INTI JOURNAL | Vol.2026, Issue 2, No.7
eISSN:2600-7320

A Scoping Review on Tripartite Motif (TRIM) Proteins in Cellular Defense against Viruses

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Abstract

For centuries, immune recognition was attributed to either innate immunity or adaptive immunity. Some of these invading viruses have been reported to be able to breach the innate defenses and escape the humoral immunity and cell-mediated response of adaptive immunity. Therefore, comprehensive immunity requires that cells to sense intracellular intruders, including viruses. The literature search was conducted following PRISMA guidelines. Database searches included PubMed, ScienceDirect, and Scopus. Studies addressing tripartite motif (TRIM) proteins, viruses, and intracellular immunity were included. A new mechanism referred to as intracellular immunity mediated by TRIM proteins is able to recognize and kill viruses. These intracellular proteins work by neutralizing a virus by interfering with its ability to infect host cells. However, at present we only have a limited understanding of this immune response to viruses in humans as well as animals. This review explores how cells effectively detect and eliminate viruses after the cell membrane is penetrated. Improving the understanding of intracellular immunity will contribute to the knowledge of intracellular immune responses, ultimately facilitating the prevention of severe viral infections in both humans and animals.

Keywords

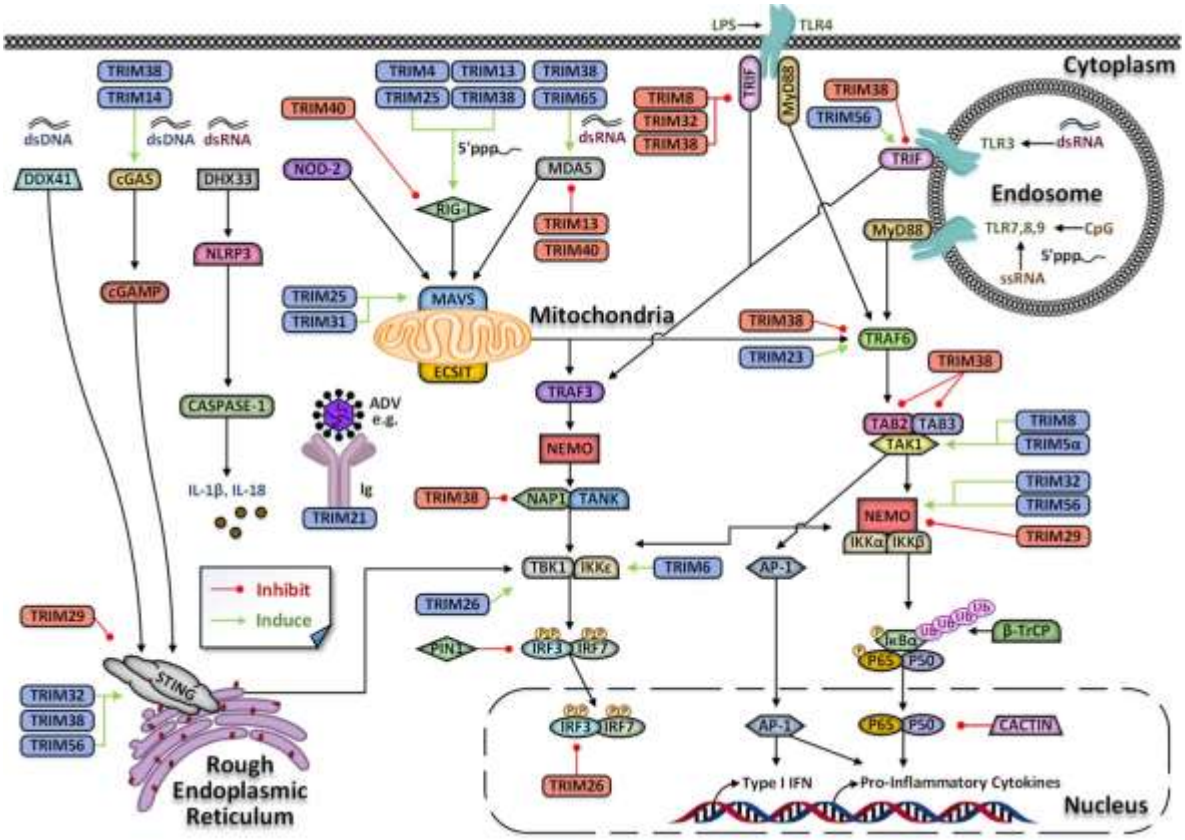
Immunity, Intracellular, Virus, TRIM

Introduction

Viral infections cause a significant challenge in both human and animal health, affecting millions around the world. In addition, viruses have profound long-term consequences, influencing humans and animals' health (Reperant et al., 2016; Sarker, 2024), hence impacting economic stability in substantial ways (Morgan & Prakash, 2006). The serious effects of these infections extend beyond immediate symptoms, potentially leading to chronic health issues, increased healthcare costs, and diminished livestock productivity (Espinosa et al., 2020; Chen et al., 2021). Addressing viral infections is essential for protecting community health and ensuring economic future. Hence, this effort is crucial for enhancing public wellbeing within our society.

Submission: 12 March 2026; **Acceptance:** 3 August 2026; **Available online:** August 2026

