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OVERVIEW OF CLASS-I TRIPARTITE MOTIF (TRIM) PROTEINS SPECIFICALLY TRIM67

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ABSTRACT

The TRIM family is a group of genes expressed during embryogenesis. This review emphasized data on Class-I TRIM genes, including TRIM1, TRIM9, TRIM36, TRIM46, TRIM67, TRIM18, and TRIM76. This article will discuss the structure and function of these genes and their roles in various physiological processes such as embryonic development, and immune regulation. Class-I TRIM proteins develop as E3 ubiquitin ligases and work with E2 ubiquitin-conjugating enzymes. TRIM9 is expressed in the stem cells of mice and linked to various neuronal functions and neurological diseases. TRIM18 is found in microtubules and cellular filaments. TRIM36 is associated with neuro-pathological mutations, while TRIM46 controls microtubule organisation during axon formation. TRIM67 plays a significant role in neuritis outgrowth, lipid phosphate phosphatase, and colorectal and lung carcinomas. It also involves cell proliferation and induces morphological changes like neuronal differentiation. TRIM67 is important in Plasticity-related gene-1 (PRG-1). Deletion of prog-1 in mice results in epileptic seizures, indicating the significance of TRIM67 in brain development and growth. TRIM76 is associated with cardiac diseases. Further identification and characterisation of novel TRIM members will provide new insights into the functions of these essential proteins in health and disease.

Keywords: Class-I, TRIM1, TRIM9, TRIM18, TRIM36, TRIM46, Trim67, TRIM76

INTRODUCTION

The Tripartite motif (TRIM) protein family has been the focus of recent research, revealing its diverse functions. This protein family, known for its tripartite motif-containing structure, comprises over 70 units, making it well-known worldwide (Wu *et al.,* 2022, Reymond *et al*., 2001) . These proteins are classified into 11 subgroups based on their unique characteristics, as identified by various studies (Carthagena *et al.,* 2009; Shigetsugu Hatakeyama, 2019).

TRIM proteins play vital roles in various physiological and pathological processes, including developmental and embryogenesis operations (Francesca Petrera and Germana Meroni, 2012). They are composed of three zinc-binding domains, namely the RING (R), Box (B) (split into B1/B2), and a C-terminal domain that can be a Coiled-Coil pattern or different domains involved in the ubiquitination process. (Pierre Boudinot *et al.,* 2011; Rienzo *et al.,* 2020). TRIM proteins are also involved in other cellular functions, such as viral response, apoptosis, and cell cycle regulation, and continuous modifications in these proteins can lead to different pathological conditions (Francesca Petrera and Germana Meroni, 2012; Tomar and Singh, 2015). The TRIM protein is linked with various C-terminal domains that determine their interactions with other proteins. As a result, TRIM proteins exhibit RING-dependent E3 ubiquitin ligase activity and can form multi-protein complexes through interactions with their Coiled-Coil (CC) and C-terminal domains (Pierre Boudinot *et al.,* 2011, Girish Patil and Shitao Li, 2019). Human TRIM proteins are classified into nine structural subsets based on their C-terminal domains, ranging from C-I to C-XI (Rienzo *et al.,* 2020).

E3 ubiquitin ligases are divided into three sub-families based on their catalytic mechanism. HECT and RBR-type ligases form a thioester intermediate with ubiquitin before its final transfer into the substrate, albeit using different structural features (Donald Spratt *et al.,* 2014;

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Buetow and Huang, 2016). Class-I and Class-IV TRIM proteins are characterised by a PRY and SPRY domain adjacent to the RING finger domain (David Rhodes *et al.,* 2005). The RING finger domain plays a significant role in the transfer of ubiquitin to RING proteins and heterologous substrates, and it is a characteristic signature of many E3 ubiquitin ligases (Shigetsugu Hatakeyama, 2019).

