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Emerging Roles of Tripartite Motif-Containing Family Proteins (TRIMs) in Eliminating Misfolded Proteins

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Protein quality control (PQC) is pivotal for eukaryotic cells to eliminate misfolded proteins and maintain cellular homeostasis. A decreased or increased capacity of PQC is associated with various diseases, e.g., neurodegenerative diseases and cancers. Recently, increasing evidences have suggested that tripartite motif-containing family proteins (TRIMs) are the key players in PQC regulation. Most TRIMs are E3 ubiquitin ligases, such as TRIM11/19/25, which, through the ubiquitination modifications, can contribute to effectively remove the cellular misfolded proteins or protein aggregates via the UPS pathway. In this review, we summarized the participation of TRIM members in misfolded protein elimination through distinct pathways, including the ubiquitin–proteasome system (UPS), autophagy system, and ER-associated degradation (ERAD).

Keywords: TRIMs, misfolded proteins, aggregates, degradation, UPS, autophagy, ERAD

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INTRODUCTION

Proteins are the basic components of cells and are involved in a broad array of cellular processes. As part of the most abundant macromolecules, the cells inevitably need to put a huge strain on the protein production and maintenance of their natural conformations (Dobson, 2003). When cells are in certain physiological states or are exposed to various stress conditions, this leads to a condition in which the correct protein conformations are lost, leading to protein misfolding (Horwich and Weissman, 1997; Balch et al., 2008; Powers and Balch, 2008). Failure to timely remove the misfolded proteins can lead to the generation of proteotoxic stress (Bucciantini et al., 2002; Costanzo and Zurzolo, 2013; Soto and Pritzkow, 2018). Thus, maintaining cellular proteostasis is a requisite for cells to perform their basal function. To achieve this, the cell employs a fairly complex protein quality control (PQC) system that is critical to sequestrate, refold, and degrade any unexpected, accumulated misfolded proteins (Balchin et al., 2016; Sontag et al., 2017). The endoplasmic reticulum (ER) is an important cellular organelle that plays critical roles in the production, processing, and transport of proteins and lipids. It is also the organelle responsible for the maturation of roughly one-half proteins, in which aberrant proteins could be generated particularly under various physiological stress conditions (Wiseman et al., 2007; Wang and Kaufman, 2016). In ER, PQC is also known as ER quality control (ERQC) (Kim et al., 2015), for which nonnative conformational proteins can be refolded and modified following activation of the

unfolded protein response (UPR) (Ron and Walter, 2007; Hetz et al., 2015) or eliminated *via* ER-associated degradation (ERAD) (Hiller et al., 1996). Studies have shown the selective degradation of harmful or exhausted organelles via a specific type of autophagic turnover such as ER-phagy. When the ER becomes overwhelmed and stressed, its fragmented components along with the aberrant protein are delivered to the lysosome where they are degraded via ER-phagy (Grumati et al., 2018).

The cell's PQC system consists of two separate but collaborated parts: (I) molecular chaperone system, which is constituted by various types of heat shock proteins (HSPs) that function to release and unfold individual misfolded proteins from aggregates (Hartl and Hayer-Hartl, 2002; Sharma et al., 2008; Kim et al., 2013); (II) the degradation system, which relies on the ubiquitin–proteasome system (UPS) and autophagy pathways (Goldberg, 2003; Finley, 2009; Wani et al., 2015). In particular, molecular chaperones – a class of protein family that are evolutionarily conserved and are widely distributed in various organisms – are essential for cell survival, including HSP60, HSP70, HSP100, small HSP, and calnexin (Richter et al., 2010). When a protein is misfolded, molecular chaperones assist in the correct folding of the misfolded protein by reversibly binding to stabilize the unstable intermediates, followed by its release and refolding to its native conformation.