Viruses are obligate intracellular pathogens that utilize specialized mechanisms to initiate endocytosis and alter endosomal cellular membranes, showcasing an intriguing area for further exploration and understanding virus-host interactions (Barrow et al., 2013). The immune system employs a vast array of complicated mechanisms and methodologies in order to successfully repel viral infections (McEwan et al., 2013). It has a vast array of specialized cells, signification molecules, and potent defenses at its disposal, all working together to detect, identify, and neutralize intruders that threaten the health of the body (Thakur et al., 2019). Hypothetically, the antibody-virus complex that successfully escapes the endosomal compartment and enters the cellular cytosol during the infection process will then encounter tripartite motif (TRIM) family proteins (Koepke et al., 2021). These proteins constitute a secondary line of immune defense, playing an important role in regulating the innate immune response (Figure 1).



Tripartite motif (TRIM); immunoglobulin (Ig); DEAD-box helicase 41 (DDX41); cyclic GMP-AMP synthase (cGAS); DEAH-box helicase 33 (DHX33); nucleotide-binding oligomerization domain-containing protein 2 (NOD-2); retinoic acid-inducible gene I (RIG-I); melanoma differentiation-associated protein (MDA5); Toll-like receptors (TLR); stimulator of IFN genes (STING); mitochondrial antiviral signaling protein (MAVS); TGF-β-activated kinase 1 (TAK1); TAK1/MAP3K7-binding protein 2 (TAB2); Myeloid differentiation primary response gene 88 (MyD88); TIR-domain-containing adapterinducing interferon-β (TRIF); NF-κB essential modulator (NEMO); nucleosome assembly protein (NAP-1); tumor necrosis factor (TNF); TNF receptor-associated factors (TRAF); TANK-binding kinase 1 (TANK); inhibitor of NF-κB (IκB); IκB kinase (IKK); TANK binding kinase 1 (TBK1); interferon (IFN); interferon regulatory factor

(IRF); phosphorylation (P); ubiquitin (Ub); double-stranded DNA (dsDNA); double-stranded RNA (dsRNA); single-stranded RNA (ssRNA); adenovirus (ADV); interleukin (IL); activator protein-1 (AP-1); Peptidyl-prolyl cis-trans isomerase NIMA-interacting 1 (PIN1); evolutionarily conserved signaling intermediate in Toll pathway (ECSIT); cysteinyl aspartate specific proteinase 1 (CASPASE-1); β-transducinrepeats containing proteins (β-TrCP).

Figure 1. Components of intracellular immunity. The TRIM proteins regulate innate immune signaling, playing dual roles in antiviral pathways marked by black arrows, and their regulation marked by green arrows and red lines (adapted from Shen et al., 2021).

