

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

Chunyan Weng^{1,*}, Rijuan Jin^{1,*}, Xiaoliang Jin^{1,*}, Zimei Yang^{1,*}, Chenghai He^{1,2}, Qiuhua Zhang¹, Jingli Xu^{1,3}, Bin Lv¹

¹Department of Gastroenterology, The First Affiliated Hospital of Zhejiang Chinese Medical University (Zhejiang Provincial Hospital of Chinese Medicine), Hangzhou, Zhejiang Province, People's Republic of China; ²Department of Gastroenterology, The Affiliated Hospital of Hangzhou Normal University, Hangzhou, Zhejiang Province, People's Republic of China; ³Department of Gastric Surgery, Zhejiang Cancer Hospital, Hangzhou, Zhejiang Province, People's Republic of China

*These authors contributed equally to this work

Correspondence: Jingli Xu; Bin Lv, Email joinleo03@163.com; lvbin@medmail.com.cn

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).

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

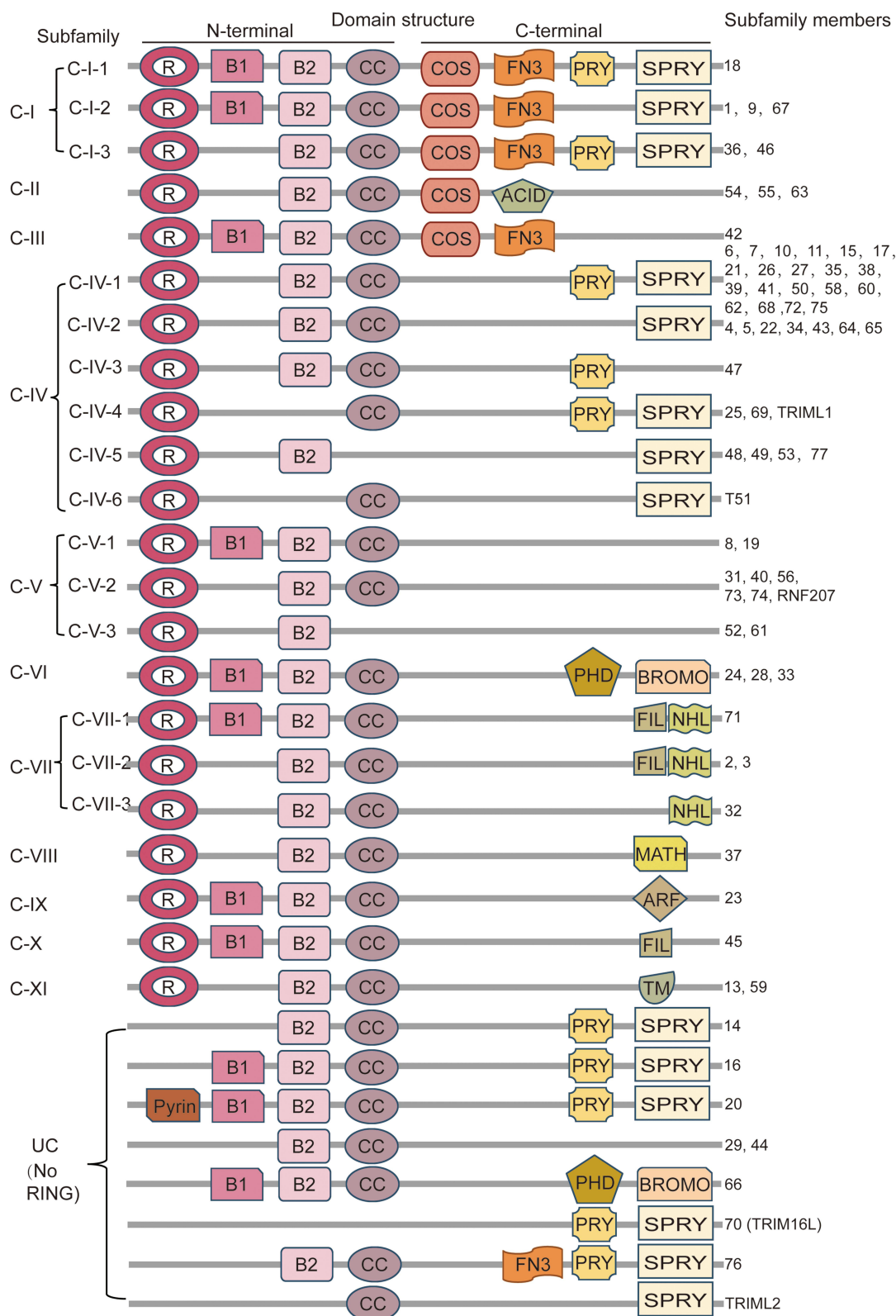


Figure 1 TRIM family structural classification. The C-terminus of TRIM proteins determines their classification from C-I to C-XI; an unclassified group lacks a RING-finger domain.

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, MATH, Meprin and TRAF-homology domain; ARF, ADP-ribosylation factor family domain; TM, transmembrane region.

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- κ B 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]

(Continued)

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- κ B signaling pathway	[67]
TRIM44	GC	Upregulated	Oncogene	Unfavorable	112		7 gastric cancer cell lines (KatolIII, 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- κ B 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]

(Continued)

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)

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- κ B 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.

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- κ B 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- κ B 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 resistance¹¹³ (Figure 2). TRIM14,⁴⁹ TRIM24,^{56,58} TRIM32⁶⁶ TRIM44,^{45,98} and TRIM59¹¹⁴ 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

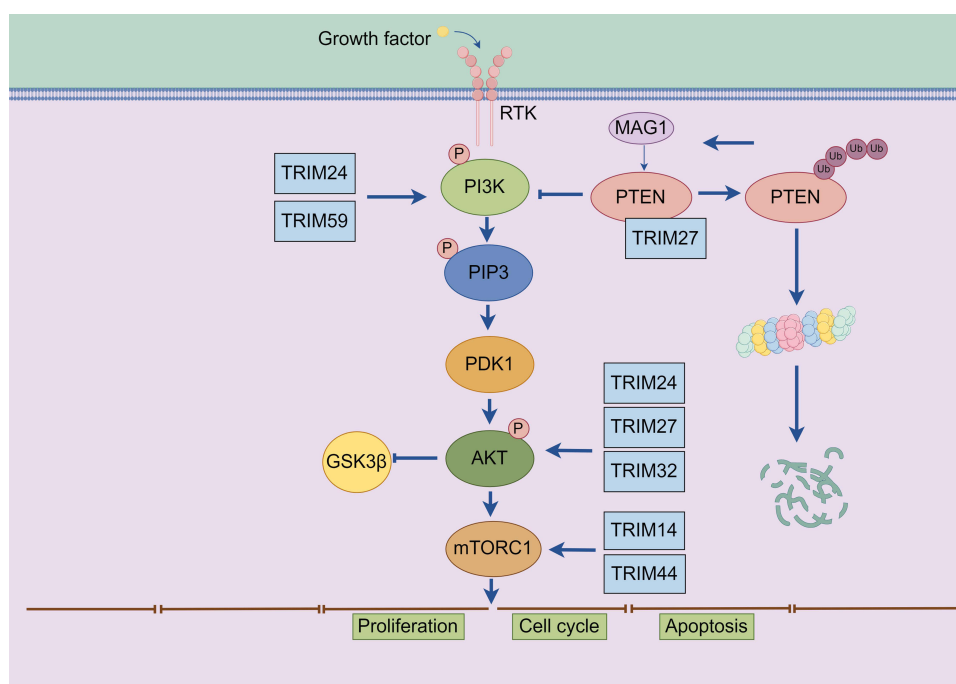


Figure 2 The interaction role between TRIM family and Akt signaling pathway in GI cancer. When growth factors induce PI3K activation, it triggers the activation of PIP3. The tumor suppressor PTEN exerts inhibitory control over PIP3 levels, thereby negatively modulating the Akt signaling cascade. PIP3-mediated 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; GSK3 β , Glycogen synthase kinase 3 β ; 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.