Meanwhile, erroneous protein aggregates that cannot be refolded can be disaggregated by chaperones as well (Saibil, 2013). Molecular chaperone system can also be overstressed, and in such condition, it directs the inundated misfolded proteins or protein aggregates to cellular clearance pathways via the ubiquitin–proteasome pathway or sequestration in autophagosomes (Kaganovich et al., 2008). The UPS and autophagy systems represents two distinct, selective, and well-regulated cellular degradative pathways, with their respective subcellular localization, mechanisms, machinery, and degradative substrates (Mishra et al., 2018). Emerging evidences have shown that these two systems have cross-talk through ubiquitination (Varshavsky, 2017; Goodier et al., 2020), implying that a complementary and synergistic function of the UPS and autophagy systems may exist (Korolchuk et al., 2009; Kwon and Ciechanover, 2017). In addition, these pathways – alone or in cooperation with each other – orchestrate the entire intracellular protein degradation (Wong and Cuervo, 2010; Chhangani et al., 2014).

Ubiquitination is accomplished by three enzymatic steps catalyzed by (1) ubiquitin-activating enzymes (E1s), (2) ubiquitin-conjugating enzymes (E2s), and (3) ubiquitin ligases (E3s). However, the specificity and efficiency of this system (protein ubiquitylation) are largely determined by the E3 ubiquitin ligases that recognize specific substrates (Zheng and Shabek, 2017). Misfolded proteins can be degraded upon the covalent attachment of ubiquitin. Ubiquitination can be either monoubiquitination (addition of a single ubiquitin molecule) or polyubiquitination (addition of a chain of ubiquitin molecules), and the fate of ubiquitinated substrates is determined by the position of the lysine by which polyubiquitination is mediated through K11, K48, K63, etc. (Hjerpe and Rodriguez, 2008; Xu et al., 2009; Sadowski et al., 2012).

For example, the K48-polyubiquitinated substrates are prone to be eliminated by UPS (Grice and Nathan, 2016), while the K63-polyubiquitinated or monoubiquitinated substrates undergo elimination by autophagy (Sun et al., 2018). Hence, the structural complexity of distinct polyubiquitin chains is sufficient to maintain the selectivity and specificity of the UPS and autophagy for each substrate (Alfano et al., 2016). This also suggests that substrates can be recognized through polyubiquitin chains of different topologies, providing degradation signals for distinct protein degradation pathways (Ohtake et al., 2016). Therefore, researches focused on ubiquitin-related enzymes have gained much attention.

The E3 ligases have a large number and has been extensively studied compared with a small number of E1s and E2s (Deshaies and Joazeiro, 2009; Berndsen and Wolberger, 2014; Buetow and Huang, 2016). TRIMs belong to E3s and over 70 members of the TRIMs have been identified in humans and mice (Hatakeyama, 2011). Most of the TRIMs consist of a highly conserved tripartite motif at N-terminus: a RING domain, one or two B-box domain, and a coiled-coil domain (Meroni and Diez-Roux, 2005; James et al., 2007; Li et al., 2014). The RING domain exhibits ubiquitin E3 ligase activity, yet there is still a limited number of TRIMs that are RING-deficient proteins. TRIM proteins can generally form homopolymers and heteropolymers with each other through their coiled-coil domain. The B-box domains are characterized as a universal domain in TRIMs, while their C-terminal domains provide TRIMs diversities. Based on their domain organization, TRIMs are categorized into 11 distinct subgroups (C-I to C-XI) (**Figure 1**).

Tripartite motif-containing family proteins play significant roles in various physiological or pathological conditions by acting as ubiquitin E3 ligases, such as cell proliferation and development, DNA damage and repair, neurodegenerative disease, innate immune response, and carcinogenesis (Nisole et al., 2005; Ozato et al., 2008; Hatakeyama, 2017). The mechanisms of TRIMs in misfolded protein clearance remain mysterious, even though it is likely a key function in many of their biological effects. Our group has demonstrated that several TRIM members, including TRIM11/5/25, are crucial for eliminating misfolded proteins (Chen et al., 2017, 2018; Liu et al., 2020). TRIM11 mediates the degradation of misfolded proteins and protein aggregates in the nucleus and cytoplasm through regulating UPS. TRIM5 may mediate protein aggregate degradation through autophagy, and TRIM25 mediates the degradation of misfolded proteins in the ER through ERAD. Other investigators discovered that TRIM13, an ER transmembrane (TM)-anchored E3 ligase, also mediates ERAD particularly for some membrane and secretory proteins from the ER (Tomar et al., 2012). TRIM13 can also orchestrate the initiation of ER-phagy via the N-degron pathway (Ji et al., 2019).