TRIM proteins were initially characterized by Reymond et al. (2001) as a conserved family of intracellular proteins defined by a conserved tripartite motif consisting of a RING domain (RING-B-box-coiled coil), followed by diverse C-terminal domains. The designation "TRIM" encompasses a vast protein family rather than a distinct individual molecule, discovered sequentially through the progressive identification of RING-B-box-coiled-coil-containing structures (Reymond et al., 2001). Recent studies have reported that TRIM proteins are involved in host immune response and defense against pathogen invasion. A commonly cited early TRIM with functional characterization is TRIM21, whose intracellular antibody receptor activity was widely reported (McEwan et al., 2013; Vaysburd et al., 2013; Rakebrandt et al., 2014; Watkinson et al., 2015; Xue et al., 2018; Wang et al., 2021).

Therefore, this review aims to explore the role of TRIM proteins in host cells against virus infections. A better understanding of this intracellular immunity will enhance the knowledge of intracellular immune responses, ultimately facilitating the prevention of severe viral infections in both humans and animals.

Methodology

Following PRISMA guidelines, a systematic literature search was conducted in PubMed, ScienceDirect, and Scopus using the following search string keywords: “Intracellular”, “Immunity”, “Tripartite motif protein”, “TRIM”, “Virus” in combination with “OR” and “AND” on 25 July 2025 (Figure 2). No limitation was used while searching databases. Reference lists of all related studies were also reviewed for any other related publications. Full-length original research articles, documents, and reports of all findings identified during the advanced search.

For inclusion, only full-length original research articles published in English were used. Articles were excluded from the review if: (i) studies did not report the TRIM proteins associated with virus infection, (ii) abstracts, case reports, congress or conference abstracts that did not include the full text, (iii) studies reported in languages other than English, and (iv) duplicate or repeated publication of the same study.

Selection of the study involved two steps: (i) the titles and abstracts of the articles were screened, and the studies that did not meet the inclusion criteria were excluded, and (ii) the full text of the selected articles was retrieved and filtered based on the same inclusion and exclusion

criteria. After evaluating the quality of the searched articles, the final articles were selected for writing the review article.