Recent studies have also highlighted the self-association properties of the CC region of TRIM proteins, which can lead to the formation of high molecular weight complexes in living organisms (Diego Esposito *et al.,* 2022) Further studies have shed light on the regulatory roles of TRIM proteins during immune signalling. While about half of known TRIM proteins have been found to enhance innate immune responses, some TRIM proteins have also been implicated in destructive regulatory roles during immune signalling (Wynne *et al.,* 2014; Gijs Versteeg *et al.,* 2013,) TRIM/RBCC proteins have been involved in various biological processes, and their mutations have been associated with multiple pathological conditions. These conditions range from Mendelian genetic diseases to cancer development and viral infections (Chaikuad *et al.,* 2022; Bawa *et al.,* 2021).

This review article aims to assess Class-I Tripartite Motif containing Proteins, specifically on TRIM-67. The objective is to explore the roles and functions of Class-I TRIM genes, which include TRIM1, TRIM9, TRIM18, TRIM36, TRIM46, TRIM67, and TRIM76. The review highlights the involvement of Class-I TRIM proteins in embryonic development, immune system regulation, host defence against viral infections, brain development, neurological diseases, microtubule organisation, cardiac diseases, and plasticity-related gene-1 (PRG-1). The article provides an overview of the structure of Class-I TRIM proteins as E3 ubiquitin ligases with the involvement of E2 ubiquitin-conjugating enzymes. Identifying and characterising novel TRIM members may provide further insights into the functions of these essential proteins in health and disease.

Ubiquitination

Regulatory proteins are known as ubiquitin. These proteins covalently attach with the above protein and participate in changes in protein firmness, its purpose, and localisation. All eukaryotic cells used ubiquitination to perform post-translational amendment mechanisms to control protein levels via proteasome-mediated proteolysis (Kawai and Akira, 2011). The ubiquitination reaction lasts in three or four steps and is regulated by a mechanism of an act of E3 ubiquitin ligases. Ubiquitin is primarily connected with "3" enzymes known as E1-ubiquitin activating, E2-ubiquitin conjugating, and E3-ubiquitin ligase. Through the subsequent activation, these enzymes bond covalently with single or additional lysine residues on mark proteins. The composition of Ubiquitin consists of 76 amino acids and seven lysine residues (K6, K11, K27, K29, K33, K48, and K63) (Bhoj and Chen, 2009). Polyubiquitin chains are likely to be made via conjugation of lysine residue with C-terminal GLY residue of ubiquitin. However, K48-related and E3-polyubiquitination are highly accepted because of targeting signal features that allow adapted proteins to experience 26S proteasome-dependent deprivation. So far, K63-linked polyubiquitination is necessary for the trafficking of reference proteins and signal transduction pathways (Liu *et al.,* 2013; Manohar *et al.,* 2019).

Ubiquitination procedure of TRIM family proteins related to three classes of enzymes. First, E1 Cysteine residue attacks the ATP-activated C terminal glycine on ubiquitin, sequent a thioester Ub-S-E1 complex, then energy from ATP and di-phosphate hydrolysis cause the placement of reactive thioester and resulting course are thermo neutral. Adjacent, a trans-thiolation reaction occurs, in which an E2 Cysteine residue attacks and replaces the E1 (Olssen and Lima, 2013). HECT sphere kinds E3-ligases contain single other trans-thiolation effects to convey the ubiquitin molecule on E3, while more frequently, RING-finger domain type ligases directly transfer ubiquitin from E2 to the substrate. The ubiquitin-activating enzyme (E1) charges ubiquitin and forms an E1-ubiquitin thioester intermediate. This activated ubiquitin is transferred to the active Cysteine of the ubiquitin-conjugating enzyme (E2) (Metzger *et al.,* 2014). The ubiquitin ligase enzyme (E3) interacts directly with the E2 and the substrate and mediates ubiquitin transfer to a lysine residue of the target protein (Glickman and Ciechanover, 2002). A large number and kind of proteins standardised by ubiquitination demand high specificity and account for the growing number of E3 ligases. Recent studies have uncovered numerous new functions of ubiquitination, independent of proteasomal degradation, which include regulation of protein activity and subcellular localisation. Different

