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E3 ubiquitin ligase-dependent regulatory mechanism of TRIM family in carcinogenesis

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ABSTRACT

Tripartite motif-containing (TRIM) proteins consist of over 80 proteins, the majority of which exhibit E3 ubiquitin ligase activity. E3 ligases have a critical role in various cellular processes by specifically recognizing and ubiquitinating substrate proteins to promote their proteasomal degradation or alter their activities. Numerous studies have indicated that TRIMs are involved in carcinogenesis through various mechanisms. However, the regulatory mechanisms delimitating TRIMs' function as E3 ligases has not yet been specifically addressed in a previous review article. In this review, we focus on recent advancements in understanding how certain TRIMs function solely as E3 ligases during cancer cell proliferation, apoptosis, and metastasis. We comprehensively summarize the target proteins of TRIMs involved in disordered signaling pathways such as Wnt/β-catenin, PI3K/AKT, NF-κB, p53, ERK, and STAT3, as well as those regulating the cell cycle and glycolysis. Following ubiquitination modification by TRIM E3 ligases, these target proteins either undergo proteasome-mediating degradation, maintain steady levels, or get activated/inactivated. This review provides a foundation for the development of E3 ligase-based cancer treatments.

KEYWORDS

TRIM proteins; Ubiquitination; Cancer; Protein degradation; Signaling pathway

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1. Introduction

The E3 ligase enzyme is essential in regulating protein ubiquitination, a post-translational modification that attaches ubiquitin to the lysine residues of substrates. This process controls various cellular processes such as protein degradation, DNA repair, and signal transduction [1]. The specific lysine sites on the ubiquitin molecule used to form the isopeptide bond determine the outcome of ubiquitination [2]. For instance, K48- or K11-polyubiquitin chains lead to proteasomal degradation, while K63-polyubiquitin regulates substrate participation in signaling transduction and the autophagy-lysosome system [3].

Protein degradation occurs when unstable N-terminus amino acid residues of misfolded, abnormal, or unnecessary proteins bind to polyubiquitin molecules [4, 5]. The process of ubiquitination in proteins involves three enzymes: ubiquitin activating enzymes (UBA, E1 enzymes), ubiquitin conjugating enzyme (UBCs, E2), and ubiquitin ligase (E3), which work together to catalyze the reaction [1, 6]. The first step in this process is the activation of ubiquitin by E1 enzymes. This is achieved by adenylating the C-terminal of ubiquitin and forming an E1~Ub intermediate through a thioester bond [7]. E2 is then recruited to the proximity of the E1~Ub thioester bond, facilitating the creation of E2~Ub intermediate by binding the E2 active site cysteine to the C-terminal carboxyl group of Ub [1, 8]. In humans, only one or two types of E1 are required to activate 40 different E2s [8], while more than 600 E3 genes are encoded to ensure precise substrate selection and provide structural and functional diversity [1, 9]. E3 ligases play a central role in the enzymatic cascade of protein ubiquitylation by recruiting substrates and E2~Ub, and facilitating the transfer of ubiquitin from E2~Ub to substrates [9].

Recently, E3 ligases have been grouped into five types: HECT (homologous to E6AP C-terminus) family, RING (really interesting new gene) family, RBR (RING-IBR-RING) family, the newly categorized PCAF-N family, and the atypical family. The structure and classification of E3 ligases have been well described in several recent reviews [1, 8, 10-13].

Tripartite motif-containing proteins (TRIM) family is an ancient RING E3 ligase family, where most members act as E3 ligase. Several reviews have summarized the involvement of TRIM family proteins in tumorigenesis, highlighting their various molecular functions that may or may not be dependent on their E3 ligase activities. However, there has been no summary yet on TRIM members that function exclusively as E3 ligase to ubiquitinate target proteins involved in cancer progression. In this review, we focus on describing the participation of individual TRIM E3 ligases and their ubiquitinated substrates (with solid evidence or reliable speculation) in cancer proliferation, apoptosis, and metastasis, which will help us to understand the cancer pathogenesis from the perspective of E3 ubiquitin ligases, develop drugs that target E3 ligases, and promote the development of proteolysis-targeting chimeras (PROTACs) technology. PROTAC has become a promising technique for targeted therapy in cancers by using two covalently-mediated ligands of PROTAC molecule to recruit E3 ligase and target protein together for proteasome degradation of target protein [14].

