 2016).

Finally, NLRX has also only one member, NLRX1, whose N-terminal domain does not fall within the four existing groups but instead carries a mitochondrial targeting sequence (Moore et al., 2008). While its role has not been fully elucidated yet, there is evidence that it is involved in negatively regulating innate immune signaling pathways (Allen et al., 2011; Moore et al., 2008; Parvatiyar and Cheng, 2011; Xia et al., 2011); however, there are also data, implicating that NLRX-1 increases ROS and thus increases NF-κB- and JNK-dependent signaling.

1.4 RIG-I-Like Receptors

Retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs) are PRRs present in all nucleated cells, where they are poised to detect cytosolic viral
RNAs (Ireton and Gale, 2011). This expression pattern is in clear contrast to TLRs, CLR, and NLRs and may reflect that RLRs are true sensors of infection rather than part of immune sampling and surveillance. This can also be discerned from the species of viral ligand that they detect. It has been clearly shown for influenza that it is progeny rather than incoming genomes that are detected by the RLR RIG-I (Rehwinkel et al., 2010). Thus, it is replicating virus and not merely inert particles that are being sensed. The RLR family has two other known members: melanoma differentiation-associated gene 5 (MDA5), and laboratory of genetics and physiology 2 (LGP2), which, like RIG-I, possess a central ATPase-containing DExD/H-box helicase domain (Dixit and Kagan, 2013). However, only RIG-I and MDA5 have N-terminal CARDs which are essential for initiation of signal transduction. LGP2 is thus thought to modulate RIG-I and MDA5 signaling instead of initiating signaling itself (Thompson et al., 2011). RIG-I and MDA5 both recognize viral RNA; however, while RIG-I senses small dsRNA that is characterized by a 5′-triphosphate group and a 3′-polyuridine-rich region, MDA5 binds long ssRNA and oligomerizes along its length (Kagan and Barton, 2014; Wu et al., 2013a). Binding of RNA to MDA5 or RIG-I leads to interaction of the N-terminal CARD with the CARD of MAVS, which is mainly located in the outer mitochondrial membrane. Upon activation, MAVS multimerizes, forming the “MAVS signalosome” and initiating downstream activation of NF-κB and IRF3 (Koshiba, 2013). Both MDA5 and RIG-I are tightly regulated through constitutive phosphorylation of their CARDs, which prevents interaction with MAVS. Upon viral infection, both sensors are rapidly dephosphorylated which results in downstream immune signaling (Gack, 2014; Maharaj et al., 2012; Sun et al., 2011; Wies et al., 2013). Ligand-free RIG-I adopts an autorepressed conformation in which the CARDs are sequestered. Binding of RNA results in a conformational change that liberates the CARDs (Kowalinski et al., 2011; Liu et al., 2017a); however, this liberation is not thought to be sufficient for RIG-I activation and thus additional activation mechanisms exist. These include ubiquitin conjugation by the E3-ligase TRIM25 to the CARDs (Gack et al., 2007), binding of unanchored K63-linked ubiquitin chains to the CARDs (Jiang et al., 2012; Zeng et al., 2010) and ATP-dependent filamentous oligomerization of RIG-I along the dsRNA (Peisley et al., 2013). All of these mechanism allow for subsequent MAVS aggregation and it has been suggested that ubiquitin promotes the formation of a RIG-I tetramer that acts as a primer for MAVS oligomerization (Peisley et al., 2014).
RLRs have been implicated in the sensing of multiple RNA viruses, with RIG-I sensing viruses such as influenza (Loo et al., 2008; Mäkelä et al., 2015), rhabdoviruses (Furr et al., 2010), HCV (Saito et al., 2008), and other flaviviruses (Chang et al., 2006), and MDA5 recognizing mainly picornaviruses (Chang et al., 2006; Gitlin et al., 2006) and caliciviruses (McCartney et al., 2008). RIG-I is also capable of detecting picornavirus infection but is antagonized by the viral 3C protease (Barral et al., 2009; Papon et al., 2009). Enveloped viruses such as West Nile virus (WNV), MV, and Sendai virus (SeV) can be sensed by both MDA5 and RIG-I (Schlee, 2013). These sensing events are not necessarily redundant as it has been shown that during WNV infection MDA5 and RIG-I cooperate in sensing RNA of the replicating virus, likely by operating at different times during the viral life cycle (Errett et al., 2013). Interestingly, RIG-I can also be activated by dsDNA viruses such as HSV-1 (Rasmussen et al., 2009) or hAdV (Minamitani et al., 2011). Here, it relies on the RNA polymerase III-dependent transcription of AT-rich regions of the viral genome into dsRNA that contain a 5′-triphosphate (Ablasser et al., 2009; Chiu et al., 2009). As further evidence that RLRs detect replicating pathogens, many viruses have evolved to antagonize RIG-I-dependent immune activation, as reviewed in Kell and Gale (2015).

1.5 AIM-Like Receptors

Absent in melanoma (AIM)-like receptors are a relatively recently discovered family of cytosolic and nuclear DNA sensors. In humans, it consists of four members: AIM-2, interferon-γ-inducible protein 16 (IFI16), myeloid cell nuclear differentiation antigen (MNDA), and pyrin and HIN domain-containing protein 1 (PYHIN1) (Gray et al., 2016). Like NLRPs, they have an N-terminal pyrin domain, but their C-terminal nucleotide-binding site is an HIN domain rather than an NACHT domain (Ratsimandresy et al., 2013). AIM2 and IFI16 are thus far the best-characterized family members. AIM2 is a potent inflammasome activator in response to cytosolic DNA. It binds DNA with its HIN domain and ASC with its pyrin domain, which results in recruitment of Caspase-1. This leads to release of IL-1β and IL-18 as well as cell death by pyroptosis (Fernandes-Alnemri et al., 2009; Hornung et al., 2009). It has been shown to promote host defense against DNA viruses such as MCMV, vaccinia virus (VV) (Rathinam et al., 2010), and hAdV (Eichholz et al., 2016; Stein and Falck-Pedersen, 2012). IFI16 activates an alternative immune response via
the ER-associated stimulator of IFN genes (STING) upon binding of dsDNA. Activation of STING promotes TBK1 activity, resulting in the induction of type I interferon (Unterholzner et al., 2010). A recent study by Gray et al. using ALR knockout mice has demonstrated that ALRs are dispensable for the IFN response to synthetic DNA as well as infection with DNA viruses and further do not contribute to the autoimmune phenotype found in Trex-1 knockout mouse models of Aicardi–Goutières syndrome (Gray et al., 2016). However, the mouse and human ALR families are significantly divergent, with 13 members in mice and only 4 known in humans (Brunette et al., 2012; Cridland et al., 2012). Furthermore, AIM2 is the only member of the family showing true orthology between mice and humans, while IFI204, initially considered to be the murine equivalent of IFI16, is now thought to be a true orthologue of IFI16 (Brunette et al., 2012), as two independent studies have shown that IFI16 is required for efficient DNA sensing in both human macrophages (Jonsson et al., 2017) and human keratinocytes (Almine et al., 2017) and that it cooperates with cGAS to achieve full activation of the type I IFN response.

1.6 OAS-Like Receptors

The oligoadenylate synthetase (OAS)-like receptors (OLRs) are a family of viral dsRNA and dsDNA sensors, which generate immune second messengers. They are characterized by a core nucleotidyl transferase domain, but have divergent C-terminal domains that explain their different ligand specificity (Kranzusch et al., 2013). OAS 1, OAS 2, and OAS 3 are the founding members of the family. Upon recognition of viral dsRNA, they produce the secondary messenger 2′-5′-linked oligoadenylate, which results in dimerization and thus activation of the endoribonuclease RNaseL. RNaseL then recognizes viral (and cellular) dsRNA and degrades it (Hornung et al., 2014). This directly interferes with the viral life cycle and the generated RNA cleavage products can be recognized by RLRs, which initiates the induction of type I IFN (Malathi et al., 2007). OAS proteins have been shown to be protective against a number of RNA viruses, such as flaviviruses like HCV (Kwon et al., 2013), DENV, and WNV (Ferguson et al., 2008; Lin et al., 2009). The function of OAS-like proteins is not well elucidated as they lack an active nucleotidyl transferase domain. They have been implicated to compete with OAS proteins and thus negatively regulate the RNaseL pathway (Choi et al., 2015; Rogozin et al., 2003), although one study has shown
that they positively regulate the RIG-I pathway (Choi et al., 2015; Zhu et al., 2014, 2015). Although only discovered in 2013 (Sun et al., 2013), cyclic GMP–AMP synthase (cGAS) is now considered the pivotal dsDNA sensor in the cytosol, since it has been shown to be absolutely required for IFN signaling in response to dsDNA. Binding of cGAS to dsDNA results in the production of cyclic guanosine monophosphate–adenosine monophosphate (cGAMP), which binds STING (Wu et al., 2013b). STING then dimerizes and interacts with TBK1, which phosphorylates IRF3 and thus leads to the induction of IFNβ. TBK1 also activates the IKK complex, resulting in the transcription of NF-κB target genes (Burdette and Vance, 2013; Sun et al., 2013). To date, cGAS has been implicated in the host’s immune defense against multiple viruses, including DNA viruses such as HSV-1 (Reinert et al., 2016), hAdV (Lam et al., 2014), and HCMV (Paijo et al., 2016), and retroviruses such as HIV (Gao et al., 2014), and surprisingly the RNA virus WNV as cGAS KO mice were more susceptible to it (Cai et al., 2014; Schoggins et al., 2014). Basal ISG (interferon-stimulated gene) expression is altered upon cGAS knockout, so this apparent ability to sense an RNA virus is almost certainly an indirect effect due to the reduction in expression levels of other sensors such as RIG-I. Constitutive cGAS activity may occur through stimulation by DNA from damaged mitochondria, sequences generated from viral RNA by cellular reverse transcriptases (Lazear and Diamond, 2016; Shimizu et al., 2014), or microbial infection (Cai et al., 2014; Gough et al., 2012). It has also been shown that cGAMP can be incorporated into nascent viral particles and thus be transferred between cells, leading to a rapid type I IFN response in newly infected cells (Bridgeman et al., 2015). Presumably this occurs in parallel with the paracrine interferon response itself. Aside from cGAS, there are several other cytosolic DNA sensors that have been identified, which do not belong to the OLR family. These include DDX41, DHDX36, DHX9, DAI, and LRRFIP1; however, there is increasing evidence that many of them are dispensable for the IFN induction in response to dsDNA (Burdette and Vance, 2013; Vance, 2016).

2. TRIM PROTEINS IN INNATE IMMUNITY

Tripartite motif-containing proteins (TRIMs) are a family which consists of up to 100 members in humans. They are ancient proteins, with orthologues of TRIM37 being found in species such as Dictyostelium discoideum and Trichomonas vaginalis (Marín, 2012); however, the family
has greatly expanded in mammals to become the largest group of E3 ubiquitin ligases. In recent years, it has become clear that many TRIMs have a function in innate immunity. Unusually for PRRs, they have been shown to function as both viral restriction factors and modulators of innate immune signaling.

2.1 Structure of TRIM Proteins

Almost all TRIMs are characterized by the presence of an RBCC motif, which consists of a RING domain, a B-box domain, and a coiled-coil domain. While some proteins might lack one of the domains, the spacing and order in which the domains occur is highly conserved (Ozato et al., 2008).

The N-terminal RING (Really Interesting New Gene) domain is a zinc-binding motif that is associated with E3-ligase activity (Metzger et al., 2012). In TRIMs, it can not only mediate ubiquitination with various linkage types but also transfer the small ubiquitin-like modifier (SUMO) and the ubiquitin like molecule ISG15 (Ozato et al., 2008).

C-terminally of the RING domain, TRIM proteins carry one or two B-box domains. B-box domains are also zinc finger domains. While all TRIM proteins have one B-box domain (B-box 2), some carry a second B-box (B-box 1) (Ozato et al., 2008). The function of the B-box in TRIM proteins is poorly understood; however, it is required for higher order assembly of some family members (Wagner et al., 2016) and is crucial for function (Koliopoulos et al., 2016).

The last constituent of the tripartite motif is the coiled-coil domain, which is also involved in maintaining quaternary structure where it mediates homodimerization and possibly tetramerization of TRIM proteins (Ozato et al., 2008).

While the N-terminal RBCC motif is conserved among all TRIM proteins, the C-terminal domains differ depending on the downstream effector functions of the TRIM protein. The most common C-terminal domain is the PRYSPRY domain, which is found in 39 human TRIM proteins and consists of an ancient PRY element and a juxtaposed SPRY element. The PRYSPRY domain mediates interactions with various ligands, such as antibody in the case of TRIM21 and retroviruses in the case of TRIM5α. Structural studies on the TRIM21 PRYSPRY domain have shown that ligand interactions occur through a canonical binding site, which consists of six variable loops, similar to antibody CDRs, whose rapid diversification may have driven the evolution of PRYSPRY domains (James et al., 2007). Other
C-terminal domains include the COS-box, which has been shown to mediate interaction with microtubules; FN3 domains, which contain a DNA-binding site; PHDs, which are usually associated with chromatin-mediated transcriptional regulation; and ARF domains, which partake in intracellular trafficking; and finally MATH domains, which have been shown to be involved in receptor binding and oligomerization (Ozato et al., 2012).