ubiquitin chain lengths are associated with diverse outcomes: while Polyubiquitin chains are usually related to proteasomal degradation, mono and di-ubiquitination have been implicated in endocytic processes (Hicke and Dunn 2003; Hicke and Dunn, 2003). The final step in the first ubiquitination event is an attack from the target protein lysine amine group, which will remove the Cysteine and form a stable isopeptide bond (McClellan *et al.,* 2019). One notable exception is the p21 protein, which appears to be ubiquitin using its N-terminal amine, thus creating a peptide bond with ubiquitin (Coulombe *et al.,* 2004).

E3-Ubiquitin ligase Enzyme

E3 enzyme is a diverse protein complex essential for projecting ubiquitination to specific substrate protein ubiquitination HECT domain type E3-ligases transfer the ubiquitin molecule into E3. The RING domain comprises 40-60 amino acids and is responsible for E3-ubiquitin ligase activity, which mediates protein pairing with ubiquitin (Esposito *et al.,* 2017). E3 performs its function in affiliation with an E1-ubiquitin activating enzyme and an E2-ubiquitin conjugating enzyme. E1 enzyme is usually divided by every ubiquitin-ligase, which utilizes ATP to trigger ubiquitin for conjugation and transfers it to an E2 enzyme. E2 usually coordinates with the E3 partner and transfers the ubiquitin to the target protein; E3-Ubiquitin attaches covalently upon a lysine residue of a target protein (Spratt *et al.,* 2012). The b-box1 structure has similarity with the RING folds; different domains like Z.Z. and U-box of E3 and E4 enzymes boost the potential with the B-box1 domain, likewise, E3 activity itself or improve the activity of Ring type E3 ligases, i.e., confers E4 enzyme activity (Wright *et al.,* 2016). The lysine of the ubiquitin moiety used for isopeptide bond formation, K48 versus K63, K11, or K29, is also crucial in determining the fate of the target protein (Tracz *et al.,* 2021). Highly distinguished, those K48-linked chains are responsible for proteasomal degradation, and K63-linked chains are involved in several types of cellular signalling via kinase activations (French *et al.,* 2021). Recent studies have shown the role of additional uncharacteristic Polyubiquitin linkage during M1, K6, K11, K27, K29, K33, or various links inside a similar sequence. Atypical Polyubiquitin chain-conjugation activities of some TRIM proteins have been revealed (Watanabe *et al.,* 2015). The nature of the modifier can be different from the classical ubiquitin peptide. Numerous ubiquitin-like peptides, SUMO, Nedd8, ISG15, etc., are being discovered and found to determine additional target facts (Li *et al.,* 2018). K27-related polyubiquitination is an exceptional change in antiviral Immunity (Song and Li, 2021).

TRIM/ RBCC proteins will focus on the growing evidence that suggests that TRIM/RBCC proteins act using the exact primary mechanism and represent a new subclass of 'particular protein RING 'finger' E3 Ubiquitin ligases (Meroni and Diez-Roux, 2005). The role of the C-terminal domain in the E3 activity is still unclear. As previously mentioned, these domains are also present in TRIM/RBCC proteins; in some cases, they interact with proteins involved in the ubiquitination process (Rajsbaum *et al.,* 2014). Hence, mono-ubiquitination and linear ubiquitination are recognized as post-translational modifications concerned with receptor internalization, trafficking, and signal transduction (Grillari *et al.,* 2010).

