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CHAPTER THIRTEEN

Intracellular Antiviral Immunity

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Contents

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.

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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 calicivirus
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

IBV	influenza B virus
IFI16	interferon-γ-inducible protein 16
IFN	interferon
IRF	interferon regulatory factor
ISG	interferon-stimulated gene
IκB	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	iligoadenylate 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

SinV	Sindbis virus
SLE	systemic lupus erythematosus
STAT	signal transducers and activators of transcription
STING	stimulator of IFN genes
SUMO	small ubiquitin-like modifier
TAB	TGF-beta-activated kinase
TANK	TRAF family member-associated NF-κB activator
TBEV	Tick-borne encephalitis virus
TBK1	TANK-binding kinase 1
TGF	transforming growth factor
TIR domain	Toll/interleukin-1 receptor domain
TLR	Toll-like receptor
TNF	tumor necrosis factor
TRAF	TNF receptor-associated factor
TRIF	TIR-domain-containing adapter-inducing interferon-β
TRIM	tripartite motif-containing protein
VSV	vesicular stomatitis virus
VV	vaccinia virus
WNV	West Nile virus
YFV	yellow fever virus
ZAP	zinc finger antiviral protein

1. 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) (Tassaneetrithep 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 CLRs 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 signaling pathways, transcriptional regulation, and autophagy. Inflammasome formation 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; Lamkanfi 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, CLRs, 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 (Ratsimandresey 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 not 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 (Jønsson 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 *R*ING domain, a *B*-box domain, and a *c*oiled-*c*oil 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 IKKε via its PRYSPRY, mediate its K48-linked ubiquitination, and thus activate IKKε 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 PRYSPRY 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

Table 1 The Role of TRIM Proteins in Innate Immunity

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		K63-linked ubiquitination and subsequent activation of TAK-1	Okumura et al. (2010)
	Epinephelus coioides TRIM8 restricts Singapore grouper iridovirus (SGIV)	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)

Continued

Table 1 The Role of TRIM Proteins in Innate Immunity—cont'd

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		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		Uchil et al. (2013)
	Restriction of retroviruses	HIV-1, N-MLV	Inhibition of viral release through interaction of the B-box with the Gag precursor protein	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 life cycle	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 parvoviruses	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. (2015); 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

Table 1 The Role of TRIM Proteins in Innate Immunity—cont'd

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)
	Negative regulation of type I IFN signaling pathway	VSV	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	Transcriptional repression	Wolf and Goff (2007); Wolf and Goff (2007)
		HIV-1	Inhibition of HIV-1 integration	Allouch et al. (2011); Figueiredo and Hope (2011)
	Negative regulation of the IRF7 signaling pathway	VSV	SUMOylation of IRF7	Liang et al. (2011)
TRIM29	Negative regulation of NF-κB and type I IFN signaling pathways	IAV	Ubiquitination and subsequent degradation of NEMO in alveolar macrophages	Xing et al. (2016)
TRIM30	Negative regulation of NF-κB signaling		TRIM30α facilitates degradation of TAB2 and TAB3	Shi et al. (2008)
	Negative regulation of NLRP3 inflammasome activation		Attenuation of ROS production	Hu et al. (2010)
TRIM31	Negative regulation of NLRP3 inflammasome activation		K48-linked ubiquitination and proteasomal degradation of NLRP3	Song et al. (2016)
	Positive regulation of the RLR signaling pathway	SeV	K63-linked polyubiquitination of MAVS which promotes MAVS aggregation	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		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)

Continued

Table 1 The Role of TRIM Proteins in Innate Immunity—cont'd

TRIM 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

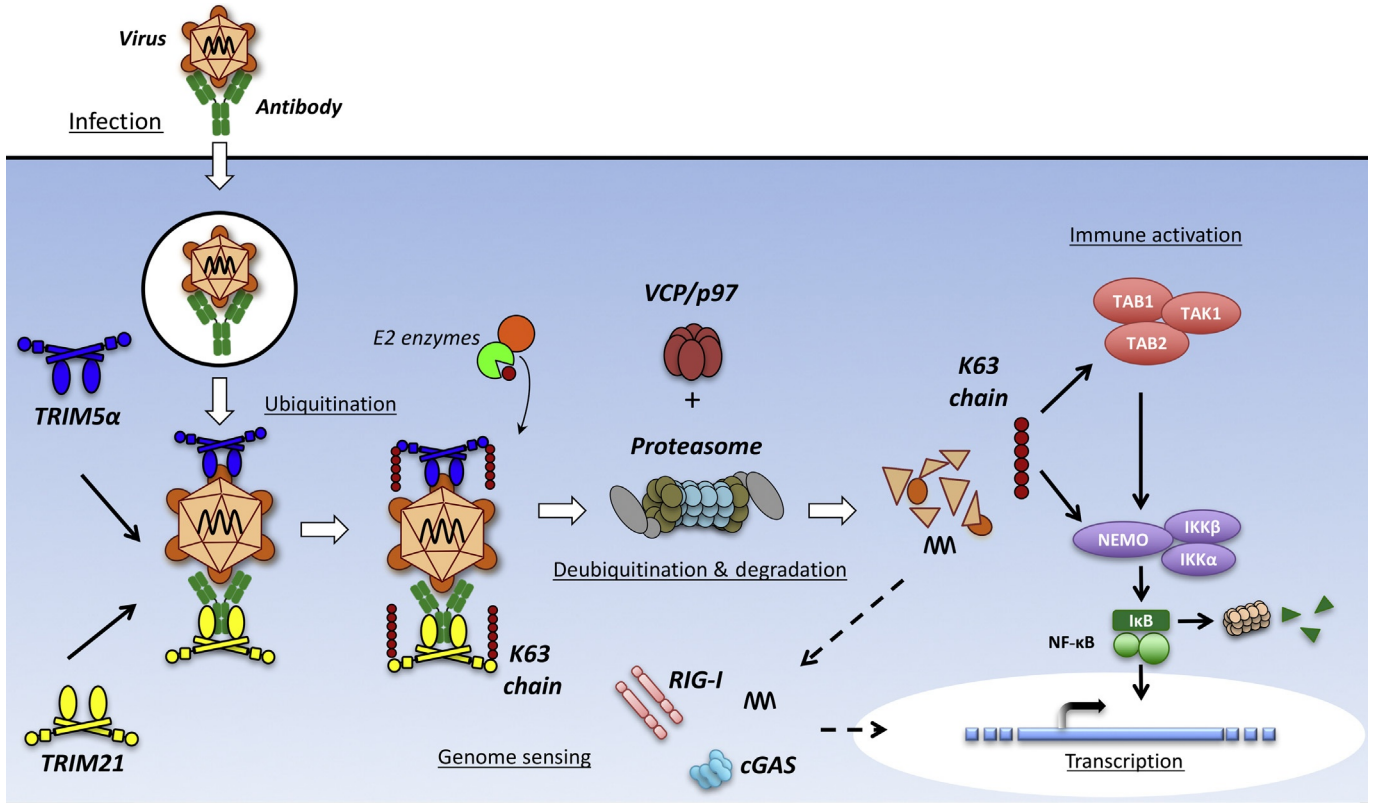

Fig. 1 The antibody-coated virus enters the cell and accesses the cytosol, where TRIM21 can bind the Fc region of the antibody; in case of a retrovirus, TRIM5α is able to bind to the viral capsid. Both TRIM21 and TRIM5α will recruit Ube2W resulting in N-terminal monoubiquitination. The E2 enzyme complex 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 erythematosus, 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 eartagging. 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 eartagging (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.

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