2.2 Functions of TRIM Proteins in Viral Restriction

The most widely studied antiviral TRIM is TRIM5α, which restricts HIV-1 in old world monkeys such as rhesus macaque (Stremlau et al., 2004). TRIM5α binds to the HIV-1 capsid via its PRYSPRY domain and is thought to form a hexagonal lattice around the virus (Ganser-Pornillos et al., 2011; Li et al., 2016) via B-box oligomerization (Wagner et al., 2016). TRIM5α restriction involves stepwise autoubiquitination (Fletcher et al., 2015) and subsequent proteasomal degradation of the viral capsid (Lukic et al., 2011; Rold and Aiken, 2008; Stremlau et al., 2006), a block to infection which occurs prior to reverse transcription. If the proteasome is inhibited or TRIM5α’s RING domain, which mediates E3-ligase activity, is deleted, RT is restored; however, HIV-1 infection is still efficiently prevented (Anderson et al., 2006; Kutluay et al., 2013; Roa et al., 2012; Wu et al., 2006). Why the two separate blocks to viral infection exist is not understood. Simultaneous with restriction of HIV-1, TRIM5α also elicits potent immune signaling via AP-1 and NF-κB, which is also dependent on its E3-ligase activity (Pertel et al., 2011). Crucially, human TRIM5α cannot restrict HIV-1, which may help to explain why the virus is so pathogenic in man. Human TRIM5α is capable of restricting N-tropic MLV (N-MLV) and equine infectious anemia virus (EIAV) (Nisole et al., 2005; Yap et al., 2004), suggesting that it is nevertheless an active antiviral. Interestingly, in new world owl monkeys, whose TRIM5α is also unable to restrict HIV, a retrotransposition of cyclophilin A (CypA), which binds the HIV-1 capsid, into the TRIM5 loci has generated the fusion protein TRIM-Cyp that renders owl monkeys resistant to HIV-1 infection (Sayah et al., 2004). TRIM-Cyp has also independently evolved in old world monkeys, in the macaque lineage via an exon-skipping mutation (Wilson et al., 2008). This highlights the intensive selective pressure that retroviral infection has on primate species and the selective advantage a functional TRIM protein can provide. Indeed, TRIM5α is thought to be the fastest evolving primate gene.
Another TRIM that has been implicated in the restriction of HIV-1 is TRIM19 (Turelli et al., 2001). While the mechanism has not been elucidated, it has been suggested that it interferes with viral replication (Turelli et al., 2001), silences gene expression (Lusic et al., 2013; Masroori et al., 2016), or indirectly interferes with reverse transcription (Dutrieux et al., 2015). Indeed, TRIM19 has been implicated in the restriction of multiple viruses, including human HCMV, VSV, and IAV (Nisole et al., 2005). The importance of TRIM19 in viral restriction is highlighted by the fact that HSV encodes a specific antagonist in the form of ICP0, which causes the degradation of TRIM19 (PML) bodies (Boutell et al., 2003). For VSV, it has been shown that TRIM19 is able to directly restrict virus by blocking viral protein expression, while HCMV and IAV are only restricted through TRIM19’s effect on type I IFN signaling. This highlights another similarity between TRIM5α and TRIM19, namely that they are able to both restrict viral infection directly and initiate innate immune signaling. However, while the signaling activity of TRIM5α is directly coupled to its mechanism of viral restriction, since both require K63-linked ubiquitination upon capsid recognition (Pertel et al., 2011), TRIM19 potentiates signaling indirectly, for instance, by recruiting Pin1 into nuclear bodies and interfering with Pin1-mediated degradation of IRF3 to positively regulate type I IFN signaling (El Asmi et al., 2014).

Several TRIM proteins have been shown to be involved in the restriction of nonretroviruses, such as flaviviruses and orthomyxoviruses. TRIM22 has been shown to restrict IAV, by mediating proteasomal degradation of the viral nucleoprotein (Di Pietro et al., 2013), HBV, and HCV (Yang et al., 2016). Another TRIM which is capable of restricting flaviviruses is TRIM79α, with one study demonstrating its importance in restricting tick-borne encephalitis virus by degrading the viral RNA polymerase (Taylor et al., 2012).

2.3 Functions of TRIM Proteins in Innate Immune Regulation

In addition to directly inhibiting viral replication, TRIMs have also been shown to alter viral infectivity through modulation of innate immune signaling pathways, via their E3-ligase activity. One example of this is the potentiation of RIG-I signaling through N-terminal CARD ubiquitination by TRIM25 (Gack et al., 2007; Zeng et al., 2010). RIG-I undergoes a conformational change in response to ligand binding and dephosphorylation (see Section 1.4), which enables TRIM25 binding. It is thought that
TRIM25-mediated ubiquitination of the CARDs facilitates the interaction of RIG-I and MAVS and thus modulates downstream IFNβ induction (Gack, 2014; Gack et al., 2007; Sanchez et al., 2016; Zeng et al., 2010). In this context, two studies have also found a role of TRIM4 in the ubiquitination of RIG-I in cooperation with TRIM25 (Sun et al., 2016; Yan et al., 2014).

TRIM6 has been shown to interact with IKKe via its PRYSRPY, mediate its K48-linked ubiquitination, and thus activate IKKe for STAT-1 phosphorylation (Rajsbaum et al., 2014), which is thought to be important in the IRF3 signaling pathway (Fitzgerald et al., 2003; Perwitasari et al., 2011). This pathway can be antagonized by Nipah virus through TRIM6 degradation by its matrix structural protein (Bharaj et al., 2016).

Similarly, TRIM14 has been implicated in the regulation of both RIG-I and cGAS signaling pathways. TRIM14 has been reported to interact with cGAS via its PRYSRPY domain and upon DNA virus infection recruit the proteasome-associated deubiquitinase (DUB) USP14 to deubiquitinate cGAS, preventing recruitment of p62 and autophagy-dependent degradation of cGAS (Jia et al., 2017). TRIM14 has also been shown to interact with MAVS and upon viral infection undergo K63-linked ubiquitination, thereby recruiting NEMO to the MAVS signalosome and activating IRF3 and NF-κB signaling pathways (Zhou et al., 2014).

TRIM proteins have also been implicated in immune cell signaling pathways. For instance, TRIM20, also referred to as Pyrin, is a key player in inflammasome activation. Interestingly, TRIM20 does not have a RING domain but instead has an N-terminal Pyrin domain and thus acts as an inflammasome activator through recruitment of ASC and subsequent activation of Caspase-1, analogous to NLRP3 and AIM2 (Latz et al., 2013; Richards et al., 2001; Yu et al., 2006). Mutations in MEFV, the gene encoding TRIM20, are associated with the autoinflammatory disease familial Mediterranean fever (FMF) (Latsoudis et al., 2017; Manukyan and Aminov, 2016; Masters et al., 2016; Park et al., 2016). The pyrin inflammasome can be activated by Rho GTPases that have been modified and inactivated by bacterial toxins (Xu et al., 2014). It is thought that Rho GTPases constitutively activate pyrin phosphorylation, which leads to the binding of inhibitory 14-3-3 proteins (Park et al., 2016). When Rho GTPases are inhibited, TRIM20 is no longer phosphorylated and becomes active. Notably, one mutation associated with FMF is S242R, which results in a loss of inhibitory 14-3-3 binding at phosphorylated S242 and might thus result in constitutive TRIM20 activation (Masters et al., 2016).
The above examples illustrate that TRIM proteins are often found synergizing with and potentiating the activity of well-established immune pathways. This highlights the notion that it is important to consider immune responses in their totality rather than focusing on the contribution of any one pathway or component. In addition to the detailed cases earlier, further examples include TRIM30α, which has been shown to negatively regulate TLR-mediated TRAF6-induced NF-κB activation by degrading TAB2 and TAB3 (Shi et al., 2008). A study by Hu et al. has also shown that TRIM30 negatively regulates the NLRP3 inflammasome. Knockdown of TRIM30 resulted in higher levels of IL-1β secretion in J774 cells as well as BMDMs in response to several NLRP3 agonists. Since there is no direct interaction of TRIM30 with members of the NLRP3 inflammasome, the authors suggest that TRIM30 attenuates the production of ROS and thus NLRP3 inflammasome activation.

TRIM23 has been implicated in the activation of NF-κB signaling in response to viral infection through polyubiquitination of NEMO (Arimoto et al., 2010). Likewise, TRIM56 has been shown to play a role in dsDNA-mediated type I IFN induction through K63 ubiquitination of STING, which promotes STING dimerization and the recruitment of TBK1 (Tsuchida et al., 2010). TRIM27 has also been suggested to regulate NF-κB signaling, via the K48-linked ubiquitination and subsequent proteasomal degradation of NOD2, thereby acting as a negative regulator of NOD2-induced NF-κB signaling (Zurek et al., 2012). TRIM38 is another TRIM that has been proposed as a negative regulation of innate immune pathways through its E3-ligase activity. Several studies have shown that TRIM38 attenuates TLR signaling pathways through K48-linked ubiquitination and degradation of TRIF (Hu et al., 2015; Xue et al., 2012), TRAF6 (Zhao et al., 2012a), and NAP1 (Zhao et al., 2012b). For a detailed review of the role of TRIM38 in innate immunity, see Hu and Shu (2017).

Consistent with a broad role of TRIM proteins in innate immune regulation, one study by Uchil et al. demonstrated that numerous TRIMs are capable of activating the innate immune signaling pathways NF-κB and AP-1 upon overexpression. The same study implicated TRIM62 as part of the TLR4 signaling pathway and TRIM15 in regulating the RIG-I signaling pathway, upstream or at the level of MAVS (Uchil et al., 2013). However, as TRIM proteins are E3 ligases that efficiently catalyze the synthesis of ubiquitin chains, this study could also be interpreted as a warning that overexpression of these enzymes may result in gain-of-function phenotypes.
These are only some examples of the diverse functions TRIM proteins, which are currently understood to have in the innate immune response. Table 1 provides a comprehensive overview of studies so far analyzing the role of individual TRIM proteins in innate immunity. Research into the antiviral roles of TRIM proteins is still in its infancy and this list is likely to grow substantially in the coming years. In many cases, current data establish a phenotype but not a molecular mechanism. An understanding of how less-studied TRIMs exert their function may be gained by considering the activity of specific TRIMs for which there are molecular, cellular, and organismal data available. The cytosolic antibody receptor TRIM21 provides an excellent such exemplar for both signaling and effector TRIM function as it simultaneously restricts antibody-coated viruses and elicits potent innate immune signaling (Mallery et al., 2010; McEwan et al., 2013); hence, its mechanism will be discussed in depth in the following sections.

2.4 The Role of TRIM21 in Innate Immunity

Human TRIM21 is a 52-kDa cytosolic protein that consists of the classical N-terminal RBCC motif and a C-terminal PRYSPRY domain. It is located on chromosome 11 in a cluster of nine TRIM proteins, all of which contain PRYSPRY regions, indicating the important role of chromosomal duplications in expanding the TRIM family (Han et al., 2011). The TRIM21 gene consists of seven exons, with exons 2–5 encoding the RBCC motif and exon 7 giving rise to the PRYSPRY domain.

TRIM21 is the only known cytosolic IgG receptor in mammals. All other known IgG receptors capture IgG via their Fc at the plasma membrane (FcγRs) or within an endosome (FcRn). TRIM21 is structurally unrelated to FcγRs and engages a different region of IgG Fc. The PRY element of TRIM21 forms a binding pocket for the C_{H2} domain of the Fc region, while the SPRY domain forms a pocket for the C_{H3} region. Binding of the antibody molecule occurs within the canonical PRYSPRY-binding site defined by its six variable loops (see Section 2.1). There are four hot spot residues in TRIM21 that are crucial for antibody interaction and their mutation abrogates all binding: D355 proximal to VL2, W381 and W383 in VL4, and F450 in VL6. They contact three hot spot residues in the IgG-Fc, located near the C-terminus of C_{H3}: H433, N434, and H435. The PRYSPRY residues in VL4 and VL6 form a hydrophobic ring around a bifurcated hydrogen bond that D355 forms with H433 and N434, shielding it from solvent (James et al., 2007; Keeble et al., 2008). Interestingly, while this binding site
| **TRIM** Protein | **Function in Innate Immunity** | **Viruses Affected** | **Mechanism** | **References** |
|------------------|-------------------------------|---------------------|--------------|---------------|
| TRIM1            | Restriction of retroviruses through initiation of innate immune signaling | N-MLV               |             | Yap et al. (2004) |
| TRIM4            | Ubiquitination of RIG-I in cooperation with TRIM25 | SeV, VSV            |             | Yan et al. (2014); Sun et al. (2016) |
| TRIM5            | Restriction of retroviruses and innate immune signaling upon capsid recognition | HIV-1, N-MLV, EIAV | Capsid binding via the PRYSPRY domain, autoubiquitination and proteasomal recruitment, stimulation of signaling pathways through unanchored K63 ubiquitin chains | Lukic et al. (2011); Pertel et al. (2011); Stremlau et al. (2004); Grütter and Luban (2012) |
| TRIM6            | Regulation of the IRF3 signaling pathway | SeV, IAV, ECMV | Generation of unanchored K48-linked ubiquitin chains that activate IKKε for STAT1 phosphorylation | Rajsbaum et al. (2014); Bharaj et al. (2016) |
| TRIM8            | Positive regulation of NF-κB target genes IL-1β and TNFα | VSV, HSV-1          | K63-linked ubiquitination and subsequent activation of TAK-1 | Okumura et al. (2010) |
| Epinephelus coioides TRIM8 restricts Singapore grouper iridovirus (SGIV) | SGIV               |                     | Epinephelus coioides TRIM8 restricts Singapore grouper iridovirus (SGIV) | Huang et al. (2016a) |
| TRIM9 short isoform | Positive regulation of IRF3 signaling pathway | VSV, HSV-1          | Autoubiquitination of TRIM9 facilitates GSK3β-mediated activation of TBK1 | Qin et al. (2016) |
| TRIM11           | Restriction of retroviruses | HIV-1               | Acceleration of HIV-1 uncoating which results in reduced reverse transcription | Yuan et al. (2014); Yuan et al. (2016) |
| Negative regulation of IFNβ production | HSV-1, VSV | Interaction with TBK1 | Lee et al. (2013) |
| Negative regulation of the AIM2 inflammasome | HSV-1, MCMV | Interaction with AIM2 via the PRYSPRY domain, autoubiquitination and recruitment of p62 which results in AIM2 degradation by autophagy | Liu et al. (2016a) |
| TRIM Protein | Function in Innate Immunity | Viruses Affected | Mechanism | References |
|--------------|-----------------------------|-----------------|-----------|------------|
| TRIM13       | Negative regulation of MDA5 signaling pathway, positive regulation of RIG-I pathway | ECMV, SeV       | K29-linked polyubiquitination of TRAF6 | Narayan et al. (2014) |
|              | Positive regulation of the TLR2-stimulated NF-κB signaling pathway | K29-linked polyubiquitination of TRAF6 | Huang and Baek (2017) |
|              | Negative regulation of NF-κB activation | Regulation of NEMO ubiquitination | Tomar and Singh (2014) |
|              | Epinephelus coioides TRIM13 negatively regulates IRF3 and MDA5 signaling pathways | RGNNV           |           | Huang et al. (2016b) |
| TRIM14       | Positive regulation of the RLR signaling pathway | SeV             | K63-linked polyubiquitination of TRIM14 after viral infection likely through interaction with MAVS results in recruitment of NEMO to the MAVS signalosome | Zhou et al. (2014) |
|              | Positive regulation of cGAS-dependent type I IFN response | HSV-1, VSV      | Recruitment of USP14 which deubiquitinates cGAS, thus preventing its p62-dependent autophagic degradation | Chen et al. (2016) |
|              | Restriction of flaviviruses | HCV             | Degradation of viral NS5A protein | Wang et al. (2016); Nenasheva et al. (2015) |
| TRIM15       | Regulation of the RIG-I signaling pathway | VSV             | Inhibition of viral release through interaction of the B-box with the Gag precursor protein | Uchil et al. (2013) |
|              | Restriction of retroviruses | HIV-1, N-MLV    |           | Uchil et al. (2008) |
| TRIM19 (PML) | Restriction of retroviruses | HIV-1 | Interference with early steps of replication | Turelli et al. (2001) |
|--------------|-----------------------------|-------|---------------------------------------------|----------------------|
|              | Cell type-specific restriction early in the viral lifecycle | | Kahle et al. (2016) |
|              | Repression of viral transcription | | Lusic et al. (2013); Masroori et al. (2016) |
|              | Stabilization of Daxx which then inhibits reverse transcription | | Dutrieux et al. (2015) |
| Restriction of paroviruses | AAV | | Mitchell et al. (2014) |
| Restriction of herpesviruses | HCMV | | Schilling et al. (2017); Wagenknecht et al. (2015) |
| Restriction of rhabdoviruses | VSV | Inhibition of viral protein synthesis | Chelbi-Alix et al. (1998) |
| Positive regulation of IFNβ | VSV, SeV, ECMV, HTLV-1, IAV, VV | Recruitment of Pin1 into nuclear bodies which prevents degradation of IRF3 (Saitoh et al., 2006) | El Asmi et al. (2014) |
| TRIM20 (pyrin) | Inflammasome activation | Inactivation of Rho GTPases results in loss of downstream pyrin phosphorylation. Phosphorylated pyrin is usually bound by inhibitory 14–3–3 proteins, and thus a loss of phosphorylation might result in activation | Richards et al. (2001); Yu et al. (2006); Masters et al. (2016); Manukyan and Aminov (2016); Park et al. (2016); Latsoudis et al. (2017); Xu et al. (2014); Vajjhala et al. (2014) |
| Regulation of NF-κB signaling | Caspase-1 cleaves an N-terminal fragment of TRIM20 that results in ASC-dependent NF-κB activation | | Chae et al. (2008) |