Here, we summarize the studies of TRIMs in misfolded protein clearance, regarding how TRIMs regulate their downstream pathways and whether they function synergistically or compensate each other. The purpose of this mini-review is to highlight the roles of TRIMs in misfolded protein degradation and describe the internal connections of TRIMs during these processes (**Figure 2**).

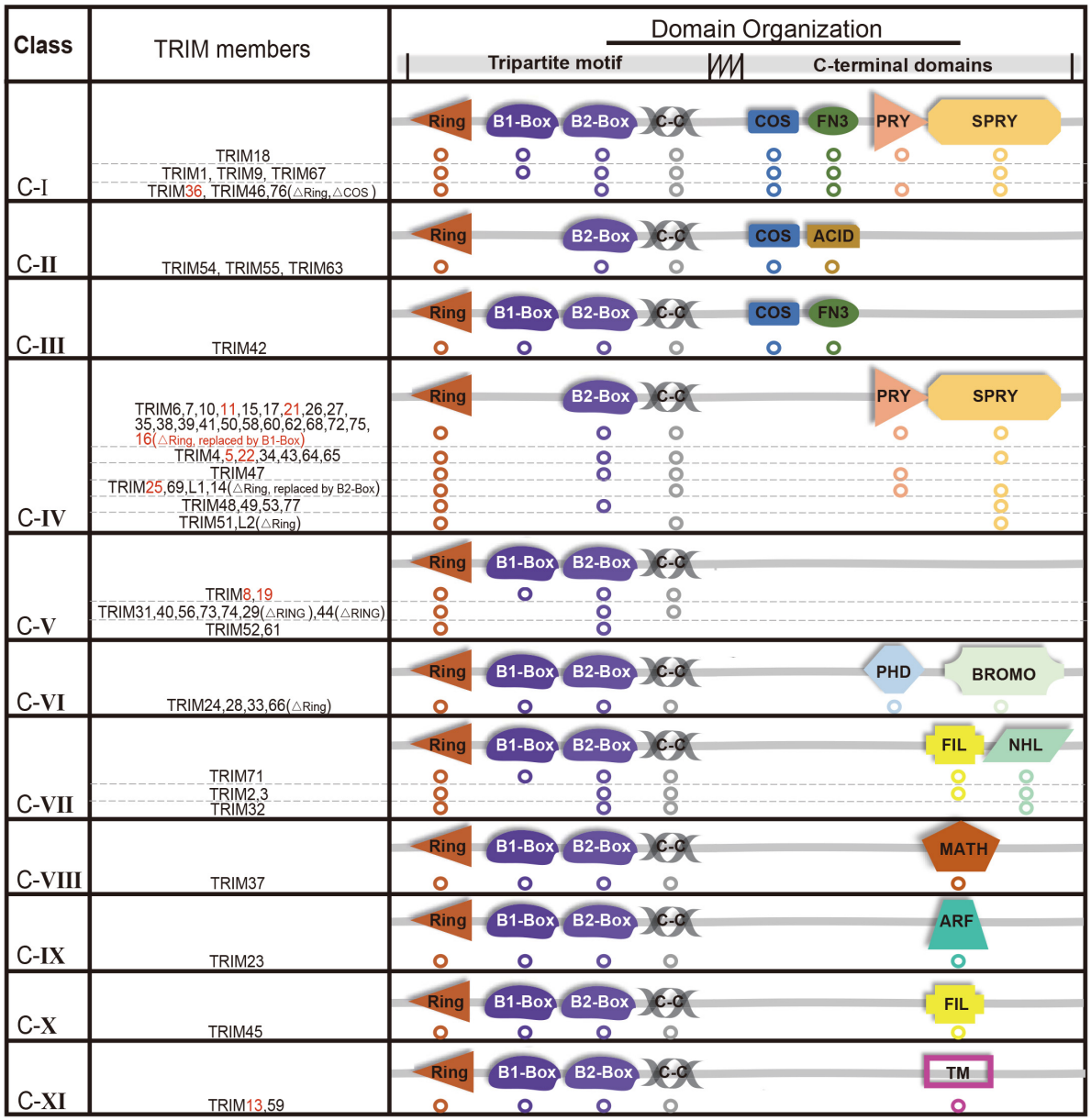

FIGURE 1 | Structure and classification of TRIMs (those mediating degradation of misfolded proteins are marked in red, which are also elaborated in this review). Based on the secondary domain organization, TRIMs are categorized into 11 distinct subgroups (C-I to C-XI). Among 10 TRIMs that are summarized in this review, over one half belongs to C-IV, and sporadic ones to C-I, C-V, or C-XI, respectively. The majority of TRIMS has a highly conserved tripartite motif (RBCC) at N-terminus, while a small number are still missing RING domain. The abbreviations of C-terminal domains are listed as follows: C-terminal subgroup One Signature domain (COS), fibronectin type III repeat domain (FN3), PRY domain, SPRY domain, acid-rich region (ACID), filamin-type IG domain (FIL), NHL domain, PHD domain, bromodomain (BROMO), Meprin and TRAF-homology domain (MATH), ADP-ribosylation factor family domain (ARF), and transmembrane region (TM). Besides, "ΔRING" means the RING domain is absent.

TRIMS IN ELIMINATING MISFOLDED PROTEINS VIA UPS

TRIM19

TRIM19, a typical RBCC ligase without any C-terminal domains, is well known as the promyelocytic leukemia protein (PML), which recruits diverse proteins to assemble PML nuclear bodies (NBs) (Nisole et al., 2013). It has been confirmed that PML NBs are involved in different cellular processes, e.g., antiviral response, DNA damage repair, and PQC (Bernardi and Pandolfi, 2007), implying a potential role of TRIM19 in removing misfolded proteins.

A polyQ stretch expansion in the nucleus of spinal or cerebellar neurons is pathologically associated with one of

