The Role of TRIM Proteins in Antiviral Defense

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Abstract. The Tripartite motif (TRIM) protein family is classified among a cohort of E3 ubiquitin ligase families. A large percentage of TRIM proteins are E3 ubiquitin ligase active and take part in a number of cellular functions. By adding ubiquitin molecules to target proteins via a variety of techniques, it can change those proteins. The important role of the TRIM protein in controlling pattern recognition receptor signaling pathways and the defense mechanisms of mammals against viruses, with a focus on protecting the host from viral infections, has been clarified by recent study. In addition to triggering crucial cell-intrinsic defense mechanisms like autophagy and transcription-dependent antiviral responses, TRIM proteins can also exhibit direct antiviral effects by obstructing particular viral components via a variety of mechanisms. Regrettably, certain viruses have developed efficient mechanisms to evade the antiviral activities exerted by specific TRIM proteins, including SARS-CoV-2. Viruses has the capacity to exploit TRIMs and the ubiquitination process directly, hence enhancing the viral replication cycle and inducing heightened pathogenicity. In this article, I have delved into research that explores the molecular mechanisms responsible for the antiviral effects of TRIM proteins. Additionally, I have examined how TRIM proteins exert their influence on various viral entities, shedding light on their crucial role in the immune response against viral infections.

Keywords: TRIM proteins; ubiquitination; pathogenesis.

1. Introduction

The TRIM (Tripartite Motif) proteins consist of more than 80 members with various E3 ubiquitin ligase functions capable of polyubiquitination modification of target proteins in different types of connections, which determines the fate of target proteins [1]. TRIM proteins have three conserved domains at the N-terminus, namely the RING domain, B-box domain, and curly helix domain (CCD); hence, the TRIM family is alternatively referred to as the RBCC family [2]. Even though members of this large family have the identical amino-terminal tripartite domain arrangement, which includes the RING-Bbox1/2-coiled coil, or RBCC motif, they can be divided into thirteen subtypes based on differences in their carboxyterminal domains [1]. Additionally, TRIM proteins have different C-terminal regions as well. The majority of eukaryotes include TRIM proteins, and the precise number of TRIM genes varies depending on the evolutionary stage of the organism. For instance, a mouse has around 64 members, a worm has about 20 members, and a fly has about 10 members [3]. Fish-specific FinTRIM proteins, also known as FTR, and human homologue TRIM proteins are both members of the TRIM protein family. FinTRIM is only found in fish. The N-terminal RBCC and the changeable C-terminal are both parts of it [4].

Numerous TRIM (Tripartite Motif) proteins are crucial for the immune system's antiviral response. The TRIM 5, 22, and 34 genes, which are found on the short arm of human chromosome 11, have been recognized as viral restriction factors. While other TRIM proteins may regulate the signal transduction pathway triggered by innate immune sensors, directing antiviral cytokine responses, some TRIM proteins may directly interfere with specific viral lifecycle stages. Virus-induced autophagy and virus eradication by autophagy are additional roles for the TRIM protein [5]. For example, the process of polyubiquitination involving K63 linkages is commonly known to modulate the activity of substrates, determine their subcellular location, or influence their ability to interact with other proteins [3]. On the other hand, ubiquitination of K48 linkages leads to the proteasomal destruction of substrates. This could result in the degradation of retroviral capsids, the production of immune signals, and participation in autophagy, cell proliferation, differentiation, and apoptosis [6].

Moreover, some TRIM proteins not only link ubiquitin to its targets but also speed up the binding of ubiquitin-like proteins (UBL), such as ISG15 or SUMO, and they use ubiquitin or UBL to change the function of a variety of substrates (originating from both hosts and viruses) [3]. In this essay, I provided background information on the TRIM protein, described how it interacts with viruses, and discussed how the TRIM protein affects various viruses.

2. TRIM Proteins: Structure and Function

The TRIM proteins exhibit a consistent structural organization consisting of three N-terminal domains, including RING, B-box, and coiled-coil [5]. The structure of cysteine and histone residues forms the RING domain, also referred to as the zinc finger domain. It has the capacity to bind to two zinc atoms and aid in the movement of ubiquitin molecules between substrates such as proteins. As a result, it acts as a distinguishing marker for several E3 ubiquitin ligases. The majority of TRIM proteins' antiviral action depends on the RING domain's regulatory ability to modify the functionality of a variety of substrates with both host and viral origins through ubiquitination or ubiquitination-like mechanisms. Nevertheless, many TRIM proteins are missing the RING domain; TRIM20, for example, has a PYRIN domain in place of the N-terminal RING domain [7].Like the RING domain, the B-box is a zinc ion-binding domain [8]. The B-box can be classified into two distinct forms, B1 and B2, based on the arrangement and distribution of cysteine and histidine residues. They play a role in facilitating the formation of several protein complexes of higher order. One to two B-box domains with zinc-binding motifs that resemble the RING domain are frequently seen in TRIM proteins. Previous studies have demonstrated that the B-box domains present in several TRIM proteins exert regulatory control over protein interactions, E3 ligase activity, and/or the formation of higher-order protein assemblies. The antiviral capabilities of some TRIM proteins rely on their ability to self-associate homomerically, in certain instances, form heteromeric assemblies. These associations are facilitated by the coiled-coil domain (CCD) [9].