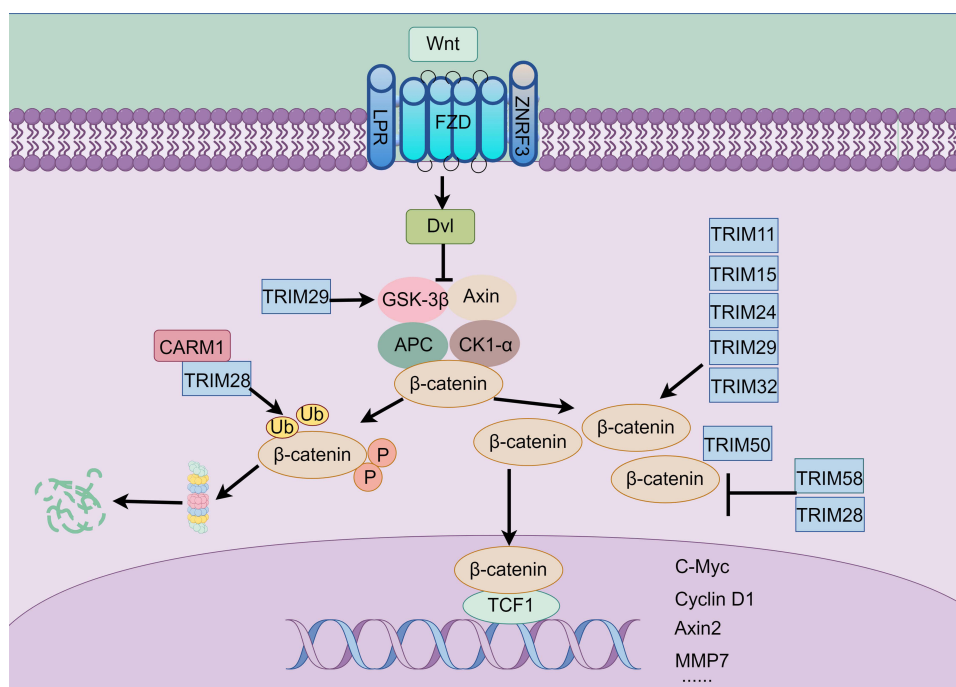


Figure 3 The interaction role between TRIM family and Wnt/ β -catenin signaling pathway in GI cancer. Activated Wnt ligand binds to the LRP5/6 co-receptor, thus recruiting GSK3 β complex to induce β -catenin expression. In the nucleus, β -catenin binds to TCF1, activating Wnt target genes. TRIM proteins also regulate the regulator of Wnt/ β -catenin signaling pathway.

Abbreviations: APC, Adenomatous polyposis coli; CK1, Casein kinase I; CARM1, coactivator-associated arginine methyltransferase1; Dvl, Dishevelled; GPI30, Glycoprotein 130; GSK-3 β , Glycogen synthase kinase 3 β ; GSK3 β 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 ESCC⁴¹ 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 activate 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

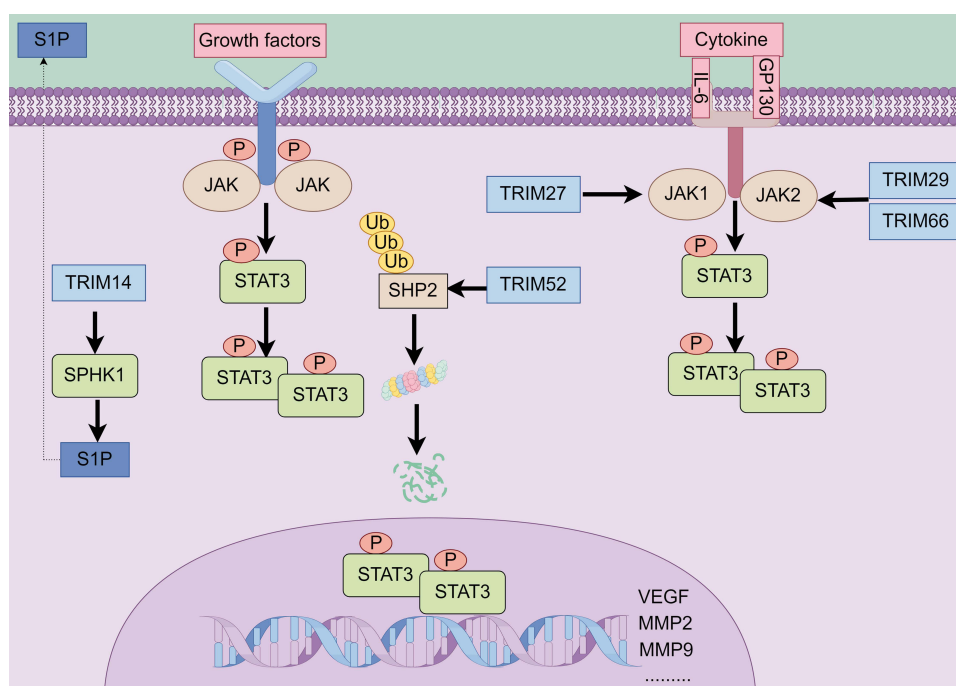


Figure 4 The interaction role between TRIM family and STAT3 signaling pathway in GI cancer. Growth factors and cytokines engage transmembrane receptors, initiating receptor-associated JAK activation. This prompts phosphorylation of receptor cytoplasmic tails, recruiting and phosphorylating cytoplasmic 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 2; 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.