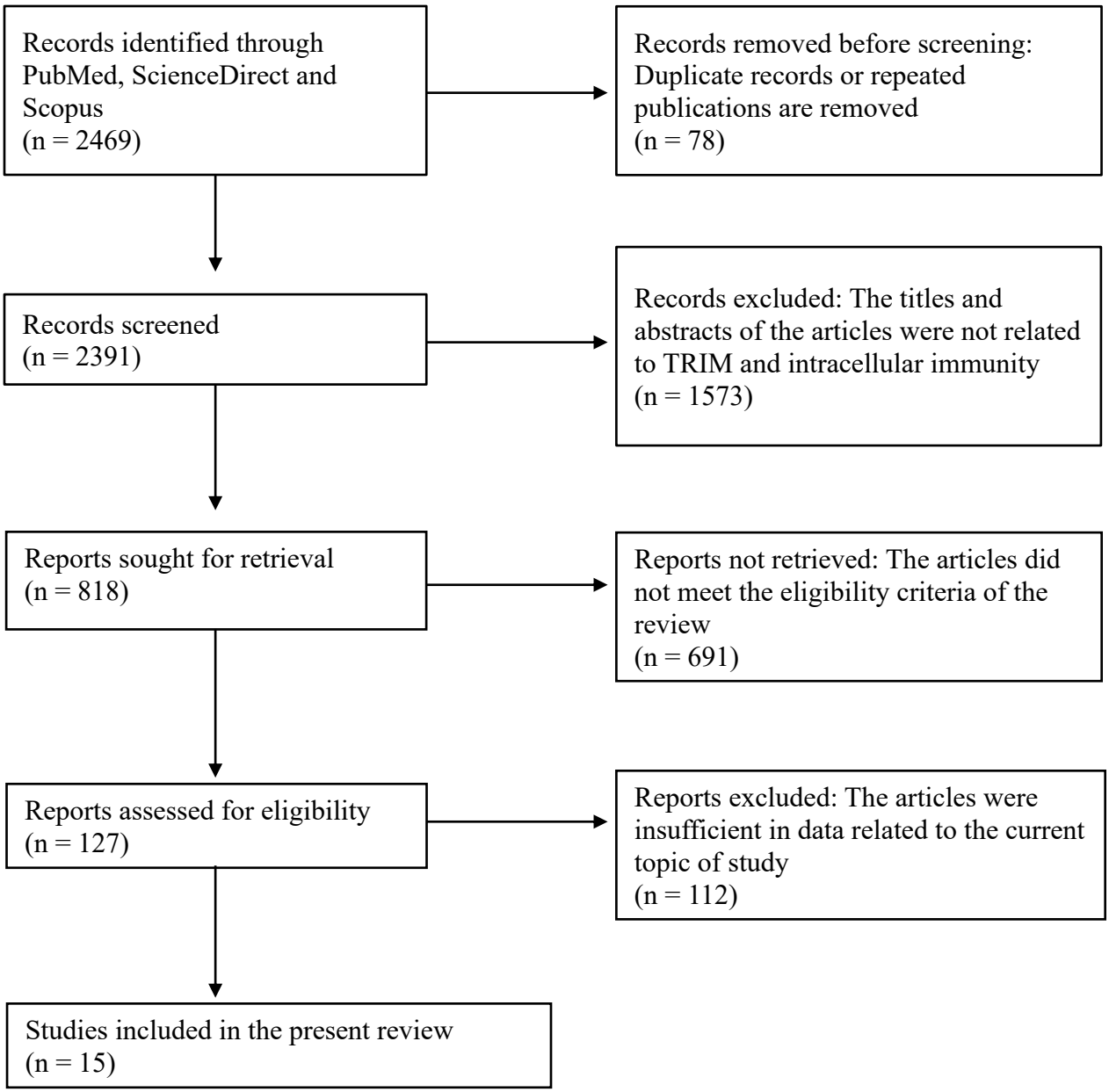


Figure 2. PRISMA flow diagram

Results and Discussion

Escaping host immunity

Certain viruses possess a strong capability to penetrate the cellular constituents of host organisms and thereby elude the primary components of the defense system of the immune system, including innate and adaptive immunity (Beachboard & Horner, 2016). These viruses employ a diverse array of evasion mechanisms to avoid recognition by the components of the immune system (Table 1).

Table 1. A summary of different viruses highlighting their non-phagocytic host cells and the diverse mechanisms they use to invade these cells.

Viruses	Non-phagocytic target cell	Evasion mechanism	References
Poxvirus	Broad range of vertebrate and invertebrate cells	Host cytokine decoy receptors	Hernaez & Alcami (2024)
Herpesvirus	Epithelial cells	Host cytokine and chemokine decoy receptors	Hernaez & Alcami (2020)
Influenza virus	Epithelial cells	Antigenic drift/shift	Amin et al. (2026)
Hepatitis C virus (HCV)	Hepatocyte	DNA rearrangement	Waly et al. (2023)
Human immunodeficiency virus (HIV)	CD4+ T-cells	i. DNA rearrangement ii. Induction of an inappropriate immune response by regulatory T-cells	Huber et al. (2024)
Epstein-Barr virus (EBV)	B cells and epithelial cells	i. Inhibition of inflammatory response ii. Hiding in safe target cells/tissue	Hu et al. (2025)
Herpes simplex virus (HSV)	Epithelial cells and sensory neurons	i. Inhibition of humoral immunity and the blocking of antigen processing and presentation ii. Hiding in safe target cells/tissue	Mei et al. (2026)

Table 1 (Continued)

Varicella zoster virus (VZV)	Neuronal cells/sensory neurons	Hiding in safe target cells/tissue (dorsal root ganglia)	D'Elia et al. (2026)

A variety of strategies are deployed to outsmart the host's defenses, showcasing the intricate battle between virus and immunity (Thakur et al., 2019). These capabilities of certain viruses to persist and be transmitted undetected provide them with a distinct disease biology.