Continued
| Table 1 The Role of TRIM Proteins in Innate Immunity—cont’d |
|-----------------------------------------------------------|
| TRIM Protein | Function in Innate Immunity | Viruses Affected | Mechanism | References |
|--------------|-----------------------------|------------------|-----------|------------|
| TRIM21       | Restriction of adenoviruses  | hAdV5, MAV-1     | Binding of the PRYSPRY domain to antibody-coated virus results in autoubiquitination and recruitment of the proteasome | Mallery et al. (2010); Vaysburd et al. (2013); Watkinson et al. (2013); Fletcher and James (2016) |
|              | Restriction of picornaviruses| FMDV             |           | Fan et al. (2016a) |
|              | Innate immune sensing of viruses | hAdV5, HRV14, FCV | Release of K63-linked ubiquitin chains by proteasome-associated DUB Poh-1 | McEwan et al. (2013); Watkinson et al. (2013); Fletcher et al. (2014) |
|              | Negative regulation of dsDNA cellular response | HSV-1 | K48-linked polyubiquitination and degradation of DDX41 | Zhang et al. (2012a) |
|              | Negative regulation of IRF signaling pathways | SeV | Polyubiquitination and degradation of IRF3, IRF5, and IRF7 | Higgs et al. (2008); Lazzari et al. (2014); Higgs et al. (2010) |
|              | Positive regulation of IRF signaling pathways | | Preventing interaction between Pin1 and IRF3, thus preventing Pin1-dependent IRF3 degradation | Kong et al. (2007) |
|              |                             |                  | Ubiquitination of IRF8 results in increased ability to stimulate IL-12p40 expression | Kong et al. (2007) |
| TRIM22 | Restriction of retroviruses | HIV-1 | Singh et al. (2011); Barr et al. (2008) |
|---|---|---|---|
| | Transcriptional silencing | | Turrini et al. (2015); Kajaste-Rudnitski et al. (2011) |
| Restriction of flaviviruses | HCV | Ubiquitination of NS5A | Yang et al. (2016) |
| | HBV | Transcriptional repression mediated by the RING and PRYSPRY domains | Yang et al. (2016) |
| Restriction of orthomyxoviruses | IAV | Degradation of the viral nucleoprotein | Di Pietro et al. (2013) |
| TRIM23 | Regulation of NF-κB signaling | SeV | K27-linked polyubiquitination of NEMO | Arimoto et al. (2010) |
| | Positive regulation of viral infectivity | YFV | Polyubiquitination of YFV NS5 promotes binding to STAT2 and suppresses type I IFN signaling | Laurent-Rolle et al. (2014) |
| | | HCMV | Interaction with HCMV UL144 facilitates association with TRAF6, which activates NF-κB signaling | Poole et al. (2009) |
| TRIM25 | Positive regulation of the RIG-I pathway | NDV, VSV, SeV | Ubiquitination of the RIG-I CARDs, which facilitates the interaction with MAVS | Gack et al. (2007); Zeng et al. (2010); Sanchez et al. (2016) |
| | Modulation of antiviral activity of zinc finger antiviral protein (ZAP) | SinV | Zheng et al. (2017); Li et al. (2017) |

*Continued*
| TRIM Protein | Function in Innate Immunity | Viruses Affected | Mechanism | References |
|--------------|----------------------------|------------------|-----------|------------|
| **TRIM26** | Positive regulation of the RLR signaling pathway | NDV, VSV | Direct interaction with TBK and likely recruitment of NEMO through autoubiquitination bridges NEMO and TBK1 and positively regulates IFNβ | Ran et al. (2016) |
| | | | Polyubiquitination and degradation of IRF3 resulting in diminished IFNβ response | Wang et al. (2015a) |
| **TRIM27** | Negative regulation of NOD2-mediated NF-κB signaling | K48-linked ubiquitination and subsequent proteasomal degradation of NOD2 | | Zurek et al. (2012) |
| **TRIM28** | Restriction of retroviruses | M-MLV, HIV-1 | Transcriptional repression | Wolf and Goff (2007); Figueiredo and Hope (2011) |
| | | | Inhibition of HIV-1 integration | |
| **TRIM29** | Negative regulation of the IRF7 signaling pathway | VSV | SUMOylation of IRF7 | Liang et al. (2011) |
| | | | Ubiquitination and subsequent degradation of NEMO in alveolar macrophages | Xing et al. (2016) |
| **TRIM30** | Negative regulation of NF-κB and type I IFN signaling pathways | IAV | TRIM30α facilitates degradation of TAB2 and TAB3 | Shi et al. (2008) |
| | | | Attenuation of ROS production | Hu et al. (2010) |
| **TRIM31** | Negative regulation of NLRP3 inflammasome activation | SeV | K48-linked ubiquitination and proteasomal degradation of NLRP3 | Song et al. (2016) |
| | | | Positive regulation of the RLR signaling pathway | Liu et al. (2017b) |
| TRIM32 | Restriction of orthomyxoviruses | IAV | Ubiquitination and degradation of IAV PB1 polymerase | Fu et al. (2015) |
|--------|--------------------------------|-----|--------------------------------------------------------|-----------------|
|        | Positive regulation of type I IFN signaling | VSV, NDV | K63-linked ubiquitination of STING which promotes interaction with TBK1 | Zhang et al. (2012b) |
| TRIM33 | Activation of NLRP3 inflammasome in response to dsRNA | VSV, HSV-1 | K63-linked ubiquitination of dsRNA sensor DHX33 (Gallouet et al., 2017) which results in DHX33–NLRP3 complex formation | Weng et al. (2014) |
|        | Regulation of *Ifnb1* expression in macrophages | | Regulatory element at the *Ifnb1* enhancer | Ferri et al. (2015) |
| TRIM35 | Negative regulation of type I IFN signaling in response to TLR9 and TLR7 activation | VSV, HSV-1 | K48-linked ubiquitination of IRF7 which results in proteasomal degradation | Wang et al. (2015b) |
| TRIM37 | Restriction of retroviruses | HIV-1 | | Tabah et al. (2014) |
| TRIM38 | Negative regulation of TLR3/4 signaling pathways | | K48-linked polyubiquitination and subsequent proteasomal degradation of TRIF | Hu et al. (2015); Xue et al. (2012) |
|        | | | K48-linked polyubiquitination and subsequent proteasomal degradation of TRAF6 | Zhao et al. (2012a) |
|        | | | VSV | K48-linked polyubiquitination and subsequent proteasomal degradation of NAP1 | Zhao et al. (2012b) |
|        | | | | Negative regulation of IL-1β and TNFα induction | Proteasomal degradation of TAB2/3 | Hu et al. (2014) |
|        | | | | Regulation of the cGAS signaling pathway | SUMOylation of cGAS and STING which results in increased stability | Hu et al. (2016) |
| Protein  | Function in Innate Immunity                                      | Viruses Affected                  | Mechanism                                                                 | References                  |
|----------|-----------------------------------------------------------------|-----------------------------------|---------------------------------------------------------------------------|-----------------------------|
| TRIM40   | Negative regulation of NF-κB signaling                          |                                   | Inhibition of NEMO through its neddylation in the gastrointestinal tract   | Noguchi et al. (2011)       |
| TRIM41   | Inhibition of flaviviruses                                       | HBV                               | Inhibition of HBV transcription                                            | Zhang et al. (2013)         |
| TRIM44   | Positive regulation of RLR signaling pathway                    | SeV                               | Stabilization of MAVS                                                      | Yang et al. (2013)          |
| TRIM45   | Negative regulation of NF-κB signaling                          |                                   |                                                                           | Shibata et al. (2012)       |
| TRIM52   | Positive regulation of NF-κB signaling                          |                                   |                                                                           | Fan et al. (2017)           |
|          | Restriction of flaviviruses                                     | JEV                               | Ubiquitination and subsequent degradation of viral NS2A protein           | Fan et al. (2016b)          |
| TRIM56   | Positive regulation of the STING signaling pathway              |                                   | K63-linked ubiquitination of STING which facilitates dimerization and TBK1 recruitment | Tsuchida et al. (2010)      |
|          | Restriction of flaviviruses and coronaviruses                   | BVDV, YFV, DENV2, hCoV-OC43       |                                                                           | Wang et al. (2011b); Liu et al. (2014) |
|          | Positive regulation of TLR3 signaling pathway                   | HCV                               |                                                                           | Shen et al. (2012)          |
|          | Restriction of orthomyxoviruses                                 | IAV, IBV                          | Inhibition of viral RNA synthesis                                          | Liu et al. (2016b)          |
|          | Restriction of retroviruses                                     | HIV-1                             |                                                                           | Kane et al. (2016)          |
| TRIM59 | Negative regulation of NF-κB and IRF3/7 signaling pathways | Kondo et al. (2012) |
| TRIM62 | Restriction of retroviruses and involvement in the TLR4 signaling pathway | N-MLV | Uchil et al. (2013) |
| TRIM65 | Positive regulator of the MDA5 signaling pathway | ECMV | K63-linked ubiquitination of MDA5, thus promoting MDA5 oligomerization and activation | Lang et al. (2016) |
| TRIM68 | Negative regulation of type I IFN signaling | | Polyubiquitination and degradation of TGF which interacts with NEMO | Wynne et al. (2014) |
| TRIM79α | Restriction of flaviviruses | TBEV | Degradation of the viral RNA polymerase | Taylor et al. (2012) |
is distant from the binding site of classic FcγRs, it overlaps with the FcRn-binding site. FcRn is important for prolonging the half-life of IgG molecules through recycling of internalized antibodies as well as transfer of IgG from mother to fetus across the placenta. The binding of FcRn to IgG can only occur at the endosomal pH of 6.5 and is markedly reduced at pH 7.4 since FcRn binding relies on the protonation of H433 and H435, which only occurs at acidic pH (Roopenian and Akilesh, 2007; Stapleton et al., 2011). In contrast, the binding of TRIM21 is pH independent and does not require protonation. TRIM21 is capable of binding all IgG subclasses with nM affinity (Keeble et al., 2008) and has also been shown to bind IgM (Mallery et al., 2010) and IgA (Bidgood et al., 2014), however with lower affinities of 17 and 50 μM, respectively.

2.5 TRIM21 Effector Mechanism

TRIM21 is an IFN-inducible, cytosolic high-affinity IgG receptor that detects antibody-coated viruses or bacteria that have entered the cytosol. In response, it mediates dual effector and sensor functions by facilitating simultaneous proteasomal degradation of virions and innate immune signaling (Fig. 1). The two critical prerequisites for this mechanism are virus penetration of the cytosol and exposure of antibody molecules to the cytosol. This means that not all virus/antibody combinations will be able to stimulate TRIM21; the antibody cannot block viral entry into the cells, e.g., through binding viral epitopes crucial for receptor engagement and the virus cannot gain access to the cytosol through a fusion mechanism that will result in shedding of the antibody. Therefore, most experiments elucidating viral neutralization and innate immune signaling mediated by TRIM21 have used either hAdV or mouse adenovirus 1 (MAV-1) as well as human rhinovirus 14 (HRV14), as they are nonenveloped viruses that penetrate the endosome during entry, carrying bound antibodies with them. In this review the term neutralization is used as defined by P.J. Klasse: “Neutralization […] is defined as the reduction in viral infectivity by the binding of antibodies to the surface of viral particles (virions), thereby blocking a step in the viral replication cycle that precedes virally encoded transcription or synthesis” (Klasse, 2014).

