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# Exploring the Mechanisms, Biomarkers, and Therapeutic Targets of TRIM Family in Gastrointestinal Cancer

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**Abstract:** Gastrointestinal region (GI) cancers are closely linked to the ubiquitination system, with the E3 ubiquitin ligase playing a crucial role by targeting various substrates. As E3 ubiquitin ligases, proteins of tripartite motif (TRIM) family play a role in cancer signaling, development, apoptosis, and formation. These proteins regulate diverse biological activities and signaling pathways. This study comprehensively outlines the functions of TRIM proteins in gastrointestinal physiology, contributing to our knowledge of the molecular pathways involved in gastrointestinal tumors. Gastrointestinal region (GI) cancers are closely linked to the ubiquitination system, with the E3 ubiquitin ligase playing a crucial role by targeting various substrates.

**Keywords:** tripartite motif, E3 ubiquitin ligase, ubiquitin–proteasome system, GI cancer, molecular pathways

## Introduction

Approximately 10 million individuals succumb to malignant tumors annually worldwide, with gastrointestinal cancer standing out as a prevalent malignancy within the digestive system.[1] Common gastrointestinal (GI) cancers involve tumors that impact various parts of the digestive system, such as the esophagus, stomach, intestines, liver, bile ducts, and pancreas.[2] Despite significant progress in surgical removal, radiation therapy, and chemotherapy, the 5-year survival rate for GI cancers remains poor.[3,4] It is the gradual alteration and influence of many genes that leads to the occurrence and development of GI tumors.[5,6] Hence, the pursuit of diagnostic markers characterized by high sensitivity and specificity holds paramount importance in enhancing the diagnostic precision of GI cancer.

As evidence has accumulated over the past ten years, abnormal degradation of oncogenic proteins or tumor suppressors by the ubiquitin proteasome system (UPS) plays a significant role in GI cancer development and progression.[7] It involves the work of ubiquitin-activating (E1), ubiquitin-conjugating (E2), and ubiquitin-ligating (E3) enzymes to facilitate the attachment of ubiquitin to lysine residues in proteins, step-by-step.[8] In humans and mice, dozens of members of TRIM family belong to the RING-type E3 ubiquitin ligases.[9] Multiple research studies have shown that several TRIM family members are linked to the onset and advancement of various types of cancer.[10–14] This suggests that we should comprehensively and thoroughly explore these members to gain a deeper understanding. Hence, we delve into the research progress concerning TRIMs associated with the predominant malignant neoplasm, gastrointestinal cancers, including esophageal squamous cell carcinoma (ESCC), gastric cancer (GC) and colorectal cancer (CRC).

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## Structure and Function of TRIM Family Proteins

The TRIM proteins are distinguished by their preserved RING domain, B-box domain, and coiled-coil region (CC) at their beginnings. TRIM proteins are categorized into subfamily C-I to C-XI based on their unique C-terminal domains, which differ from the N-terminal domains. Specifically, the C-terminal regions of TRIM proteins contain various domains COS (cos-box) domain, Fibronectin type-III domain (FN3), PRY domain, B30.2/SPRY domain (SPRY), acid-rich region (ACID), filamin type I domain (FIL), NHL domain, PHD domain, bromodomain (BRD), Meprin and TRAF-homology domain (MATH), ADP-ribosylation factor family domain (ARF), and transmembrane region (TM). An additional subfamily, known as UC, consists of 8 TRIM proteins that do not contain a RING domain (Figure 1). In addition, the functions of each domain name are shown in Table 1.

### N-Terminal

#### The RING Domain

The RING domain lies approximately 10–20 amino acids from the initial methionine. Initially, it was anticipated that the RING domain would be involved in DNA binding and identification.[27] Rad18, a yeast protein belonging to the first group of RNF proteins, can facilitate histone ubiquitination through its RING domain.[28] Past decades have demonstrated that the RING domain, when coupled with two zinc atoms, creates a RING finger structure resembling the zinc finger structure.[14,29] This structure facilitates the ubiquitination process by serving as a stable binding site for E2. The presence of this RING finger domain is a common feature among numerous E3 ubiquitin ligases.[30]

#### The B-Box Regions

The B-box is a zinc-binding motif unique to TRIM proteins that can bind either one or two zinc atoms, locating after the RING finger domain. Due to the B-box domain's structure resembling the RING finger, it gains ubiquitination capability for substrates.[15] The B-box domain can be classified into two types based on their amino acid sequence: type 1 B-boxes (B-box1) and type 2 B-boxes (B-box2).[31] There is evidence that the B1 box domain can function as an E3 ligase or boost the activity of the RING type E3 ligases. Also, the B-box2 domain, which is primarily connected to RING and coiled-coil domains, may have an effect on TRIM protein function.[15] It could potentially impact the control of the RING domain function or work alongside the B-box1 domain, potentially influencing substrate recognition and/or E3 ligase activity.

#### Coiled-Coil Domain

The coil–coil domain has 2 or 3 motifs, typically varying in length between 100 and 200 residues. These proteins have mechanical characteristics due to the basic arrangement, consisting of α helices twisted to form a rope-like structure, which is supported by hydrophobic interactions. Within the TRIM family, it facilitates both homodimeric interactions among its members and heterodimeric interactions between its members and other proteins. The coiled-coil domain has the ability to influence interactions between TRIM and various proteins, both heteromeric and homomeric, which ultimately dictates where they are located within the cell.[32,33]

### C-Terminal

The majority of TRIMs are found in the cytoplasm, making it crucial to comprehend their mechanisms of action and the types of substrates they interact with, which are determined by the C-terminal of TRIMs. In general, this region of TRIM proteins identifies certain targets and serves as a unique identifier to differentiate one TRIM protein from another. Typically, a COS domain appears after the coiled-coil domain, then the PRY-SPRY domain appears. Among them, the PRY-SPRY domain acts as a protein–protein interaction module.[21,34,35]

C-I subgroup members significantly influenced microtubule cytoskeleton interactions.[18] Specifically, the C-II subgroup contains COS-ACID domains, which possess abundant glutamate regions and function as E3 ubiquitin ligases to facilitate ubiquitin-mediated degradation of muscle proteins.[20] Noteworthy, C-I and C-III subgroups possess FN3 domain. Research suggests that this domain may have a broad range of molecular interactions due to its scaffold's ability to accommodate various loop lengths and coupling with other protein domains.[19] C-IV subgroup members possess the Plant homeodomain-bromodomain (PHD-BROMO) domain, which has been categorized as a gene regulator by

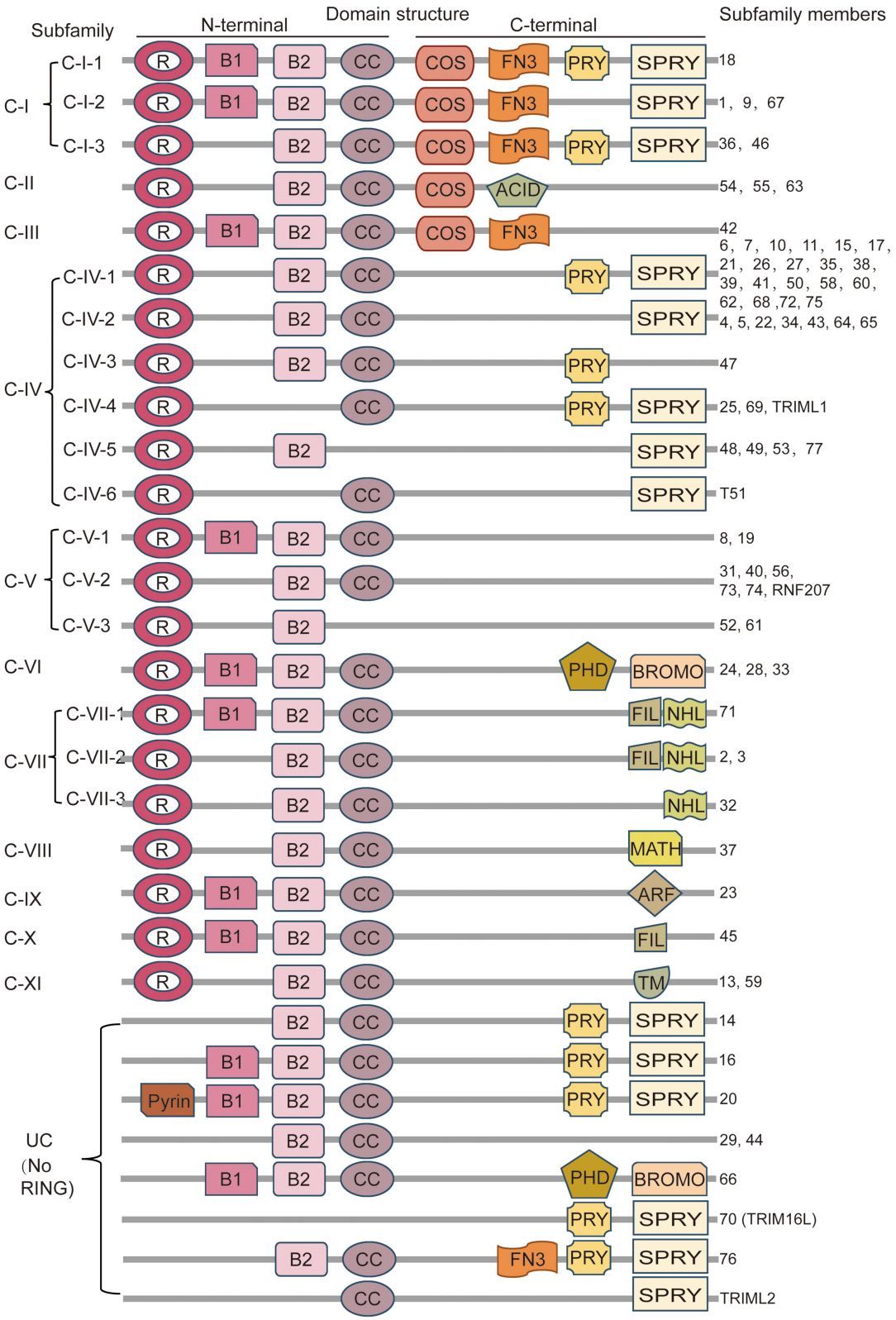


**Figure 1** TRIM family structural classification. The C-terminus of TRIM proteins determines their classification from C-I to C-XI; an unclassified group lacks a RING-finger domain.