Hernaez & Alcami (2024) demonstrated the poxviruses' ability to escape host immunity by producing host cytokine decoy receptors. Poxviruses secrete a family of proteins that can bind to and neutralize cytokines and chemokines, which is one mechanism by which the host defense systems may be modulated. These proteins are mimic-like analogues of host decoy cytokine receptors but possess unique characteristics that may render them more efficient.

Hernaez & Alcami (2020) reported that herpesviruses also have the ability to escape host immunity by encoding secreted versions of cytokine receptors as a unique strategy to evade the host immune response. The herpesviruses produce proteins secreted from infected cells that sequester cytokines, thereby acting as decoy receptors, thus preventing cytokine action. The decoy receptors function by structurally mimicking host cell receptors to intercept and neutralize the immune signals of the host.

Amin et al. (2026) described the ability of influenza viruses to evade host immune defenses, particularly through antigenic drift and antigenic shift mutations. The most common targets are the virus surface glycoproteins hemagglutinin (HA) and neuraminidase (NA), which serve as the primary site of the host immune response. To escape immune recognition, evolutionary selection pressure drives the virus to acquire mutations through drift or shift mechanisms without eliminating the HA and NA protein binding function.

Waly et al. (2023) reported that hepatitis C viruses (HCV) escape the immune defense system through a DNA arrangement that encodes the immunoglobulin heavy chain. The arrangement lays on the genetic mutation of HCV due to the prone error RNA-dependent RNA polymerase (RdRp). The proteins encoded (ie: NS3-4A and NS5A) are able to disrupt the host's immune defense.

Huber et al. (2024) described the ability of human immunodeficiency virus (HIV) to escape the immune system primarily by DNA rearrangement and induction of inappropriate immune response by regulatory T-cells. DNA rearrangement alters the surface protein structure, which causes difficulty for antibodies to recognize and bind the virus, or the proteins produced can mimic host proteins, which tricks the host immune system. Moreover, the disruption of T-cells causes incoordination of the host's immune response against the virus.

Hu et al. (2025) demonstrated that Epstein-Barr virus (EBV) is able to avoid the immune defense system by inhibiting the host inflammatory response and hiding itself in the safe target host's cells or tissue.

Mei et al. (2026) reported that the herpes simplex virus (HSV) evades the host immune system by suppressing humoral immunity, the key to antibody synthesis, and disrupting antigen processing and presentation. The virus avoids detection by concealing itself within safe target cells and tissues.

D'Elia et al. (2026) reported that varicella zoster virus (VZV) remains dormant and avoids detection by the host immune system by hiding in safe target cells or tissues, particularly the dorsal root ganglia.

Components of intracellular immunity

Recent years have highlighted the fact that numerous cells possess sensor and effector mechanisms to effectively manage intracellular viruses. Therefore, a new mechanism was proposed by which cells recognize and kill the viruses intracellularly and is referred as intracellular immunity (McEwan et al., 2013).

The tripartite motif (TRIM) proteins are a critical component of intracellular immunity, and this is the first line of defense in the cellular universe. TRIM proteins are reported to have originated early in eukaryotic evolution and developed into a highly diversified family of E3 ubiquitin ligases (Marin, 2012). The evolution of the TRIM family is divided into two distinct evolutionary groups: (i) Group 1; highly diverse C-terminal domains, stable and highly conserved across species, and (ii) Group 2; strictly defined by a C-terminal domain, highly volatile, and experienced positive selection and expansion (Boudinot et al., 2011). TRIM proteins are crucial in modulating the innate immune response, particularly in viral infections. By modulating several signaling pathways, TRIM proteins orchestrate an effective immune response and hence enable the cell to detect and resist the attacks of viruses. Their complex function underscores their importance in immune homeostasis and efficient response to pathogens (Keeble et al., 2008; Rakebrandt et al., 2014; Watkinson et al., 2015; Vunjak & Versteeg, 2019; Wang et al., 2021). TRIM proteins are structurally characterized by two parts: the tripartite motif or N-terminal domain comprising a really interesting new gene (RING) domain, a B-box domain, and a coiled-coil domain (CCD), and the C-terminal domains (Figure 3).