Once the virus has accessed the cytosol, TRIM21 binds the Fc region of an antibody with a 1:1 stoichiometry (one TRIM21 dimer to one heterodimeric IgG), with the coiled-coil domain mediating TRIM21 dimerization. Binding of the antibody activates the E3-ligase activity of
The antibody-coated virus enters the cell and accesses the cytosol, where TRIM21 can bind the Fc region of the antibody; in case of a retrovirus, TRIM5α is able to bind to the viral capsid. Both TRIM21 and TRIM5α will recruit Ube2W resulting in N-terminal monoubiquitination. The E2 enzyme complex Ube2N/Ube2V2 then extends the N-terminal ubiquitin through K63-linked chains. Ubiquitination results in recruitment of the proteasome, the virus, or virus/antibody complex become degraded, while the proteasome-associated DUB Poh1 simultaneously releases the K63-linked ubiquitin chains, which can stimulate innate immune pathways downstream. TRIM21 has been shown to stimulate NF-κB, AP-1, as well as IRF3, IRF5, and IRF7 pathways, while TRIM5α only stimulates NF-κB and AP-1 signaling pathways. In the case of TRIM21 it has been shown that viral degradation of hAdV and HRV results in exposure of the viral DNA or RNA genome which can be sensed further downstream by cGAS or RIG-I, respectively, initiating a second wave of innate immune signaling.
TRIM21 through a still unknown mechanism. It is thought that TRIM21 first recruits the E2 enzyme Ube2W, which monoubiquitinates the N-terminus of TRIM21. Subsequently, the E2 enzyme complex Ube2N/Ube2V2 polyubiquitinates TRIM21 through K63 chain extension of the N-terminal ubiquitin. This mechanism of autoubiquitination is analogous to the mechanism the TRIM5α uses (Fletcher et al., 2015). Cellular depletion of Ube2N also results in loss of TRIM21 K48 ubiquitination, suggesting that there may be additional E2 enzymes recruited to TRIM21 resulting in mixed or branched chains. It is not known whether the antibody or the virus also becomes ubiquitinated. Following ubiquitination, it has been shown that PohI, a proteasome-associated DUB, is required for the removal of K63-linked ubiquitin chains, which is pivotal for both TRIM21-mediated neutralization and signaling. The virus:antibody:TRIM21 complex is then degraded by the proteasome in cooperation with the AAA ATPase p97/VCP (Hauler et al., 2012), while the liberated K63 chains activate innate immune signaling through NF-κB, AP-1 as well as IRF3, IRF5, and IRF7 signaling pathways (McEwan et al., 2013). This results in the induction of proinflammatory cytokines such as IL-6, CCL4, and TNFα as well as IFNβ. Interestingly, while TRIM21-dependent neutralization has only been demonstrated for hAdV (and recently for foot-and-mouth disease virus (FMDV) in swines (Fan et al., 2016a)), TRIM21-dependent signaling could be demonstrated for hAdV, HRV14, feline calicivirus (FCV), as well as Salmonella enterica. Furthermore, TRIM21 is important in exposing the respective dsDNA and ssRNA genomes of hAdV and HRV, through degradation of the viral capsid, thus making them accessible to sensing by cGAS and RIG-I, and driving a second wave of signal induction after the first wave initiated by TRIM21 (Watkinson et al., 2015).

While the neutralization and signaling activities of TRIM21 are coupled, they have different response thresholds. Neutralization of hAdV could be observed with as little as 1.6 antibodies per virus in IFNα-treated MEF cells (McEwan et al., 2012). Similarly, TRIM21’s neutralization activity is tolerant to mutations in the Fc region that decrease the antibody’s affinity for TRIM21 to the point that it is even capable of neutralizing virus with an H433K mutant, which displays a 100-fold decrease in affinity for TRIM21. Conversely, signaling is highly sensitive to changes in affinity. In cells where Fc mutant I253A (which has approximately a twofold lower affinity for TRIM21 than the wild-type (WT) antibody) does not impact neutralization, signaling is almost completely lost. This phenotype can be partially rescued by increasing antibody concentration, but this mutant’s signaling
activity is always significantly lower than WT (McEwan et al., 2012). In line with this observation, it has been shown that TRIM21 effector functions strongly correlate with antibody off-rate, more so than simply affinity for the antigen, a trend that is again more pronounced for TRIM21’s signaling output than its neutralization function (Bottermann et al., 2016). It is intuitive that signaling would be regulated more strictly and have thresholds, since TRIM21’s neutralization activity cannot be harmful for the host, while the initiation of potent immune signaling can have potentially severe consequences. During an immune response, this may ensure that TRIM21 signaling only activates immune transcription in the presence of high-affinity IgG or significant viral challenge. However, this separate threshold allows for neutralization function during the early stages of an immune response where viremia is lower and where antibodies are derived from the natural or low-affinity IgM repertoire. This is supported by the fact that in vivo, TRIM21 can protect naïve mice from fatal MAV-1 infection, where the protective antibody effect can only result from natural or low-affinity IgM that is produced prior to affinity maturation. Moreover, immune signaling in naïve mice after challenge with MAV-1 shows no TRIM21 dependence (Vaysburd et al., 2013). Conversely, mice that received MAV-1 immune sera prior to challenge with MAV-1 were not only better protected from fatal infection in a TRIM21-dependent manner (Vaysburd et al., 2013), but they also showed strong TRIM21-dependent upregulation of proinflammatory cytokines (Watkinson et al., 2013).

Recently, it has been shown that TRIM21 can also inhibit tau seeds, which is the source of pathological tau that exhibits prion-like properties (Iqbal et al., 2015), in a manner similar to neutralizing antibody-bound viruses (McEwan et al., 2017). This suggests that the protection mediated by TRIM21 extends to nonclassical pathogens, such as proteopathic agents. This also highlights that TRIM21 is agnostic to the nature of the infectious agent. TRIM21 is essentially a DAMP sensor for antibodies that mislocalize to the cytosol—something that should only happen if normal cellular compartmentalization has been compromised.

2.6 The Role of TRIM21 in Innate Immune Regulation and Autoimmunity

Systemic lupus erythematosus (SLE) is an autoimmune disorder that is characterized by erythematous, fatigue as well as joint pain and swelling. While its cause and origin are still unknown, it is often associated with autoantibodies against TRIM21. The same is true for the autoimmune disorder
Sjögren’s syndrome, where the presence of TRIM21 autoantibodies has served as a diagnostic tool for decades (Fujimoto et al., 1997). One hypothesis of how TRIM21 may contribute to these autoimmune disorders is that autoantibodies against it might undergo bipolar bridging, involving simultaneous engagement of their Fc and Fab regions. This could result in the formation of large aggregated immune complexes that cannot be cleared by Fcγ-mediated phagocytosis, thereby contributing to pathogenesis (James et al., 2007). Another study has shown that macrophages from SLE-prone mice do not fully mature their lysosomes, which has been suggested to result in a defect in clearance of apoptotic cells, an accumulation of nuclear antigens and leakage of DNA and IgG into the cytosol, which then activates AIM2 and TRIM21 (Monteith et al., 2016). Furthermore, there has been evidence that TRIM21 is involved in not only the initiation of immune signaling but also its regulation. TRIM21 has been implicated in the polyubiquitination and subsequent degradation of IRF transcription factors IRF3, IRF5, and IRF7 and thus in the negative regulation of IFNβ signaling (Higgs et al., 2008, 2010; Lazzari et al., 2014; Oke and Wahren-Herlenius, 2012). However, other studies contradict a negative regulatory role and have shown that TRIM21 positively upregulates type I IFN signaling through interference with the Pin1–IRF3 interaction (Yang et al., 2009), which usually results in IRF3 degradation (Saitoh et al., 2006), or through ubiquitination and thus stabilization of IRF8 (Kong et al., 2007). One study using TRIM21 KO mice has suggested that while mice are phenotypically normal when left unmanipulated, they develop symptoms consistent with autoimmune disorders upon metal ear-tagging. In mice that spontaneously become autoimmune, proinflammatory cytokines such as IL-6 and IL-17 (Espinosa et al., 2009) are upregulated. However, one drawback of this study was that the TRIM21 KO generated in these mice was not complete, but through homologous recombination targeted to exon 5. This means that the RING, B-box, and coiled-coil domains of TRIM21 are still intact and in frame with the native promoter, while the PRYSPRY domain has been knocked out, meaning that the catalytic part of TRIM21 is still present. On the other hand, Yoshimi et al. generated TRIM21 KO mice where the entire sequence encoding the TRIM21 mRNA was replaced by eGFP. In this study, it was shown that TRIM21 expression is prevalent in many tissues, while particularly high expression levels are observed in immune cells. Interestingly, these mice did not display any autoimmune phenotypes upon ear-tagging (Yoshimi et al., 2010). However, MEF cells from these TRIM21 KO mice displayed higher levels of proinflammatory cytokines
after TNFα stimulation than MEFs from WT animals as well as enhanced NF-κB promoter activity. The ubiquitination of IRF3 and IRF8 was reduced in the TRIM21 KO MEFs, but ISG expression in BMDMs was not affected. This suggests that knockout of TRIM21 can impact the regulation of proinflammatory cytokines; however, it is not clear whether this plays a role in autoimmune disease.

In summary, TRIM21 is a unique innate immune sensor in that it is a cytosolic IgG receptor that is capable of both neutralization and initiation of innate immune signaling. Unlike other innate immune sensors, which often recognize PAMPs associated with the pathogen itself, TRIM21 is not specific to a particular pathogen or antigen as its activation depends on the presence of antigen-bound antibody rather than the antigen itself. Future work will seek to further elucidate the activation and regulatory mechanisms of TRIM21, which will hopefully also give further insights into its role in autoimmune disease.

ACKNOWLEDGMENTS

M.B. and L.C.J. received funding from the Medical Research Council (UK; U105181010) and through a Wellcome Trust Investigator Award.

REFERENCES

Abais, J.M., Xia, M., Zhang, Y., Boini, K.M., Li, P.-L., 2015. Redox regulation of NLRP3 inflammasomes: ROS as trigger or effector? Antioxid. Redox Signal. 22, 1111–1129.
Ablasser, A., et al., 2009. RIG-I-dependent sensing of poly(dA:dT) through the induction of an RNA polymerase III-transcribed RNA intermediate. Nat. Immunol. 10, 1065–1072.
Akira, S., Takeda, K., 2004. Toll-like receptor signalling. Nat. Rev. Immunol. 4, 499–511.
Allen, I.C., et al., 2009. The NLRP3 inflammasome mediates in vivo innate immunity to influenza A virus through recognition of viral RNA. Immunity 30, 556–565.
Allen, I.C., et al., 2011. NLRX1 protein attenuates inflammatory responses to infection by interfering with the RIG-I-MAVS and TRAF6-NF-κB signaling pathways. Immunity 34, 854–865.
Allouch, A., et al., 2011. The TRIM family protein KAP1 inhibits HIV-1 integration. Cell Host Microbe 9, 484–495.
Almine, J.F., et al., 2017. IFI16 and cGAS cooperate in the activation of STING during DNA sensing in human keratinocytes. Nat. Commun. 8, 14392.
Anderson, J.L., et al., 2006. Proteasome inhibition reveals that a functional preintegration complex intermediate can be generated during restriction by diverse TRIM5 proteins. J. Virol. 80, 9754–9760.
Arimoto, K., et al., 2010. Polyubiquitin conjugation to NEMO by triparite motif protein 23 (TRIM23) is critical in antiviral defense. Proc. Natl. Acad. Sci. U.S.A. 107, 15856–15861.
Barlan, A.U., Griffin, T.M., McGuire, K.A., Wiertz, C.M., 2011. Adenovirus membrane penetration activates the NLRP3 inflammasome. J. Virol. 85, 146–155.
Barr, S.D., Smiley, J.R., Bushman, F.D., 2008. The interferon response inhibits HIV particle production by induction of TRIM22. PLoS Pathog. 4, 1–11.
Barral, P.M., Sarkar, D., Fisher, P.B., Racaniello, V.R., 2009. RIG-I is cleaved during picornavirus infection. Virology 39, 171–176.

Bharaj, P., et al., 2016. The matrix protein of nipah virus targets the E3-ubiquitin ligase TRIM6 to inhibit the IKKε kinase-mediated type-I IFN antiviral response. PLoS Pathog. 12, 1–27.

Bidgood, S.R., Tam, J.C.H., McEwan, W.A., Mallery, D.L., James, L.C., 2014. Translocalized IgA mediates neutralization and stimulates innate immunity inside infected cells. Proc. Natl. Acad. Sci. U.S.A. 111, 13463–13468.

Bieback, K., et al., 2002. Hemagglutinin protein of wild-type measles virus activates toll-like receptor hemagglutinin protein of wild-type measles virus activates toll-like receptor 2 signaling. J. Virol. 76, 8729–8736.

Bottermann, M., et al., 2016. Antibody-antigen kinetics constrain intracellular humoral immunity. Sci. Rep. 6, 37457.

Boutell, C., Orr, A., Everett, R.D., 2003. PML residue lysine 160 is required for the degradation of PML induced by herpes simplex virus type 1 regulatory protein ICP0 PML residue lysine 160 is required for the degradation of PML induced by herpes simplex virus type 1 regulatory protein ICP0. Society 77, 8686–8694.

Bridgeman, A., et al., 2015. Viruses transfer the antiviral second messenger cGAMP between cells. Science 349, 1228–1232.

Broz, P., Von Moltke, J., Jones, J.W., Vance, R.E., Monack, D.M., 2010. Differential requirement for caspase-1 autoproteolysis in pathogen-induced cell death and cytokine processing. Cell Host Microbe 8, 471–483.

Brunette, R.L., et al., 2012. Extensive evolutionary and functional diversity among mammalian AIM2-like receptors. J. Exp. Med. 209, 1969–1983.

Burdette, D.L., Vance, R.E., 2013. STING and the innate immune response to nucleic acids in the cytosol. Nat. Immunol. 14, 19–26.

Cai, X., Chiu, Y.H., Chen, Z.J., 2014. The cGAS–cGAMP-STING pathway of cytosolic DNA sensing and signaling. Mol. Cell 54, 289–296.

Chae, J.J., Wood, G., Richard, K., Jaffé, H., Colburn, N.T., Masters, S.L., Gumucio, D.L., Shoham, N.G., Kastner, D.L., 2008. The familial Mediterranean fever protein, pyrin, is cleaved by caspase-1 and activates NF-kB through its N-terminal fragment. Blood 12, 6–7.