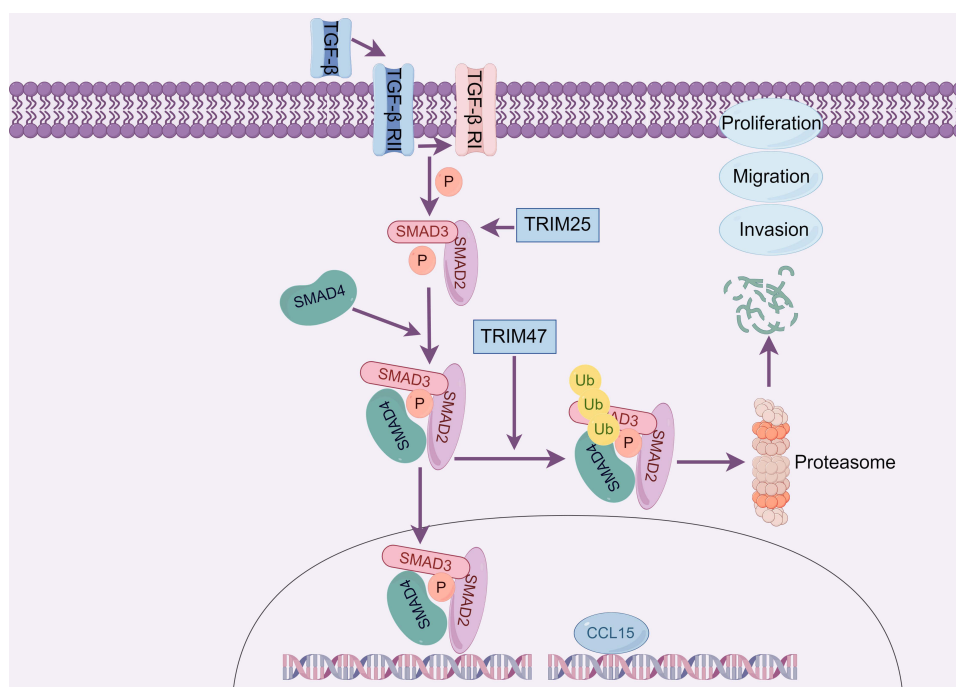


Figure 5 The role of the TRIM family in the TGF- β signaling pathway in GI cancer. Upon TGF- β activation, TGFBR1 phosphorylates the SMAD2/3 complex, facilitating its association with SMAD4. This complex translocates into the nucleus to modulate targeted gene expression. TRIM proteins, such as TRIM25 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 degrading 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) signaling⁹⁹ (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 Consistent 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

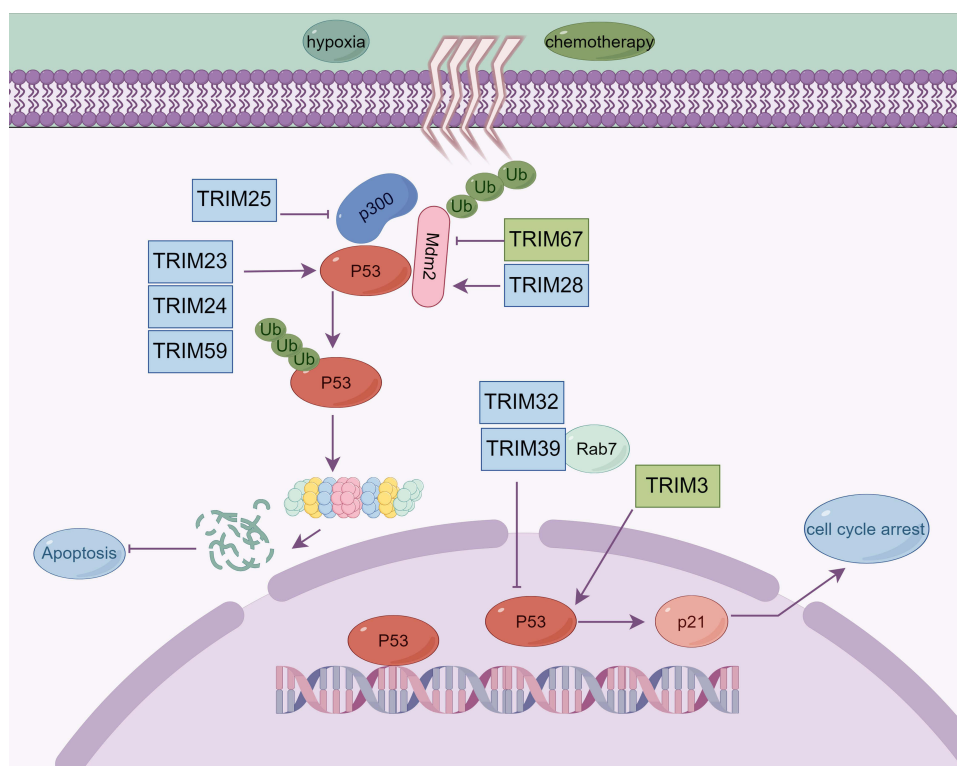


Figure 6 The interaction role between TRIM family and p53 signaling pathway in GI cancer. MDM2 binds to p53, facilitating p53's ubiquitination and degradation to suppress cell apoptosis. Certain TRIMs facilitate p53 stabilization. TRIM67 directly targeting to MDM2, thus preventing p53 proteasomal degradation. 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- κ B Signaling Pathway

YAP and NF- κ B 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 DANCER/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- κ B signaling.^{131–133} By neddylating the inhibitor of NF- κ B 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- κ B 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 TRIM59¹⁰³ 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 TRIM24.¹⁵⁶ 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.

Funding

This work was supported by the National Natural Science Foundation of China (grant no. 81600426, 81770535).

Disclosure

Conflicts of interest are not declared by the authors.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *Ca A Cancer J Clin*. 2021;71(3):209–249. doi:10.3322/caac.21660
2. Arnold M, Abnet CC, Neale RE, et al. Global burden of 5 major types of gastrointestinal cancer. *Gastroenterology*. 2020;159(1):335–349.e315. doi:10.1053/j.gastro.2020.02.068
3. Thrift AP. Global burden and epidemiology of Barrett oesophagus and oesophageal cancer. *Nat Rev Gastroenterol Hepatol*. 2021;18(6):432–443. doi:10.1111/jgh.12157
4. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *Ca A Cancer J Clin*. 2018;68(6):394–424. doi:10.3322/caac.21492
5. Shi B, Liu WW, Yang K, Jiang GM, Wang H. The role, mechanism, and application of RNA methyltransferase METTL14 in gastrointestinal cancer. *Mol Cancer*. 2022;21:163. doi:10.1186/s12943-022-01634-5
6. Tong Y, Gao H, Qi Q, et al. High fat diet, gut microbiome and gastrointestinal cancer. *Theranostics*. 2021;11(12):5889–5910. doi:10.7150/thno.56157
7. Park J, Cho J, Song EJ. Ubiquitin-proteasome system (UPS) as a target for anticancer treatment. *Arch Pharmacol Res*. 2020;43:1144–1161. doi:10.1007/s12272-020-01281-8