Class I TRIM

The TRIM family unit is subdivided into classes based on their carboxy-terminal domains. TRIM9 and TRIM67 are the least evolutionarily conserved class I TRIMs. Class I subunit is defined by the C-terminal FNIII and spray domains, which may bind to microtubules (Menon e*t al.,* 2021). Other members of Class-I are TRIM1, TRIM18, TRIM36, TRIM46, and TRIM76. These proteins are established by juxtaposing a PRY and a SPRY domain, also known as PRY/SPRY domain (Pierre Boudinot *et al.,* 2011) . PRY/SPRY domain promotes protein-protein interactions (Yu *et al.,* 2019). B-boxes have not been found in any other proteins. they are the best determinant of the TRIM family, and the general function of B-Boxes, mutations in these domains have been associated with developmental abnormalities and they appear to be involved in viral recognition by some TRIMs (Wagner *et al.,* 2016). The function of Class-I TRIM E3 ligases has been established, but little is known about their specific interaction and expression patterns during vertebrate development. Short and Cox used a bioinformatics approach to categorize TRIM proteins (Girish Patil and Shitao Li, 2019).

TRIM 1

The protein TRIM1 may be a key player in regulating immune responses to pathogens and other immune-related processes, as well as in

neuropathology, specifically in Parkinson's disease (P.D.) (MacMahon Copas *et al.,* 2021) P.D. is a neurodegenerative disorder that results in motor symptoms such as tremors, rigidity, and bradykinesia due to the loss of dopaminergic neurons in the substantia nigra region of the brain (Aubrey Schonhoff *et al.,* 2020). Recent studies have found that TRIM1's involvement in biological processes may differ in P.D. patient-derived induced pluripotent stem cells (iPSCs) neuronal progenitors and neurons compared to control cells (Xu *et al.,* 2016).

Research has shown that TRIM1 expression is altered in P.D. patients and animal models, specifically reduced in the substantia nigra of P.D. patients, which suggests a potential link between TRIM1 and the pathogenesis of P.D (Panicker *et al.,* 2021). TRIM1 has also been found to regulate cellular processes such as autophagy, which is responsible for recycling cellular components and maintaining cellular homeostasis (Adrienne Stormo *et al.,* 2022). Dysregulated autophagy has been linked to the development of P.D. and TRIM1 has been shown to play a role in modulating this process in iPSCs-derived neuronal progenitors and neurons from P.D. patients (Panicker *et al.,* 2021; Ahsan Usmania *et al.,* 2021).

In addition to autophagy, TRIM1 has been implicated in mitochondrial dynamics, another cellular process associated with P.D. pathogenesis (Yuzuru Imai *et al.,* 2011). P.D. patients and animal models have observed mitochondrial dysfunction and impaired dynamics. Recent studies have suggested that TRIM1 may regulate mitochondrial dynamics through its E3 ubiquitin ligase activity, although the exact mechanisms require further investigation (Kah-Leong Lim *et al.,* 2012). These findings highlight the potential therapeutic applications of TRIM1 in P.D. and other neurodegenerative disorders and the importance of further research into its involvement in cellular processes (Martin Lang *et al.,* 2022, Valentina Nicoletti *et al.,* 2021).

TRIM 9

C-I subfamily of TRIM proteins, including TRIM-9, MIDI, and MID2, have neuronal functions and are associated with neurological diseases (Timothy Cox, 2012). Its primary function in Cytoplasmic variable neuropathology decreased in the affected brain areas in P.D. and dementia with Lewy bodies (Yan Zhu *et al.,* 2022) Transcription of the gene differs in P.D. patients derived ipscs neural progenitors and neurons in comparison with control cells associated with paraneoplastic neurological syndrome (Simona Aversano *et al.,* 2022; Chris Woodard *et al.,* 2014). Trim 9 functions in Stem cells during mouse embryogenesis expressed mainly in CNS, in particular developing neocortex dorsal thalamus and midbrain basal area of the hindbrain and in the spinal cord, in the adult brain is detected in the parkinjie cells of the cerebellum in the hippocampus and the cortex (Vivian Chen *et al.*, 2017). Ubiquitin netrin 1 receptor DCC and thereby decrease dendritic and axonal branching of adult-born hippocampal neurons as well as cortical neurons influences on hippocampal-dependent spatial learning and memory in the Morris water maze (Jayne Aiken and Georgia Buscaglia, 2016). Ubiquitinates polymerase VASP modulates the filopodia density and stability in response to netrin in cortical neurons, interacts with SNAP25, and thereby inhibits SNARE complex formation upon exocytosis in axon branches (Shalini Menon *et al.,* 2021; Melissa Plooster *et al.,* 2017).