Chang, T.H., Liao, C.L., Lin, Y.L., 2006. Flavivirus induces interferon–beta gene expression through a pathway involving RIG-I-dependent IRF-3 and PI3K-dependent NF-kB activation. Microbes Infect. 8, 157–171.

Chelbi-Alix, M.K., Quignon, F., Pelicano, L., Koken, M.H., de Thé, H., 1998. Resistance to virus infection conferred by the interferon-induced promyelocytic leukemia protein. J. Virol. 72, 1043–1051.

Chen, M., et al., 2016. TRIM14 inhibits cGAS degradation mediated by selective autophagy receptor p62 to promote innate immune responses. Mol. Cell 64, 105–119.

Chiu, Y.-H., MacMillan, J.B., Chen, Z.J., 2009. RNA polymerase III detects cytosolic DNA and induces type-I interferons through the RIG-I pathway. Cell 138, 576–591.

Choi, U.Y., Kang, J.S., Hwang, Y.S., Kim, Y.J., 2015. Oligoadenylate synthase-like (OASL) proteins: dual functions and associations with diseases. Exp. Mol. Med. 47, e144.

Compton, T., et al., 2003. Human cytomegalovirus activates inflammatory cytokine responses via CD14 and toll-like receptor 2. J. Virol. 77, 4588–4596.

Cridland, J.A., et al., 2012. The mammalian PYHIN gene family: phylogeny, evolution and expression. BMC Evol. Biol. 12, 140.

Dambuza, I.M., Brown, G.D., 2015. C-type lectins in immunity: recent developments. Curr. Opin. Immunol. 32, 21–27.

de Witte, L., Abt, M., Schneider-Schaubies, S., van Kooyk, Y., Geijtenbeek, T.B.H., 2006. Measles virus targets DC-SIGN to enhance dendritic cell infection. J. Virol. 80, 3477–3486.
Diebold, S.S., 2004. Innate antiviral responses by means of TLR7-mediated recognition of single-stranded RNA. Science 303, 1529–1531.
Di Pietro, A., et al., 2013. TRIM22 inhibits influenza A virus infection by targeting the viral nucleoprotein for degradation. J. Virol. 87, 4523–4533.
Dixit, E., Kagan, J.C., 2013. Intracellular pathogen detection by RIG-I-like receptors. Adv. Immunol. 117, 99–125.
Drummond, R.A., Brown, G.D., 2013. Signalling C-type lectins in antimicrobial immunity. PLoS Pathog. 9, 9–11.
Duewell, P., et al., 2010. NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals. Nature 464, 1357–1361.
Dutrieux, J., et al., 2015. PML/TRIM19–dependent inhibition of retroviral reverse-transcription by Daxx. PLoS Pathog. 11, 1–22.
Eichholz, K., et al., 2016. Immune–complexed adenovirus induce AIM2–mediated pyroptosis in human dendritic cells. PLoS Pathog. 12, e1005871.
El Asmi, F., et al., 2014. Implication of PMLIV in both intrinsic and innate immunity. PLoS Pathog. 10 (2), e1003975. https:/doi.org/10.1371/journal.ppat.1003975.
Errett, J.S., Suthar, M.S., McMillan, A., Diamond, M.S., Gale, M., 2013. The essential, non-redundant roles of RIG-I and MDA5 in detecting and controlling west Nile virus infection. J. Virol. 87, 11416–11425.
Espinosa, A., et al., 2009. Loss of the lupus autoantigen Ro52/Trim21 induces tissue inflammation and systemic autoimmunity by disregulating the IL–23–Th17 pathway. J. Exp. Med. 206, 1661–1671.
Fan, W., et al., 2016a. Swine TRIM21 restricts FMDV infection via an intracellular neutralization mechanism. Antiviral Res. 127, 32–40.
Fan, W., et al., 2016b. TRIM52 inhibits Japanese encephalitis virus replication by degrading the viral NS2A. Sci. Rep. 6, 33698.
Fan, W., et al., 2017. TRIM52: a nuclear TRIM protein that positively regulates the nuclear factor–kappa B signaling pathway. Mol. Immunol. 82, 114–122.
Farhat, K., et al., 2007. Heterodimerization of TLR2 with TLR1 or TLR6 expands the ligand spectrum but does not lead to differential signaling. J. Leukoc. Biol. 83, 692–701.
Ferguson, W., Dvora, S., Gallo, J., Orth, A., Boissinot, S., 2008. Long-term balancing selection at the West Nile virus resistance gene, Oas1b, maintains transspecific polymorphisms in the house mouse. Mol. Biol. Evol. 25, 1609–1618.
Fernandes-Alnemri, T., et al., 2009. AIM2 activates the inflammasome and cell death in response to cytoplasmic DNA. Nature 458, 509–513.
Ferre, F., et al., 2015. TRIM33 switches off Ifnb1 gene transcription during the late phase of macrophage activation. Nat. Commun. 6, 8900.
Figueiredo, A., Hope, T.J., 2011. KAPs off for HIV–1 integration. Cell Host Microbe 9, 447–448.
Fiola, S., Gosselin, D., Takada, K., Gosselin, J., 2010. TLR9 contributes to the recognition of EBV by primary monocytes and plasmacytoid dendritic cells. J. Immunol. 185, 3620–3631.
Fitzgerald, K.A., et al., 2003. IKKε and TBK1 are essential components of the IRF3 signaling pathway. Nat. Immunol. 4, 491–496.
Fletcher, A.J., James, L.C., 2016. Coordinated neutralization and immune activation by the cytosolic antibody receptor TRIM21. J. Virol. 90, 4856–4859.
Fletcher, A.J., Mallory, D.L., Watkinson, R.E., Dickson, C.F., James, L.C., 2014. Sequential ubiquitination and deubiquitination enzymes synchronise the dual sensor and effector functions of TRIM21. Proc. Natl. Acad. Sci. U.S.A. 112, 10014–10019.
Fletcher, A.J., et al., 2015. TRIM5α requires Ube2W to anchor Lys63-linked ubiquitin chains and restrict reverse transcription. EMBO J. 34, 1–18.
Franchi, L., et al., 2008. Intracellular NOD-like receptors in innate immunity, infection and disease. Cell. Microbiol. 10, 1–8.
Franchi, L., Warner, N., Viani, K., Nuñez, G., 2009. Function of Nod-like receptors in microbial recognition and host defense. Immunol. Rev. 227, 106–128.
Fu, B., et al., 2015. TRIM32 senses and restricts influenza A virus by ubiquitination of PB1 polymerase. PLoS Pathog. 11, 1–23.
Fujimoto, M., et al., 1997. Prevalence and clinical relevance of 52-kDa and 60-kDa Ro/SS-A autoantibodies in Japanese patients with systemic sclerosis. Ann. Rheum. Dis. 56, 667–670.
Furr, S.R., Moerdyk-Schauwecker, M., Grdzelishvili, V.Z., Marriott, I., 2010. RIG-I mediates nonsegmented negative-sense RNA virus–induced inflammatory immune responses of primary human astrocytes. Glia 58, 1620–1629.
Gack, M.U., 2014. Mechanisms of RIG-I-like receptor activation and manipulation by viral pathogens. J. Virol. 88, 5213–5216.
Gack, M.U., et al., 2007. TRIM25 RING-finger E3 ubiquitin ligase is essential for RIG-I-mediated antiviral activity. Nature 446, 916–920.
Gallouet, A.-S., et al., 2017. Macrophage production and activation are dependent on TRIM33. Oncotarget 8, 5111–5122.
Ganser-Pornillos, B.K., et al., 2011. Hexagonal assembly of a restricting TRIM5 protein. Proc. Natl. Acad. Sci. U.S.A. 108, 534–539.
Gao, D., et al., 2014. Cyclic GMP-AMP synthase is an innate immune sensor of HIV and other retroviruses. Science 341, 903–906.
Geijtenbeek, T.B.H., Gringhuis, S.I., 2009. Signalling through C-type lectin receptors: shaping immune responses. Nat. Rev. Immunol. 9, 465–479.
Geijtenbeek, T.B., et al., 2000. DC-SIGN, a dendritic cell-specific HIV-1-binding protein that enhances trans-infection of T cells. Cell 100, 587–597.
Gitlin, L., et al., 2006. Essential role of mda-5 in type I IFN responses to polyriboinosinic: polyriboctydilic acid and encephalomyocarditis picornavirus. Proc. Natl. Acad. Sci. U.S.A. 103, 8459–8464.
Gough, D.J., Messina, N.L., Clarke, C.J.P., Johnstone, R.W., Levy, D.E., 2012. Constitutive type I interferon modulates homeostatic balance through tonic signaling. Immunity 36, 759–785.
Gray, E.E., et al., 2016. The AIM2-like receptors are dispensable for the interferon response to intracellular DNA. Immunity 45, 255–266.
Grüttler, M.G., Luban, J., 2012. TRIM5 structure, HIV-1 capsid recognition, and innate immune signaling. Curr. Opin. Virol. 2, 142–150.
Guo, H., Callaway, J.B., Ting, J.P.-Y., 2015. Inflammasomes: mechanism of action, role in disease and therapeutics. Nat. Med. 21, 677–687.
Han, K., Lou, D.I., Sawyer, S.L., 2011. Identification of a genomic reservoir for new trim genes in primate genomes. PLoS Genet. 7 (12), e1002388.
Hashimoto, M., et al., 2006. Lipoprotein is a predominant toll-like receptor 2 ligand in staphylococcus aureus cell wall components. Int. Immunol. 18, 355–362.
Hauer, F., Mallory, D.L., McEwan, W.A., Bidgood, S.R., James, L.C., 2012. AAA ATPase p97/VCP is essential for TRIM21-mediated virus neutralization. Proc. Natl. Acad. Sci. U.S.A. 109, 19733–19738.
Hayashi, F., et al., 2001. The innate immune response to bacterial flagellin is mediated by Toll-like receptor 5. Nature 410, 1099–1103.
Heid, M.E., et al., 2013. Mitochondrial reactive oxygen species induces NLRP3-dependent lysosomal damage and inflammasome activation. J. Immunol. 191, 5230–5238.
Hemmi, H., et al., 2000. A toll-like receptor recognizes bacterial DNA. Nature 408, 740–745.
Higgs, R., Gabhann, J.N., Larbi, N.B., Breen, E.P., Fitzgerald, K.A., Jeffries, C.A., 2008. The E3 ubiquitin ligase Ro52 negatively regulates IFN-β production post-pathogen recognition by polyubiquitin-mediated degradation of IRF3. J. Immunol. 181, 1780–1786.

Higgs, R., et al., 2010. Self protection from anti-viral responses—Ro52 promotes degradation of the transcription factor IRF7 downstream of the viral toll-like receptors. PLoS One 5, 1–7.

Hornung, V., Latz, E., 2010. Critical functions of priming and lysosomal damage for NLRP3 activation. Eur. J. Immunol. 6, 620–623.

Hornung, V., et al., 2009. AIM2 recognizes cytosolic dsDNA and forms a caspase-1 activating inflammasome with ASC. Nature 458, 514–518.

Hornung, V., Hartmann, R., Ablaser, A., Hopfner, K.-P., 2014. OAS proteins and cGAS: unifying concepts in sensing and responding to cytosolic nucleic acids. Nat. Rev. Immunol. 14 (8), 521.

Hoving, J.C., Wilson, G.J., Brown, G.D., 2014. Signalling C-type lectin receptors, microbial recognition and immunity. Cell. Microbiol. 16, 185–194.

Hu, M.-M., Shu, H.-B., 2017. Multifaceted roles of TRIM38 in innate immune and inflammatory responses. Cell. Mol. Immunol. 14, 331–338.

Hu, Y., et al., 2010. Tripartite-motif protein 30 negatively regulates NLRP3 inflammasome activation by modulating reactive oxygen species production. J. Immunol. 185, 7699–7705.

Hu, M.-M., et al., 2014. TRIM38 inhibits TNFα- and IL-1β-triggered NF-κB activation by mediating lysosome-dependent degradation of TAB2/3. Proc. Natl. Acad. Sci. U.S.A. 111, 1509–1514.

Hu, M.-M., et al., 2015. TRIM38 negatively regulates TLR3/4-mediated innate immune and inflammatory responses by two sequential and distinct mechanisms. J. Immunol. 195, 4415–4425.

Hu, M.M., et al., 2016. Sumoylation promotes the stability of the DNA sensor cGAS and the adaptor STING to regulate the kinetics of response to DNA virus. Immunity 45, 555–569.

Huang, B., Baek, S., 2017. Trim13 potentiates toll-like receptor 2-mediated nuclear factor κB activation via K29-linked polyubiquitination of tumor necrosis factor receptor-associated factor 6. Mol. Pharmacol. 91, 307–316.

Huang, Y., et al., 2016a. Fish TRIM8 exerts antiviral roles through regulation of the proinflammatory factors and interferon signaling. Fish Shellfish Immunol. 54, 435–444.

Huang, Y., et al., 2016b. Grouper TRIM13 exerts negative regulation of antiviral immune response against nodavirus. Fish Shellfish Immunol. 55, 106–115.

Ichinohe, T., Lee, H.K., Ogura, Y., Flavell, R., Iwasaki, A., 2009. Inflammasome recognition of influenza virus is essential for adaptive immune responses. J. Exp. Med. 206, 79–87.

Ichinohe, T., Pang, I.K., Iwasaki, A., 2010. Influenza virus activates inflammasomes via its intracellular M2 ion channel. Nat. Immunol. 11, 404–410.

Iqbal, K., Liu, F., Gong, C.-X., 2015. Tau and neurodegenerative disease: the story so far. Nat. Rev. Neurol. 12, 15–27.

Ireton, R.C., Gale, M., 2011. RIG-I like receptors in antiviral immunity and therapeutic applications. Virus 3, 906–919.

James, L.C., Keeble, A.H., Khan, Z., Rhodes, D.a., Trowsdale, J., 2007. Structural basis for PRYSPRY-mediated tripartite motif (TRIM) protein function. Proc. Natl. Acad. Sci. U.S.A. 104, 6200–6205.