**Abbreviations**: R, RING-finger domain; B1, B-box domain 1; B2, B-box domain 2; CC, coiled-coil domain; COS, cos box; FN3, fibronectin type III repeat; PRY, PRY domain; SPRY, SPRY domain; ACID, acid-rich region; FIL, filamin-type IG domain; NHL, NHL domain; PHD, PHD domain; BROMO, bromodomain; MATH, Meprin and TRAF-homology domain; ARF, ADP-ribosylation factor family domain; TM, transmembrane region.


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**Table 1** Functions of Different TRIM Domains

| Domain | Functions | Refs |
|---|---|---|
| RING | It promotes the transfer of ubiquitin to the substrate by binding to the ubiquitin coupling enzyme (UBE2 or E2) during the ubiquitination process | [14] |
| B-BOX | The B1 domain may exhibit E3 ligase activity or potentiate the effect of the RING domain. B2 can also contribute to RING domain efficacy or synergize with B1 | [15] |
| COILED-COIL | Coiled-coil domains mediate the formation of homodimers or heteropolymers in TRIM proteins, playing a crucial role in the assembly and localization of macromolecular protein complexes | [16] |
| PYRIN | It regulates inflammation and apoptosis | [17] |
| COS | Interaction between Cos and the microtubule cytoskeleton | [18] |
| FN3 | Pharmaceutical scaffolds based on FN3 | [19] |
| ACID | In addition to regulating ubiquitin-mediated protein degradation, ACID is an acidic region rich in glutamate | [20] |
| PRY-SPRY | PRY-SPRY is a protein-protein interaction and RNA binding region that plays a role in innate immune response and viral protein recognition. | [17] |
| PHD-BROMO | DNA-binding and transcriptional activation properties are found in PHD-BROMO domain, which are more protein-to-protein interaction modules | [21] |
| FIL | It regulates both TRIM-NHL mRNA and the immune system | [22] |
| NHL | A specific RNA sequence or structure can bind to NHL | [23] |
| ARF | By hydrolyzing GTP, ARF plays a role in intracellular transport | [24] |
| MATH | The MATH domain, common to other ubiquitin ligases known as TRAFs, facilitates protein–protein interactions and enables the formation of both hetero- and homo-oligomeric structures through self-interaction. | [25] |
| TM | It is necessary for TM to suppress the inflammatory response to pathogenic DNAs. | [26] |

**Abbreviations**: ACID, acid-rich region; ARF, ADP-ribosylation factor family domain; B-BOX, B-box domain; Coiled-coil, coiled-coil domain; COS, cos box; FIL, filamin-type IG domain; FN3, fibronectin type III repeat; MATH, Meprin and TRAF-homology domain; NHL, NHL domain; PHD-BROMO, PHD-BROMO bromodomain; PRY, PRY domain; SPRY, SPRY domain; TM, transmembrane region.

bringing together multiple regulators of transcription and chromatin, regulating numerous signaling pathways crucial for typical tumor growth and development.[36]

C-VII to C-X possessed FIL, NHL, MATH, or/and ARF domain. Four TRIM proteins have a filamin-type immunoglobulin domain, one type of FIL domain. TRIM45 possesses only the FIL domain at its end of the C-terminus participating in various tumor progression signal transduction pathways.[37] In addition to the above domain, TRIM2, TRIM3, and TRIM71 include an NHL domain, composed of repeat NCL-I/HT2A/LIN-41. As for the MATH and ARF domains, TRIM37's MATH domain promotes auto-oligomerization, and TRIM23's ARF domain induces autophagy in response to viruses.[24] TRIM13 and TRIM59 both possess a transmembrane domain located at the end of the C-terminal region. Both of these proteins are found in the ER and are essential for restraining inflammatory responses to pathogenic DNAs.[38,39] However, none of the typical C-terminal domains are present in the C-V subgroups. Typically, these unclassified TRIMs lack RING domains, but can still control inflammatory pathways.[40]

## The Role of TRIM in GI Cancer

The members of TRIM family can be classified as oncogenes or cancer suppressors according to their unique roles. We summarize and elucidate important roles of various TRIM proteins in GI malignancies (Table 2).

**Table 2** Summary of TRIMs Roles in GI Cancer

| Gene | Cancer Type | Expression | Gene Type | Prognostic | Tested Tissues | | Tested Cells | Cell Functions | Pathway | Refs |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Primary Tissue | Normal Tissue | | | | |
| TRIM15 | ESCC | Upregulated | Oncogene | NA | 38 | 38 | 1 esophageal epithelial cell line (HET-1A); 5 ESCC cell lines (EC9706, EC-1, KYSE-410, KYSE-150, TE-1 cells) | Proliferation, migration, invasion, EMT | Wnt/β-catenin signaling pathway | [41] |
| TRIM27 | ESCC | Upregulated | Oncogene | NA | 25 | 18 | 1 esophageal epithelial cells (HECC); 4 ESCC cell lines (TE-1, TE-11, EAC-109, KYSE150) | Proliferation, apoptosis | PI3/AKT signaling pathway | [42] |
| TRIM28 | ESCC | Upregulated | Oncogene | None | 136 | 37 | NA | Metastasis | NA | [43] |
| TRIM37 | ESCC | Upregulated | Oncogene | Unfavorable | 441 | NA | Specimens of the adjacent noncancerous esophageal tissue; esophageal Eca109 cells | NA | NF-κB signaling pathway | [44] |
| TRIM44 | ESCC | Upregulated | Oncogene | Unfavorable | 100 | 100 | 1 esophageal epithelial cells (HECC); 5 ESCC cell lines (KYSE140, KYSE150, EC109, EC9706, KYSE510) | Proliferation, migration, invasion, EMT | PI3K-AKT /mTOR pathway | [45] |
| TRIM3 | GC | Downregulated | Tumor suppressor | Favorable | 20 | 20 | 1 normal gastric epithelial cell line (GES-1); 2 GC cell line (SGC-7901, MGC-803) | Proliferation, migration, EMT | NA[ | [46] |
| TRIM11 | GC | Upregulated | Oncogene | Unfavorable | 36 | 36 | 1 normal gastric epithelial cell line (GES-1); 4 GC cell line (MGC-803, AGS, SGC-7901, HGC-27) | Proliferation, migration, invasion, EMT | Activating β-Catenin Signaling | [47] |
| TRIM3 | GC | Upregulated | Tumor suppressor | Favorable | 40 | 40 | NA | Proliferation, apoptosis, cell cycle | NA | [48] |
| TRIM14 | GC | Upregulated | Oncogene | Unfavorable | 117 | 117 | 1 normal gastric epithelial cell line (GES-1); 5 GC cell line (MKN45, MGC803, BGC823, SGC7901, AGS) | Migration, invasion, metastatic, EMT | AKT/mTOR pathway | [49] |
| TRIM15 | GC | Downregulated | Tumor suppressor | Favorable | 134 | 134 | 2 GC cell line (AGS, MKN-1) | Invasion | NA | [50] |
| TRIM15 | GC | Upregulated | Oncogene | Unfavorable | 275 | 275 | 2 GC cell line (MGC80-3, HGC-27) | Migration, invasion, EMT, metastasis | NA | [51] |

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**Table 2** (Continued).