2. Structure characters of TRIMs

The TRIM family is composed of more than 80 members [15] and is involved in a range of biological processes,

including proliferation, apoptosis, cell cycle, viral and antiviral response, and oncogenesis. As shown in Figure 1, members of the TRIM family are characterized by an N-terminal RING finger domain, one or two B boxes (B1 box and B2 box), and a coiled-coil domain (CCD), which is also known as RING, B-box, and coiled-coil (RBCC) family [16]. The spatial arrangement of these domains is evolutionarily conserved. In some TRIM proteins, one of the three domains can be substituted with linkers, while leaving the domain order unchanged [17]. The RING domain, which contains two zinc-binding motifs with a Cys3HisCys4 amino acid motif, allows TRIM proteins to function as E3 ligases in most cases [18]. The function of TRIM proteins as E3 ligases requires homo- or hetero-dimerization [19]. However, for certain TRIMs, the distance between the two RINGs is too great to allow for intra-dimeric RING-RING contact. To compensate for this, higher oligomerization of TRIMs may be necessary to activate its E3 ligase activity [17]. The B box domains, which include B1 and B2, are zinc-finger domains. Some TRIM proteins only have the B2 domain, indicating its essential role [19, 20]. The B1 box may possess E3 ligase activity itself or enhance the activity of RING type E3 ligases [20]. The CCD domain contributes to interactions among TRIM members and can also facilitate higher-order oligomerization of TRIMs [18, 20, 21]. It is worth noting that certain TRIM proteins lack the RING domain but still possess conserved B-boxes and CCD domains.

The RBCC domain is followed by variable C-terminal domains that have different lengths and properties, typically involved in recognizing substrates. Based on the structural diversity of the C-terminus, TRIM proteins can be classified into 12 different groups from C-I to C-XI (Figure 1), including one uncategorized group (UC) which lacks the RING domain [22]. The C-terminal region of TRIM family proteins consists of COS (C-terminal subgroup one signature), FN3 (fibronectin type 3), PRY-SPRY domain (a.k.a B30.2, the most common C-terminal domain), PHD (plant homeodomain), BROMO bromodomain, TM (transmembrane domain), NHL (NHL domain), ACID (acid-rich domain), ARF (ADP-ribosylation factor family domain), FIL (filamin-type IG domain), MATH (Meprin and TRAF-homology domain), or uncharacterized sequences [15, 16, 20, 23, 24]. The PRY-SPRY domain, only found in vertebrates, is a single globular domain containing the N-terminal PRY (~60 amino acids) and the well-conserved C-terminal SPRY (~140 amino acids) [25-27]. Although the core β-strands of PRY-SPRY domain are widely conserved, the loops between the β-strands are highly variable and capable of recognizing various substrates through binding [17]. The SPRY domain can independently bind to its substrate, as seen in the case of TRIM11 binding to pleckstrin homology domain leucine-rich repeats protein phosphatase 1 (PHLPP1) [28]. Reports have shown that the PRY-SPRY domain is crucial for innate immune response, recognition of viral proteins and subcellular localization of certain TRIM proteins [25, 26]. In addition to the PRY-SPRY domain, the NHL domain and PHD-BROMO domain also contribute to the physical interactions of TRIM with their substrates, such as TRIM71, TRIM24, and TRIM28 [23, 29, 30]. Thus, the C-terminal domains of TRIM members are variable and are critical in determining substrate specificity. These domains can also exhibit enzymatic activity or bind to chromatin [31-34].