Jia, X., et al., 2017. The ubiquitin ligase RNF125 targets innate immune adaptor protein TRIM14 for ubiquitination and degradation. J. Immunol. 198, 1601322. https://doi.org/10.4049/jimmunol.1601322.
Jiang, X., et al., 2012. Ubiquitin-induced oligomerization of the RNA sensors RIG-I and MDA5 activates antiviral innate immune response. Immunity 36, 959–973.

Jiang, S., Li, X., Hess, N.J., Guan, Y., Tapping, R.I., 2016. TLR10 is a negative regulator of both MyD88-dependent and -independent TLR signaling. J. Immunol. 196, 3834–3841.

Jonsson, K.L., et al., 2017. IFI16 is required for DNA sensing in human macrophages by promoting production and function of cGAMP. Nat. Commun. 8, 14391.

Kagan, J.C., Barton, G.M., 2014. Transduction by pattern-recognition receptors, Cold Spring Harb. Perspect. Biol. 1–16.

Kagan, J.C., Barton, G.M., 2016. Emerging principles governing signal transduction by pattern-recognition receptors. Cold Spring Harb. Perspect. Biol. 33, 395–401.

Kahle, T., et al., 2016. TRIM19/PML restricts HIV infection in a cell type-dependent manner. Virus 8, 1–18.

Kajaste-Rudnitski, A., et al., 2011. TRIM22 inhibits HIV-1 transcription independently of its E3 ubiquitin ligase activity, tat, and NF-κB-responsive long terminal repeat elements. J. Virol. 85, 5183–5196.

Kane, M., et al., 2016. Identification of interferon-stimulated genes with antiretroviral activity. Cell Host Microbe 20, 392–405.

Kang, J.Y., et al., 2009. Recognition of lipopeptide patterns by toll-like receptor 2-toll-like receptor 6 heterodimer. Immunity 31, 873–884.

Kanneganti, T.-D., 2010. Central roles of NLRs and inflammasomes in viral infection. Nat. Rev. Immunol. 10, 688–698.

Kawai, T., Akira, S., 2010. The role of pattern-recognition receptors in innate immunity: update on Toll-like receptors. Nat. Immunol. 11, 373–384.

Kawasaki, T., Kawai, T., 2014. Toll-like receptor signaling pathways. Front. Immunol. 5, 1–8.

Kayagaki, N., et al., 2013. Noncanonical inflammasome activation by intracellular lps independent of tlr4. Science 130, 1246–1249.

Keeble, A.H., Khan, Z., Forster, A., James, L.C., 2008. TRIM21 is an IgG receptor that is structurally, thermodynamically, and kinetically conserved. Proc. Natl. Acad. Sci. U.S.A. 105, 6045–6050.

Kell, A.M., Gale Jr., M., 2015. RIG-I in RNA virus recognition. Virology 479–480, 110–121. https://doi.org/10.1016/j.virol.2015.02.017.RIG-I.

Kim, Y.K., Shin, J.S., Nahm, M.H., 2016. NOD-like receptors in infection, immunity, and diseases. Yonsei Med. J. 57, 5–14.

Klasse, P.J., 2014. Review article neutralization of virus infectivity by antibodies: old problems in new perspectives. Adv. Biol. 2014. pii: 157895.

Koliopoulos, M.G., Esposito, D., Christodoulou, E., Taylor, I.A., Rittinger, K., 2016. Functional role of TRIM E 3 ligase oligomerization and regulation of catalytic activity. EMBO J. 35, 1–15.

Kondo, T., Watanabe, M., Hatakeyama, S., 2012. TRIM59 interacts with ECSIT and negatively regulates NF-κB and IRF-3/7-mediated signal pathways. Biochem. Biophys. Res. Commun. 422, 501–507.

Kong, H.J., et al., 2007. Cutting edge: autoantigen Ro52 is an interferon inducible E3 ligase that ubiquitinates IRF-8 and enhances cytokine expression in macrophages. J. Immunol. 179, 26–30.

Koshiba, T., 2013. Mitochondrial-mediated antiviral immunity. Biochim. Biophys. Acta 1833, 225–232.

Kowalinski, E., et al., 2011. Structural basis for the activation of innate immune pattern-recognition receptor RIG-1 by viral RNA. Cell 147, 423–435.

Kranzusch, P.J., Lee, A.S., Berger, J.M., Jennifer, A., 2013. Structure of human cGAS reveals a conserved family of second-messenger enzymes in innate immunity. Cell Rep. 3, 1362–1368.
Krug, A., et al., 2004. TLR9-dependent recognition of MCMV by IPC and DC generates coordinated cytokine responses that activate antiviral NK cell function. Immunity 21, 107–119.

Kutluay, S.B., Perez-Caballero, D., Bieniasz, P.D., 2013. Fates of retroviral core components during unrestricted and TRIM5-restricted infection. PLoS Pathog. 9 (3), e1003214. https://doi.org/10.1371/journal.ppat.1003214.

Kwon, Y.-C., Kang, J.-I., Hwang, S.B., Ahn, B.-Y., 2013. The ribonuclease L-dependent antiviral roles of human 2’,5’-oligoadenylate synthetase family members against hepatitis C virus. FEBS Lett. 587, 156–164.

Lam, E., Stein, S., Falck-Pedersen, E., 2014. Adenovirus detection by the cGAS/STING/TBK1 DNA sensing cascade. J. Virol. 88, 974–981.

Lamkanfi, M., Dixit, V.M., 2014. Review mechanisms and functions of inflammasomes. Cell 157, 1013–1022.

Lang, X., et al., 2016. TRIM65-catalized ubiquitination is essential for MDA5-mediated antiviral innate immunity. J. Exp. Med. 214, 459–473. https://doi.org/10.1084/jem.20160592.

Latsoudis, H., et al., 2017. Differential expression of miR-4520a associated with pyrin mutations in familial mediterranean fever (FMF). J. Cell. Physiol. 232, 1326–1336.

Latz, E., Xiao, T.S., Stutz, A., 2013. Activation and regulation of the inflammasomes. Nat. Rev. Immunol. 13, 397–411.

Laurent-Rolle, M., et al., 2014. The interferon signaling antagonist function of yellow fever virus NS5 protein is activated by type I interferon. Cell Host Microbe 16, 314–327.

Lawrence, T.M., Hudacek, A.W., de Zoete, M.R., Flavell, R.A., Schnell, M.J., 2013. Rabies virus is recognized by the NLRP3 inflammasome and activates interleukin-1 release in murine dendritic cells. J. Virol. 87, 5848–5857.

Lazear, H.M., Diamond, M.S., 2016. New insights into innate immune restriction of west Nile virus infection. Curr. Opin. Virol. 1848, 3047–3054.

Lazzari, E., et al., 2014. TRIPartite motif 21 (TRIM21) differentially regulates the stability of interferon regulatory factor 5 (IRF5) isoforms. PLoS One 9, 1–10.

Lee, Y., Song, B., Park, C., Kwon, K.S., 2013. TRIM11 negatively regulates IFNβ production and antiviral activity by targeting TBK1. PLoS One 8, 1–12.

Lee, S.M.Y., et al., 2014. Toll-like receptor 10 is involved in induction of innate immune responses to influenza virus infection. Proc. Natl. Acad. Sci. U.S.A. 111, 3793–3798.

Lee, J., et al., 2015. TNF-α induced by hepatitis C virus via TLR7 and TLR8 in hepatocytes supports interferon signaling via an autocrine mechanism. PLoS Pathog. 11, 1–19.

Lester, S.N., Li, K., 2014. Toll-like receptors in antiviral innate immunity. J. Mol. Biol. 426, 1246–1264.

Li, J., et al., 2015. DDX19A senses viral RNA and mediates NLRP3-dependent inflammasome activation. J. Immunol. 195, 5732–5749.

Li, Y.L., et al., 2016. Primate TRIM5 proteins form hexagonal nets on HIV-1 capsids. eLife 5, 1–33.

Li, M.M.H., et al., 2017. TRIM25 enhances the antiviral action of zinc-finger antiviral protein (ZAP). PLoS Pathog. 13, 1–25.

Liang, Q., et al., 2011. Tripartite motif-containing protein 28 is a small ubiquitin-related modifier E3 ligase and negative regulator of IFN regulatory factor 7. J. Immunol. 187, 4754–4763.

Lin, R.J., et al., 2009. Distinct antiviral roles for human 2’,5’-oligoadenylate synthetase family members against dengue virus infection. J. Immunol. 183, 8035–8043.

Liu, B., et al., 2014. Overlapping and distinct molecular determinants dictating the antiviral activities of TRIM5α against flaviviruses and coronavirus. J. Virol. 88, 13821–13835.

Liu, T., et al., 2016a. TRIM11 suppresses AIM2 inflammasome by degrading AIM2 via p62-dependent selective autophagy. Cell Rep. 16, 1988–2002.

Lam, E., Stein, S., Falck-Pedersen, E., 2014. Adenovirus detection by the cGAS/STING/TBK1 DNA sensing cascade. J. Virol. 88, 974–981.

Lamkanfi, M., Dixit, V.M., 2014. Review mechanisms and functions of inflammasomes. Cell 157, 1013–1022.

Lang, X., et al., 2016. TRIM65-catalized ubiquitination is essential for MDA5-mediated antiviral innate immunity. J. Exp. Med. 214, 459–473. https://doi.org/10.1084/jem.20160592.

Latz, E., Xiao, T.S., Stutz, A., 2013. Activation and regulation of the inflammasomes. Nat. Rev. Immunol. 13, 397–411.

Laurent-Rolle, M., et al., 2014. The interferon signaling antagonist function of yellow fever virus NS5 protein is activated by type I interferon. Cell Host Microbe 16, 314–327.

Lawrence, T.M., Hudacek, A.W., de Zoete, M.R., Flavell, R.A., Schnell, M.J., 2013. Rabies virus is recognized by the NLRP3 inflammasome and activates interleukin-1 release in murine dendritic cells. J. Virol. 87, 5848–5857.

Lazear, H.M., Diamond, M.S., 2016. New insights into innate immune restriction of west Nile virus infection. Curr. Opin. Virol. 1848, 3047–3054.

Lazzari, E., et al., 2014. TRIPartite motif 21 (TRIM21) differentially regulates the stability of interferon regulatory factor 5 (IRF5) isoforms. PLoS One 9, 1–10.

Lee, Y., Song, B., Park, C., Kwon, K.S., 2013. TRIM11 negatively regulates IFNβ production and antiviral activity by targeting TBK1. PLoS One 8, 1–12.

Lee, S.M.Y., et al., 2014. Toll-like receptor 10 is involved in induction of innate immune responses to influenza virus infection. Proc. Natl. Acad. Sci. U.S.A. 111, 3793–3798.

Lee, J., et al., 2015. TNF-α induced by hepatitis C virus via TLR7 and TLR8 in hepatocytes supports interferon signaling via an autocrine mechanism. PLoS Pathog. 11, 1–19.

Lester, S.N., Li, K., 2014. Toll-like receptors in antiviral innate immunity. J. Mol. Biol. 426, 1246–1264.

Li, J., et al., 2015. DDX19A senses viral RNA and mediates NLRP3-dependent inflammasome activation. J. Immunol. 195, 5732–5749.

Li, Y.L., et al., 2016. Primate TRIM5 proteins form hexagonal nets on HIV-1 capsids. eLife 5, 1–33.

Li, M.M.H., et al., 2017. TRIM25 enhances the antiviral action of zinc-finger antiviral protein (ZAP). PLoS Pathog. 13, 1–25.

Liang, Q., et al., 2011. Tripartite motif-containing protein 28 is a small ubiquitin-related modifier E3 ligase and negative regulator of IFN regulatory factor 7. J. Immunol. 187, 4754–4763.

Lin, R.J., et al., 2009. Distinct antiviral roles for human 2’,5’-oligoadenylate synthetase family members against dengue virus infection. J. Immunol. 183, 8035–8043.

Liu, B., et al., 2014. Overlapping and distinct molecular determinants dictating the antiviral activities of TRIM5α against flaviviruses and coronavirus. J. Virol. 88, 13821–13835.

Liu, T., et al., 2016a. TRIM11 suppresses AIM2 inflammasome by degrading AIM2 via p62-dependent selective autophagy. Cell Rep. 16, 1988–2002.
Liu, B., et al., 2016b. The C-terminal tail of TRIM56 dictates antiviral restriction of influenza A and B viruses by impeding viral RNA synthesis. J. Virol. 90, 4369–4382.

Liu, Y., Olagnier, D., Lin, R., 2017a. Host and viral modulation of RIG-I-mediated antiviral immunity. Front. Immunol. 7, 1–12.

Liu, B., et al., 2017b. The ubiquitin E3 ligase TRIM31 promotes aggregation and activation of the signaling adaptor MAVS through Lys63-linked polyubiquitination. Nat. Immunol. 18, 214–224.

Loo, Y.-M., et al., 2008. Distinct RIG-I and MDA5 signaling by RNA viruses in innate immunity. J. Virol. 82, 335–345.

Lu, Y.C., Yeh, W.C., Ohashi, P.S., 2008. LPS/TLR4 signal transduction pathway. Cytokine 42, 145–151.

Luisoni, S., et al., 2015. Co-option of membrane wounding enables virus penetration into cells. Cell Host Microbe 18, 75–85.

Lukic, Z., et al., 2011. TRIM5α associates with proteasomal subunits in cells while in complex with HIV-1 virions. Retrovirology 8, 93.

Lund, J.M., et al., 2004. Recognition of single-stranded RNA viruses by Toll-like receptor 7. Proc. Natl. Acad. Sci. U.S.A. 101, 5598–5603.

Lusic, M., et al., 2013. Proximity to PML nuclear bodies regulates HIV-1 latency in CD4+ T cells. Cell Host Microbe 13, 665–677.

Maharaj, N.P., Wies, E., Stoll, A., Gack, M.U., 2012. Conventional protein kinase C-α (PKC-α) and PKC-β negatively regulate RIG-I antiviral signal transduction. J. Virol. 86, 1358–1371.

Mäkelä, S.M., et al., 2015. RIG-I signaling is essential for influenza B virus-induced rapid interferon gene expression. J. Virol. 89, 12014–12025.

Malathi, K., Dong, B., Gale, M.J., Silverman, R.H., 2007. Small self-RNA generated by RNase L amplifies antiviral innate immunity. Nature 448, 816–819.