| Gene | Cancer Type | Expression | Gene Type | Prognostic | Tested Tissues | | Tested Cells | Cell Functions | Pathway | Refs |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Primary Tissue | Normal Tissue | | | | |
| TRIM16 | GC | Downregulated | Tumor suppressor | None | 40 | 40 | NA | NA | NA | [52] |
| TRIM16 | GC | Upregulated | Oncogene | NA | 10 | 10 | 1 normal gastric epithelial cell line (GES-1); 6 GC cell line (AGS, BGC-823, HGC-27, SGC-7901, MKN-28, NCI-N87) | Invasion, migration | NA | [53] |
| TRIM21 | GC | Downregulated | Tumor suppressor | Favorable | 64 | 64 | 2 GC cell lines (SGC7901, BGC823) | Proliferation, apoptosis | NA | [54] |
| TRIM23 | GC | Upregulated | Oncogene | Unfavorable | 81 | 40 | 1 normal gastric epithelial cell line (GES-1); 6 GC cell lines (MKN45, BGC823, MGC803, HGC27, SGC7901, AGS) | NA | NF-kB signaling | [55] |
| TRIM24 | GC | Upregulated | Oncogene | Unfavorable | 133 | 20 | 5 GC cell lines (BGC-823, AGS, SGC-7901, MKN-1, HGC-27) | Proliferation | Akt signaling pathway | [56] |
| TRIM24 | GC | Upregulated | Oncogene | Unfavorable | 90 | 60 | 1 normal gastric epithelial cell line (GES-1); 5 GC cell lines (AGS, BGC823, MGC803, HGC-27, SGC7901) | Proliferation, migration, invasion, apoptosis, metastasis, cell cycle | Wnt/β-catenin signaling pathway | [57] |
| TRIM24 | GC | Upregulated | Oncogene | Unfavorable | 12 | 12 | 1 normal gastric epithelial cell line (GES-1); 5 GC cell lines (AGS, BGC823, MGC803, HGC-27, SGC7901) | Proliferation | PI3K/AKT and Wnt/β-catenin pathways | [58] |
| TRIM25 | GC | Downregulated | Tumor suppressor | Favorable | 90 | 82 | 3 GC cell lines (BGC823, SGC7901, MGC803) | NA | NA | [59] |
| TRIM29 | GC | Upregulated | Oncogene | NA | NA | NA | 1 normal gastric epithelial cell line (GES-1); 2 GC cell lines (BGC823, MGC803) | Proliferation, cell cycle, apoptosis | Wnt/β-catenin signaling | [60] |
| TRIM29 | GC | Upregulated | Oncogene | Unfavorable | 124 | 124 | NA | NA | NA | [61] |
| TRIM31 | GC | Upregulated | Oncogene | NA | 39 | 71 | 293 cells, AsPC-1 | Colony formation | NA | [62] |
| TRIM31 | GC | Upregulated | Oncogene | NA | NA | NA | 293 cell, AsPC-1 pancreatic cancer cells | None | NA | [63] |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| TRIM32 | GC | Upregulated | Oncogene | Unfavorable | 142 | 0 | 2 GC cell lines (MKN45; MKN74 cells) | Proliferation, apoptosis | NA | [64] |
| TRIM32 | GC | Upregulated | Oncogene | Unfavorable | 81 | 20 | 1 normal gastric epithelial cell line (GES-1); 4 GC cell lines (SGC7901, BGC823, AGS, MKN28) | Proliferation, migration, invasion, colony formation | β-catenin signaling pathway | [65] |
| TRIM32 | GC | Upregulated | Oncogene | Unfavorable | 876 | NA | 1 normal gastric epithelial cell line (GES-1); 5 GC cell lines (NCI-N87, MKN74, HGC27, AGS, MKN45) | Proliferation, apoptosis | Akt signaling pathway | [66] |
| TRIM40 | GC/ CRC | Downregulated | Oncogene | NA | NA | NA | HEK293T, HeLa, SW480, IEC-6 cells lines | NA | NF-κB signaling pathway | [67] |
| TRIM44 | GC | Upregulated | Oncogene | Unfavorable | 112 | | 7 gastric cancer cell lines (KatoIII, NUGC4, HGC27, MKN7, MKN28, MKN45, MKN74) | Proliferation, migration and invasion | NA | [68] |
| TRIM47 | GC | Upregulated | Oncogene | Unfavorable | 136 | 30 | 1 GC cell line (AGS) | Apoptosis, EMT | NF-κB signaling pathway | [69] |
| TRIM50 | GC | Downregulated | Tumour suppressor | NA | 415 | 34 | 1 normal gastric epithelial cell line (GES-1); 7 GC cell lines (AGS, BGC-823, HGC-27, MGC-803, MKN-28, MKN-45, SGC-7901) | Proliferation, cell cycle, Migration, Invasion, | Wnt/β-Catenin Signaling Pathway | [70] |
| TRIM54 | GC | Upregulated | Oncogene | Unfavorable | 4 | 4 | 1 normal gastric epithelial cell line (GES-1); 3 GC cell lines (AGS, HGC27, MGC-803) | Proliferation, migration, invasion, metastasis | NA | [71] |
| TRIM58 | GC | Downregulated | Tumour suppressor | Favorable | 23 | 23 | 1 normal gastric epithelial cell line (GES-1); 5 GC cell lines (MKN45, BGC823, HGC27, AGS, SNU719) | Proliferation, cell cycle | β-catenin signaling | [72] |
| TRIM59 | GC | Upregulated | Oncogene | Unfavorable | 156 | 122 | 1 normal gastric epithelial cell line (GES-1); 7 GC cell lines (MKN45, AGS, SGC7901, BGC823, N87, SNU1, SNU5) | Proliferation, clone formation, and migration | P53 Signaling Pathway | [73] |

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**Table 2** (Continued).

| Gene | Cancer Type | Expression | Gene Type | Prognostic | Tested Tissues | | Tested Cells | Cell Functions | Pathway | Refs |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Primary Tissue | Normal Tissue | | | | |
| TRIM3 | CRC | Downregulated | Tumour suppressor | NA | NA | NA | 2 CRC cell lines (HCT116, DLD-1) | Proliferation, clone formation, migration, invasion | P53 Signaling Pathway | [74] |
| TRIM6 | CRC | Upregulated | Oncogene | Unfavorable | 125 | 35 | 1 normal colorectal mucosa cell line (FHC); 4 CRC cell lines (LOVO, Sw620, HCT-8, HCT116) | Proliferation, cell cycle | NA | [75] |
| TRIM8 | CRC | Downregulated | Tumour suppressor | NA | NA | NA | HCT116 | Proliferation, colony | N-MYC pathway | [76] |
| TRIM11 | CRC | Upregulated | Oncogene | Unfavorable | 23 | 23 | 4 CRC cell lines (DLD-1, HT29, Sw480, HCT116) | Proliferation, apoptosis | miR-24-3p/ TRIM11 axis | [77] |
| TRIM14 | CRC | Upregulated | Oncogene | NA | 40 | 40 | 4 CRC cell lines (Sw620, Caco2, LOVO, HT29) | Migration, invasion | SPHK1/STAT3 pathway | [78] |
| TRIM15 | CRC | Downregulated | Tumor suppressor | NA | 32 | 32 | 1 normal colorectal mucosa cell line, CCD18Co; 3 CRC cell lines (HCT116, HT-29, LOVO) | Migration, colony formation | NA | [79] |
| TRIM21 | CRC | Downregulated | Tumor suppressor | NA | 39 | 14 | NA | Proliferation, EMT | NA | [80] |
| TRIM23 | CRC | Upregulated | Oncogene | Unfavorable | 60 | 60 | 1 normal colorectal mucosa cell line, FHC; 5 CRC cell lines (Sw480, HT29, SW1116, HCT116, SW620) | Proliferation, cell cycle, metastasis | P53 Signaling Pathway | [81] |
| TRIM24 | CRC | Upregulated | Oncogene | Unfavorable | 80 | 80 | 1 normal colorectal mucosa cell line (NCM460); 5 CRC cell lines (HCT116, LOVO, Sw620, HT29, NM460) | Proliferation, colony formation | YAP signaling | [82] |
| TRIM24 | CRC | Upregulated | Oncogene | Unfavorable | 97 | NA | NA | NA | NA | [83] |
| TRIM24 | CRC | Upregulated | Oncogene | NA | NA | NA | 1 CRC cell (HCT116) | Proliferation, colony formation, cell cycle, apoptosis | NA | [84] |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| TRIM25 | CRC | Upregulated | Oncogene | NA | NA | NA | 5 CRC cell lines (H1299, U2OS, MCF7, HCT116, HCT116 p53-/-) | NA | P53 Signaling Pathway | [84] |
| TRIM25 | CRC | Upregulated | Oncogene | NA | 11 | NA | 2 CRC cell lines (HCT116, HT29) | Proliferation, migration, invasion | TGF-β signaling | [85] |
| TRIM25 | CRC | NA | Oncogene | NA | NA | NA | 2 CRC cell lines (RKO, DLD-1); HEK293 cells | Apoptosis | NA | [86] |
| TRIM27 | CRC | Upregulated | Oncogene | Unfavorable | 80 | 80 | 1 normal colorectal mucosa cell line (NCM460); 5 CRC cell lines (LOVO, HCT116, Sw480, DLD-1 and HT29) | Proliferation, invasion, metastasis, apoptosis, cell cycle, EMT, colony formation | AKT signaling pathway | [87] |
| TRIM27 | CRC | Upregulated | Oncogene | NA | NA | NA | 2 CRC cell lines (HT29, RKO); HEK293; HeLa | NA | STAT3 signaling | [88] |
| TRIM28 | CRC | Upregulated | Oncogene | Unfavorable | 137 | NA | NA | NA | P53 Signaling Pathway | [89] |
| TRIM28 | CRC | Upregulated | Oncogene | Unfavorable | 19 | NA | NA | NA | P53 Signaling Pathway | [90] |
| TRIM28 | CRC | Downregulated | Tumor suppressor | Favorable | 15 | 15 | 1 normal colorectal mucosa cell line (NCM460); 5 CRC cell lines (LOVO, HCT116, SW48, DLD-1, HT-29); HEK293T cell | Migration, invasion, metastasis | WNT/β-catenin signaling pathway | [91] |
| TRIM29 | CRC | Upregulated | Oncogene | Unfavorable | 90 | 90 | 7 CRC cell lines (HCT116, SW620, SW480, SW1116, LOVO, HT29; RKO) | Proliferation, migration, invasion, apoptosis, metastasis, Cell cycle | p53 signaling pathway and JAK2/STAT3 signaling pathway | [92] |
| TRIM32 | CRC | Upregulated | Oncogene | NA | NA | NA | 1 normal colorectal mucosa cell line (CRL-1831); 2 CRC cell lines (HCT116, RKO), H1299; H460; MCF7; CRL-1831; CRL-10742 cells | Apoptosis, cell cycle | p53 Signaling Pathway | [93] |