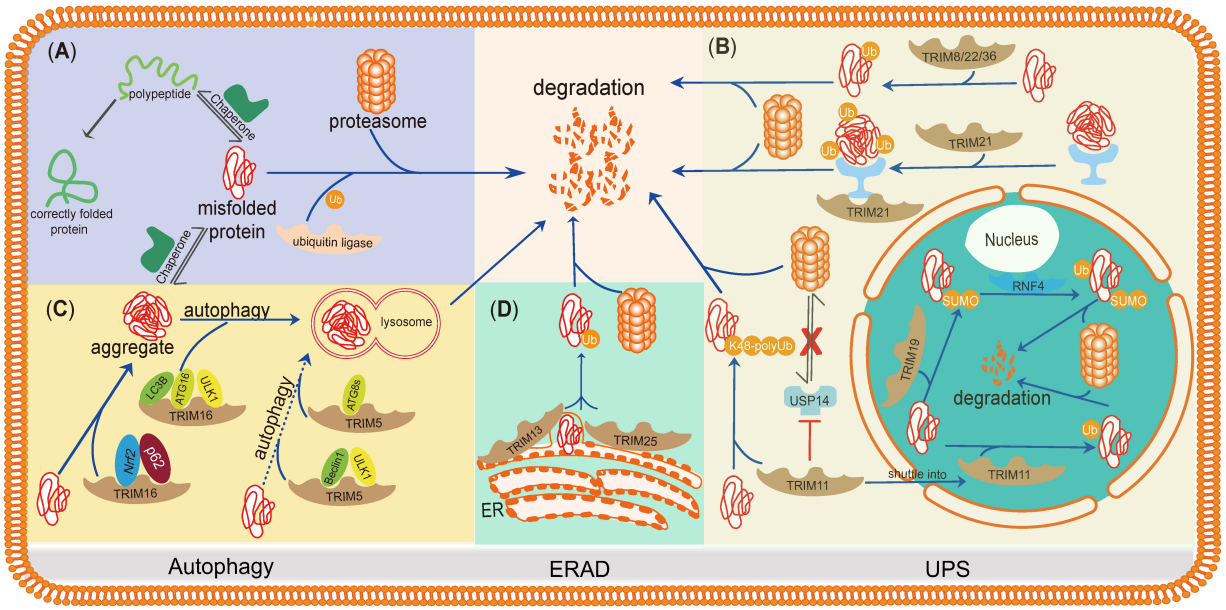

FIGURE 2 | TRIMs mediate degradation of misfolded proteins or protein aggregates through the UPS, autophagy, and ERAD. TRIMs are widely involved in misfolded proteins clearance through distinct mechanisms, and some of them even play dual roles and function in different organelles. **(A)** The basic mechanism of degradation of misfolded proteins in PQC. **(B)** TRIM19 (PML), as well as TRIM11, participates in degradation of misfolded proteins in the nucleus via UPS, while the latter also works in cytosol by enhancing the activity of proteasome. TRIM21, as a cytoplasmic Fc receptor, is of high affinity to the complexes composed by aggregates and specific antibody and then activates UPS. Besides, TRIM8/22/36 are also supposed to promote misfolded proteins' degradation through UPS. **(C)** TRIM16 promotes misfolded proteins into aggregates by interacting with Nrf2 and p62 and then enhances the biogenesis of autophagosome and autophagy-mediated aggregate removal. TRIM5 acts as an autophagic scaffold protein for Beclin1 and ULK1, which interacts with Atg8s for selective autophagy. **(D)** Upon ER stress, TRIM25 triggers ERAD to degrade misfolded proteins through ROS-associated pathways potentially. TRIM13, a membrane-bound protein of ER, also contributes to ERAD with its transmembrane domain.

the neurodegenerative diseases spinocerebellar ataxias (SCAs) (Janer et al., 2006). SCA1 gene Ataxin-1 encodes pathogenic protein Atxn1-82Q, but not the normal protein Atxn1-30Q, forming protein aggregates in the nucleus, which could be co-localized and decreased by TRIM19 (Guo et al., 2014). Notably, more distinct sites on TRIM19 were identified to directly recognize multiple misfolded proteins [i.e., the CC region of the TRIM/RBCC motif (SRS1) and the 63 amino acid residues at its C terminus (SRS2)] in the nucleus. Mechanistically, TRIM19 first acts as a small ubiquitin-like modifier (SUMO) E3 ligase by conjugating SUMO to misfolded proteins, which are recognized and ubiquitinated by a SUMO-targeted ubiquitin ligase called RING finger protein 4 (RNF4). Through the sequential SUMOylation and ubiquitination, misfolded proteins in cancer cells are efficiently degraded via the proteasome (Guo et al., 2014); furthermore, the capacity of TRIM19 to mediate the degradation of Atxn1-82Q protein aggregates in differentiated acute promyelocytic leukemia (APL) cells was found to be markedly reduced (Chen et al., 2017). Thus, the function of TRIM19 provides a new insight, suggesting that maintenance of malignant phenotypes may rely on effective clearance of misfolded proteins.

TRIM11

TRIM11 is structurally characterized by a typical TRIM/RBCC (RING, B-box, and coiled-coil) motif at its N-terminus and a PRY/SPRY domain at its C-terminus. Extensive studies have demonstrated the critical roles of TRIM11 in the processes of neurogenesis as well as oncogenesis (Niikura et al., 2003; Tuoc and Stoykova, 2008; Wang et al., 2016).