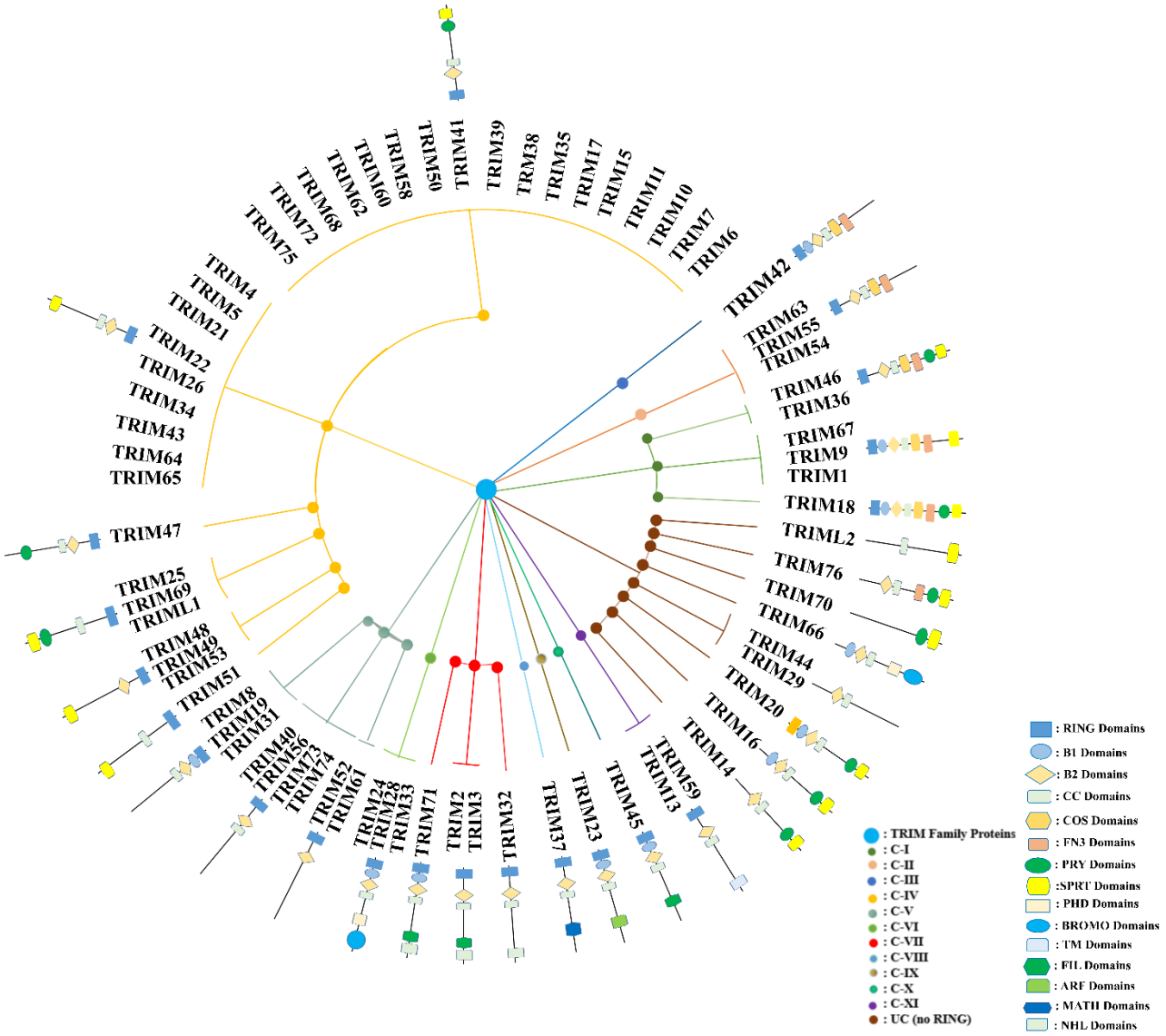

Figure 1. TRIMs classification according to the structural diversity of their C-terminus. For example, TRIM4, 5, 21, 22, 26, 34, 43, 64, and 65 share a common structural feature and TRIM6, 7, 10, 11, 15, 17, 35, 38, 39, 41, 50, 58, 60, 62, 68, 72, and 75 have a same structure feature. All diagrams are drawn through the Figdraw platform (https://www.figdraw.com/static/index.html).

3. TRIMs as E3 ubiquitin ligases in cancer cell proliferation, apoptosis, and metastasis

Cancer is a complex disease characterized by ten hallmarks, including sustained proliferative signaling, evading growth suppressors, resistance to cell death, limitless replicative potential, sustained angiogenesis, invasion and metastasis capability, avoiding immune destruction, elevated tumor inflammation, reprogramming energy metabolism, and genome instability and mutation [35]. Understanding the molecular mechanisms behind these hallmarks will speed up the discovery of new diagnostic and therapeutic strategies.

This review focuses on three primary features of cancer: cell proliferation, apoptosis, and metastasis. The role of TRIM E3 ligases in carcinogenesis varies depending on the context, with both positive and negative effects

observed in different cancer types and in response to different stimuli. The molecular mechanisms underlying these effects involve both the E3 ligase activity of TRIMs and other non-E3 ligase functions. However, existing reviews on the TRIM proteins in cancer tend not to distinguish those involve E3 ligase activity from those do not. Therefore, this review specifically summarizes the involvement of TRIMs as E3 ligases in cancer proliferation, apoptosis, and metastasis, which would contribute to the development of E3 ligase-based drug discovery.

In the following section, we'll summarize how TRIMs play a role as E3 ligases in regulating cancer progression through their involvement in a range of signaling pathways, such as PI3K/AKT, NF-κB, and others, as well as biological processes like cell cycle regulation and glycolysis. It's worth noting that these signaling pathways also have a significant impact on the regulation of cell cycle and glycolysis, and crosstalk exists between them.

3.1. TRIMs as E3 ligase in regulating cell cycle

The abnormal growth of cancer cells, characterized by uncontrolled cell cycling and reduced susceptibility to cell death, can result in malignancy. Researches have revealed that TRIM6, 7, 11, 25, 28, 32, 59, and 62 can regulate cell proliferation in an E3 ligase-dependent manner by targeting key regulators of cell cycle (Figure 2, the effects of TRIM7 and TRIM59 on the cell cycle are described in later sections). For instance, TRIM6 promotes cell proliferation in colorectal cancer cells (CRC) by interacting with, ubiquitinating and degrading transcriptional activating factor 21 (TIS21), an anti-proliferative protein involved in the regulation of G2/M arrest [36]. TRIM25 has been shown to promote the generation of breast cancer (BC) in vivo by facilitating ubiquitination-dependent proteolysis of 14-3-3σ, leading to G2 arrest and contributing to cisplatin (DDP) resistance [37, 38].