(*Continued*)



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**Table 2** (Continued).

| Gene | Cancer Type | Expression | Gene Type | Prognostic | Tested Tissues | | Tested Cells | Cell Functions | Pathway | Refs |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Primary Tissue | Normal Tissue | | | | |
| TRIM37 | CRC | Upregulated | Oncogene | NA | 30 | 30 | 2 CRC cell lines (SW480; SW620) | Proliferation, colony formation, invasion, EMT | NA | [94] |
| TRIM37 | CRC | Upregulated | Oncogene | NA | NA | NA | 1 normal colorectal mucosa cell line (NCM460); 3 CRC cell lines (Sw480, HT-29, HCT116) | Proliferation, migration, invasion | Wnt/β-Catenin Signaling Pathway | [95] |
| TRIM39 | CRC | Upregulated | Oncogene | Unfavorable | 367 | NA | 7 CRC cell lines (HCT116, LOVO, DLD-1, HT29, SW48, Sw480, Caco2); HEK293T | Colony formation, migration, invasion | p53 Signaling Pathway | [96] |
| TRIM40 | CRC | Downregulated | Tumor suppressor | NA | NA | NA | 1 CRC cell SW480, HEK293T, HeLa | NA | NF-κB signaling pathway | [67] |
| TRIM44 | CRC | NA | NA | NA | NA | NA | 1 normal colorectal mucosa cell line (HIEC); 5 CRC cell lines (SW480, Caco-2, SW620, HCT116, HT29) | Proliferation | LINC00265/ miR-216b-5p/ TRIM44 | [97] |
| TRIM44 | CRC | Up-regulated | Oncogene | Unfavorable | 123 | 3 | 1 normal colorectal mucosa cell line (NCM460); 3 CRC cell lines (SW620, LOVO, HCT116) | Proliferation, migration, invasion | Akt/mTOR signaling | [98] |
| TRIM47 | CRC | Upregulated | Oncogene | Unfavorable | 280 | 280 | 1 normal colorectal mucosa cell line (FHC); 8 CRC cell lines (HCT116, HT29, Sw480, RKO, SW620, Caco2, LOVO, SW1116) | Proliferation, metastasis | TRIM47-SMAD4-CCL15 axis | [99] |
| TRIM52 | CRC | Upregulated | Oncogene | Unfavorable | 80 | 80 | 1 normal colorectal mucosa cell line (HIEC); 5 CRC cell lines (SW480, LOVO, SW620, HT29, RKO) | Proliferation, apoptosis | STAT3 signaling pathway | [100] |
| TRIM55 | CRC | Downregulated | Tumor suppressor | Favorable | 101 | 36 | 1 normal colorectal mucosa cell line (FHC); 4 CRC cell lines (DLD1, HCT116, SW620, Sw480) | Migration, invasion, apoptosis, cell cycle | NA | [101] |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| TRIM58 | CRC | Downregulated | Tumor suppressor | Favorable | 81 | 81 | 11 CRC cell lines (HCT8, KM12, Caco-2, DLD-1, HCT116, LOVO, HT-29, SW480, SW620, RKO, HCT15) | Proliferation, colony formation, migration, invasion, EMT | Wnt-β-catenin signaling pathway | [102] |
| TRIM59 | CRC | Upregulated | Oncogene | Unfavorable | 90 | 90 | 1 normal colorectal mucosa cell line (NCM460); 6 CRC cell lines (Caco-2, Sw480, HT-29, LOVO, DLD-1, HCT116) | Proliferation, colony formation, apoptosis, migration, invasion, metastasis, EMT | PI3K/AKT signaling pathway | [103] |
| TRIM59 | CRC | Upregulated | Oncogene | Unfavorable | 80 | 16 | 1 normal colorectal mucosa cell line (NCM460); 6 CRC cell lines (HCT116, SW480, SW620, HT29, Caco2, NCM460) | Proliferation, migration, invasion, cell cycle, apoptosis | NA | [104] |
| TRIM65 | CRC | Upregulated | Oncogene | Unfavorable | 194 | 160 | 1 normal colorectal mucosa cell line (NCM460); 11 CRC cell lines (HCT8, KM12, Caco-2, DLD-1, HCT116, LOVO, HT-29, Sw480, SW620, RKO, HCT15) | Proliferation, colony formation, migration, invasion, metastasis | NA | [105] |
| TRIM66 | CRC | Upregulated | Oncogene | NA | 17 | 17 | 1 normal colorectal mucosa cell line (NCM460); 4 CRC cell lines (HCT116, HT29, CaCo2, SW620) | Proliferation, migration, invasion, EMT | JAK2/STAT3 signaling pathway | [106] |
| TRIM67 | CRC | Downregulated | Tumor suppressor | Favorable | 138 | 138 | 2 normal colorectal mucosa cell line (NCM460, GES1); 3 CRC cell lines (HCT116, RKO, LOVO) | Proliferation, apoptosis, cell cycle | p53 signaling pathway | [107] |
| TRIM68 | CRC | Upregulated | Oncogene | Unfavorable | NA | NA | 2 CRC cell lines (HCT116, SW1116); HEK293T cell | Proliferation, colony formation, cell cycle, apoptosis | NA | [108] |

**Abbreviations**: ESCC, Esophageal squamous cell carcinoma; CRC, Colorectal cancer; GC, Gastric cancer; NA, Not mentioned; EMT, Epithelial–mesenchymal transition.


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## TRIM Proteins Regulate Targets Stability

The TRIM family consists of proteins that have E3 ubiquitin ligase activity, and they regulate tumor progression or suppression by adjusting the stability of target proteins. Autophagy is a significant intracellular degradation system, alongside the ubiquitin-proteasome system. TRIM27, TRIM37, TRIM6, TRIM65, and TRIM39 exhibit increased expression in tumor tissues of GI cancer compared to normal tissues, potentially influencing the progression of GI cancer through the ubiquitin-proteasome system.

### TRIM Proteins Regulate Tumor Progression via Ubiquitin–Proteasome Pathway

TRIM27 and TRIM37 were reported to be over-expressed in tumor tissues, relating to the ubiquitin-proteasome pathway in ESCC and/or CRC.[42,44,87] Initially, TRIM27 acts as an E3 ligase to increase the poly-ubiquitination of tensin homologue protein (PTEN), leading to PIP3 dephosphorylation of and PIP2 regeneration of, which reduces PI3K signaling, activating AKT signaling pathway and ultimately inhibiting cell apoptosis in ESCC.[42] TRIM37 is another E3 ligand in ESCC. Following genotoxic stimulation, TRIM37 quickly moves into the nucleus and directly interacts with TRAF6 to facilitate the mono-ubiquitination of NEMO at K309.[44] Blocking the interaction between TRIM37 and TRAF6 also prevented NEMO mono-ubiquitination, increasing cells' sensitivity to DNA-damaging chemotherapeutic treatments by inhibiting NF-kB signaling.

Comparatively, to adjacent normal tissues, GC tissues express less TRIM25. TRIM25 enhances ubiquitination of SP1 at K610, resulting in the down-expressed MMP2 level and the inhibition of angiogenesis in GC.[59] Besides, TRIM54 also up-expressed in GC tumor tissues, promoting GC progression by ubiquitin FLNC.[71] Given the complex function of FLNC in cancers, the deep mechanism needs to be further explored. However, TRIM21 is down-expressed in GC tumor tissue, exerting as a tumor suppressor.[54] Reduced expression of EZH1 by TRIM21 leads to enhanced anti-tumor effects of Apatinib by overcoming chemoresistance in various tumor types.

TRIM59, TRIM23, TRIM24, and TRIM32 can act as an E3 ligase by binding with p53, a key tumor suppressor that affects the development and/or advancement of human cancers. TRIM59 and TRIM23 could potentially be linked to tumor depth and metastasis in GC.[55,102] Furthermore, TRIM59 and TRIM23 enhance the growth of cancer cells by directly interacting with p53 and increasing p53 ubiquitination.[81,102] Like TRIM23, TRIM24 and TRIM32 are also capable of directly interacting with p53 and facilitating p53 degradation through ubiquitination.[93,109] Remarkably, a complex feedback loop modulates TRIM24/TRIM32 and p53 expression post-DNA damage. Initially, ATM kinase phosphorylates TRIM24 at S768, subsequently inducing its self-ubiquitination. Later, the late stage of DNA damage promotes phosphorylation and activation of p53, further inducing TRIM24 or TRIM32 transcription.[93,109] Elevated TRIM24 or TRIM32 then degrades p53 via ubiquitination, aiding tumor cell survival. Consequently, targeting to TRIM24 and TRIM32 holds promise in augmenting the efficacy of chemotherapy.