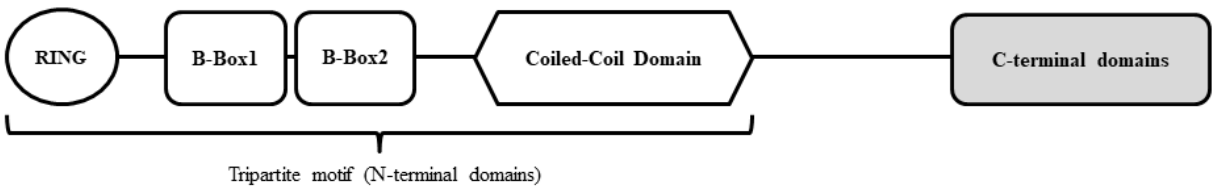


Figure 3. The organization of TRIM protein (adapted from Shen et al., 2021).

Most TRIMs are E3 ubiquitin ligases, where RING domains have ubiquitin ligase activity (Vunjak & Versteeg, 2019). RING domain is critical in TRIM's activity as an E3 ubiquitin ligase, allowing the effective and specific transfer of ubiquitin molecules (Shen et al., 2021). The domain is fundamental for the activation of TRIM's enzymatic activity to regulate protein degradation and maintain homeostasis in the cell (Vunjak & Versteeg, 2019). Two kinds of B-Box are recognized:

B-Box1 and B-Box2. While the precise function of the B-Box domain is unknown, it is generally believed to be significant for the assembly and interaction that occurs between TRIM proteins and their various partners (Zheng & Peterlin, 2005). At the core of this interaction is the superhelix CCD structure of the coiled-coil domain that is responsible for promoting both homo- and heterodimerization of TRIM proteins. This dynamic pairing is required for their diverse biological functions, indicating the importance of these protein interactions in cellular processes (Li et al., 2011; Esposito et al., 2017). The highly diverse C-terminal domains are subdivided into 11 groups comprising 80 family members (Shen et al., 2021). The role of each domain in this region is unique depending on its distinctive localization (Figure 4).