8. Aliabadi F, Sohrabi B, Mostafavi E, Pazoki-Toroudi H, Webster TJ. Ubiquitin-proteasome system and the role of its inhibitors in cancer therapy. *Open Biol*. 2021;11:200390. doi:10.1098/rsob.200390
9. Hatakeyama S. TRIM proteins and cancer. *Nat Rev Cancer*. 2011;11(11):792–804. doi:10.1038/nrc3139
10. Elabd S, Meroni G, Blattner C. TRIMming p53's anticancer activity. *Oncogene*. 2016;35(43):5577–5584. doi:10.1038/ncr.2016.33
11. Huang N, Sun X, Li P, et al. TRIM family contribute to tumorigenesis, cancer development, and drug resistance. *Exp Hematol Oncol*. 2022;11:75. doi:10.1186/s40164-022-00322-w
12. Rajsbaum R, Garcia-Sastre A, Versteeg GA. TRIMmunity: the roles of the TRIM E3-ubiquitin ligase family in innate antiviral immunity. *J Mol Biol*. 2014;426(6):1265–1284. doi:10.1016/j.jmb.2013.12.005
13. Fong KW, Zhao JC, Song B, Zheng B, Yu J. TRIM28 protects TRIM24 from SPOP-mediated degradation and promotes prostate cancer progression. *Nat Commun*. 2018;9:5007. doi:10.1038/s41467-018-07475-5
14. Cai C, Tang YD, Zhai J, Zheng C. The RING finger protein family in health and disease. *Signal Transduct Target Ther*. 2022;7(1):300. doi:10.1038/s41392-022-01152-2
15. Massiah MA, Simmons BN, Short KM, Cox TC. Solution structure of the RBCC/TRIM B-box1 domain of human MID1: b-box with a RING. *J Mol Biol*. 2006;358:532–545. doi:10.1016/j.jmb.2006.02.009
16. Reymond A, Meroni G, Fantozzi A, et al. The tripartite motif family identifies cell compartments. *EMBO J*. 2001;20(9):2140–2151. doi:10.1093/emboj/20.9.2140
17. James LC, Keeble AH, Khan Z, Rhodes DA, Trowsdale J. Structural basis for PRYSPRY-mediated tripartite motif (TRIM) protein function. *Proc Natl Acad Sci USA*. 2007;104(15):6200–6205. doi:10.1073/pnas.0609174104
18. Cox TC. The microtubule-associated C-I subfamily of TRIM proteins and the regulation of polarized cell responses. *Adv Exp Med Biol*. 2012;770:105–118. doi:10.1007/978-1-4614-5398-7_8
19. Bloom L, Calabro V. FN3: a new protein scaffold reaches the clinic. *Drug Discov Today*. 2009;14(19–20):949–955. doi:10.1016/j.drudis.2009.06.007
20. Perera S, Mankoo B, Gautel M. Developmental regulation of MURF E3 ubiquitin ligases in skeletal muscle. *J Musc Res Cell Motil*. 2012;33(2):107–122. doi:10.1007/s10974-012-9288-7
21. D'Cruz AA, Babon JJ, Norton RS, Nicola NA, Nicholson SE. Structure and function of the SPRY/B30.2 domain proteins involved in innate immunity. *Protein Sci*. 2013;22(1):1–10. doi:10.1002/pro.2185
22. Wang Y, Li Y, Qi X, et al. TRIM45, a novel human RBCC/TRIM protein, inhibits transcriptional activities of Elk-1 and AP-1. *Biochem Biophys Res Commun*. 2004;323(1):9–16. doi:10.1016/j.bbrc.2004.08.048