TRIM6 was overexpressed in CRC, promoting tumor cell proliferation and decreasing sensitivity to oxaliplatin and 5-fluorouracil.[75] It has been found that TRIM6 lead to TIS21 ubiquitination, while TRIM6 E3 catalytic mutant (C15A) cannot influence the stability of TIS21. Subsequently, the decrease of TIS21 caused by TRIM6 overexpression eventually leads to increased phosphorylation of FOXM1, resulting in tumor progress. TRIM65 also over expressed in CRC. In the same way, TRIM65 focuses on ARHGAP35, a protein that deactivates Rho GTPase and hinders its function, marking it for breakdown through ubiquitination. This process leads to the promotion of migration and invasion in CRC. Moreover, the phosphorylation of TRIM65 at S167, S367, T413, S166, S172, and S181 seemed to attenuate its oncogenic activity.[105]

### TRIM Proteins Regulate Tumor Progression via Autophagy Pathway

Autophagy is a primary cellular degradation mechanism alongside the ubiquitin-proteasome system.[110] Recent studies indicate that multiple TRIM proteins serve as receptors for autophagy and are involved in autophagosome formation. TRIM39 was also over-expressed in tumor tissues, predicting clinical outcomes of CRC patients. Functionally, TRIM39 binds to Rab7 and enhances its function by preventing its ubiquitination at the lysine 191 site.[96] Prior research has identified Rab7 as playing a crucial function in the maturation of autophagosomes. Additional findings indicated that reducing TRIM39 levels hinders the flow of autophagy in a manner dependent on Rab7 activity, consequently impeding the breakdown of p53 through autophagy.

## TRIM Proteins' Functions in Signal Pathways

Previous studies have demonstrated that the TRIM family engages in diverse cellular pathways, whose cascades are intricately linked to carcinogenesis, including AKT, Wnt/β-catenin, STAT3, TGF-β, p53, NF-κB pathways. A wealth of research has evidenced that TRIM proteins effectively regulate these pathways by modulating the expression of downstream targets within the context of cancer.

### TRIM Proteins in Akt Signaling

Akt signaling is crucial in coordinating essential cellular functions such as cell growth, viability, energy regulation, movement, and reactions to various stressors and treatments.[111] Activating PI3K-AKT pathway leads to changes in cellular metabolism by increasing the function of multiple transporters and enzymes, which helps meet the growth needs of rapidly dividing cells.[110] The effectiveness of PI3K inhibitors in clinical settings has been questioned due to negative effects like high blood sugar and resistance to treatment, while AKT inhibitors face limitations due to their numerous downstream targets and complex interactions with other signaling pathways.[112]

Several TRIM members influence Akt signaling in gastrointestinal cancer, predicting a worse prognosis and promoting cancer cells proliferation, invasion, metastasis, and apoptosis resistance[113] (Figure 2). TRIM14,[49] TRIM24,[56,58] TRIM32[66] TRIM44,[45,98] and TRIM59[114] were frequently over-expressed in tumor tissues in GI cancer. They stimulate tumor cells' growth and metastasis by activation of Akt signaling pathway. Notably, participation in the AKT/mTOR signaling pathway induced by TRIM44 further influences STAT3 phosphorylation, a point of convergence for many oncogenic pathways, while Akt inhibitor rescued the phosphorylation of STAT3 and cancer-promoting effect of TRIM44.[115]

### TRIM Proteins in Wnt/β-Catenin Signaling

Dysregulation of the Wnt/β-catenin pathway is linked to the reappearance of cancer, the migration of cancer cells, and the avoidance of the immune system.[116,117] As a crucial member of the canonical Wnt-signaling cascade, β-catenin activates

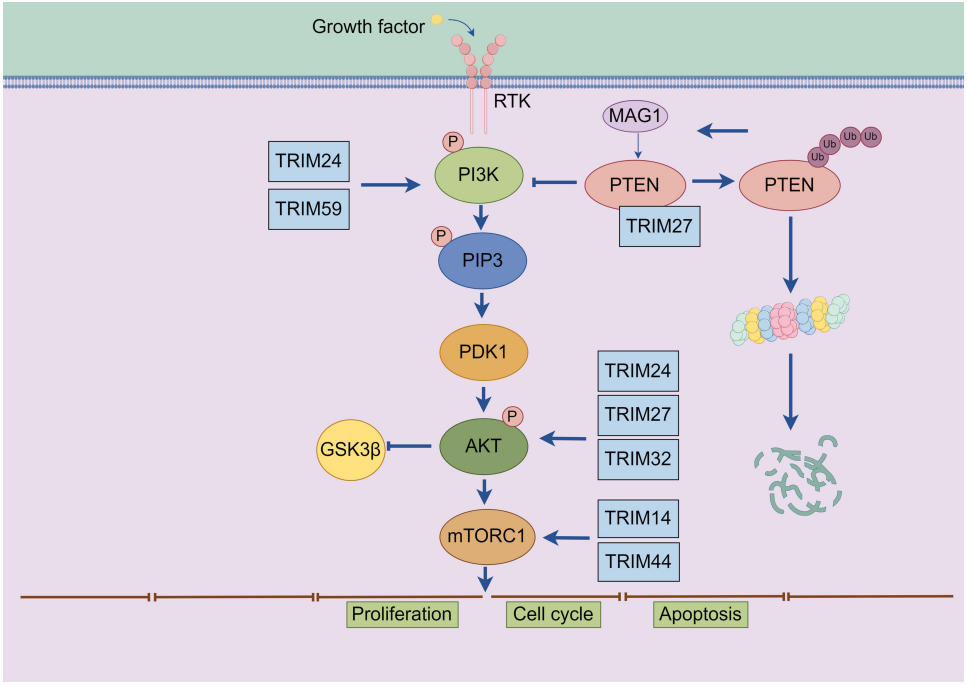


**Figure 2** The interaction role between TRIM family and Akt signaling pathway in GI cancer. When growth factors induce PI3K activation, it triggers the activation of PIP3. The tumor suppressor PTEN exerts inhibitory control over PIP3 levels, thereby negatively modulating the Akt signaling cascade. PIP3-mediated recruitment and subsequent activation of PDK1 leads the activation of Akt, further stimulating the activity of mammalian target of mTORC1. Subsequently, Akt signaling fosters the upregulation of target gene expression. Furthermore, TRIM protein regulates the regulator of Akt signaling pathway.

**Abbreviations**: Akt, Protein kinase B; GSK3β, Glycogen synthase kinase 3β; mTORC1, Mammalian target of rapamycin complex 1; P, Phosphorylation; PDK1, Phosphoinositide-dependent kinase-1; PI3K, Phosphoinositide 3-kinase; PIP3, Phosphatidylinositol (3,4,5)- trisphosphate; PTEN, Phosphatidylinositol 3,4,5-trisphosphate 3-phosphatase and dual-specificity protein phosphatase PTEN; RTK, receptor tyrosine kinase; Ub, ubiquitin.

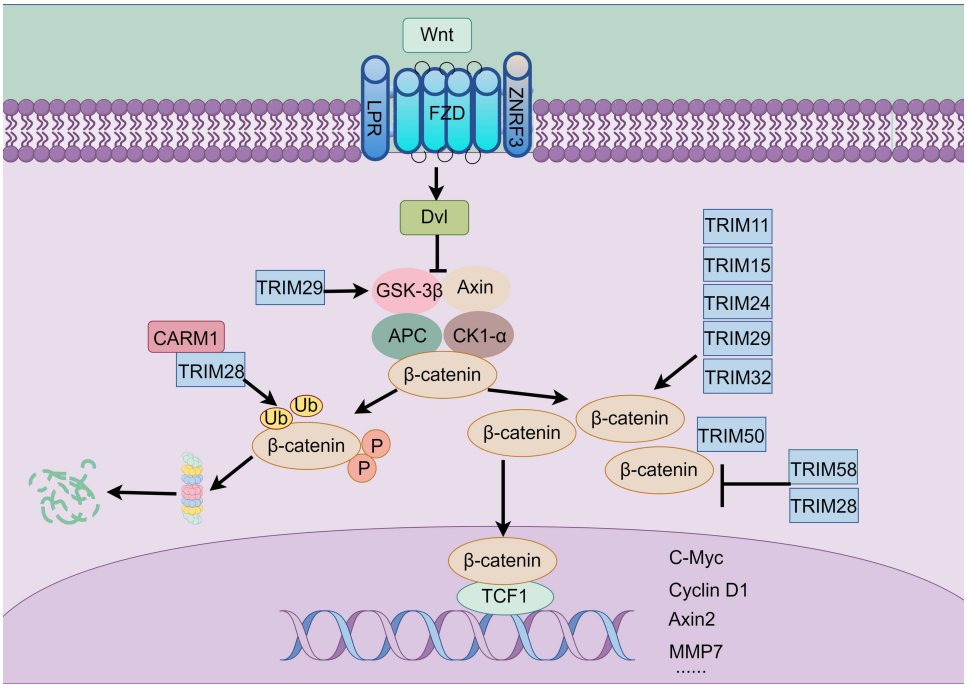


**Figure 3** The interaction role between TRIM family and Wnt/β-catenin signaling pathway in GI cancer. Activated Wnt ligand binds to the LRP5/6 co-receptor, thus recruiting GSK3β complex to induce β-catenin expression. In the nucleus, β-catenin binds to TCF1, activating Wnt target genes. TRIM proteins also regulate the regulator of Wnt/β-catenin signaling pathway.

**Abbreviations**: APC, Adenomatous polyposis coli; CK1, Casein kinase 1; CARM1, coactivator-associated arginine methyltransferase1; Dvl, Dishevelled; GP130, Glycoprotein 130; GSK-3β, Glycogen synthase kinase 3β; GSK3β complex, disrupts the destruction complex; LRP, Low density lipoprotein receptor-related protein; TCF1, T cell factor 1; P, Phosphorylation; Ub, ubiquitin; ZNRF3, zinc and ring finger 3.

several genes responsible for maintaining the multi-potency of stem cells, serving as a co-activator of the TCF/LEF transcription factors.[118] Multiple research studies have indicated the interaction between TRIM proteins and Wnt/β-catenin pathway in GI tumors (Figure 3).