The interaction between UBE2S, an E2 ubiquitin-conjugating enzyme, and TRIM28 enhances the ubiquitination and degradation of p27, a cyclin-dependent kinase inhibitor. This facilitates G1/S phase transition of hepatocellular carcinoma (HCC) cells, resulting in the increased expressions of G1/S phase transition-related proteins, such as cyclin-dependent kinase 2 (CDK2), CDK4, cyclin D1, and cyclin E1[39]. In contrast, TRIM32 has been considered as a tumor suppressor of human neuroblastoma cells through positively regulating asymmetric cell division. This was achieved by promoting the ubiquitination and degradation of MYCN on spindle poles after its phosphorylation by CDK1/cyclinB [40]. Similarly, TRIM62 suppresses the proliferation of cervical cancer cells by ubiquitinating and degrading cellular Jun proto-oncogene (c-Jun). This results in the downregulation of Cyclin D1, a positive regulator of the G1 to S phase transition, and the upregulation of p27, an inhibitor of cell progression to S phase. Consequently, the cell cycle is blocked in G1 phase [41]. However, it should be noted that the proteasomal degradation of c-Jun is an although reliable speculation that requires further exploration.

Due to the limited number of reports on TRIMs as E3 ligases in cell cycle and the complex regulatory mechanisms involved in cell cycle, further research is needed to fully understand the role of TRIMs as E3 ligases in regulating the cell cycle.

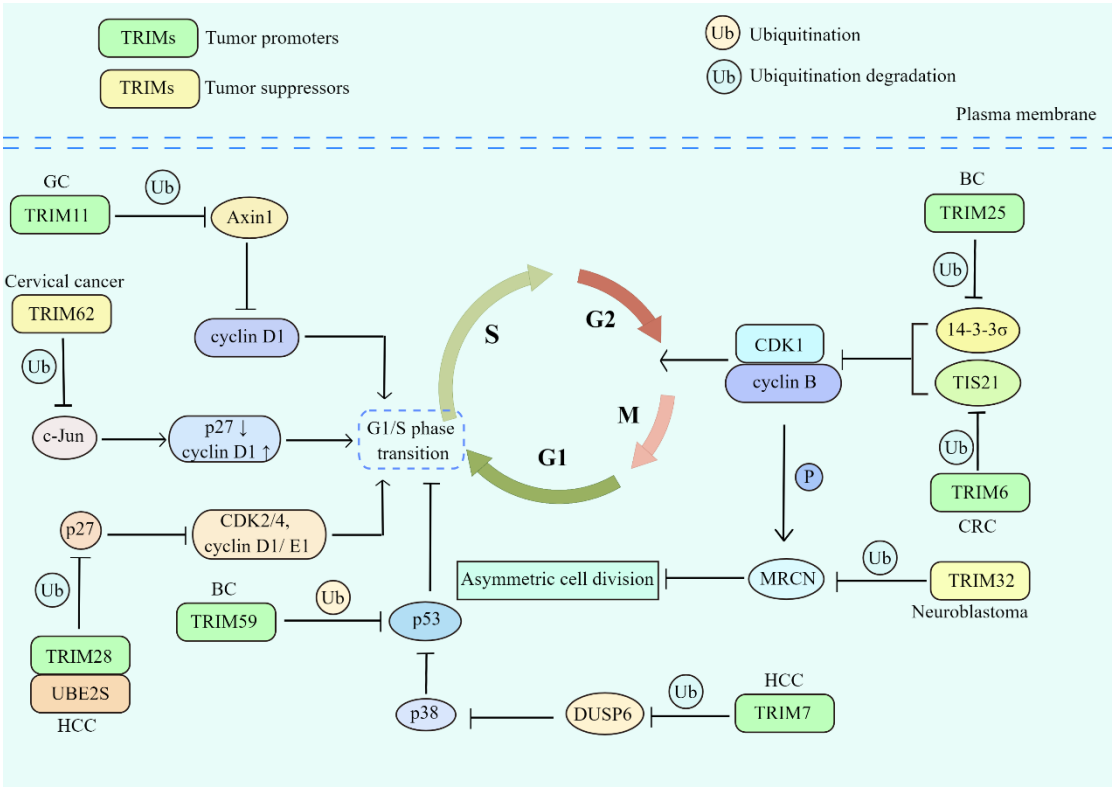

Figure 2. TRIMs as E3 ligase in regulating cell cycle of cancer cells. Notably, two TRIMs, namely TRIM7 and TRIM59, are described in later sections. Briefly, TRIM7 promotes cell cycle progression of HCC cells by facilitating polyubiquitination-mediated degradation of dual specificity phosphatase 6 (DUSP6) [42]. TRIM59 upregulates ubiquitination of p53, thereby promoting cell cycle progression of BC [43].