23. Connacher RP, Goldstrohm AC. Molecular and biological functions of TRIM-NHL RNA-binding proteins. *WIREs RNA*. 2021;12(2):e1620. doi:10.1002/wrna.1620
24. Sparrer KMJ, Gableske S, Zurenski MA, et al. TRIM23 mediates virus-induced autophagy via activation of TBK1. *Nat Microbiol*. 2017;2:1543–1557. doi:10.1038/s41564-017-0017-2
25. Brigant B, Metzinger-le Meuth V, Rochette J, Metzinger L. TRIMming down to TRIM37: relevance to inflammation, cardiovascular disorders, and cancer in MULLIBREY nanism. *Int J Mol Sci*. 2018;20(1):67. doi:10.3390/ijms20010067
26. Li X, Yu Z, Fang Q, et al. The transmembrane endoplasmic reticulum-associated E3 ubiquitin ligase TRIM13 restrains the pathogenic-DNA-triggered inflammatory response. *Sci Adv*. 2022;8(4):eabh0496. doi:10.1126/sciadv.abh0496
27. Freemont PS, Hanson IM, Trowsdale J. A novel cysteine-rich sequence motif. *Cell*. 1991;64(3):483–484. doi:10.1016/0092-8674(91)90229-r (1991)
28. Bailly V, Lauder S, Prakash S, Prakash L. Yeast DNA repair proteins Rad6 and Rad18 form a heterodimer that has ubiquitin conjugating, DNA binding, and ATP hydrolytic activities. *J Biol Chem*. 1997;272(37):23360–23365. doi:10.1074/jbc.272.37.23360
29. Barlow PN, Luisi B, Milner A, Elliott M, Everett R. Structure of the C3HC4 domain by 1H-nuclear magnetic resonance spectroscopy. A new structural class of zinc-finger. *J Mol Biol*. 1994;237(2):201–211. doi:10.1006/jmbi.1994.1222
30. Joazeiro CAP, Weissman AM. RING finger proteins: mediators of ubiquitin ligase activity. *Cell*. 2000;102(5):549–552. doi:10.1016/s0092-8674(00)00077-5
31. Torok M, Etkin LD. Two B or not two B? Overview of the rapidly expanding B-box family of proteins. *Differentiation*. 2001;67(3):63–71. doi:10.1046/j.1432-0436.2001.067003063.x
32. Napolitano LM, Meroni G. TRIM family: pleiotropy and diversification through homomultimer and heteromultimer formation. *IUBMB Life*. 2012;64(1):64–71. doi:10.1002/iub.580
33. Meroni G, Diez-Roux G. TRIM/RBCC, a novel class of single protein RING finger E3 ubiquitin ligases. *BioEssays*. 2005;27(11):1147–1157. doi:10.1002/bies.20304
34. Yu Y, Liang L, Jin Y, Yin Y. The TRIM14 PRYSPRY domain mediates protein interaction via its basic interface. *FEBS Lett*. 2019;593(10):1122–1129. doi:10.1002/1873-3468.13386
35. Yap MW, Nisole S, Stoye JP. A single amino acid change in the SPRY domain of human Trim5alpha leads to HIV-1 restriction. *Curr Biol*. 2005;15:73–78. doi:10.1016/j.cub.2004.12.042
36. Herquel B, Ouararhni K, Davidson I. The TIF1α-related TRIM cofactors couple chromatin modifications to transcriptional regulation, signaling and tumor suppression. *Transcription*. 2011;2(5):231–236. doi:10.4161/trns.2.5.17725
37. Zhang J, Zhang C, Cui J, et al. TRIM45 functions as a tumor suppressor in the brain via its E3 ligase activity by stabilizing p53 through K63-linked ubiquitination. *Cell Death Dis*. 2017;8:e2831. doi:10.1038/cddis.2017.149
38. Han T, Guo M, Gan M, et al. TRIM59 regulates autophagy through modulating both the transcription and the ubiquitination of BECN1. *Autophagy*. 2018;14(12):2035–2048. doi:10.1080/15548627.2018.1491493
39. Tomar D, Singh R, Singh AK, Pandya CD, Singh R. TRIM13 regulates ER stress induced autophagy and clonogenic ability of the cells. *BBA*. 2012;1823:316–326. doi:10.1002/bies.20304
40. Kawai T, Akira S. Regulation of innate immune signalling pathways by the tripartite motif (TRIM) family proteins. *EMBO Mol Med*. 2011;3:513–527. doi:10.1002/emmm.201100160
41. Zhang L, Qin B, Zou B, et al. Knockdown of TRIM15 inhibits the proliferation, migration and invasion of esophageal squamous cell carcinoma cells through inactivation of the Wnt/β-catenin signaling pathway. *J Bioenerg Biomembr*. 2021;53(2):213–222. doi:10.1007/s10863-021-09872-w
42. Ma L, Yao N, Chen P, Zhuang Z. TRIM27 promotes the development of esophagus cancer via regulating PTEN/AKT signaling pathway. *Can Cell Inter*. 2019;19:283. doi:10.1186/s12935-019-0998-4
43. Liu B, Li X, Liu F, et al. Expression and significance of TRIM 28 in squamous carcinoma of Esophagus. *Pathol Oncol Res*. 2019;25:1645–1652. doi:10.1007/s12253-018-0558-6
44. Wu G, Song L, Zhu J, et al. An ATM/TRIM37/NEMO axis counteracts genotoxicity by activating nuclear-to-cytoplasmic NF-κB signaling. *Cancer Res*. 2018;78:6399–6412. doi:10.1158/0008-5472.Can-18-2063
45. Xiong D, Jin C, Ye X, et al. TRIM44 promotes human esophageal cancer progression via the AKT/mTOR pathway. *Cancer Sci*. 2018;109(10):3080–3092. doi:10.1111/cas.13762
46. Fu H, Yang H, Zhang X, et al. Exosomal TRIM3 is a novel marker and therapy target for gastric cancer. *J Exp Clin Cancer Res*. 2018;37(1):162. doi:10.1186/s13046-018-0825-0
47. Lan Q, Tan X, He P, et al. TRIM11 promotes proliferation, migration, invasion and EMT of gastric cancer by activating β-catenin signaling. *Onco Targets Ther*. 2021;14:1429–1440. doi:10.2147/ott.S289922
48. Farhadi J, Goshayeshi L, Motavalizadehkakhky A, Mehrzad J, Mehrad-Majd H. Decreased expression of TRIM3 gene predicts a poor prognosis in gastric cancer. *J Gastrointest Cancer*. 2022;53(1):179–186. doi:10.1007/s12029-020-00563-0
49. Wang F, Ruan L, Yang J, Zhao Q, Wei W. TRIM14 promotes the migration and invasion of gastric cancer by regulating epithelial-to-mesenchymal transition via activation of AKT signaling regulated by miR-195-5p. *Oncol Rep*. 2018;40:3273–3284. doi:10.3892/or.2018.6750
50. Chen W, Lu C, Hong J. TRIM15 exerts anti-tumor effects through suppressing cancer cell invasion in gastric adenocarcinoma. *Med Sci Monitor*. 2018;24:8033–8041. doi:10.12659/msm.911142
51. Zhou W, Chen H, Ruan Y, Zeng X, Liu F. High expression of TRIM15 is associated with tumor invasion and predicts poor prognosis in patients with gastric cancer. *J Invest Surg*. 2021;34(8):853–861. doi:10.1080/08941939.2019.1705443
52. Afshar J, Mehrzad J, Mehrad-Majd H, Goshayeshi L, Saeidi J. Prognostic significance of tripartite motif containing 16 expression in patients with gastric cancer. *Asian Pac J Cancer Prev*. 2021;22(8):2445–2451. doi:10.31557/apjcp.2021.22.8.2445
53. Yan Y, Shen Z, Gao Z, et al. Long noncoding ribonucleic acid specific for distant metastasis of gastric cancer is associated with TRIM 16 expression and facilitates tumor cell invasion in vitro. *J Gastroenterol Hepatol*. 2015;30(9):1367–1375. doi:10.1111/jgh.12976
54. Ping M, Wang S, Guo Y, Jia J. TRIM21 improves apatinib treatment in gastric cancer through suppressing EZH1 stability. *Biochem Biophys Res Commun*. 2022;586:177–184. doi:10.1016/j.bbrc.2021.07.040
55. Yao Y, Liu Z, Guo H, et al. Elevated TRIM23 expression predicts poor prognosis in Chinese gastric cancer. *Pathol Res Pract*. 2018;214:2062–2068. doi:10.1016/j.prp.2018.10.010