Mallery, D.L., et al., 2010. Antibodies mediate intracellular immunity through tripartite motif-containing 21 (TRIM21). Proc. Natl. Acad. Sci. U.S.A. 107, 19985–19990.

Manukyan, G., Aminov, R., 2016. Update on pyrin functions and mechanisms of familial Mediterranean fever. Front. Microbiol. 7, 1–8.

Marín, I., 2012. Origin and diversification of TRIM ubiquitin ligases. PLoS One 7 (11), e50030. https://doi.org/10.1371/journal.pone.0050030.

Mastroori, N., Merindol, N., Berthoux, L., 2016. The interferon-induced antiviral protein PML (TRIM19) promotes the restriction and transcriptional silencing of lentiviruses in a context-specific, isoform-specific fashion. Retrovirology 13, 19.

Masters, S.L., et al., 2016. Familial autoinflammation with neutrophilic dermatosis reveals a regulatory mechanism of pyrin activation. Sci. Transl. Med. 8, 332ra45.

McCartney, S.A., et al., 2008. MDA-5 recognition of a murine norovirus. PLoS Pathog. 4, 1–7.

McEwan, W.A., et al., 2012. Regulation of virus neutralization and the persistent fraction by TRIM21. J. Virol. 86, 8482–8491.

McEwan, W.A., et al., 2013. Intracellular antibody-bound pathogens stimulate immune signaling via the Fc receptor TRIM21. Nat. Immunol. 14, 327–336.

McEwan, W.A., et al., 2017. Cytosolic Fc receptor TRIM21 inhibits seeded tau aggregation. Proc. Natl. Acad. Sci. U.S.A. 114, 201607215.

Metzger, M.B., Hristova, V.A., Weissman, A.M., 2012. HECT and RING finger families of E3 ubiquitin ligases at a glance. J. Cell Sci. 125, 531–537.

Minamitani, T., Iwakiri, D., Takada, K., 2011. Adenovirus virus-associated RNAs induce type I interferon expression through a RIG-I-mediated pathway. J. Virol. 85, 4035–4040.

Mitchell, A.M., Hirsch, M.L., Li, C., Samulski, R.J., 2014. Promyelocytic leukemia protein is a cell-intrinsic factor inhibiting parvovirus DNA replication. J. Virol. 88, 925–936.
Mitoma, H., et al., 2013. The DHX33 RNA helicase senses cytosolic RNA and activates the NLRP3 inflammasome. Immunity 39, 123–135.
Monteith, A.J., et al., 2016. Defects in lysosomal maturation facilitate the activation of innate sensors in systemic lupus erythematosus. Proc. Natl. Acad. Sci. U.S.A. 113, E2142–E2151.
Moore, C.B., et al., 2008. NLRX1 is a regulator of mitochondrial antiviral immunity. Nature 451, 573–577.
Muñoz-Planillo, R., Kuffa, P., Giovanny Martínez-Colón, B.L.S., Rajendiran, T.M., Núñez, G., 2013. K+ efflux is the common trigger of NLRP3 inflammasome activation by bacterial toxins and particulate matter. Immunity 38, 1142–1153.
Murawski, M.R., et al., 2009. Respiratory syncytial virus activates innate immunity through Toll-like receptor 2. J. Virol. 83, 1492–1500.
Narayan, K., et al., 2014. TRIM13 is a negative regulator of MDA5–mediated type I interferon production. J. Virol. 88, 10748–10757.
Nenasheva, V.V., et al., 2015. Enhanced expression of trim14 gene suppressed Sindbis virus reproduction and modulated the transcription of a large number of genes of innate immunity. Immunol. Res. 62, 255–262.
Nisole, S., Stoye, J.P., Saïb, A., 2005. TRIM family proteins: retroviral restriction and antiviral defence. Nat. Rev. Microbiol. 3, 799–808.
Noguchi, K., et al., 2011. Trim40 promotes neddylation of IKKα and is downregulated in gastrointestinal cancers. Carcinogenesis 32, 995–1004.
Odendall, C., Kagan, J.C., 2017. Activation and pathogenic manipulation of the sensors of the innate immune system. Microbes Infect. 19, 229–237. https://doi.org/10.1016/j.micinf.2017.01.003.
Oke, V., Wahren-Herlenius, M., 2012. The immunobiology of Ro52 (TRIM21) in autoimmunity: a critical review. J. Autoimmun. 39, 77–82.
Okumura, F., Matsunaga, Y., Katayama, Y., Nakayama, K.I., Hatakeyama, S., 2010. TRIM8 modulates STAT3 activity through negative regulation of PIAS3. J. Cell Sci. 123, 2238–2245.
Oliveira-Nascimento, L., Massari, P., Wetzler, L.M., 2012. The role of TLR2 in infection and immunity. Front. Immunol. 3, 1–17.
Oosting, M., et al., 2014. Human TLR10 is an anti-inflammatory pattern-recognition receptor. Proc. Natl. Acad. Sci. U.S.A. 111, E4478–E4484.
Osorio, F., Reis e Sousa, C., 2011. Myeloid C–type lectin receptors in pattern recognition and host defense. Immunity 34, 651–664.
Ozato, K., Shin, D.-M., Chang, T.-H., Morse, H.C., 2008. TRIM family proteins and their emerging roles in innate immunity. Nat. Rev. Immunol. 8, 849–860.
Ozato, K., Shin, D., Chang, T., Morse, H., 2012. TRIM family proteins and their emerging roles in innate immunity. Nat. Rev. Immunol. 8, 849–860.
Paijo, J., et al., 2016. cGAS senses human cytomegalovirus and induces type I interferon responses in human monocyte–derived cells. PLoS Pathog. 12, 1,–24.
Papon, L., et al., 2009. The viral RNA recognition sensor RIG-I is degraded during encephalomyocarditis virus (EMCV) infection. Virology 393, 311–318.
Park, Y.H., Wood, G., Kastner, D.L., Chae, J.J., 2016. Pyrin inflammasome activation and RhoA signaling in the autoinflammatory diseases FMF and HIDS. Nat. Immunol. 17, 914–921.
Parvatiyar, K., Cheng, G., 2011. NOD so fast: NLRX1 puts the brake on inflammation. Immunity 34, 821–822.
Peisley, A., Wu, B., Yao, H., Walz, T., Hur, S., 2013. RIG-I forms signaling-competent filaments in an ATP-dependent, ubiquitin-independent manner. Mol. Cell 51, 573–583.
Peisley, A., Wu, B., Xu, H., Chen, Z.J., Hur, S., 2014. Structural basis for ubiquitin-mediated antiviral signal activation by RIG-I. Nature 509, 110–114.
Pertel, T., et al., 2011. TRIM5 is an innate immune sensor for the retrovirus capsid lattice. Nature 472, 361–365.

Perwitasari, O., Cho, H., Diamond, M.S., Gale, M., 2011. Inhibitor of kB kinase ε (IKKε), STAT1, and IFIT2 proteins define novel innate immune effector pathway against West Nile virus infection. J. Biol. Chem. 286, 44412–44423.

Poole, E., et al., 2009. Identification of TRIM23 as a cofactor involved in the regulation of NF-κB by human cytomembranovirus. J. Virol. 83, 3581–3590.

Qin, Y., et al., 2016. TRIM9 short isoform preferentially promotes DNA and RNA virus-induced production of type I interferon by recruiting GSK3β to TBK1. Cell Res. 26, 613–628.

Rajan, J.V., Warren, S.E., Miao1, E.A., Aderem, A., 2010. Activation of the NLRP3 inflammasome by intracellular poly I:C. FEBS Lett. 584, 4627–4632.

Rajan, J.V., Rodriguez, D., Miao, E.A., Aderem, A., 2011. The NLRP3 inflammasome detects encephalomyocarditis virus and vesicular stomatitis virus infection. J. Virol. 85, 4167–4172.

Rajsbaum, R., Versteeg, G.A., Schmid, S., Maestre, A.M., Belicha-Villanueva, A., Martínez-Romero, C., Patel, J.R., Morrison, J., Pisanelli, G., Miorin, L., Laurent-Rolle, M., Moulton, H.M., Stein, D.A., Fernandez-Ses, A., Sastre, A.G., 2014. Unanchored K48-linked poly-ubiquitin synthesized by the E3-ubiquitin ligase TRIM6 stimulates the interferon-IKKε kinase mediated antiviral response. Immunity 40, 880–895.

Rallabhandi, P., et al., 2012. Respiratory syncytial virus fusion protein-induced toll-like receptor 4 (TLR4) signaling is inhibited by the TLR4 antagonists Rhodobacter sphaeroides lipopolysaccharide and eritoran (E5564) and requires direct interaction with MD-2. mBio 3 (4), e00218-12. https://doi.org/10.1128/mBio.00218-12.

Ran, Y., et al., 2016. Autoubiquitination of TRIM 26 links TBK 1 to NEMO in RLR-mediated innate antiviral immune response. J. Mol. Cell Biol. 8, 31–43.

Rasmussen, S.B., et al., 2009. Herpes simplex virus infection is sensed by both toll-like receptors and RIG-like receptors, which synergize to induce type I interferon production. J. Virol. 90, 74–78.

Rathinam, V.A.K., et al., 2010. The AIM2 inflammasome is essential for host defense against cytosolic bacteria and DNA viruses. Nat. Immunol. 11, 395–402.

Ratsimandresy, R.A., Dorfleutner, A., Stehlik, C., 2013. An update on PYRIN domain-containing pattern recognition receptors: from immunity to pathology. Front. Immunol. 4, 1–20.

Rehwinkel, J., et al., 2010. RIG-I detects viral genomic RNA during negative-strand RNA virus infection. Cell 140, 397–408.

Reinert, L.S., et al., 2016. Sensing of HSV-1 by the cGAS-STING pathway in microglia orchestrates antiviral defense in the CNS. Nat. Commun. 7, 13348.

Richards, N., et al., 2001. Interaction between pyrin and the apoptotic speck protein (ASC) modulates ASC-induced apoptosis. J. Biol. Chem. 276, 39320–39329.

Roa, A., et al., 2012. RING domain mutations uncouple TRIM5 restriction of HIV-1 from inhibition of reverse transcription and acceleration of uncoating. J. Virol. 86, 1717–1727.

Rogozin, I.B., Aravind, L., Koonin, E.V., 2003. Differential action of natural selection on the N and C-terminal domains of 20k−5′ oligoadenylate synthetases and the potential nuclease function of the C-terminal domain. J. Mol. Biol. 326, 1449–1461.

Rold, C.J., Aiken, C., 2008. Proteasomal degradation of TRIM5α during retrovirus restriction. PLoS Pathog. 4 (5), e1000074. https://doi.org/10.1371/journal.ppat.1000074.

Roopenian, D.C., Akilesh, S., 2007. FcRn: the neonatal Fc receptor comes of age. Nat. Rev. Immunol. 7, 715–725.

Sabbah, A., et al., 2009. Activation of innate immune antiviral responses by Nod2. Nat. Immunol. 10, 1073–1080.
Saito, T., Owen, D.M., Jiang, F., Marcotrigiano, J., Gale Jr., M., 2008. Innate immunity induced by composition-dependent RIG-I recognition of hepatitis C virus RNA. Nature 454, 523–527.

Saitoh, T., et al., 2006. Negative regulation of interferon-regulatory factor 3-dependent innate antiviral response by the prolyl isomerase Pin1. Nat. Immunol. 7, 598–605.

Sanchez, J.G., et al., 2016. Mechanism of TRIM25 catalytic activation in the antiviral RIG-I pathway. Cell Rep. 16, 1315–1325.

Sancho, D., Reis e Sousa, C., 2012. Signaling by myeloid C-type lectin receptors in immunity and homeostasis. Annu. Rev. Immunol. 30, 491–529.

Sayah, D.M., Sokolskaja, E., Berthoux, L., Luban, J., 2004. Cyclophilin A retrotransposition into TRIM5 explains owl monkey resistance to HIV–1. Nature 430, 569–573.

Schenk, M., Belisle, J.T., Modlin, R.L., 2009. TLR2 looks at lipoproteins. Immunity 31, 847–849.

Schilling, E.-M., Scherer, M., Reuter, N., Schweininger, J., Muller, Y.A., Stamminger, T., 2017. The human cytomegalovirus IE1 protein antagonizes PML nuclear body-mediated intrinsic immunity via the inhibition of PML de novo SUMOylation. J. Virol. 91, 1–17.

Schlee, M., 2013. Master sensors of pathogenic RNA–RIG-I like receptors. Immunobiology 218, 1322–1335.

Schoggins, J.W., et al., 2014. Pan-viral specificity of IFN-induced genes reveals new roles for cGAS in innate immunity. Nature 505, 691–695.

Shen, Y., et al., 2012. TRIM56 is an essential component of the TLR3 antiviral signaling pathway. J. Biol. Chem. 287, 36404–36413.

Shi, M., et al., 2008. TRIM30α negatively regulates TLR-mediated NF-κB activation by targeting TAB2 and TAB3 for degradation. Nat. Immunol. 9, 369–377.

Shibata, M., Sato, T., Nukiwa, R., Ariga, T., Hatakeyama, S., 2012. TRIM45 negatively regulates NF-κB-mediated transcription and suppresses cell proliferation. Biochem. Biophys. Res. Commun. 423, 104–109.

Shimizu, A., et al., 2014. Characterisation of cytoplasmic DNA complementary to non-retroviral RNA viruses in human cells. Sci. Rep. 4, 1–9.

Singh, R., et al., 2011. Association of TRIM22 with the type 1 interferon response and viral control during primary HIV-1 infection. J. Virol. 85, 208–216.

Song, H., et al., 2016. The E3 ubiquitin ligase TRIM31 attenuates NLRP3 inflammasome activation by promoting proteasomal degradation of NLRP3. Nat. Commun. 7, 13727.

Stapleton, N.M., et al., 2011. Competition for FcRn-mediated transport gives rise to short half-life of human IgG3 and offers therapeutic potential. Nat. Commun. 2, 599.

Stein, S.C., Falck-Pedersen, E., 2012. Sensing adenovirus infection: activation of interferon regulatory factor 3 in RAW 264.7 cells. J. Virol. 86, 4527–4537.