3.2. TRIMs as E3 ligase in regulating the PI3K/AKT signaling pathway

TRIMs, including TRIM7, 11, 14, 15,16, 21, 25, 27, 29, 37,46, and 59, act as E3 ligases to regulate cancer growth, metastasis, and death by modulating the PI3K/AKT signaling pathway (Figure 3). In particular, TRIM11 and TRIM29 induce K48-linked ubiquitination degradation of PHLPP1, a negative regulator of the PI3K/AKT pathway, which activates the AKT signaling pathway and leads to proliferation and metastasis of HCC cells and CRC cells, respectively [44, 45]. Other studies demonstrate that TRIM14 and TRIM37 activate the PI3K/AKT pathway by ubiquitinating and degrading another negative regulator of the PI3K/AKT pathway, phosphatase and tensin homolog (PTEN) lipid phosphatase, to augment growth in CRC and maintain stemness in pancreatic cancer (PC) cells, respectively [46, 47]. Similarly, both TRIM46 and TRIM59 can activate the AKT/HK2 pathway and glycolysis, likely through interaction with PHLPP2 or PTEN, respectively, and subsequent increase in their ubiquitination and degradation, resulting in DDP resistance and proliferation in non-small cell lung cancer (NSCLC) [48, 49] (also displayed in Figure 8). Moreover, TRIM25 interacts with PTEN phosphatase and facilitates its ubiquitination (such as K63-linked), leading to a reduction in its phosphatase activity and subsequent activation of the PI3K/AKT signaling pathway. This leads to NSCLC cell proliferation, HCC cell migration, or HCC cells resistance to epirubicin (EPI) [50-52]. TRIM27, also named Ret finger protein (RFP), is capable of decreasing PTEN phosphatase activity by stimulating atypical polyubiquitination of PTEN. This leads to enhanced progression of esophageal squamous cell carcinoma (ESCC), prostate cancer, and BC, and increased resistance to TRAIL-induced apoptosis [53, 54]. TRIM21 and TRIM31 activate the PI3K/AKT pathway by mediating ubiquitination and degradation of Elongin A (ELOA) or tuberous sclerosis complex protein (TSC1/2), two negative regulators of the PI3K/AKT pathway, eventually leading

to tumorigenesis and metastasis of CRC or HCC cells [55, 56]. In addition, TRIM15 activates the PI3K/AKT pathway by inducing K63-linked polyubiquitination of LIM and SH3 domain protein 1 (LASP1), a negative regulator of PTEN expression. This results in increased phosphorylation of AKT and tyrosine kinase inhibitor resistance in HCC[57].

In contrast to the positive role of the above mentioned TRIMs in the PI3K/AKT pathway, TRIM13 and TRIM21 have been found to deactivate AKT through mediating proteasomal degradation of AKT in non-tumor cells [58, 59]. In clear cell renal cell carcinoma (ccRCC) and HCC, TRIM7 deactivates the Src-activated PI3K/AKT pathway by directing ubiquitin-proteasome degradation of Src. This suppression of the pathway leads to a decrease in cell migration, invasion, and growth [60, 61]. In human glioblastoma (GBM) cells, TRIM21 inhibits the PI3K/AKT pathway by inducing polyubiquitination and degradation of PFK1 platelet isoform (PFKP). However, this degradation can be prevented by PFKP phosphorylation at S386, which is mediated by the activated PI3K/AKT pathway [62]. Furthermore, TRIM35 deactivates the AKT signaling by inducing ubiquitination-mediated degradation of PDK1, which eventually reduces cell proliferation and increases cell apoptosis in BC cells [63]. Lastly, TRIM16 can polyubiquitinate and degrade Vimentin to suppress lung cancer metastasis. However, this degradation can be blocked by AKT/STAT3-induced upregulation of lncRNA VAL (Vimentin associated lncRNA, LINC01546) [64].

Taken together, several key nodes of the PI3K/AKT signaling pathway appear to be susceptible to TRIM E3 ligases during cancer progression. This implies that the expression levels of these constituents are critical in driving cancer development and can easily be modified by external stimuli. Although targeting AKT using PI3K inhibitors has immense therapeutic potential, it is challenging due to the adverse effects caused by complex crosstalk with other pathways and the involvement of numerous downstream substrates [65]. Given the interactions between TRIM E3 ligase and key targets of the AKT signaling pathway, it is hypothesized that implementing techniques such as PROTACs or screening for small molecule drugs or peptide synthetics that regulate these interactions would enable more precise intervention to this pathway, diminish side effects, and offer a promising option for treating tumors.