TRIM15 was found to be highly expressed in ESCC[41] and GC,[50,51] leading to the upregulation of β-catenin, C-myc, and CyclinD1 specifically in ESCC.[41] In GC and CRC, TRIM24, TRIM32, TRIM37 and TRIM11 activated Wnt/β-catenin signal to induce the tumor progression.[47,57,65,95] TRIM11 specifically enhances the expression of β-catenin and further facilitates its transfer from cytoplasm to nucleus. Conversely, reducing TRIM11 levels leads to an accumulation of Axin2,[47] which directly interact with β-catenin and enhance its degradation through the proteasome-ubiquitin system. This process may be due to TRIM11's E3 ligand function to promote Axin2 ubiquitination, which needs further verifying.

In contrast to the above, TRIM16, TRIM50, TRIM58, and TRIM28 were down-expressed in GC and/or CRC tumor tissues.[52,70,72,91,102] TRIM16 suppress β-catenin signaling pathway.[52] Additionally, TRIM50 and TRIM58 have the ability to bind with β-catenin, resulting the breakdown of β-catenin.[70,72] Further experiments confirmed that TRIM50 induce β-catenin degradation through protease-ubiquitin system and TRIM58 could significantly induce ubiquitination of β-catenin. TRIM28 was also identified as a tumor-suppressor. The PHD/Bromo domain in TRIM28 was found to bind with co-activator-associated arginine methyltransferase1 (CARM1), preventing CARM1 from being degraded by the proteasome. As a consequence of this interaction, Wnt signaling was subsequently suppressed, dependent on CARM1 expression.[91]

## TRIM Proteins in STAT3 Signaling

The abnormal and continuous stimulation of STAT3 leads to the formation of tumors, primarily caused by excessive specific cytokines, or malfunctioning regulators.[119] Various types of cancer progression are influenced by the continuous activation of STAT3, which is driven by multiple tyrosine kinases, including JAK1, JAK2, EGFR, and BMX, but also by

other stimulators like IL-6, IL-11, and S1P.[120,121] In addition, protein tyrosine phosphatases (PTPs) such as PTP1B, TCPTP, SHP1, and SHP278 also negatively regulate STAT3 signaling.[122] Thus, understanding the relevance of TRIM family and STAT3 signaling is critical for tumor therapy.

An excessive amount of TRIM-mediated STAT3 activation has been reported in GI cancer (Figure 4). TRIM14 enhanced the expression of sphingosine kinase 1 (SPHK1), an enzyme responsible for producing S1P, leading to the phosphorylation of STAT3 at Y705.[78] STAT3 activation promotes the expression of MMP2, MMP9, and VEGF, which facilitates CRC invasion and migration. Previous research has demonstrated that IL-6 is capable of attracting and triggering STAT3 activation via the IL-6R/gp130/JAK pathway in the cytosol.[123] Zhang et al showed that TRIM27 was found in retromer-positive structures, a well-preserved heteropentameric complex crucial for reusing proteins from endosomes to trans-Golgi networks or cell membranes, and serves as a connector for bringing gp130, JAK1, and STAT3 to the retromer, enhancing the activity of JAK1, gp130, and STAT3 through IL-6 stimulation.[88] Moreover, TRIM52 may function as an E3 ligase, enhancing the ubiquitination of SHP2 and its proteasomal breakdown, leading to an elevation in STAT3 phosphorylation.[100] Other TRIM proteins, such as TRIM29 and TRIM66, also could active JAK/STAT3 signaling, promoting GI cancer cells proliferation, migration, and invasion.[92,106]

## TRIM Proteins in TGF-β Signaling

Secreted cytokines from the TGF-β superfamily are critical to the regulation of growth, survival, cell death, dormancy, self-degradation, and aging in cells.[124] It attaches to its receptor type II and activates its type I counterpart, triggering the phosphorylation of the receptor-regulated SMAD2/3. This enables it to join with SMAD4 and enter the nucleus to connect with specific enhancers in target genes, initiating transcription.[125] TGF-β signaling pathway suppresses proliferation and encourages cell-cycle stoppage and cell death in both healthy and precancerous cells. In advanced cancer cells, the activation of this pathway may promote the transition from epithelial to mesenchymal cells, as well as increase stemness and mobility, ultimately boosting tumor growth and spread.[126]

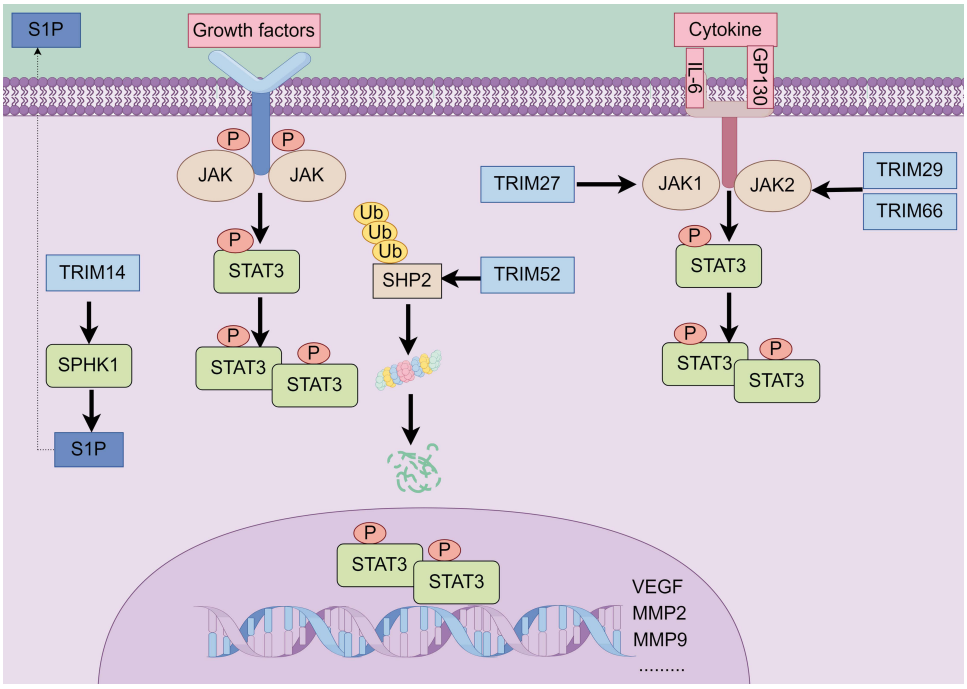


**Figure 4** The interaction role between TRIM family and STAT3 signaling pathway in GI cancer. Growth factors and cytokines engage transmembrane receptors, initiating receptor-associated JAK activation. This prompts phosphorylation of receptor cytoplasmic tails, recruiting and phosphorylating cytoplasmic STAT3. Activated STAT3 forms dimers, transfers to nucleus, and induce target gene expression. TRIMs (eg, TRIM14, TRIM27, TRIM29, TRIM52, TRIM66) modulate JAK/STAT signaling. TRIM29 and TRIM66 activate JAK2/STAT3, while TRIM27 activates JAK1/STAT3. TRIM52 promotes SHP2 polyubiquitination and degradation, thereby enhancing STAT3 phosphorylation.
**Abbreviations**: GP130, Eukaryotic Glycoprotein 130; JAK, Janus Kinase; JAK1, Janus kinase 1; JAK2, Janus kinase 1; IL-6, Interleukin 6; P, Phosphorylation; SHP2, SH2 domain-containing protein-tyrosine phosphatase-2; SPHK1, Recombinant Sphingosine Kinase 1; STAT3, Signal transducer and activator of transcription 3; Ub, ubiquitin; VEGF, vascular endothelial growth factor.

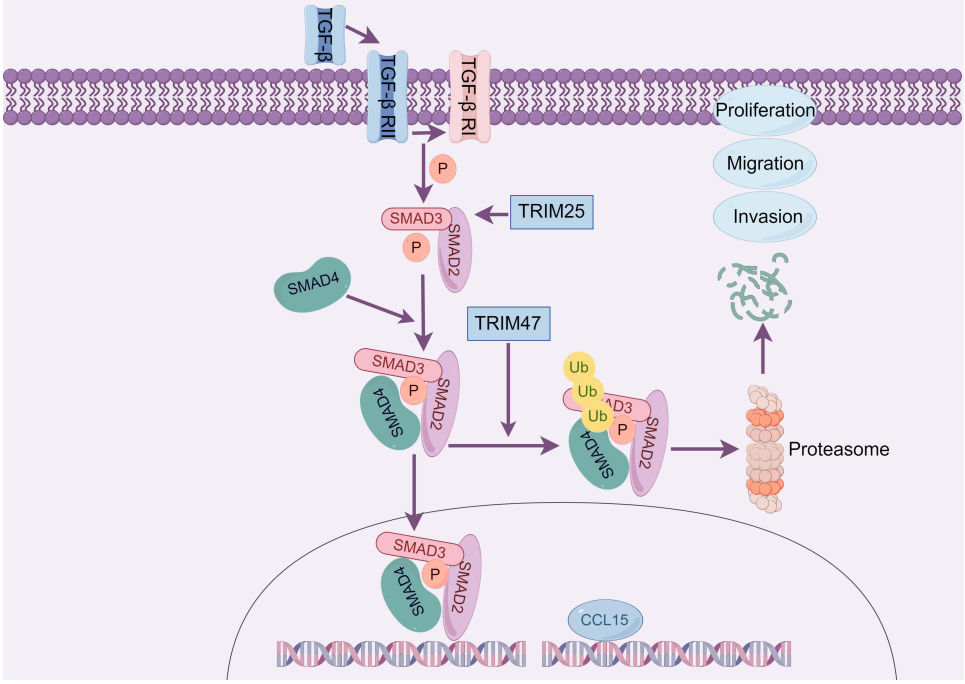


**Figure 5** The role of the TRIM family in the TGF-β signaling pathway in GI cancer. Upon TGF-β activation, TGFBR1 phosphorylates the SMAD2/3 complex, facilitating its association with SMAD4. This complex translocates into the nucleus to modulate targeted gene expression. TRIM proteins, such as TRIM25 and TRIM47, play crucial roles in TGF-β signaling pathway modulation. TRIM25 enhances TGF-β signaling pathway activity by promoting the phosphorylation of SMAD2/3. Conversely, TRIM47 negatively regulates TGF-β-Smad signaling by enhancing the ubiquitination and subsequent degradation of Smad4.