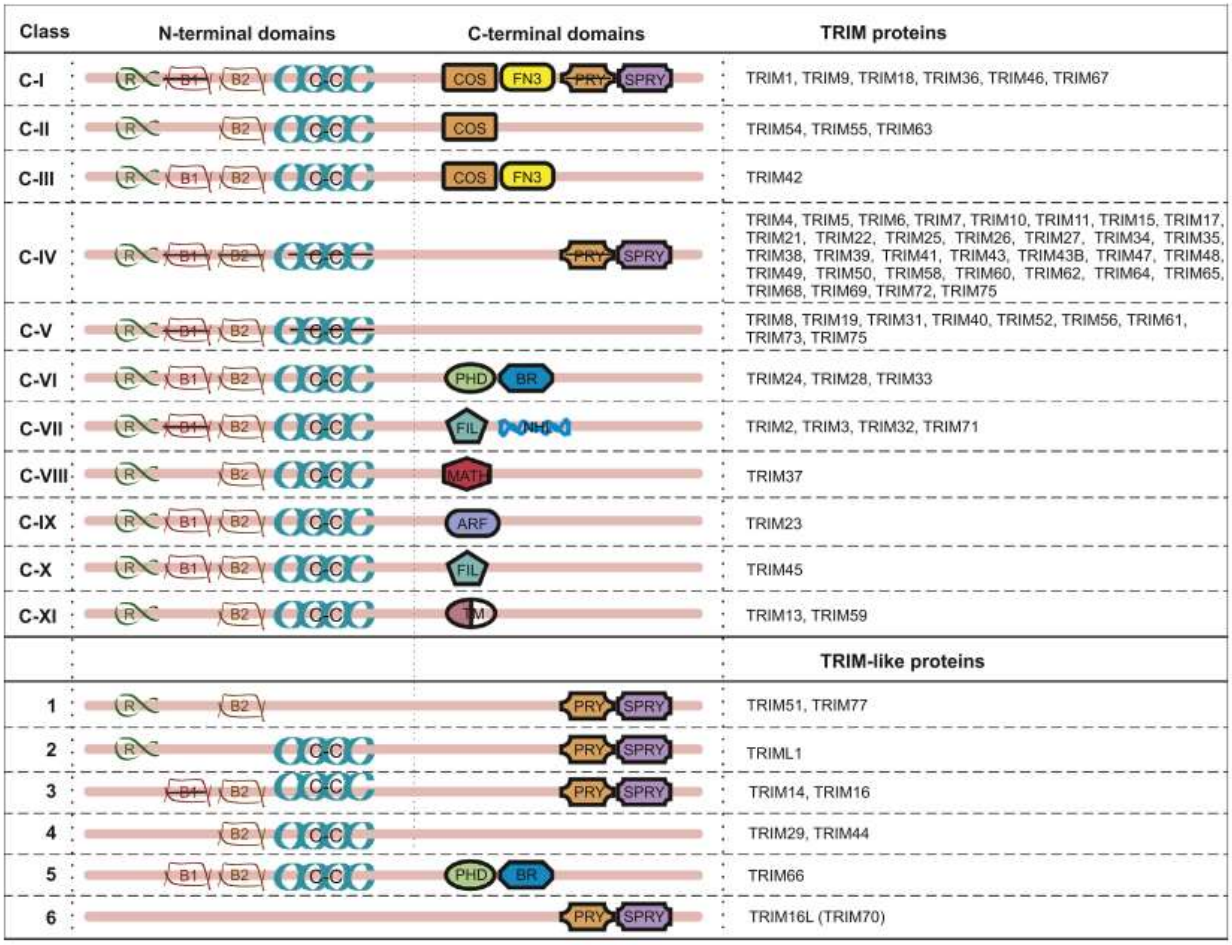


Figure 4. Classification of TRIM family proteins (adapted from Borlepawar et al., 2019).

Hence, several sub-family members of TRIM proteins and other intracellular proteins were found to play important roles in intracellular antiviral activities (Table 2).

Table 2. The components and mechanisms of action of different TRIM proteins in protecting cells from viral infections.

Name	Mechanism of action of intracellular immunity against viral infection	References
Tripartite motif-containing protein 5 (TRIM5)	Restricts virus replication (eg; HIV).	Stremlau et al. (2004)
Tripartite motif-containing protein 19 (TRIM19)	Restricts virus replication (eg; VSV and HSV).	Geoffroy & Chelbi-Alix (2011)
Tripartite motif-containing protein 21 (TRIM21)	Expresses a cytosolic Fc receptor which is significant in providing robust protective immunity against nonenveloped viruses.	Rakebrandt et al. (2014)
	Mediates intracellular neutralization of antibody-opsonized viruses, a mechanism referred to as antibody-dependent intracellular neutralization (ADIN).	Mallery et al. (2010); Vaysburd et al. (2013)
	Initiate antibody-dependent immune activation.	McEwan et al. (2013)
	Inhibits virus replication via direct targeting and degradation of the nucleocapsid protein by the proteasomal pathway, as seen with PEDV.	Wang et al. (2021)
	Accelerates virus uncoating, thereby exposing the viral genome and activating the RIG-I (retinoic acid-inducible gene I) and cGAS (cyclic GMP–AMP synthase) pathways, leading to the induction of a potent innate immune response.	Watkinson et al. (2015)
	Targets and degrades the viral DNA sensor, DEAD (Asp-Glu-Ala-Asp) box polypeptide 41 (DDX41).	Zhang et al. (2013)