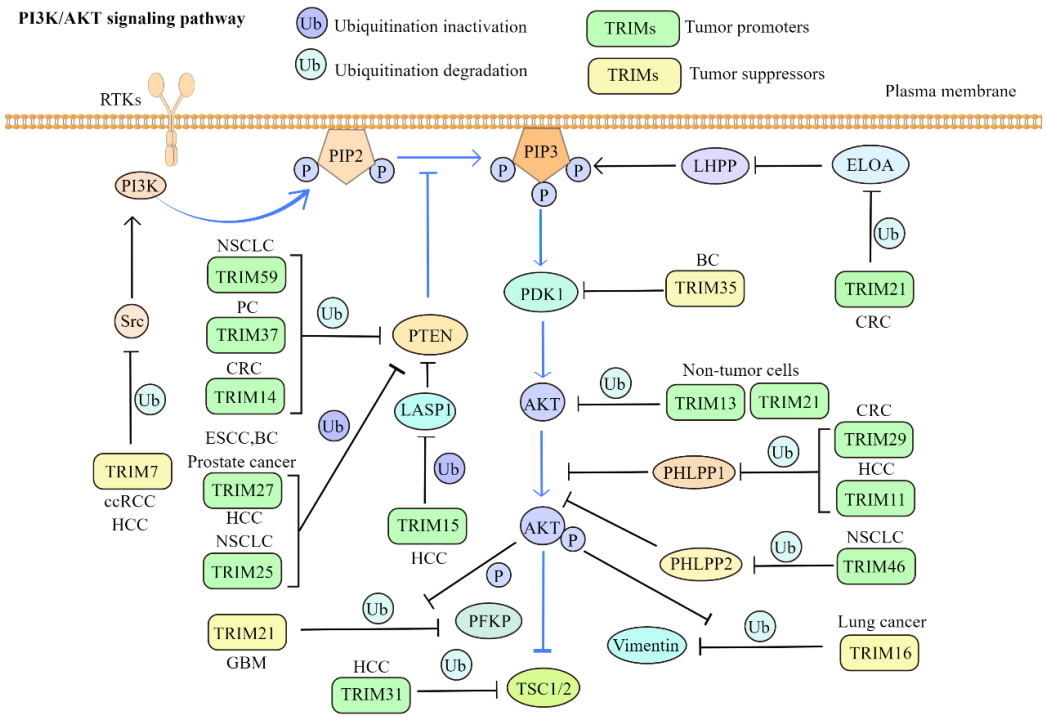

Figure 3. TRIMs as E3 ligase in regulating the PI3K/AKT signaling pathway of cancer cells. The blue arrows indicate the main cascade reaction process of the PI3K/AKT pathway.

3.3 TRIMs as E3 ligases in regulating the NF-κB signaling pathway

TRIM3, 7, 13, 22, 27, 31, 32, 37, 46, 47, 56, and 71 are crucial E3 ligases involved in regulating the NF-κB signaling pathway, which has significant implications for cancer development (Figure 4). In the cytoplasm, IκB-α binds to NF-κB, thereby blocking its nuclear localization and preventing its activation. After phosphorylation, IκB-α undergoes ubiquitination and proteasomal degradation, releasing NF-κB for activation [66]. TRIM13, TRIM22, TRIM27, and TRIM71 activate the NF-κB signaling pathway by ubiquitin-mediated proteasomal degradation of nuclear IκB-α/NFKBIA. This results in increased cell proliferation in multiple myeloma (MM), GBM, renal cell carcinoma (RCC), or NSCLC [66-69].

TRIM22 can also activate NF-κB signaling by interacting with IKKγ and promoting its K63-linked ubiquitination, which eventually facilitates cell proliferation in GBM [69]. Furthermore, TRIM31 and TRIM37 facilitate the activation of NF-κB signaling by mediating the K63 polyubiquitination of tumor necrosis factor receptor-associated factor 2 (TRAF2), ultimately leading to gemcitabine resistance in PC cells, DDP resistance in NSCLC cells, and the promotion of NSCLC cell proliferation, respectively [70, 71]. TRIM37 promotes the activation of the NF-κB signaling pathway by facilitating the mono-ubiquitination of NF-κB essential modulator (NEMO) in the nucleus and the export of NEMO from the nucleus. This confers resistance to DDP and promotes the development of esophageal cancer [72]. In addition, TRIM47 activates NF-κB signaling by mediating lysine 27-linked polyubiquitination of PKC-ε and facilitating the formation of a ternary complex that includes TRIM47, PKC-ε and PKD3. This effect promotes cell proliferation and tamoxifen resistance of BC [73].