As a structural framework for enabling protein-protein interactions, the C-terminal domain preferentially interacts with particular proteins to carry out a variety of tasks [1, 10]. The SPRY and PRY-SPRY domains have a high level of selectivity in protein binding and are frequently used as scaffolds for protein-protein interactions. The PRY-SPRY domain has characteristics that are comparable to those seen in TRIM21 and Fc receptors. The process of attaching to the cytoskeleton, specifically the microtubule networks, is facilitated by the C-terminal Cos domain. Moreover, certain TRIM proteins incorporate NHL repeat sequences, hypothesized to enhance protein-protein interactions because to their hexagonal propeller-like structure. The TRIM family includes a number of C-terminal domains, such as the fibronectin type 3 (FN3) domain, which has DNA and heparin binding sites. The MATH domain also has the capacity to support self-correlation. E3 ubiquitin ligases play a significant role in the substrate identification process. Based on the architecture of their domains, E3 ubiquitin ligases have been divided into two separate families: the homologous E6-AP COOH terminus (HECT) family and the RING-finger-containing protein family. Due to the presence of the RING domain, the TRIM protein is given the ability to function as an E3 ubiquitin ligase during the ubiquitination process. The TRIM protein interacts with the substrate as a result, changing its final outcome [5].

3. TRIM protein and virus

3.1. Influenza A virus (IAV)

Influenza, also referred to as the flu, is a respiratory ailment caused by the influenza virus (IAV), which is a widely distributed viral infection. Human avian influenza, often known as avian influenza in humans, is a highly contagious respiratory infection caused by many subtypes of avian influenza. A viral pathogen. The prevailing indicators of infection typically include pyrexia, coughing, rhinorrhea, among others. It can also cause pneumonia, which has the potential to induce failure in

vital organs such as the heart, kidneys, and other bodily systems, resulting in a considerable mortality risk. It has been made clear what part TRIM41 plays in the fight against IAV. The SPRY domain of nucleoprotein is the protein target of TRIM41, and TRIM41 overexpression prevents IAV replication in lung epithelial cells. Since mutant TRIM41 missing E3 ligase is unable to regulate infection, TRIM41 E3 ligase is necessary for viral suppression [11].

Konstantin et al. identified a multitude of TRIM proteins that exhibit virus-species-specific regulation of autophagy. Additionally, they discovered that specific TRIM proteins, such TRIM23, are necessary for rapamycin- and virus-induced autophagy induction. The presence of TRIM23's RING E3 ligase and ADP-ribosylation factor (ARF) GTPase activity was discovered to be necessary for its participation in autophagy-mediated viral restriction. The TRIM23-TBK1-p62 axis plays a crucial role in the process of selective autophagy. The suppression of endogenous TRIM23 expression resulted in a notable decrease in autophagy triggered by both IAV and rapamycin, suggesting a significant involvement of TRIM23 in the autophagic pathway. Concurrently, the deletion of TRIM25 resulted in a significant reduction in the formation of GFP-LC3B puncta induced by IAV [12]. Furthermore, based on recent research findings, Khan et al.'s study has determined that TRIM22 is becoming increasingly important in the fight against the influenza A virus (IAV). Infection with influenza A virus (IAV) induces the production of interferon, a signaling protein that further enhances the creation of TRIM22. In adenocarcinomic human alveolar basal epithelial A549 cells, the TRIM22 protein has been observed to cause restriction of the influenza A virus (IAV). Exogenous TRIM22 causes a 100-fold decrease in virus infectivity in MDCK cells, which is a considerable drop. It has been proven that the expression of restriction action requires the link between TRIM22 and viral nucleoproteins [11]. The promyelocytic leukemia protein (PML), also known as TRIM19, gives protection against the influenza A virus (IAV), according to a different experiment. The inhibition of viral replication is associated with PML overexpression. PML and IAV were transfected into hamster CHO cells and mouse GP+E86 cells. With a suppression ranging from 100 to 125 times, the study showed a considerable decrease in the IAV viral load [13].