TRIM18 (MID1)

Of the nine subfamilies identified, defined by different domains found within the C-terminal half, MID1 is classified as part of the C-I subfamily, including MID2, TRIM9, TNL, TRIM36, and TRIFIC (Katharine Wright *et al.,* 2016). The C-I subfamily consists of the FNIII and B30.2 domains; interestingly, all are associated with microtubules (Timothy Cox, 2012). Reanalysis of the C-I subgroup led to the identification of a relatively conserved 60 amino acid region, termed the C-terminal subgroup One Signature (COS) box, at the C-terminal end of the CC domain (Kieran Short and Timothy Cox, 2006).

Mutation of TRIM18 is found in Opitz syndrome, G/BBB syndrome, which is an X-lin recessive disorder; characterized by hypertelorism, hypospadias, genital-urinary defects, lip-palate-laryngotracheal clefts, imperforate anus, developmental delay and congenital heart defects cleft lip/palate, hypospadias, and hypertelorism (Roger Stevenson *et al.,* 2013). Homo interaction with TRIM 27 is required during embryogenesis for proper development Mutations of MID1 are associated with X-linked Opitz G syndrome, characterized by midline anomalies. MID1 is connected with the microtubules and works as a ubiquitin E3 ligase, targeting protein Phosphatase 2A for ubiquitin-mediated regulation (Rossella Baldini *et al.,* 2020).

Table 1. Illustrate: Class-I TRIM its Domains, isoform mapping, adult and embryonic expression, in vitro in vivo and I. M. expression, cellular locality, and its function (Asami *et al.,* 2023, Venuto and Merla *et al.,* 2019, Reymond *et al.,* 2001)

ClassI TRIM Names	Synonyms	Molecular Position	Domains	Isoforms Mapping	Adult Expression	Embryonic Expression	In Vivo expression	In vitro Expression	I.M.	Cellular Localization	Function
TRIM1	MID2	642-aa protein	R B1,B2, CC, COS, FN3, SPRY	X.Q. 22-25 (R.H.)	UBIQUITUS	Heart, Kidney, CNS, Thymus, eye	+	-	+	Filamentous C Microtubules	Inhibits MLV (virus) entry, gene expression and release
TRIM9	MIDI and MID2 KIAA0282, RNF91	1-710	R, B1,B2, CC, COS, FN3, SPRY, RFP	(3) 14 q 21-24 (RH)	Brain 4.4 Kb, Right Hemisphere of cerebellum, cerebral cortex	CNS, Kidney, Lens, Gut	+	+	+	Cytoskeleton Speckles (N) Microtubules	associated with neurological diseases, innate Immunity
TRIM18	MID1	60-aa	MID1 R, B1,B2,CC, COS, FN3, PRY, SPRY	(2) xp 22-3	Ubiquitous 5kb	CNS Gastrointestinal Tract	+	-	-	Cellular filaments. Microtubules	Mutated in Opitz syndrome type I
TRIM36	RBCC728, RNF98	33-84. 154-192. 207-249. 271-345.	R, B1, B2 CC, COS, FN3, SPRY	5 q 22	Expressed in 160 organs, highest expression in sperm.	Expressed in 160 organs,	+	+	+	Cytoskeleton Microtubule and mitotic spindles M.T. cytoskeleton in HeLa cells	Transferase Degradation of target protein axon specification, neuronal polarity, neuronal migration Anencephaly (APH), chromosomal segregation Cell cycle regulation.
TRIM46	TRIFIC	33-59. 172-231. 222-263	R1, R2 B-Box, CC, COS, FN3, SPRY	Q7Z4K81-5.	Expressed in 119 organs Right hemisphere of cerebellum. Proximal axon of Purkinje cells in cerebellum	Expressed in 119 organs Right hemisphere of cerebellum	+	+	-	Microtubule MT cytoskeleton in HeLa cells	Controls microtubule organization during axon formation
TRIM67		PRGs PRG-1 PRG-2 and 80 K-H	R, B1,B2, CC, COS, FN3, SPRY	80K-H	Ubiquitous, Brain	Brain, Cerebellum Lungs Intestine	+	+	-	-	TRIM67 may function as a positive regulator for PRG-1 innate Immunity, viral infection, carcinogenesis, and development
TRIM 76					Heart, Left ventricular.		+	-	-	-	Associated with cardiac disease