56. Miao Z-F, Wang Z-N, Zhao -T-T, et al. TRIM24 is upregulated in human gastric cancer and promotes gastric cancer cell growth and chemoresistance. *Virchows Arch*. 2015;466(5):525–532. doi:10.1007/s00428-015-1737-4
57. Fang Z, Deng J, Zhang L, et al. TRIM24 promotes the aggression of gastric cancer via the Wnt/ β -catenin signaling pathway. *Oncol Lett*. 2017;13(3):1797–1806. doi:10.3892/ol.2017.5604
58. Fang Z, Zhang L, Liao Q, et al. Regulation of TRIM24 by miR-511 modulates cell proliferation in gastric cancer. *J Exp Clin Cancer Res*. 2017;36(1):17. doi:10.1186/s13046-017-0489-1
59. Chen JJ, Ren Y-L, Shu C-J, et al. JP3, an antiangiogenic peptide, inhibits growth and metastasis of gastric cancer through TRIM25/SP1/MMP2 axis. *J Exp Clin Cancer Res*. 2020;39(1):118. doi:10.1186/s13046-020-01617-8
60. Qiu F, Xiong JP, Deng J, Xiang XJ. TRIM29 functions as an oncogene in gastric cancer and is regulated by miR-185. *Int J Clin Exp Pathol*. 2015;8:5053–5061.
61. Kosaka Y, Inoue H, Ohmachi T, et al. Tripartite motif-containing 29 (TRIM29) is a novel marker for lymph node metastasis in gastric cancer. *Ann Surg Oncol*. 2007;14(9):2543–2549. doi:10.1245/s10434-007-9461-1
62. Sugiura T, Miyamoto K. Characterization of TRIM31, upregulated in gastric adenocarcinoma, as a novel RBCC protein. *J Cell Biochem*. 2008;105(4):1081–1091. doi:10.1002/jcb.21908
63. Sugiura T. The cellular level of TRIM31, an RBCC protein overexpressed in gastric cancer, is regulated by multiple mechanisms including the ubiquitin-proteasome system. *Cell Biol Int*. 2011;35:657–661. doi:10.1042/cbi20100772
64. Ito M, Migita K, Matsumoto S, et al. Overexpression of E3 ubiquitin ligase tripartite motif 32 correlates with a poor prognosis in patients with gastric cancer. *Oncol Lett*. 2017;13(5):3131–3138. doi:10.3892/ol.2017.5806
65. Wang C, Xu J, Fu H, et al. TRIM 32 promotes cell proliferation and invasion by activating β -catenin signalling in gastric cancer. *J Cell Mol Med*. 2018;22(10):5020–5028. doi:10.1111/jcmm.13784
66. Wang J, Fang Y, Liu T. TRIM32 promotes the growth of gastric cancer cells through enhancing AKT activity and glucose transportation. *Biomed Res Int*. 2020;2020:4027627. doi:10.1155/2020/4027627
67. Noguchi K, Okumura F, Takahashi N, et al. TRIM40 promotes neddylation of IKK and is downregulated in gastrointestinal cancers. *Carcinogenesis*. 2011;32(7):995–1004. doi:10.1093/carcin/bgr068
68. Kashimoto K, Komatsu S, Ichikawa D, et al. Overexpression of TRIM44 contributes to malignant outcome in gastric carcinoma. *Cancer Sci*. 2012;103(11):2021–2026. doi:10.1111/j.1349-7006.2012.02407.x
69. Xia Y, Wei Z, Huang W, Wei X, He Y. Trim47 overexpression correlates with poor prognosis in gastric cancer. *Neoplasma*. 2021;68(02):307–316. doi:10.4149/neo_2020_200708N706
70. Li R, Xu P, Jin X, et al. TRIM50 inhibits proliferation and metastasis of gastric cancer via promoting β -catenin degradation. *J Oncol*. 2022;2022:5936753. doi:10.1155/2022/5936753
71. Cao H, Li Y, Chen L, et al. Tripartite motif-containing 54 promotes gastric cancer progression by upregulating K63-linked ubiquitination of filamin C. *Asia Pac J Clin Oncol*. 2022;18:669–677. doi:10.1111/ajco.13747
72. Liu X, Long Z, Cai H, Yu S, Wu J. TRIM58 suppresses the tumor growth in gastric cancer by inactivation of β -catenin signaling via ubiquitination. *Cancer Biol Ther*. 2020;21(3):203–212. doi:10.1080/15384047.2019.1679554
73. Zhou Z, Ji Z, Wang Y, et al. TRIM59 is up-regulated in gastric tumors, promoting ubiquitination and degradation of p53. *Gastroenterology*. 2014;147(5):1043–1054. doi:10.1053/j.gastro.2014.07.021
74. Piao M-Y, Cao H-L, He -N-N, et al. Potential role of TRIM3 as a novel tumour suppressor in colorectal cancer (CRC) development. *Scand J Gastroenterol*. 2016;51(5):572–582. doi:10.3109/00365521.2015.1124285
75. Zheng S, Zhou C, Wang Y, et al. TRIM6 promotes colorectal cancer cells proliferation and response to thiostrepton by TIS21/FoxM1. *J Exp Clin Cancer Res*. 2020;39(1):23. doi:10.1186/s13046-019-1504-5
76. Mastropasqua F, Marzano F, Valletti A, et al. TRIM8 restores p53 tumour suppressor function by blunting N-MYC activity in chemo-resistant tumours. *Mol Cancer*. 2017;16(1):67. doi:10.1186/s12943-017-0634-7
77. Yin Y, Zhong J, Li S-W, et al. TRIM11, a direct target of miR-24-3p, promotes cell proliferation and inhibits apoptosis in colon cancer. *Oncotarget*. 2016;7(52):86755–86765. doi:10.18632/oncotarget.13550
78. Jin Z, Li H, Hong X, et al. TRIM14 promotes colorectal cancer cell migration and invasion through the SPHK1/STAT3 pathway. *Can Cell Inter*. 2018;18(1):202. doi:10.1186/s12935-018-0701-1
79. Lee OH, Lee J, Lee KH, et al. Role of the focal adhesion protein TRIM15 in colon cancer development. *BBA*. 2015;1853(2):409–421. doi:10.1016/j.bbamer.2014.11.007
80. Zhou G, Wu H, Lin J, et al. TRIM21 is decreased in colitis-associated cancer and negatively regulates epithelial carcinogenesis. *Inflamm Bowel Dis*. 2021;27(4):458–468. doi:10.1093/ibd/izaa229
81. Han Y, Tan Y, Zhao Y, et al. TRIM23 overexpression is a poor prognostic factor and contributes to carcinogenesis in colorectal cancer. *J Cell Mol Med*. 2020;24:5491–5500. doi:10.1111/jcmm.15203
82. Xie W, Zhang Y, Wang B, et al. Tripartite motif containing 24 regulates cell proliferation in colorectal cancer through YAP signaling. *Cancer Med*. 2020;9(17):6367–6376. doi:10.1002/cam4.3310
83. Wang F-Q, Han Y, Yao W, Yu J. Prognostic relevance of tripartite motif containing 24 expression in colorectal cancer. *Pathol Res Pract*. 2017;213(10):1271–1275. doi:10.1016/j.prp.2017.08.008
84. Wang J, Zhu J, Dong M, et al. Knockdown of tripartite motif containing 24 by lentivirus suppresses cell growth and induces apoptosis in human colorectal cancer cells. *Oncol Res*. 2014;22(1):39–45. doi:10.3727/096504014x14078436005012
85. Sun N, Xue Y, Dai T, Li X, Zheng N. Tripartite motif containing 25 promotes proliferation and invasion of colorectal cancer cells through TGF- β signaling. *Biosci Rep*. 2017;37(4). doi:10.1042/bsr20170805
86. Nasrullah U, Haussler U, Biyanee A, et al. Identification of TRIM25 as a negative regulator of Caspase-2 expression reveals a novel target for sensitizing colon carcinoma cells to intrinsic apoptosis. *Cells*. 2019;8(12):1622. doi:10.3390/cells8121622
87. Zhang Y, Feng Y, Ji D, et al. TRIM27 functions as an oncogene by activating epithelial-mesenchymal transition and p-AKT in colorectal cancer. *Int J Oncol*. 2018;53(2):620–632. doi:10.3892/ijo.2018.4408
88. Zhang HX, Xu ZS, Lin H, et al. TRIM27 mediates STAT3 activation at retromer-positive structures to promote colitis and colitis-associated carcinogenesis. *Nat Commun*. 2018;9:3441. doi:10.1038/s41467-018-05796-z