3.2. Human immunodeficiency virus (HIV)

The majority of viruses that are impacted by TRIM proteins are retroviruses. [11]. The AIDS virus, sometimes referred to as the human immunodeficiency virus, is a retrovirus that impairs the human immune system. When infected, this virus attacks and gradually damages the human immune system, leading the host to lose protection and eventually die from secondary infections or cancer. AIDS is the terminal stage of human immunodeficiency virus infection, with a high fatality rate.

The original work used recombinant HIV-1 that produced green fluorescent protein and TRIM5 obtained from Old World monkeys to determine a link between HIV-1 and Trim proteins. These components were introduced into human HeLa cells for experimentation. The findings indicated that HIV-1 was capable of cellular entry in Old World monkey cells, but it was unable to undergo the process of reverse transcription. The key suppressive component was identified as TRIM5, which exhibits species-specific functionality due to the fact that the simian immunodeficiency virus is less vulnerable to TRIM5 activity compared to HIV-1. The differential in susceptibility can be attributed to variations in the viral capsid [14]. Simultaneous findings were reported regarding the antiviral properties of TRIM5 against HIV-2, as well as significant reductions in HIV-2 levels [11].

In addition, the reduced TRIM5 expression brought on by SiRNA is seen to contribute to the increased infectivity of HIV2. This demonstrates the flexibility of TRIM5 and its potential efficacy against various HIV genotypes [11]. According to Neagu et al. (year), human TRIM5 has been proposed as a promising option for gene therapy. This study involved the development of an HIV-1 inhibitor through the fusion of cyclophilin A and human TRIM5, replacing the fusion protein AoT5Cyp known for its capacity to impede HIV-1 infection. The study found that when given to human cell lines, three out of the total 13 designs showed promise for lowering HIV-1 infection [15]. A connection between the overexpression of HIV-1 and TRIM22 was discovered by another investigation [16]. Several other TRIM family members, including TRIM21, TRIM34, and TRIM5

delta, were seen to have elevated levels in a real-time expression analysis of HIV-1-infected patients. This data suggests that these proteins might play a functional role [17].

3.3. Hepatitis B virus (HBV)

Hepatitis B virus has a complicated life cycle. As part of the replication process, they use reverse transcription. Hepatitis B is still a major public health concern today. Acute or chronic HBV infection can cause a number of diseases and health issues. In addition to hepatitis, HBV infection can also result in cirrhosis and hepatocellular carcinoma. Hepatitis B surface antigen is detected in an estimated 350 million people worldwide, with prevalence ranging from 0.20% to 22.38% [11]. The involvement of TRIM41 in the inhibition of HBV virus transcription was identified by Ramisha Khan and colleagues. The E3 ligase and the C-terminal domain of TRIM41 work together to block this process. In a study, NTRIM22 has been recognized as a potential biotherapeutic due to its ability to selectively target the major promoter of the HBV gene and effectively decrease HBV gene expression in a manner that is dependent on the dosage [18]. In a separate investigation, a cellular expression system consisting of human hepatocytes was subjected to co-transfection with TRIM proteins and HBV DNA. The findings of the expression and gel assay tests showed that the secretion of HBV e antigen (HBeAG) and HBV surface antigen (HBsAG) had significantly decreased by 50%. The action of TRIM41 hinders the transcriptional activity of viral genes by impeding the functionality of HBV Enhancer I and Enhancer II/core promoters. Several other members of the TRIM family, namely TRIM5, TRIM6, TRIM11, TRIM14, TRIM25, TRIM26, and TRIM31, have been identified as potential contributors to the reduction in hepatitis B virus (HBV) gene expression [19].

The expression of TRIM56 in HepG2-NTCP cells and liver tissues infected with HBV responded to IFN therapy, according to a study by Xing Tian et al. Furthermore, it was discovered that TRIM56 was a potent inhibitor of IFN-induced HBV proliferation. The ring and C-terminal domains of TRIM56 showed the HBV replication inhibitory activity. The presence of the C-terminal domain was discovered to be necessary for the translocation of TRIM56 from the cytoplasm to the nucleus during hepatitis B virus (HBV) infection. Subsequent examination revealed that the ring domain of TRIM56 selectively directed its ubiquitination activity towards IκBα. The modification resulted in the phosphorylation of p65, thereby inhibiting HBV core promoter activity and impeding HBV replication. The involvement of p65 is essential in the NF-κB signaling pathway for the inhibition of HBV replication. According to their study, the researchers have demonstrated that TRIM56 plays a significant role as an antiviral immune effector by suppressing the transcription of HBV covalently closed circular DNA through its interaction with the NF-κB signal pathway [20].The involvement of TRIM41 in the inhibition of HBV virus transcription was identified by Ramisha Khan and colleagues. The E3 ligase and the C-terminal domain of TRIM41 work together to block this process. In a study, it has been determined that NTRIM22 exhibits potential as a biotherapeutic agent due to its ability to specifically target the major promoter of the HBV gene and effectively decrease HBV gene expression in a manner that is dependent on the dosage administered [18]. In a separate investigation, a cellular expression system consisting of human hepatocyte cells was subjected to co-transfection with TRIM proteins and HBV DNA. The HBV e antigen (HBeAG) and HBV surface antigen (HBsAG) secretion was shown to have significantly decreased by a factor of two in both expression and gel assay assays. It was discovered that TRIM41 inhibits viral gene transcription by preventing the HBV Enhancer I and Enhancer II/core promoters from functioning properly. Several other members of the TRIM family, namely TRIM5, TRIM6, TRIM11, TRIM14, TRIM25, TRIM26, and TRIM31, have been identified as potential contributors to the decrease in hepatitis B virus (HBV) gene expression [19].