The mechanism of microtubule association is not known. Nowadays, a 60-amino acid region known as the C-terminal subgroup One Signature (COS) box/domain was identified at the C-terminal end of the coiled-coil (CC) domain that assists microtubule localization (Dongming Sun *et al.,* 2001). The MID1 (TRIM18) protein contains the prototypical RING–B-box–Coiled-coil (RBCC) domains observed in the tripartite motif (TRIM) protein family (Michael Massiah *et al.,* 2006). MID1 exhibits ubiquitin E3 ligase activities and targets the catalytic subunit of PP2A (PP2Ac), alpha4, and the fused kinase for polyubiquitination (Du *et al.,* 2013). In cells, MID1 is shown to associate with microtubules throughout the cell life cycle. It is not clear whether the microtubule association involves MID1 directly binding microtubules or binding a transport protein or another microtubule-binding protein. Mutations within the C-terminal half of MID1 have been shown to result in MID1-forming cytoplasmic "'clumps' or aggregates instead of associating with the microtubules (Beatriz Aranda-Orgillés *et al.,* 2008).

TRIM36

TRIM36, TRIM/RBCC family protein, RBCC is one of the large protein families concerned with many biological processes likewise cell proliferation, cell differentiation, transcriptional development regulation, apoptosis, and tumorigenesis (Ning Uang *et al.,* 2022). TRIM 36 associated with Neuropathology mutations with autosomal recessive anencephaly defined by the lack of brain tissue and cranium stem cell knockdown of trim36 inhibits smile formation from mesodermal tissue during early embryogenesis of Xenopus leavis (Nivedita Singh *et al.,* 2017). E3 ubiquitin-protein ligase, Zinc binding protein RBCC728, brings subsequent proteasomal degradation and ubiquitination of target proteins. Also Concerned with cell cycle regulation and chromosome segregation, possibly function in the acrosome reaction and fertilization. Few studies refer to TRIM36 origin disorganized spindles in HeLa cells, ring finger protein 98 (Santina Venuto and Giuseppe Merla *et al.,* 2019).

TRIM36 is made up of 10 axons and codes for a 728 amino-acid long protein of 83-kDa. Diagnosed via RT-PCR that TRIM36 expressed

in the human fetal brain and in other tissues of 18 weeks old aborted fetus also discovers its function in neurogenesis (Michael Lopez and Shamim Mohiuddin, 2023).

TRIM46

Recently identified TRIM46 is microtubule-associated protein active in the arrangement of parallel microtubule bundles joined by cross-bridges in the proximal axon; it is Necessary for the unvarying placement and maintenance of the parallel microtubule nervous tissue, which are important for prompt cargo transfer and trafficking in axons (Sam van Beuningen *et al.,* 2015). It is mainly found in recently specified axon and play vital role in axon specification. Besides, it helps in the organization of unvarying M.T. placement in axons. Furthermore, it is associated with a paraneoplastic neurological syndrome, stem cell control, neuronal polarity, and proper neural migration in vitro and in vivo (Jason *et al.,* 2010).

TRIM46 is joined with ubiquitin E3 ligase activity; it is not coupled with ubiquitin-conjugating E2 enzymes (Fiesel *et al.,* 2014). Moreover, for the confirmation of specific antibodies of TRIM46 the RING finger domain comprises a conserved Cys3HisCys4 motif which is necessary for proper folding of the RING finger and its possible E3 ubiquitin-protein ligase activity (Mary Canning *et al.,* 2004).