89. Fitzgerald S, Sheehan KM, O'Grady A, et al. Relationship between epithelial and stromal TRIM 28 expression predicts survival in colorectal cancer patients. *J Gastroenterol Hepatol*. 2013;28(6):967–974. doi:10.1111/jgh.12157
90. Fitzgerald S, Espina V, Liotta L, et al. Stromal TRIM28-associated signaling pathway modulation within the colorectal cancer microenvironment. *J Transl Med*. 2018;16(1):89. doi:10.1186/s12967-018-1465-z
91. Cui J, Hu J, Ye Z, et al. TRIM28 protects CARM1 from proteasome-mediated degradation to prevent colorectal cancer metastasis. *Sci Bull*. 2019;64(14):986–997. doi:10.1016/j.scib.2019.05.024
92. Xu W, Xu B, Yao Y, et al. RNA interference against TRIM29 inhibits migration and invasion of colorectal cancer cells. *Oncol Rep*. 2016;36(3):1411–1418. doi:10.3892/or.2016.4941
93. Liu J, Zhang C, Wang XL, et al. E3 ubiquitin ligase TRIM32 negatively regulates tumor suppressor p53 to promote tumorigenesis. *Cell Death Differ*. 2014;21(11):1792–1804. doi:10.1038/cdd.2014.121
94. Hu CE, Gan J. TRIM37 promotes epithelial-mesenchymal transition in colorectal cancer. *Mol Med Rep*. 2017;15:1057–1062. doi:10.3892/mmr.2017.6125
95. Zhao P, Guan HT, Dai ZJ, et al. Knockdown of Tripartite Motif-Containing Protein 37 (TRIM37) inhibits the proliferation and tumorigenesis in colorectal cancer cells. *Onco Res*. 2017;25(1):115–122. doi:10.2147/OTT.S228637
96. Hu J, Ding X, Tian S, et al. TRIM39 deficiency inhibits tumor progression and autophagic flux in colorectal cancer via suppressing the activity of Rab7. *Cell Death Dis*. 2021;12(4):391. doi:10.1038/s41419-021-03670-3
97. Sun S, Li W, Ma X, Luan H. Long noncoding RNA LINC00265 promotes glycolysis and lactate production of colorectal cancer through regulating of miR-216b-5p/TRIM44 axis. *Digestion*. 2020;101(4):391–400. doi:10.1159/000500195
98. Li CG, Hu H, Yang XJ, Huang CQ, Yu XQ. TRIM44 promotes colorectal cancer proliferation, migration, and invasion through the Akt/mTOR signaling pathway. *Onco Targets Ther*. 2019;12:10693–10701. doi:10.2147/ott.S228637
99. Liang Q, Tang C, Tang M, et al. TRIM47 is up-regulated in colorectal cancer, promoting ubiquitination and degradation of SMAD4. *J Exp Clin Cancer Res*. 2019;38(1):159. doi:10.1186/s13046-019-1143-x
100. Pan S, Deng Y, Fu J, et al. TRIM52 promotes colorectal cancer cell proliferation through the STAT3 signaling. *Can Cell Inter*. 2019;19(1):57. doi:10.1186/s12935-019-0775-4
101. Lin M, Fang Z, Lin X, et al. TRIM55 inhibits colorectal cancer development via enhancing protein degradation of c-Myc. *Cancer Med*. 2023;12(12):13511–13521. doi:10.1002/cam4.6020
102. Liu M, Zhang X, Cai J, et al. Downregulation of TRIM58 expression is associated with a poor patient outcome and enhances colorectal cancer cell invasion. *Oncol Rep*. 2018;40(3):1251–1260. doi:10.3892/or.2018.6525
103. Sun Y, Ji B, Feng Y, et al. TRIM59 facilitates the proliferation of colorectal cancer and promotes metastasis via the PI3K/AKT pathway. *Oncol Rep*. 2017;38(1):43–52. doi:10.3892/or.2017.5654
104. Wu W, Chen J, Wu J, et al. Knockdown of tripartite motif-59 inhibits the malignant processes in human colorectal cancer cells. *Oncol Rep*. 2017;38(4):2480–2488. doi:10.3892/or.2017.5896
105. Chen D, Li Y, Zhang X, et al. Ubiquitin ligase TRIM65 promotes colorectal cancer metastasis by targeting ARHGAP35 for protein degradation. *Oncogene*. 2019;38(37):6429–6444. doi:10.1038/s41388-019-0891-6
106. He T, Cui J, Wu Y, Sun X, Chen N. Knockdown of TRIM66 inhibits cell proliferation, migration and invasion in colorectal cancer through JAK2/STAT3 pathway. *Life Sci*. 2019;235:116799. doi:10.1016/j.lfs.2019.116799
107. Wang S, Zhang Y, Huang J, et al. TRIM67 activates p53 to suppress colorectal cancer initiation and progression. *Cancer Res*. 2019;79(16):4086–4098. doi:10.1158/0008-5472.Can-18-3614
108. Tan Z, Liu X, Yu E, et al. Lentivirus-mediated RNA interference of tripartite motif 68 inhibits the proliferation of colorectal cancer cell lines SW1116 and HCT116 in vitro. *Oncol Lett*. 2017;13(4):2649–2655. doi:10.3892/ol.2017.5787
109. Jain AK, Allton K, Duncan AD, Barton MC. TRIM24 is a p53-induced E3-ubiquitin ligase that undergoes ATM-mediated phosphorylation and autodegradation during DNA damage. *Mol Cell Biol*. 2014;34(14):2695–2709. doi:10.1128/mcb.01705-12
110. Hatakeyama S. TRIM family proteins: roles in autophagy, immunity, and carcinogenesis. *Trends Biochem Sci*. 2017;42(4):297–311. doi:10.1016/j.tibs.2017.01.002
111. Yu L, Wei J, Liu P. Attacking the PI3K/Akt/mTOR signaling pathway for targeted therapeutic treatment in human cancer. *Semi Cancer Biol*. 2022;85:69–94. doi:10.1016/j.semcancer.2021.06.019
112. Lee MJ, Jin N, Grandis JR, Johnson DE. Alterations and molecular targeting of the GSK-3 regulator, PI3K, in head and neck cancer. *Biochim Biophys Acta Mol Cell Res*. 2020;1867:118679. doi:10.1016/j.bbamer.2020.118679
113. Vunjak M, Versteeg GA. TRIM proteins. *Curr Biol*. 2019;29:R42–R44. doi:10.1016/j.cub.2018.11.026
114. Shen H, Zhang J, Zhang Y, et al. Knockdown of tripartite motif 59 (TRIM59) inhibits proliferation in cholangiocarcinoma via the PI3K/AKT/mTOR signalling pathway. *Gene*. 2019;698:50–60. doi:10.1016/j.gene.2019.02.044
115. Grossman SR, Perez M, Kung AL, et al. p300/MDM2 complexes participate in MDM2-mediated p53 degradation. *Molecular Cell*. 1998;2(4):405–415. doi:10.1016/s1097-2765(00)80140-9
116. Wang Z, Li Z, Ji H. Direct targeting of β -catenin in the Wnt signaling pathway: current progress and perspectives. *Med Res Rev*. 2021;41:2109–2129. doi:10.1002/med.21787
117. Liu J, Xiao Q, Xiao J, et al. Wnt/ β -catenin signalling: function, biological mechanisms, and therapeutic opportunities. *Signal Transduct Target Ther*. 2022;7(1):3. doi:10.1038/s41392-021-00762-6
118. White BD, Chien AJ, Dawson DW. Dysregulation of Wnt/ β -catenin signaling in gastrointestinal cancers. *Gastroenterology*. 2012;142(2):219–232. doi:10.1053/j.gastro.2011.12.001
119. Zou S, Tong Q, Liu B, et al. Targeting STAT3 in cancer immunotherapy. *Mol Cancer*. 2020;19(1):145. doi:10.1186/s12943-020-01258-7
120. Heichler C, Scheibe K, Schmied A, et al. STAT3 activation through IL-6/IL-11 in cancer-associated fibroblasts promotes colorectal tumour development and correlates with poor prognosis. *Gut*. 2020;69(7):1269–1282. doi:10.1136/gutjnl-2019-319200
121. Johnson DE, O'Keefe RA, Grandis JR. Targeting the IL-6/JAK/STAT3 signalling axis in cancer. *Nat Rev Clin Oncol*. 2018;15:234–248. doi:10.1038/nrclinonc.2018.8
122. Yip SC, Saha S, Chernoff J. PTP1B: a double agent in metabolism and oncogenesis. *Trends Biochem Sci*. 2010;35:442–449. doi:10.1016/j.tibs.2010.03.004