The expression of all TRIM genes in the human mammary epithelial cell (HMEC) transformation model was analyzed, and the results revealed that TRIM11 is amplified in a series of cancer cell lines and tissues, e.g., breast carcinoma, gliomas, and lung cancer. TRIM11 promotes the degradation of misfolded and aggregated proteins in tumor cells' nucleus or cytosol; for instance, forced expression of TRIM11 was shown to reduce the inclusions formed by Atxn1-82Q and Httax1p-97QP (Chen et al., 2017).

Notably, the RING domain of TRIM11 is required to perform its functions. On one hand, this domain catalyzes the conjugation of K48-polyubiquitin to various types of substrates, thus, ensuring adequate concentration of substrate for UPS (Chen et al., 2017, 2018). On the other hand, it directly enhances the proteasome activity by interacting with the ubiquitin-like (UBL) domain of ubiquitin-specific protease 14 (also called USP14, which removes ubiquitin chains from substrates) which deterred the interaction between USP14 and the 19S subunit of the proteasome (Chen et al., 2018). Collectively, these studies revealed that TRIM11 effectively clears misfolded proteins through promoting the activity of proteasome.

TRIM21

TRIM21/Ro52 is another member of the TRIM protein family that possesses a PRY/SPRY domain at its C-terminus, along with a typical RBCC motif at the N-terminus modulating its ubiquitin E3 ligase activity (Takahata et al., 2008). Reports have shown that TRIM21 has a high affinity to immunoglobulins (Keeble et al., 2008); thus, it acts mainly as an Fc receptor in the cytoplasm, to recognize the antigen–antibody complex (Kimura et al., 2015; Bottermann et al., 2018).

During immune defensive response against viral or bacterial infection, TRIM21 triggers pathogen neutralization by mediating UPS and valosin-containing protein (VCP, a molecular unfoldase) to eliminate such pathogens (McEwan et al., 2012). Similar to pathogen infection, misfolded tau proteins can be assembled, transferred, and spread in neurons leading to neuron cell apoptosis and induction of neurodegenerative disease. The accumulation of tau proteins has been associated with both acute neurological dysfunctions such as traumatic brain injury (TBI) and chronic neurodegenerative disorders like Alzheimer's disease (Bloom, 2014; Edwards et al., 2020).

In addition, robust cis p-tau proteins that are found in TBI models were targeted and ablated by monoclonal antibodies (mAbs) (Kondo et al., 2015). These mAbs gained entry into the neurons via TRIM21 and then neutralized the tau aggregates, which was accompanied by TRIM21 recruitment (McEwan et al., 2017). Therefore, it inspires us to consider whether there are more similarities between invasion of pathogen and aggregation of misfolded proteins, and it raises our interest in investigating the critical roles of TRIM21 in several neuron system diseases via UPS.

TRIM8, TRIM22, and TRIM36

TRIM8, TRIM22, and TRIM36 belong to a different subclass of TRIM family. They can be significantly upregulated during cell transformation and effectively promote the elimination of misfolded proteins in transformed cells (Chen et al., 2017). This class of TRIMs was observed to be upregulated along with the proteasome in tumor cells during cell transformation (Chen et al., 2017). Hence, we propose that TRIM8/22/36 enhance misfolded protein degradation probably through the UPS pathway; however, the mechanism through which they perform this function needs further investigation.

TRIMS IN ELIMINATING MISFOLDED PROTEINS/AGGREGATES VIA AUTOPHAGY

TRIM16

TRIM16 (also termed as estrogen-responsive B box protein-EBBP) has a missing RING domain at the N-terminus but harbors two B-box domains that possess RING-like folds, which still has the E3 ligase activity, a coiled-coil region, and a C-terminal PRY-SPRY domain.