TRIM67

TRIM67 is the least studied vertebrate Class I TRIM that is the closest paralog of TRIM9. TRIM67 plays an important role in brain development and behaviour. TRIM67 'homologs were more evolutionarily conserved than vertebrate TRIM9 homologs, TRIM67 protein was most enriched in the embryonic cortex and the adult cerebellum. High expressions of TRIM67 throughout the developing hippocampus, the cortex, and most structures of the nascent diencephalon, some data indicate TRIM9 and TRIM67 interact and may heterodimerize (Nicholas Boyer *et al.,* 2018).

Effects in stem cells promote neural differentiation, including neuritogenesis and negatively regulate RNA signalling via ubiquitination and degradation of 80-KH (Hiroaki Yaguchi *et al.,* 2012) required for appropriate brain development, cognitive ability and social behaviour of mice. Neuropathology associated with the paraneoplastic neurological syndrome (Devine *et al.,* 2021). Interferons (IFNs) type I and type II motivate numerous TRIM proteins; TRIM proteins have an essential function in anti-microbial and antiviral systems. Few studies conclude that TRIM9 and TRIM67 both have similar amino acid sequences, acknowledge the role of TRIM67 as E3 ubiquitin ligase for 80K-H and expression of TRIM67 suppressed the growth of N1E-115 cells and prompt neurite outgrowth (Ling Wang and Shunbin Ning, 2021).

Expression of TRIM67 in adult mice denotes that it enhanced in the cerebellum as compared to other brain parts, while in embryo, TRIM67 expressions were noticed in the midbrain, developing cortex and diencephalon. However, in adult mice, deletion of TRIM67 results in a complex set of behavioural inadequacy and malformation of various brain regions and axonal fiber tracts, whereas mice deficient with Trim67 do not fully phenocopy the axon tract defects (Nicholas Boyer *et al.,* 2018). While information from humans concludes that the TRIM67 gene is not connected with any human illness, TRIM67 is the least biological process preserved vertebrate Class-I TRIM, dissimilar from the invertebrate TRIM ortholog (Nicholas Boyer *et al.,* 2018; Fan *et al.,* 2022).

TRIM67 mutant animals were suffering from congnital and behavioural insufficiency. Mice deficient Trim67 exhibit knockout impairments in sensorimotor gating, congenital flexibility, special memory, muscle function, social novelty preference and cause aberrant anatomy of numerous brain regions, hippocampus, thalamus, striatum and corpus callosum (Nicholas Boyer *et al.,* 2018; Sven Dekeyzer *et al.,* 2017). TRIM67 is a transcriptional reference of p53 gene indicated via Chromatin immunoprecipitation (ChIP) assay. Onto cellular emphasis, p53 gene joins with TRIM67-promoter and generates the impressive up-regulation of TRIM67, thus constituting a TRIM67/p53 self-amplifying loop that boosts p53 induced cell development, suppression and apoptosis (Shiyan Wang *et al.,* 2019). Recent investigations show that TRIM67 ubiquitin ligase activity is required for cognitive ability, proper brain development and social behavior in mice, although numerous of these investigations still lack from past 40 years (Denise Montell, 2019).

Possibility to such an extent that TRIM67 composed to inflect netrin-1 mutualist axonal effect. TRIM67 is an ample multi-domain protein constitutes N-terminal tripartite motif domains a RING field that confers ligase activity, a coiled coil domain and a B-box domain (Pratibha Kumari *et al.,* 2021). In addition, it contains a

COS domain and an FN3 domain that may permit interaction with microtubules and a SPRY domain which typically engages new binding partners (Shigetsugu Hatakeyama, 2019). Performing structure-function analysis by expressing versions lacking individual domains, the authors find that all domains participate in the axon-branching response to netrin (Nicholas Boyer *et al.,* 2020). TRIM67 negatively impacts TRIM9 function via ubiquitination. This acknowledged ubiquitination of TRIM9 would likely be nondegradative, like that of VASP, as author fined no differences in TRIM9 protein levels in the absence of TRIM67 (Shalini Menon *et al.,* 2021).