Differently, TRIM7 inactivates the NF-κB signaling pathway by interacting with p65 (RelA), a critical subunit of transcription factor NF-kB dimers, and promoting its ubiquitination and degradation, leading to inhibition of NSCLC cell proliferation [74]. TRIM13 may also inhibit NF-κB signaling through TRIM13-mediated ubiquitination of tumor necrosis factor receptor-associated factor 6 (TARF6), a transforming growth factor-beta-activated kinase 1 (TAK1) activator, inducing apoptosis in NSCLC cells [75, 76]. TRIM3 inhibits NF-κB signaling by interacting with and triggering E3 ligase-mediated proteasomal degradation of α-Actinin-4 (ACTN4), negatively regulating metastasis of esophageal squamous cell carcinoma cells [77].

Lastly, TRIM32, TRIM46 and TRIM56 activate the NF-κB signaling by degrading the inhibitors of this pathway. Specifically, these TRIMs associate with Piasy, peroxisome proliferator-activated receptor α (PPARα), or sin3-associated polypeptide of 18 (SAP18), respectively, and facilitate ubiquitination and degradation of them to activate the NF-κB signaling. These effects enhance human epidermal carcinogenesis, promote osteosarcoma growth and cell cycle progression, inhibit apoptosis, or facilitate migration, invasion, and angiogenesis of Kaposi's sarcoma [78-81]. Similarly, TRIM7 activates the NF-κB signaling through binding to and ubiquitinating the K184 site of breast cancer metastasis suppressor 1 (BRMS1), a tumor suppressor in osteosarcoma and its inhibitory role on epithelial-to-mesenchymal transition (EMT) linked to NF-κB signaling. This promotes invasion, migration and chemoresistance of osteosarcoma cells [82, 83].

To conclude, TRIM proteins regulate the NF-κB pathway in cancer through ubiquitination of various nodal proteins, leading to activation or inhibition of this pathway. Identifying regulatory mechanisms of TRIM family members on the NF-κB signaling pathway in cancer cells could provide valuable insights for precise intervention. To this end, screening for small molecules or peptides that affect the interaction of TRIMs with their targets and applying PROTACs technique would be a beneficial initiative for targeted applications.