TRIM16 was reported to bolster the turnover of stress-induced misfolded proteins by positively regulating the nuclear factor erythroid 2-related factor 2 (Nrf2) and autophagy signaling pathways (Jena et al., 2018b, 2019). TRIM16 binds to Nrf2, inducing K63-ubiquitination of Nrf2 and enhancing p62-Kelch-like ECH-associated protein 1 (KEAP1) interaction, which displaces Nrf2 from KEAP1 and prevents Nrf2 from proteasomal degradation (Jena et al., 2018a). As a positive feedback loop, the activated Nrf2 then converts misfolded proteins into aggregates by induction of p62, TRIM16, and other ubiquitin system genes. Recent studies demonstrated that TRIM16 is capable of assembling the autophagy machinery that contains TRIM16 (which acts as a scaffold protein), unc-51 Like Autophagy Activating Kinase 1 (ULK1), ATG16, and LC3B, which governed autophagosome biogenesis, and thus accelerate protein aggregates sequestration and clearance (Jena et al., 2018a; New and Thomas, 2019). Taken together, TRIM16 acts as a central player in eliminating misfolded proteins/protein aggregates during exposure to oxidative/proteotoxic stress by modulating the autophagy pathway.

TRIM5

TRIM5 has a similar structure to TRIM11 except for the absence of a PRY domain at its C-terminus. As an innate immune activator and a ubiquitin E3 ligase, TRIM5 is highly relevant in retroviral restriction such as anti-HIV infection (Pertel et al., 2011; Fletcher et al., 2018).

TRIM5 can be significantly upregulated during cell transformation to eliminate misfolded proteins/aggregates effectively (Chen et al., 2017). Mandell et al. (2014) screened all TRIMs involved in autophagy and identified that TRIM5 acts as a scaffold protein that interacts with the key members of autophagy like protein ULK1 and Beclin1. TRIM5 also served as a selective autophagic receptor mediating substrates' autophagic degradation (Mandell et al., 2014). Thus, TRIM5 promotes the removal of misfolded proteins/aggregates most likely via the autophagy pathway.

TRIMS IN ELIMINATING MISFOLDED PROTEINS VIA ERAD

TRIM25

TRIM25, known as the estrogen-responsive finger protein (EFP), possesses a typical N-terminal TRIM/RBCC motif and a C-terminal PRY/SPRY domain that has been extensively studied in innate immunity (Zou and Zhang, 2006; Versteeg et al., 2013). Previous studies showed that TRIM25 mainly acted as an E3 ligase and mediated ubiquitination of various key molecular biomarkers such as retinoic acid-inducible gene 1 (RIG-I) for antiviral response and peroxisome proliferator-activated receptor-gamma (PPARγ) for metabolism (Gack et al., 2007; Lee et al., 2018).

Since the ER is fundamental for protein and lipid biosynthesis as well as protein posttranslational processing and transportation,

various physiological or pathological processes can lead to an accumulation of misfolded proteins in the ER resulting in a condition called ER stress (Wu and Kaufman, 2006). To cope with ER stress, cells rely on ERQC systems such as the UPR and ER-associated protein degradation (ERAD) (Guerriero and Brodsky, 2012; Hetz and Saxena, 2017). Recently, our group identified that TRIM25 is significantly induced upon ER stress, which promotes ERAD and finally restores ER homeostasis (Liu et al., 2020). Moreover, we found that TRIM25 expression is associated with hepatocellular carcinoma (HCC) progression and high TRIM25 expression correlates with poor patient survival in HCC (Liu et al., 2020). This reveals that TRIM25 modulates the ER homeostasis and could serve as a potential target for HCC therapy. In summary, TRIM25 is a novel ERQC player, mediating misfolded protein clearance via the ERAD.

TRIM13

TRIM13 is another member of the TRIM protein family that is encoded by the Ret Finger Protein 2 (RFP2) gene that consists of RING, B-box, and coiled-coil domains. Besides, TRIM13 also contains a TM domain, which is required for its ER localization (Lerner et al., 2007). Interestingly, this TM domain is only found in TRIM13 and TRIM59 among all the TRIM members.