TRIM67 energizing restored p53 gene, make it enable to sensitized colorectal cells carcinoma toward chemotherapy in Vitro and in vivo. TRIM67 functions as a pivotal tumor suppressor in colorectal carcinoma and was a potential target for enhanced chemotherapy responsiveness (Shiyan Wang *et al.,* 2019). TRIM67 revealed earlier during the development phase than TRIM9, that's why might be it carries TRIM9-independent work. TRIM67 might heterodimerizes or homodimerize with additional distant relatives (Nicholas Boyer *et al.,* 2018).

TRIM9-mutualist ubiquitination Deleted in colorectal cancer (DCC) as well limit axon branches by blocking intracellular signaling and exocytosis of new membrane. TRIM67 heterodimerizes with TRIM9 because Trim9 is nearest paralog of TRIM67 and attached to (DCC), a deliberate neuronal path-finding receptor (Melissa Plooster *et al.,* 2017).

Trim 76

TRIM-76 is a protein with a tripartite motif domain, which is a defining feature of TRIM proteins. It plays a crucial role in regulating innate immune responses by interacting with and promoting the degradation of IRF3, a key regulator of type I interferon response. This allows TRIM-76 to modulate the production of type I interferon and the subsequent antiviral response (Maria Giraldo, 2020).

Beyond innate Immunity, TRIM-76 is involved in other cellular processes such as the regulation of NF-κB, a transcription factor that regulates inflammation and immune responses. It also plays a role in the regulation of p53, a tumor suppressor protein frequently mutated in cancer (Fan *et al.,* 2022; Tao Zhang *et al.,* 2016). By stabilizing p53, TRIM-76 induces cell cycle arrest and apoptosis in cancer cells, acting as a tumor suppressor in certain contexts. However, it has also been shown to promote the growth and survival of cancer cells by stabilizing HIF-1α, a protein involved in cell metabolism and survival under hypoxic conditions (Toshinori Ozaki and Akira Nakagawara, 2011). In viral infections, TRIM-76 has been found to be involved in the replication of various viruses, including HIV, West Nile virus, and dengue virus. Therefore, targeting TRIM-76 could be a potential strategy for the development of antiviral therapies (Supreeti Mahajan *et al.,* 2021; Ahammad *et al.,* 2019).

TRIM-76 has also been studied in the context of autoimmune diseases, where it regulates the activity of STAT3, a key player in the development of autoimmune diseases like rheumatoid arthritis and multiple sclerosis. Thus, inhibiting the activity of STAT3 using TRIM-76 may have therapeutic potential for these diseases (Peter Gregersen, 2009). TRIM-76 has also been studied in the context of autoimmune diseases, where it regulates the activity of STAT3, a key player in the development of autoimmune diseases like rheumatoid arthritis and multiple sclerosis. Thus, inhibiting the activity of STAT3 using TRIM-76 may have therapeutic potential for these diseases (Jennifer Huynh *et al.,* 2017). TRIM-76 has also been used as a building block for the development of protein-based materials with potential biomedical applications in tissue engineering and drug delivery (Jennifer Gagner *et al.,* 2014).

CONCLUSION

TRIM proteins have gained attention due to their crucial role in immune signaling pathways. Recent studies have uncovered the intricate mechanisms of TRIM protein self-association, catalytic activity, and substrate recognition. However, despite this knowledge, further research is needed to comprehend the mechanisms of this complex protein family fully. Changes in TRIM genes have been linked to various diseases, but the specific molecular effects of these alterations are not yet fully understood. Investigating the molecular-level phenomena caused by amino acid sequence modifications in TRIM proteins is necessary to uncover the pathophysiology of relevant diseases and the role of C-I TRIM proteins. A thorough analysis of all C-I TRIM proteins can provide valuable insights into disease pathophysiology. Further research on novel TRIMs is crucial for developing new strategies for diagnosis, treatment, and drug development in medical science.

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