**Abbreviations**: P, Phosphorylation; SMAD, Mothers against decapentaplegic homolog; TCF1, T cell factor 1; TGF-β, Transforming Growth Factor-β; TGFBR1, Type I TGF-β Receptor; TGFBR2, Type II TGF-β Receptor; Ub, ubiquitin.

So far, the association between TRIMs of GI tumors and this signaling pathway has been established.[85,99] TRIM25 plays an important part in promoting CRCs malignancy by increasing Smad2 and Smad4 phosphorylation.[85] In the previous section, it was explained that TRIM47 inhibited TGF-β-Smad signaling by ubiquitinating and degradating SMAD4.[99] Loss of SMAD4 also led to an increase in C-C motif chemokine ligand 15 (CCL15), promoting CRC progression through chemokine receptor 1 (CCR1) signaling[99] (Figure 5).

## TRIM Proteins in p53 Signaling Pathway

P53, a well-known cancer inhibitor, is commonly altered in various forms of cancer. Oncogenes or cellular stress activate p53, causing it to respond and activate a variety of genes associated with cell cycle regulation, DNA repair, aging, and programmed cell death. It has been discovered the interaction functions of p53 and TRIM family members (Figure 6).

TRIM3, TRIM67 and TRIM25 can upregulate p53 expression in GI cancer. TRIM3 upregulated p53 and its downstream targets such as p21 and GADD45 in CRC cells.[74] The increase in p53 levels could be attributed to the prolonged stability of p53 resulting from TRIM3 overexpression, leading to an extended half-life of p53.[74] Additionally, TRIM67 binds with the p53's C-terminal region, disrupting the communication between MDM2 and p53 in CRC. This results in a reduction of MDM2-mediated ubiquitination of p53.[107] Consisting with this, TRIM25 prevents MDM2 from interacting with p300,[127] an essential requirement for p53 polyubiquitination.[115] However, the upregulation of p53 mediated by TRIM53 did not result in an increase in apoptosis, due to the decreased acetylation of p53, which is required for p53's transcriptional activity to grow-arresting and pro-apoptotic target genes.[128] TRIM28 also could down-regulate MDM2 expression to increase p53 expression and deacetylation of p53, inhibiting p53's tumor-suppressive activity in CRC.[90]

Interestingly, TRIM29, categorized as one of the TRIM proteins that inhibit p53, does not have the usual RING domain. The p300-dependent acetylation of TRIM29 at Lys116 causes TRIM29 to interact with p53, causing p53 to remain in the cytoplasm and inhibit its transcription of its target genes in the nucleus.[129]

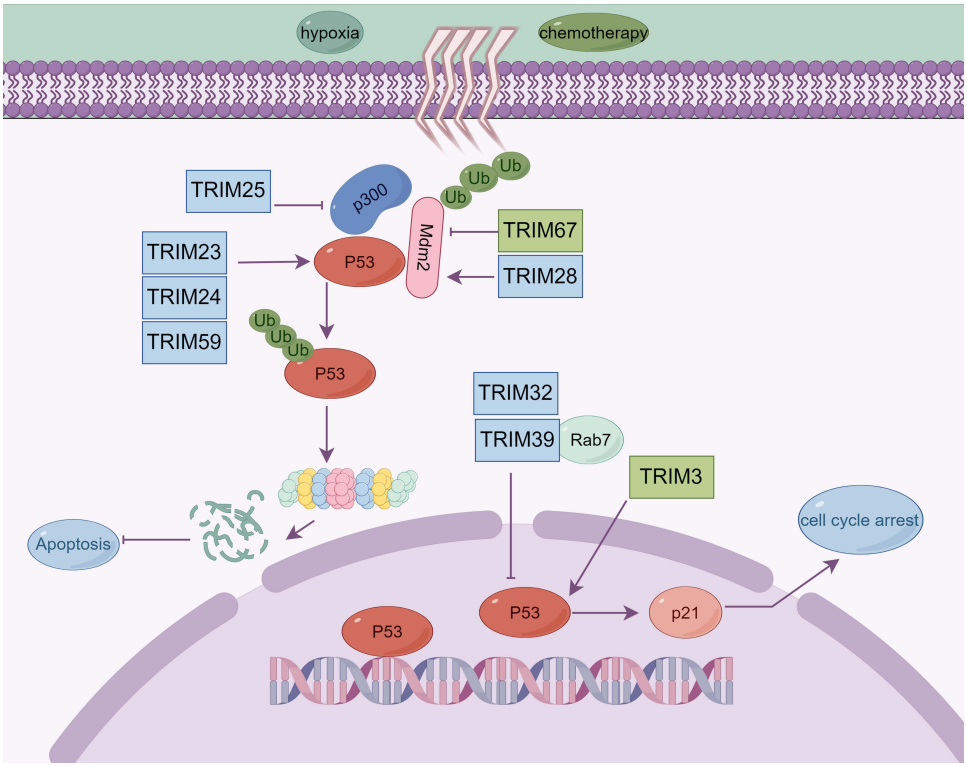


**Figure 6** The interaction role between TRIM family and p53 signaling pathway in GI cancer. MDM2 binds to p53, facilitating p53's ubiquitination and degradation to suppress cell apoptosis. Certain TRIMs facilitate p53 stabilization. TRIM67 directly targeting to MDM2, thus preventing p53 proteasomal degradation. Similarly, TRIM25 disrupts the formation of a ternary complex involving p53, Mdm2, and p300, which is crucial for p53 degradation.
**Abbreviations**: MDM2, Mouse double minute 2; Rab7, Ras-related GTP binding protein 7; Ub, ubiquitin.

### TRIM Proteins in YAP, NF-κB Signaling Pathway

YAP and NF-κB signaling pathway play an important role in controlling programmed cell death.[130] Nonetheless, limited research has been conducted on the correlation between TRIMs and those signaling pathways in GI tumors. The TRIM24 recruited by the DANCR/KAT6A complex specifically binds to acetylated lysine 23 of histone H3 (H3K23), leading to its direct binding to the YAP promoter, further activating YAP transcription and ultimately boosting the proliferation of CRC cells.[82] TRIM40 and TRIM47 might affect NF-κB signaling.[131–133] By neddylating the inhibitor of NF-κB kinase subunit gamma, TRIM40 prevented the inflammation-related carcinogenesis in the GI tumors.[67] Additional research is necessary to elucidate the impact of TRIM-mediated control of NF-κB in various disease states, particularly in the context of anti-cancer immune response and tumor resilience.

## Impact of TRIM Proteins on Characteristics of Cancer Development

### TRIM Family in Cell Cycle

Cells go through the cell cycle in four stages: the G1 phase (preparation for growth), the S phase (replication of DNA), the G2 phase (growth and preparation for division), and the M phase (phase of division).[84] Proper control of cell division is crucial for preserving the regular functions of tissues and organs, whereas disruptions in the cell division process are a common characteristic in numerous types of cancer.[134] Irregular TRIM protein expressions result in the cell cycle advances abnormally and continuous cell division.