123. Yu H, Lee H, Herrmann A, Buettner R, Jove R. Revisiting STAT3 signalling in cancer: new and unexpected biological functions. *Nat Rev Cancer*. 2014;14(11):736–746. doi:10.1038/nrc3818
124. Peng D, Fu M, Wang M, Wei Y, Wei X. Targeting TGF- β signal transduction for fibrosis and cancer therapy. *Mol Cancer*. 2022;21(1):104. doi:10.1186/s12943-022-01569-x
125. Tzavlaki K, Moustakas A. TGF- β signaling. *Biomolecules*. 2020;10(3):487. doi:10.3390/biom10030487
126. Yeh HW, Lee SS, Chang CY, Lang YD, Jou YS. A new switch for TGF β in cancer. *Cancer Res*. 2019;79(15):3797–3805. doi:10.1158/0008-5472.Can-18-2019
127. Zhang P, Elabd S, Hammer S, et al. TRIM25 has a dual function in the p53/Mdm2 circuit. *Oncogene*. 2015;34(46):5729–5738. doi:10.1038/onc.2015.21
128. Brooks CL, Gu W. The impact of acetylation and deacetylation on the p53 pathway. *Protein Cell*. 2011;2(6):456–462. doi:10.1007/s13238-011-1063-9
129. Yuan Z, Villagra A, Peng L, et al. The ATDC (TRIM29) protein binds p53 and antagonizes p53-mediated functions. *Mol Cell Biol*. 2010;30(12):3004–3015. doi:10.1128/mcb.01023-09
130. Zhou W, Lim A, Edderkaoui M, et al. Role of YAP signaling in regulation of programmed cell death and drug resistance in cancer. *Int J Bio Sci*. 2024;20(1):15–28. doi:10.7150/ijbs.83586
131. Ji J, Ding K, Luo T, et al. TRIM22 activates NF- κ B signaling in glioblastoma by accelerating the degradation of I κ B α . *Cell Death Differ*. 2021;28(1):367–381. doi:10.1038/s41418-020-00606-w
132. Xi X, Bao Y, Zhou Y, et al. Oncogenic gene TRIM10 confers resistance to cisplatin in osteosarcoma cells and activates the NF- κ B signaling pathway. *Cell Biol Int*. 2021;45(1):74–82. doi:10.1002/cbin.11468
133. Fan W, Liu X, Zhang J, et al. TRIM67 suppresses TNF α -triggered NF- κ B activation by competitively binding beta-TrCP to I κ B α . *Front Immunol*. 2022;13:793147. doi:10.3389/fimmu.2022.793147
134. Liu J, Peng Y, Wei W. Cell cycle on the crossroad of tumorigenesis and cancer therapy. *Trends Cell Biol*. 2022;32(1):30–44. doi:10.1016/j.tcb.2021.07.001
135. Hume S, Dianov GL, Ramadan K. A unified model for the G1/S cell cycle transition. *Nucleic Acids Res*. 2020;48(22):12483–12501. doi:10.1093/nar/gkaa1002
136. Bertoli C, Skotheim JM, de Bruin RA. Control of cell cycle transcription during G1 and S phases. *Nat Rev Mol Cell Biol*. 2013;14(8):518–528. doi:10.1038/nrm3629
137. Burgess DJ. Apoptosis: refined and lethal. *Nat Rev Cancer*. 2013;13(2):79. doi:10.1038/nrc3462
138. Su Z, Yang Z, Xu Y, Chen Y, Yu Q. Apoptosis, autophagy, necroptosis, and cancer metastasis. *Mol Cancer*. 2015;14(1):48. doi:10.1186/s12943-015-0321-5
139. Carneiro BA, El-Deiry WS. Targeting apoptosis in cancer therapy. *Nat Rev Clin Oncol*. 2020;17:395–417. doi:10.1038/s41571-020-0341-y
140. Singh P, Lim B. Targeting apoptosis in cancer. *Curr Oncol Rep*. 2022;24(3):273–284. doi:10.1007/s11912-022-01199-y
141. Chen B, Dragomir MP, Yang C, et al. Targeting non-coding RNAs to overcome cancer therapy resistance. *Signal Transduct Target Ther*. 2022;7(1):121. doi:10.1038/s41392-022-00975-3
142. Toden S, Zumwalt TJ, Goel A. Non-coding RNAs and potential therapeutic targeting in cancer. *Biochimica Et Biophysica Acta*. 2021;1875(1):188491. doi:10.1016/j.bbcan.2020.188491
143. Zaninotto G, Bennett C, Boeckxstaens G, et al. The 2018 ISDE achalasia guidelines. *Dis Esophagus*. 2018;31:doy071. doi:10.1093/dote/doy071
144. Xiao M, Liang Z, Yin Z. Long non-coding RNA ZFPM2-AS1 promotes colorectal cancer progression by sponging miR-137 to regulate TRIM24. *Mol Med Rep*. 2021;23(2). doi:10.3892/mmr.2020.11737
145. Lei R, Feng L, Hong D. ELFN1-AS1 accelerates the proliferation and migration of colorectal cancer via regulation of miR-4644/TRIM44 axis. *Cancer Biomark*. 2020;27(4):433–443. doi:10.3233/cbm-190559
146. Cheng Z, Wang HZ, Li X, et al. MicroRNA-184 inhibits cell proliferation and invasion, and specifically targets TNFAIP2 in Glioma. *J Exp Clin Cancer Res*. 2015;34(1):27. doi:10.1186/s13046-015-0142-9
147. Caratozzolo MF, Micale L, Turturo MG, et al. TRIM8 modulates p53 activity to dictate cell cycle arrest. *Cell Cycle*. 2012;11:511–523. doi:10.4161/cc.11.3.19008
148. Manasanch EE, Orlowski RZ. Proteasome inhibitors in cancer therapy. *Nat Rev Clin Oncol*. 2017;14:417–433. doi:10.1038/nrclinonc.2016.206
149. Tan CRC, Abdul-Majeed S, Cael B, Barta SK. Clinical pharmacokinetics and pharmacodynamics of bortezomib. *Clin Pharmacokinet*. 2019;58:157–168. doi:10.1007/s40262-018-0679-9
150. Nakata W, Hayakawa Y, Nakagawa H, et al. Anti-tumor activity of the proteasome inhibitor bortezomib in gastric cancer. *Int J Oncol*. 2011;39(6):1529–1536. doi:10.3892/ijo.2011.1141
151. Yue D, Sun X. Ixazomib promotes CHOP-dependent DR5 induction and apoptosis in colorectal cancer cells. *Cancer Biol Ther*. 2019;20(3):284–294. doi:10.1080/15384047.2018.1529095
152. Mañas A, Chen W, Nelson A, Yao Q, Xiang J. Bax Δ 2 sensitizes colorectal cancer cells to proteasome inhibitor-induced cell death. *Biochem Biophys Res Commun*. 2018;496:18–24. doi:10.1016/j.bbrc.2017.12.156
153. Bennett J, Fedorov O, Tallant C, et al. Discovery of a chemical tool inhibitor targeting the bromodomains of TRIM24 and BRPF. *J Med Chem*. 2016;59(4):1642–1647. doi:10.1021/acs.jmedchem.5b00458
154. Zhan Y, Kost-Alimova M, Shi X, et al. Development of novel cellular histone-binding and chromatin-displacement assays for bromodomain drug discovery. *Epigen Chromat*. 2015;8:37. doi:10.1186/s13072-015-0026-4
155. Palmer WS, Poncet-Montange G, Liu G, et al. Structure-guided design of IACS-9571, a selective high-affinity dual TRIM24-BRPF1 bromodomain inhibitor. *J Med Chem*. 2016;59:1440–1454. doi:10.1021/acs.jmedchem.5b00405
156. Gechijian LN, Buckley DL, Lawlor MA, et al. Functional TRIM24 degrader via conjugation of ineffectual bromodomain and VHL ligands. *Nat Chem Biol*. 2018;14(4):405–412. doi:10.1021/acs.jmedchem.5b00405
157. Li K, Crews CM. PROTACs: past, present and future. *Chem Soc Rev*. 2022;51(12):5214–5236. doi:10.1039/d2cs00193d

Drug Design, Development and Therapy

Dovepress

Publish your work in this journal

Drug Design, Development and Therapy is an international, peer-reviewed open-access journal that spans the spectrum of drug design and development through to clinical applications. Clinical outcomes, patient safety, and programs for the development and effective, safe, and sustained use of medicines are a feature of the journal, which has also been accepted for indexing on PubMed Central. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/drug-design-development-and-therapy-journal>