Reports have shown that TRIM13 can recognize ERAD substrate CD3δ and degraded it via UPS, which relies on its RING domain (Lerner et al., 2007). In a condition of ER stress, TRIM13 also contributes to autophagosome biogenesis through its strong interaction with p62 and double FYVE-containing protein 1 (DFCP1). The deletion construct of the coiled-coil domain of TRIM13 represses autophagy regulation (Tomar et al., 2012). Additionally, TRIM13 has been found to regulate the activation of caspase-8 to induce autophagy, leading to tumor cell death in tumors (Tomar et al., 2013). These studies enrich our understanding of the critical roles played by TRIM13 in ERAD and suggest that TRIM13 may be a tumor suppressor.

DISCUSSION AND FUTURE PROSPECTS

In this review, we summarized the defined roles of TRIM proteins in misfolded protein clearance. These TRIM members can be localized at the nucleus, cytoplasm, or ER and facilitate the degradation of misfolded and aggregated proteins through distinct pathways, including the UPS, autophagy, and ERAD. Recent studies revealed that TRIM5 and TRIM16, serve as autophagy receptors for cargo recruitment providing the possibility that TRIM members can collaborate to regulate autophagy-mediated misfolded proteins' clearance (Kimura et al., 2017; New and Thomas, 2019). In previous studies, TRIM5 has been shown to shuttle into the nucleus, where it forms heterodimer with TRIM19 (PML) or TRIM16 resulting in PML NBs (Stremlau et al., 2004; Diaz-Griffero et al., 2011; Bell et al., 2012); thus, indicating a synergistic effect of autophagy and UPS on misfolded protein removal. In addition, the complex of MAGE-A3/6-TRIM28 could target 5′ AMP-activated protein kinase (AMPK) for ubiquitination and proteasome-mediated degradation resulting in significant autophagy inhibition (Pineda et al., 2015). Together, these reports suggest a positive feedback loop and the existence of a cross-talk between the UPS and autophagy pathways. Thus, it is imperative to investigate the cooperation among the TRIM protein members in the degradation of misfolded protein via the UPS, autophagy, or their combination.

Of note, TRIM proteins not only act as E3 ligases but also may have extensive, yet unidentified roles. For example, TRIM19 (PML) possesses SUMOylation ligase activity in the nucleus (Guo et al., 2014), and other TRIMs with a SUMOylation ligase activity include TRIM5, TRIM27, and TRIM36 (Chu and Yang, 2011). Misfolded proteins may undergo sequential SUMOylation and ubiquitination mediated by one or several TRIM members. Moreover, the association between SUMOylation and ubiquitination and their roles in misfolded protein degradation provides a better understanding of those TRIMs containing TRIM19-like RBCC structure and is worth further exploration (Wang et al., 2018).

We have proven that the effective removal of misfolded proteins is required for oncogenesis and that TRIM members (like TRIM11) are upregulated and play critical roles during oncogenic transformation (Chen et al., 2017); this suggests that TRIM proteins can serve as novel therapeutic targets for clinical treatment of cancer. An approach has recently been developed to acutely and rapidly degrade endogenous proteins, which is based on TRIM21 and UPS pathway (Clift et al., 2017, 2018). This method, which can also precisely target the aberrant proteins in the cell, may contribute to developing other novel therapeutics for diseases associated with misfolded proteins such as cancers and neurodegenerative diseases.

To conclude, TRIM proteins are involved in misfolded protein clearance through distinct mechanisms, and the identification of other TRIM members capable of efficient misfolded proteins removal is imperative. More importantly, there exists a strong connection between TRIM proteins and proteostasis – a condition that can affect tumorigenesis and neurodegeneration. It is of key importance to further elucidate the relationships and dynamics between TRIMs and proteostasis as this is crucial for the development of novel therapeutic intervention by targeting relevant TRIMs in cancer, neurodegenerative diseases, and other associated pathologies.

AUTHOR CONTRIBUTIONS

LZ, LA, XW, YL, and LC contributed to the acquisition of data, interpretation of data, and drafting the article. LZ and LC contributed to analyze the data and wrote the manuscript. All authors contributed to the manuscript revision and read and approved the submitted version.

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