TRIM family is crucial in controlling the G1/S phase transitions and is involved in regulating cell cycle progression through diverse mechanisms. Certain TRIM proteins can impact CDKs, CKIs, and cyclins to control G1 phase advancement.[135,136] Silencing TRIM24, TRIM29, TRIM23, TRIM27, and TRIM68 result in the G1-S phase arrest of GC or CRC cells.[57,60,81,87,108] However, TRIM50 overexpression decrease CDK4 and Cyclin D1 expression, inducing

GC cell arrest in the G0/G1 phase.[70] Furthermore, increased TRIM58 led to a significant decrease in C-myc, Cyclin D1, and survivin, ultimately halting cell proliferation.[72]

During the G2/M transition, TRIM protein may influence cell preparation and entry into mitosis by regulating proteins such as mitotic kinase. Increased levels of TRIM6 have been linked to excessive growth of CRC cells, whereas reducing TRIM6 enhances responsiveness to chemotherapeutic drugs, leading to G2/M phase arrest in CRC.[75] Furthermore, TRIM55 has been shown to have a strong relation to the genes involved in G2/M checkpoint and Myc signaling.[101]

### TRIM Family in Apoptosis

As cell death, apoptosis is characterized by blebbing of the cell membrane, shrinkage of the cell, nuclear fragmentation, chromatin condensation, and fragmentation of chromosomal DNA.[137–139] Various intracellular stimuli, such as DNA damage, lack of growth factors, and oxidative stress, trigger the inherent apoptotic pathway. The process depends on the creation of a complicated structure known as the apoptosome, which consists of procaspase-9, Apaf-1, and cytochrome c. A number of proteins such as Bx, Bak, Bcl-2, and Bcl-xL get involved in controlling cytochrome c release from the mitochondria and affect the membrane permeability of the mitochondria.[140]

Parts of TRIMs exert their carcinogenic function by inhibiting apoptosis. TRIM27 could inhibit cell apoptosis in esophagus cancer, and its knockdown significantly increases the percentage of apoptosis.[42] In addition, TRIM47 and TRIM32 knockdown successfully decreased Bcl-2 or increased cleaved caspase 3 and cleaved PARP in GC.[64,69] Similarly, several TRIM proteins act as apoptosis inhibitors in CRC. Numerous research studies have indicated that silencing TRIM24,[84] TRIM29,[92] TRIM52,[100] or TRIM59[103] led to a notable reduction in Bcl-2 levels or an elevation in Bax levels, while upregulation of TRIM55 inhibited the expression of Bcl-2.[101]

Several TRIM members act as tumor suppressors in GI cancers by inducing cell apoptosis. For example, TRIM55 enhanced the expressions of cleaved-caspase 3, BAX, and BAK, indicating the significant role of TRIM55 in cell apoptosis.[101] Elevated levels of TRIM67 led to a notable rise in cell death-associated proteins, such as activated caspase-3, −7, −8, −9, and PARP, by activating the p53/MDM2 pathway.[107] Furthermore, other TRIM proteins, such as TRIM3, also induce tumor apoptosis through Bcl-2 expression in GC.[48] Interestingly, TRIM21 significantly improves chemosensitivity to classic chemotherapeutic agents, whereas TRIM21 knockdown markedly decreased the apoptosis in apatinib-incubated GC cells.[54]

## Upstream Noncoding RNA Regulators of TRIM Family in GI Cancer

Non-coding RNAs (ncRNAs) act an important role in biological functions, including cancer, instead of protein-coding transcripts.[141] In general, depending on their length (200 nucleotides), ncRNAs can be divided into small ncRNAs (sncRNAs) and long ncRNAs (lncRNAs). MicroRNAs (miRNAs) is one type of sncRNAs.[142] Prior research has shown that TRIM proteins can also engage with ncRNAs in order to carry out their diagnostic and therapeutic functions, as indicated in Table 3.

By binding to 3′ untranslated regions (3′UTRs), miRNAs inhibit the expression of their target genes post-transcriptionally.[146] Within GC, miR-20a and miR-195-5p were found to have a suppressive function on the TRIM3 and TRIM14 mRNA levels through their interaction with the UTRs.[46,49] This interaction ultimately inhibits GC cell proliferation and migration.[46,49] TRIM24 is a direct target of miR-511, showing an inverse correlation in GC.[58] Additionally, miR-185 inhibited malignant behavior by inactivating Wnt and repressing TRIM29 expression.[60] In CRC, miR-24-3p can directly target and control TRIM11 expression, inhibiting cell proliferation and inducing apoptosis.[77] There is a reduction in TRIM8 mRNA in cancerous tissues due to the suppressive effects of miR-17-5R and miR-10, which could be targeting TRIM8's mRNA.[76] Conversely, TRIM8 has the ability to directly engage with p53, enhancing p53's stability through the promotion of MDM2 degradation.[147] Furthermore, the active p53 by miR-17-5p and miR-106b knockdown further induce miR-34a, which could negatively regulate N-MYC (a transcription factor activated miR-17-5p and miR-106b), increasing p53 tumor-suppressor function by the feed-forward loop.[76]

**Table 3** TRIMs are the Targets of Non-Coding RNAs in GI Cancer

| Gene | Cancer Type | Upstream | Associated Molecules or Mechanisms | Refs |
|---|---|---|---|---|
| TRIM3 | GC | miR-20a | Downregulating expression of TRIM3 | [143] |
| TRIM14 | GC | miR-195-5p | Upregulating expression of TRIM14 | [49] |
| TRIM16 | GC | SDMGC | Upregulating expression of TRIM16 | [53] |
| TRIM24 | GC | miR-511 | miR-511 regulates TRIM24 through translational inhibition | [58] |
| TRIM29 | GC | miR-185 | Up-regulation of miR-185 repressed TRIM29 expression | [60] |
| TRIM8 | CRC | miR-17-5p | MiR-17-5p directly targets the 30 UTR of TRIM8 repressing its expression | [76] |
| TRIM11 | CRC | Mir-24-3p | miR-24-3p downregulation can promote TRIM11 upregulation | [77] |
| TRIM24 | CRC | ZFPM2 - AS1 | ZFPM2-AS1 positively regulated TRIM24 expression by sponging miR-137 | [144] |
| TRIM44 | CRC | LINC00265 | Directly bounding to miR-216b-5p and negatively regulating miR-216b-5p, and increases the expression of TRIM44 | [97] |
| TRIM44 | CRC | ELFN1-AS1 | ELFN1-AS1 targeted miR-4644 to augment TRIM44 level | [145] |

LncRNAs have also been shown to affect tumor growth by regulating the TRIM family. Increasing the lncRNA SDMGC expression leads to the positive regulation of TRIM16 expression, which enhances the progression of GC.[53] In addition, lncRNAs typically function as a molecular sponge for specific miRNAs, increasing the levels of downstream targets.[53,97,144,145] By interacting with miR-137, ZFPM2-AS1 increased TRIM24 expression, causing CRC cells to proliferate, migrate, and invade.[144] Likewise, ELFN1-AS1 functions as a molecular decoy for miR-4644, leading to elevated levels of TRIM44 mRNA and protein in CRC cells.[145] LINC00265 has the ability to directly attach to miR-216b-5p and suppress its activity, leading to an elevation in TRIM44 levels within CRC cells.[97]

## Conclusion and Prospect

Here, we summarize recent advances in multiple roles played by TRIM family members in GI cancer. There has been a growing body of evidence showing that patients with digestive tract tumors express high amounts of TRIM proteins compared to non-cancerous tissues. The high levels of many TRIM proteins are strongly linked to patient survival, making TRIMs promising targets for treatment and new indicators for detecting and evaluating gastrointestinal cancer early on, as well as for providing therapy. The significant contribution of these cancer-promoting TRIMs to the development of gastrointestinal cancer is supported by evidence from experiments involving both reduced and increased activity in gastrointestinal cancer cell lines, as well as from studies using xenograft models. Conversely, some individuals are consistently decreased in gastrointestinal cancer and demonstrate tumor-inhibiting functions.

Given that TRIM proteins primarily function through the UPS, it appears possible to inhibit TRIM proteins in gastrointestinal cancer using proteasomal inhibitors.[148] Compounds that inhibit proteasomes, such as bortezomib, ixazomib, and carfilzomib, have demonstrated efficacy in treating gastrointestinal cancer.[149–152] Furthermore, it suggests that focusing on TRIM proteins could be a treatment option for cancer. The growing interest in TRIM proteins has spurred the development of drug designs, particularly those targeting TRIM24. Knapp and Bradner reported in 2015 and 2016 that three inhibitors, Compound 34,[153] IACS-6558,[154] and IACS-9571,[155] were created to target the TRIM24 bromodomain. These inhibitors showed micromolar or nanomolar efficacy. Moreover, the compound dTRIM24, degrading TRIM24 selectively and bifunctionally, may result in greater inhibition effectiveness compared to IACS-9571, which targets the same TRIM244.[156] These research studies suggest that TRIM24 could be a new focus for developing drugs to treat different types of cancer. Additionally, investigating various natural and synthetic substances that can hinder tumor growth by targeting TRIM proteins, either directly or indirectly, could be engaging research endeavors. In summary, focusing on the bromodomain as a target to discover potential small-molecule inhibitors for TRIMs shows promise in cancer therapy.

Proteolysis-targeting chimeras (PROTACs) are heterobifunctional molecules with two ligands, one attaching to a protein of interest (POI) and the other bringing in an E3 ubiquitin ligase. The close interaction caused by chemicals between the POI and E3 ligase leads to the tagging with ubiquitin and eventual breakdown of the POI by the UPS.[157] PROTACs have the ability to directly target TRIM proteins. An example is how dTRIM24 is able to bring in VHL E3-

ligase to trigger powerful and specific breakdown of TRIM24.[43,156] TRIM proteins can also serve as vehicles in PROTACs, enabling the targeted down-regulation of certain oncoproteins to alleviate gastrointestinal cancer. Developing new PROTACs ligand compounds is difficult due to the requirement of attaching to the correct-binding site with a limited number of ubiquitin sites and leaving enough room to extend the ubiquitin chain.

Despite significant advancements in comprehending the TRIM proteins linked to cancer, no TRIM protein-based treatments are currently being tested in clinical testing. To date, the FDA has not approved any drug or treatment that focuses on targeting ubiquitin E3 ligases. Thus, identifying TRIM proteins as potential targets for treating cancerous conditions could prove to be difficult. Therefore, additional translational research and clinical trials are necessary to create new biomarkers and treatments based on TRIM for individuals with cancer.

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## Disclosure

Conflicts of interest are not declared by the authors.

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