Table 2 (continued)

	Enhances antiviral activity against RNA virus infections by inducing K27-linked polyubiquitination of the MAVS (mitochondrial antiviral signaling) protein.	Xue et al. (2018)
	Suppress viral function by selectively targeting and degrading the VP1 fused with Fc, such as in the case of FMDV.	Fan et al. (2016)
Tripartite motif-containing protein 22 (TRIM22)	Restricts virus replication (eg; HIV).	Hattlmann et al. (2012)
Tripartite motif-containing protein 25 (TRIM25)	Enhances innate immunity by selectively targeting and ubiquitinating the viral RNA receptor RIG-I.	Chen et al. (2018)
Tripartite motif-containing protein 31 (TRIM31)	The mechanism is by a direct interaction with the MAVS protein whereby it triggers the K63-linked polyubiquitination of critical lysine residues at Lys10, Lys311, and Lys461 positions on MAVS, thereby regulating antiviral signaling with precision.	Liu et al. (2017)
Tripartite motif-containing protein 56 (TRIM56)	Promotes the ubiquitination of cGAS to affect viral growth.	Seo et al. (2018)

Among TRIM proteins, the sub-family of TRIM21 is widely studied for its role in regulating intracellular immunity. TRIM21 is a cytosolic protein that is ubiquitously expressed and induced by type I interferon (Rhodes & Isenberg, 2017). The protein boasts high affinity for binding antibodies and possesses a number of significant domains: a RING-type E3 ubiquitin ligase domain, a B-box domain, and a coiled-coil domain that together form an antiparallel homodimer. Crucially, the C-terminal PRYSPRY domain enables it to bind two heavy chains of an antibody at once, which enables TRIM21 to bind efficiently with all four subclasses of IgG (IgG1, IgG2, IgG3, and IgG4) with similar levels of affinity (Reusch et al., 2024). In addition, it also binds to IgA and IgM, but with lower affinity (Foss et al., 2016). This differs from classical antibody receptors, which are specific to certain isotypes and subclasses.

On recognizing a virus with an antibody attached, TRIM21 is rapidly activated, and it induces the formation of ubiquitin chains (Rhodes & Isenberg, 2017). The ubiquitin chains cause proteasomal degradation of the virus and also amplify immune signaling, constituting an

immediate response while creating a long-term antiviral state within the host (Ozato et al., 2008). Essentially, TRIM21 allows entry-blocking antibodies incapable of blocking viral entry on viral particles to prevent viral replication following entry (Fan et al., 2016). Additionally, the TRIM21-mediated ubiquitination event ensures recruitment of the proteasomes, thereby inducing degradation of the antibody-bound virus particles (Van Tol et al., 2017).

Conclusion

Understanding intracellular antibody immunity mechanisms and TRIM protein function has significant relevance to vaccine and therapeutics design for the future. Several studies demonstrate that intracellular immune controls are centered on TRIM proteins. Stimulation of TRIM during vaccination could enhance the generation of a protective response that is stronger. This is achieved through TRIM-mediated proteasomal degradation of virus-encoded proteins followed by assistance in peptide generation for the process of antigen presentation. Hence, the stimulation of TRIM provides essential costimulatory signals to professional immune cells in the framework of the innate immune system.

Therefore, a comprehensive understanding of the multifaceted functions of TRIM proteins, their detailed structural characteristics, their regulatory mechanism, their activation, and the nature of enzymatic catalysis must be studied. These multifaceted aspects are areas of present and future studies, which have the potential to further understanding of these essential proteins.

Acknowledgements

The author would like to thank the Director General of the Department of Veterinary Services Malaysia, Director of Veterinary Research Division, DVS, and Director of Veterinary Research Institute for their kind permission to publish this paper. There are no grant or funding bodies to be acknowledged for preparing this paper.

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