Stremlau, M., et al., 2004. The cytoplasmic body component TRIM5alpha restricts HIV-1 infection in Old World monkeys. Nature 427, 848–853.

Stremlau, M., et al., 2006. Specific recognition and accelerated uncoating of retroviral capsids by the TRIM5 restriction factor. Proc. Natl. Acad. Sci. U.S.A. 103, 5514–5519.

Sun, Z., Ren, H., Liu, Y., Teeling, J.L., Gu, J., 2011. Phosphorylation of RIG-I by casein kinase II inhibits its antiviral response. J. Virol. 85, 1036–1047.

Sun, L., Wu, J., Du, F., Chen, X., Chen, Z.J., 2013. Cyclic GMP-AMP synthase is a cytosolic DNA sensor that activates the type-I interferon pathway. Science 257, 2432–2437.

Sun, X., et al., 2016. A hierarchical mechanism of RIG-I ubiquitination provides sensitivity, robustness and synergy in antiviral immune responses. Sci. Rep. 6, 29263.

Tabah, A.A., Tardif, K., Mansky, L.M., 2014. Anti-HIV–1 activity of trim 37. J. Gen. Virol. 95, 960–967.

Takeda, K., Akira, S., 2005. Toll-like receptors in innate immunity. Int. Immunol. 17, 1–14.
Tassaneetrithep, B., et al., 2003. DC-SIGN (CD209) mediates dengue virus infection of human dendritic cells. J. Exp. Med. 197, 823–829.

Tatematsu, M., Nishikawa, F., Seya, T., Matsumoto, M., 2013. Toll-like receptor 3 recognizes incomplete stem structures in single-stranded viral RNA. Nat. Commun. 4, 1833.

Tatematsu, M., Seya, T., Matsumoto, M., 2014. Beyond dsRNA: toll-like receptor 3 signaling in RNA-induced immune responses. Biochem. J. 458, 195–201.

Taylor, R. T., et al., 2012. TRIM79α, an interferon-stimulated gene product, restricts tick-borne encephalitis virus replication by degrading the viral RNA polymerase. Cell Host Microbe 10, 185–196.

Thompson, M. R., Kaminski, J. J., Kurt-Jones, E. A., Fitzgerald, K. A., 2011. Pattern recognition receptors and the innate immune response to viral infection. Virus 3, 920–940.

Tomar, D., Singh, R., 2014. TRIM13 regulates ubiquitination and turnover of NEMO to suppress TNF induced NF-κB activation. Cell. Signal. 26, 2606–2613.

Triantafilou, K., et al., 2005. Human cardiac inflammatory responses triggered by coxsackie B viruses are mainly toll-like receptor (TLR) 8-dependent. Cell. Microbiol. 7, 1117–1126.

Tsuchida, T., et al., 2010. The ubiquitin ligase TRIM56 regulates innate immune responses to intracellular double-stranded DNA. Immunity 33, 765–776.

Turelli, P., et al., 2001. Cytoplasmic recruitment of INI1 and PML on incoming HIV pre-integration complexes: interference with early steps of viral replication. Mol. Cell 7, 1245–1254.

Turrini, F., et al., 2015. HIV-1 transcriptional silencing caused by TRIM22 inhibition of Sp1 binding to the viral promoter. Retrovirology 12, 104.

Uchil, P. D., Quinlan, B. D., Chan, W. T., Luna, J. M., Mothes, W., 2008. TRIM E3 ligases interfere with early and late stages of the retroviral life cycle. PLoS Pathog. 4 (2), e16. https://doi.org/10.1371/journal.ppat.0040016.

Uchil, P. D., et al., 2013. TRIM protein–mediated regulation of inflammatory and innate immune signaling and its association with antiretroviral activity. J. Virol. 87, 257–272.

Unterholzner, L., et al., 2010. IFI16 is an innate immune sensor for intracellular DNA. Nat. Immunol. 11, 997–1004.

Vajjhala, P. R., et al., 2014. Identification of multifaceted binding modes for pyrin and ASC pyrin domains gives insights into pyrin inflammasome assembly. J. Biol. Chem. 289, 23504–23519.

Vance, R. E., 2016. Cytosolic DNA sensing: the field narrows. Immunity 45, 227–228.

Vaysburd, M., et al., 2013. Intracellular antibody receptor TRIM21 prevents fatal viral infection. Proc. Natl. Acad. Sci. U.S.A. 110, 12397–12401.

Villano, J. S., Rong, F., Cooper, T. K., 2014. Bacterial infections in Myd88-deficient mice. Comp. Med. 64, 110–114.

Wagenknecht, N., et al., 2015. Contribution of the major ND10 proteins PML, hDaxx and sp100 to the regulation of human cytomegalovirus latency and lytic replication in the monocytic cell line THP-1. Virus 7, 2884–2907.

Wagner, J. M., et al., 2016. Mechanism of B-box 2 domain-mediated higher-order assembly of the retroviral restriction factor TRIM5α. eLife 5, 1–26.

Wang, C. H., et al., 2011a. TLR7 and TLR8 gene variations and susceptibility to hepatitis C virus infection. PLoS One 6, 6–13.

Wang, J., et al., 2011b. TRIM56 is a virus- and interferon-inducible E3 ubiquitin ligase that restricts pestivirus infection. J. Virol. 85, 3733–3745.

Wang, X., et al., 2014. RNA viruses promote activation of the NLRP3 inflammasome through a RIP1–RIP3–DRP1 signaling pathway. Nat. Immunol. 15, 1126–1133.

Wang, P., Zhao, W., Zhao, K., Zhang, L., Gao, C., 2015a. TRIM26 negatively regulates interferon beta production and antiviral response through polyubiquitination and degradation of nuclear IRF3. PLoS Pathog. 11, e1004726.
Wang, Y., et al., 2015b. TRIM35 negatively regulates TLR7- and TLR9-mediated type I interferon production by targeting IRF7. FEBS Lett. 589, 1322–1330.

Wang, S., et al., 2016. TRIM14 inhibits hepatitis C virus infection by SPRY domain-dependent targeted degradation of the viral NS5A protein. Sci. Rep. 6, 32336.

Watkinson, R.E., Tam, J.C., Vaysburd, M.J., James, L.C., 2013. Simultaneous neutralization and innate immune detection of a replicating virus by TRIM21. J. Virol. 87, 7309–7313.

Watkinson, R.E., McEwan, W.A., Tam, J.C.H., Vaysburd, M., James, L.C., 2015. TRIM21 promotes cGAS and RIG-I sensing of viral genomes during infection by antibody-opsonized virus. PLoS Pathog. 11 (10), e1005253. https://doi.org/10.1371/journal.ppat.1005253.

Weng, L., et al., 2014. The E3 ubiquitin ligase tripartite motif 33 is essential for cytosolic RNA-induced NLRP3 inflammasome activation. J. Immunol. 193, 3676–3682.

Wies, E., Wang, M.K., Maharaj, N.P., Chen, K., Shenghua Zhou, R., Finberg, W., Gack, M.U., 2013. Dephosphorylation of the RNA sensors RIG-I and MDA5 by the phosphatase PP1 is essential for innate immune signaling. Immunity 38, 437–449.

Wilson, S.J., et al., 2008. Independent evolution of an antiviral TRIMCyp in rhesus macaques. Proc. Natl. Acad. Sci. U.S.A. 105, 3557–3562.

Wolf, D., Goff, S.P., 2007. TRIM28 mediates primer binding site-targeted silencing of murine leukemia virus in embryonic cells. Cell 131, 46–57.

Wu, X., Anderson, J.L., Campbell, E.M., Joseph, A.M., Hope, T.J., 2006. Proteasome inhibitors uncouple rhesus TRIM5alpha restriction of HIV-1 reverse transcription and infection. Proc. Natl. Acad. Sci. U.S.A. 103, 7465–7470.

Wu, B., et al., 2013a. Structural basis for dsRNA recognition, filament formation, and antiviral signal activation by MDA5. Cell 152, 276–289.

Wu, J., Sun, L., Chen, X., Du, F., Shi, H., Chen, C., Chen, Z.J., 2013b. Cyclic-GMP-AMP is an endogenous second messenger in innate immune signaling by cytosolic DNA. Science 339, 826–830.

Wynne, C., et al., 2014. TRIM68 negatively regulates IFN beta production by degrading TRK fused gene, a novel driver of IFN beta downstream of anti-viral detection systems. PLoS One 9 (7), e101503.

Xia, X., Cui, J., Wang, H.Y., Liang, Z., Matsueda, S., Wang, Q., Yang, X., Hong, J., Songyang, Z., Chen, Z.J., Wang, R.–F., 2011. NLRX1 negatively regulates TLR–induced NF–kB signaling by targeting. Immunity 34, 843–853.

Xing, J., et al., 2016. Identification of a role for TRIM29 in the control of innate immunity in the respiratory tract. Nat. Immunol. 17, 1373–1380.

Xu, H., et al., 2014. Innate immune sensing of bacterial modifications of Rho GTPases by the Pyrin inflammasome. Nature 513, 237–241.

Xue, Q., et al., 2012. TRIM38 negatively regulates TLR3-mediated IFN–β signaling by targeting TRIF for degradation. PLoS One 7 (10), e46825.

Yan, J., Li, Q., Mao, A., Hu, M., Shu, H., 2014. TRIM4 modulates type I interferon induction and cellular antiviral response by targeting RIG-I for K 63-linked ubiquitination. J. Mol. Cell Biol. 6, 154–163.

Yang, K., et al., 2009. TRIM21 is essential to sustain IFN regulatory factor 3 activation during antiviral response. J. Immunol. 182, 3782–3792.

Yang, B., et al., 2013. Novel function of Trim44 promotes an antiviral response by stabilizing VISA. J. Immunol. 190, 3613–3619.

Yang, C., et al., 2016. Interferon alpha (IFNα)-induced TRIM22 interrupts HCV replication by ubiquitinating NS5A. Cell. Mol. Immunol. 13, 94–102.

Yap, M.W., Nisole, S., Lynch, C., Stoye, J.P., 2004. Trim5alpha protein restricts both HIV–1 and murine leukemia virus. Proc. Natl. Acad. Sci. U.S.A. 101, 10786–10791.

Yoshimi, R., et al., 2010. Gene disruption study reveals a non-redundant role for TRIM21/RO52 in NF-κB-dependent cytokine expression in fibroblasts. J. Immunol. 182, 7527–7538.
Yu, J.-W., et al., 2006. Cryopyrin and pyrin activate caspase-1, but not NF-κB, via ASC oligomerization. Cell Death Differ. 13, 236–249.

Yuan, T., Yao, W., Huang, F., Sun, B., Yang, R., 2014. The human antiviral factor TRIM11 is under the regulation of HIV-1 Vpr. PLoS One 9 (8), e104269. https://doi.org/10.1371/journal.pone.0104269.

Yuan, T., Yao, W., Tokunaga, K., Yang, R., Sun, B., 2016. An HIV-1 capsid binding protein TRIM11 accelerates viral uncoating. Retrovirology 13, 72.

Zeng, W., et al., 2010. Reconstitution of the RIG-I pathway reveals a signaling role of unanchored polyubiquitin chains in innate immunity. Cell 141, 315–330.

Zhang, Z., et al., 2012a. The E3 ubiquitin ligase TRIM21 negatively regulates the innate immune response to intracellular double-stranded DNA. Nat. Immunol. 14, 172–178.

Zhang, J., Hu, M.M., Wang, Y.Y., Shu, H.B., 2012b. TRIM32 protein modulates type I interferon induction and cellular antiviral response by targeting MITA/STING protein for K63-linked ubiquitination. J. Biol. Chem. 287, 28646–28655.

Zhang, S., Guo, J.T., Wu, J.Z., Yang, G., 2013. Identification and characterization of multiple TRIM proteins that inhibit hepatitis B virus transcription. PLoS One 8 (8), e70001. https://doi.org/10.1371/journal.pone.0070001.

Zhao, Y., Shao, F., 2015. The NAIP-NLRC4 inflammasome in innate immune detection of bacterial flagellin and type III secretion apparatus. Immunol. Rev. 265, 85–102.

Zhao, Y., et al., 2011. The NLRC4 inflammasome receptors for bacterial flagellin and type III secretion apparatus. Nature 477, 596–600.

Zhao, W., Wang, L., Zhang, M., Yuan, C., Gao, C., 2012a. E3 ubiquitin ligase tripartite motif 38 negatively regulates TLR-mediated immune responses by proteasomal degradation of TNF receptor-associated factor 6 in macrophages. J. Immunol. 188, 2567–2574.

Zhao, W., et al., 2012b. Tripartite motif-containing protein 38 negatively regulates TLR3/4- and RIG-I-mediated IFN- production and antiviral response by targeting NAP1. J. Immunol. 188, 5311–5318.

Zheng, X., et al., 2017. TRIM25 is required for the antiviral activity of zinc-finger antiviral protein (ZAP). J. Virol. 91, JVI.00088–17.

Zhou, Z., et al., 2014. TRIM14 is a mitochondrial adaptor that facilitates retinoic acid-inducible gene-I-like receptor-mediated innate immune response. Proc. Natl. Acad. Sci. U.S.A. 111, E245–E254.

Zhu, J., Huang, X., Yang, Y., 2007. Innate immune response to adenoviral vectors is mediated by both toll-like receptor-dependent and -independent pathways. J. Virol. 81, 3170–3180.

Zhu, J., Zhang, Y., Ghosh, A., Cuevas, R.A., Forero, A., Dhar, J., Ibsen, M.S., Schmidt-Burgk, J.L., Schmidt, T., Ganapatiraju, M.K., Fujita, T., Hartmann, R., Barik, S., Hornung, V., Coyne, C.B., Sarkar, S.N., 2014. Antiviral activity of human oligoadenylate synthetases-like (OASL) is mediated by enhancing retinoic acid-inducible gene I (RIG-I) signaling. Immunity 40, 936–948.

Zhu, J., Ghosh, A., Sarkar, S.N., 2015. OASL—a new player in controlling antiviral innate immunity. Curr. Opin. Virol. 12, 15–19.

Zurek, B., et al., 2012. TRIM27 negatively regulates NOD2 by ubiquitination and proteasomal degradation. PLoS One 7 (7), e41255. https://doi.org/10.1371/journal.pone.0041255.