3.4. SARS-CoV-2

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) causes COVID-19, a respiratory ailment that is the root of the COVID-19 pandemic. The virus is airborne and usually spreads between people through close contact, as well as through aerosols and respiratory droplets

that are formed when coughing and sneezing, talking, breathing, and other exhalations. By attaching to the membrane protein known as ACE2, which controls the renin-angiotensin system, it enters human cells. At the same time, infection with A can also affect many body organs or tissues, including the lungs and respiratory system, which has resulted in the death of several people all over the world.

The level of ACE2 expression can play a role in determining an individual's susceptibility to and the severity of COVID-19 infection, as SARS-CoV-2 relies on ACE2 for cellular entry in human cells through binding. Consequently, it is crucial to comprehend how ACE2 expression is controlled. Type II pneumocytes have been found to co-express the SARS-CoV-2 receptor and the antiviral restriction protein TRIM28. In addition, TRIM28 is recognized to contribute to immunological response, endogenous retrovirus latency, and antiviral restriction. TRIM28 was discovered by Yinfang Wang et al. to be a new regulator of ACE2 expression and SARS-CoV-2 cell entrance. A549 cells and primary pulmonary alveolar epithelial cells (PAEpiCs) can both be infected with pseudotyped SARS-CoV-2, according to their research, which shows that TRIM28 knockdown aids this process. Not only that, but they also found that interleukin-2 depletion and granzyme B blocking in the co-culture media only partially reversed the effects of NK cells' suppression of TRIM28 and promotion of ACE2 expression in lung epithelial cells in co-culture. Additionally, activation of IFN-receptor 2 (IFNGR2) was a factor in how TRIM28 knockdown enhanced IFN-induced ACE2 expression in A549 and PAEpiCs. The increased ACE2 caused by the co-culture of NK cells and TRIM28 knockdown in A549 cells was somewhat suppressed by dexamethasone [21].

In a study conducted by Nidhal Raheem Juhi Al Å Kaabi et al., i was discovered that people with the TRIM22 genotypes rs1063303 GG, rs7935564 GG, and rs7113258 TT had noticeably more severe COVID-19 infections than people with the genotypes rs1063303 CC, rs7935564 AA, and rs7113258 AA, who had improved COVID-19 symptoms. Additionally, it was found that patients with the TRIM22 genotypes rs1063303 CC, rs7935564 AA, and rs7113258 AA (39.0%) had a more significant response to COVID-19 infection than patients with other genotypes. Nevertheless, deceased individuals exhibited higher viral loads and lower PCR Ct values. Low-density lipoprotein (LDL), cholesterol, PCR Ct value, and 25-hydroxyvitamin D levels were found to negatively correlate with the severity of COVID-19 infection. On the other hand, it was discovered that a positive link existed between higher levels of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and particular genotypes of TRIM22 (rs1063303 GG, rs7113258 TT, and rs3824949 GG) [22].

4. Conclusion

This review examines the attributes, organization, and role of the TRIM protein family, elucidating their substantial influence on diverse viruses such as Influenza A virus (IAV), Human Immunodeficiency Virus (HIV), Hepatitis B virus (HBV), and Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). In conclusion, this study emphasizes the TRIM proteins' ubiquitous structure and emphasizes the significance of their role in the immune response to viral infections. TRIM proteins exhibit E3 ubiquitin ligase activity, which grants them the ability to combat viral infections through the modulation of the ubiquitination process or the facilitation of ubiquitin-like modifiers (UBLs) binding. This comprehensive study emphasizes the efficacy and promise of TRIM proteins as antiviral factors, demonstrating their potential in the ongoing fight against viral infections.

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