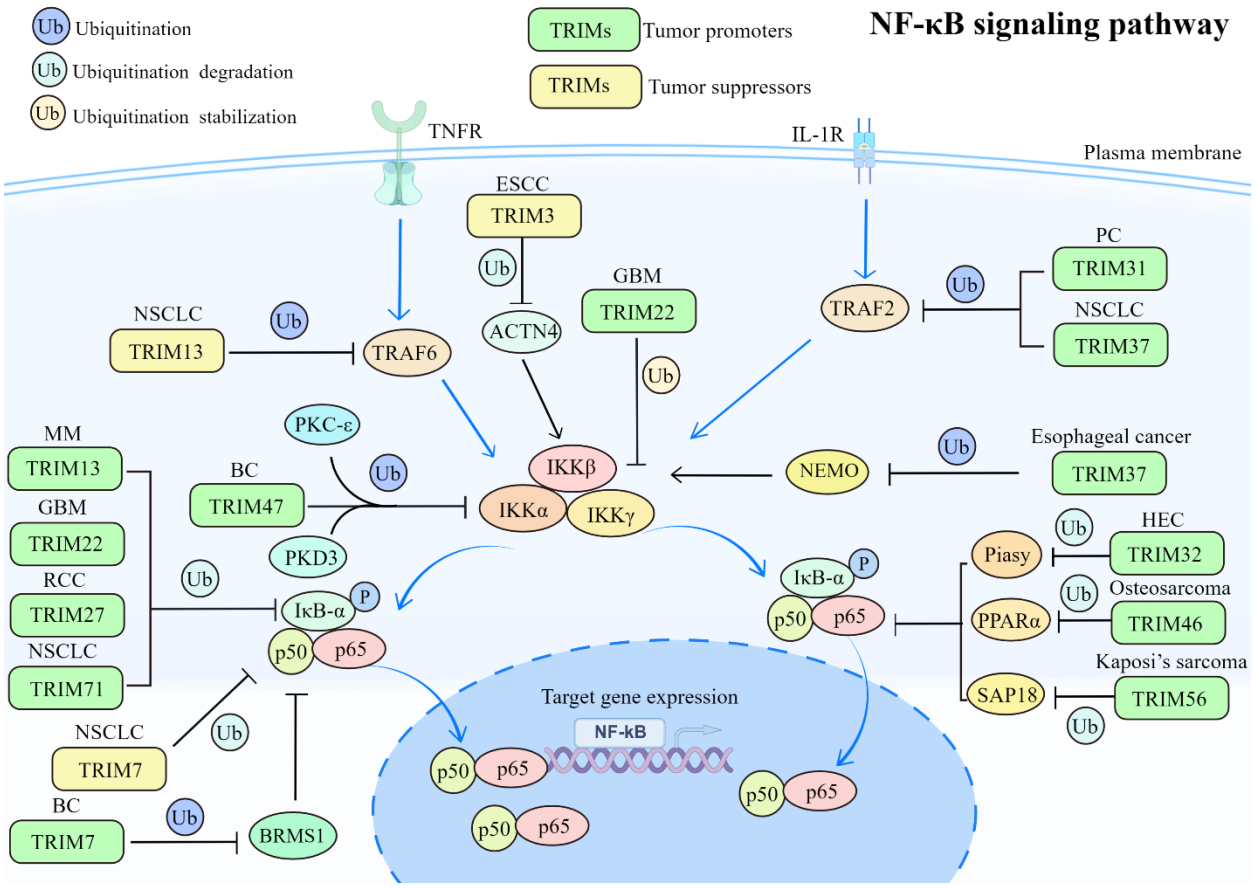

Figure 4. TRIMs as E3 ligase in regulating the NF-κB signaling pathway of cancer cells.

3.4 TRIMs as E3 ligase in regulating the p53 signaling pathway

p53, a key tumor suppressor, plays a critical role in regulating cell growth and maintaining genome integrity under cellular stress via direct controlling the expression of genes that are involved in various cellular processes, including cell cycle, DNA repair, apoptosis, and senescence [84]. TRIMs, including TRIM3, 13, 21, 23, 24, 25, 28, 29, 31, 32, 39, 45, 47, 58, 59, 65, and 71, have been identified as E3 ligases to regulate this pathway (Figure 5). Specifically, TRIM3 promotes K48-mediated ubiquitination and degradation of p53, leading to BC cell proliferation and suppression of apoptosis [85]. Similarly, TRIM23, TRIM24, TRIM25, TRIM28, TRIM31, TRIM32, TRIM39, TRIM47, TRIM59, and TRIM65, promote p53 degradation, leading to cell proliferation, metastasis, or resistance to anoikis or to other drugs in CRC, BC, HCC, MM, NSCLC, esophageal cancer, RCC, gastric cancers (GC), osteosarcoma [86-98]. TRIM59 functions as E3 ligase to induce p53 ubiquitination, leading to the promotion of cell proliferation, migration, invasion, cell cycle transition, and paclitaxel resistance in BC [43] (TRIM59's effect on cell cycle shown in Figure 2). In contrast, TRIM71 represses ovarian cancer cell growth in vitro and in vivo via ubiquitinating and degrading mutant p53 protein. This mutant p53 is different to wildtype p53 and is known to enhance cancer cell proliferation and metastasis [99].

Certain TRIMs can deactivate or activate p53 signaling by promoting ubiquitination of upstream regulators of this pathway. For example, TRIM29 (ataxia-telangiectasia group D, ATDC) suppresses p53 activation by increasing ubiquitin-proteasome degradation of tat-interactive protein 60 (Tip60), a cellular acetyltransferase of p53, and decreasing p53 acetylation at K120. This promotes the proliferation and oncogenic transformation of CRC cells [100]. Similarly, TRIM58 inactivates p53 by interacting with, ubiquitinating and degrading dead-box RNA helicase

3 (DDX3), a positive regulator of the p53/p21 signaling pathway. This leads to the increased doxorubicin resistance in BC cells [101]. TRIM21 destabilizes p53 to promote proliferation and metastasis of BC cells through mediating the ubiquitination and degradation of guanosine 5'-monophosphate synthase (GMPS) or human antigen R (HuR), two positive regulators of p53 stabilization or activation [102-104]. In contrast, TRIM13 stabilizes p53 through mediating ubiquitination and degradation of mouse double minute 2 (MDM2) (a E3 ligase of p53 to facilitate its degradation), ultimately promoting irradiation-induced apoptosis in normal cells [58].

Several other TRIMs activate p53 through ubiquitinating it. For instance, TRIM31 promotes stabilization and activation of p53 by directly facilitating K63-linked ubiquitination of p53 while inhibiting MDM2-mediated K48-linked ubiquitination through competitive inhibition of the MDM2-p53 interaction. This ultimately limits cell growth in BC [105]. The similar mechanism of stabilizing p53 by ubiquitinating it was employed by TRIM45 and TRIM3 (speculative) in glioblastoma cells or in CRC cells, respectively, to suppress proliferation and tumorigenicity [106, 107].

Therefore, TRIM E3 ligases play a crucial role in precisely controlling the p53 signaling pathway by either degrading, stabilizing, activating, or inactivating it. A potential therapeutic strategy for TRIM E3 ligases that degrade or inactivate p53 is to interfere with their interaction using small molecule drugs or peptides. On the other hand, for TRIM E3 ligases that can activate the p53 pathway, small molecule drugs or peptides that enhance their interaction can promote tumor cell death. Furthermore, advances in biomaterials have offered additional options, such as introducing genes of TRIM E3 ligases that stabilize p53 or small molecule drugs (mentioned above) into cells using nanobiomaterials to enhance p53 signaling activity and improve tumor treatment.

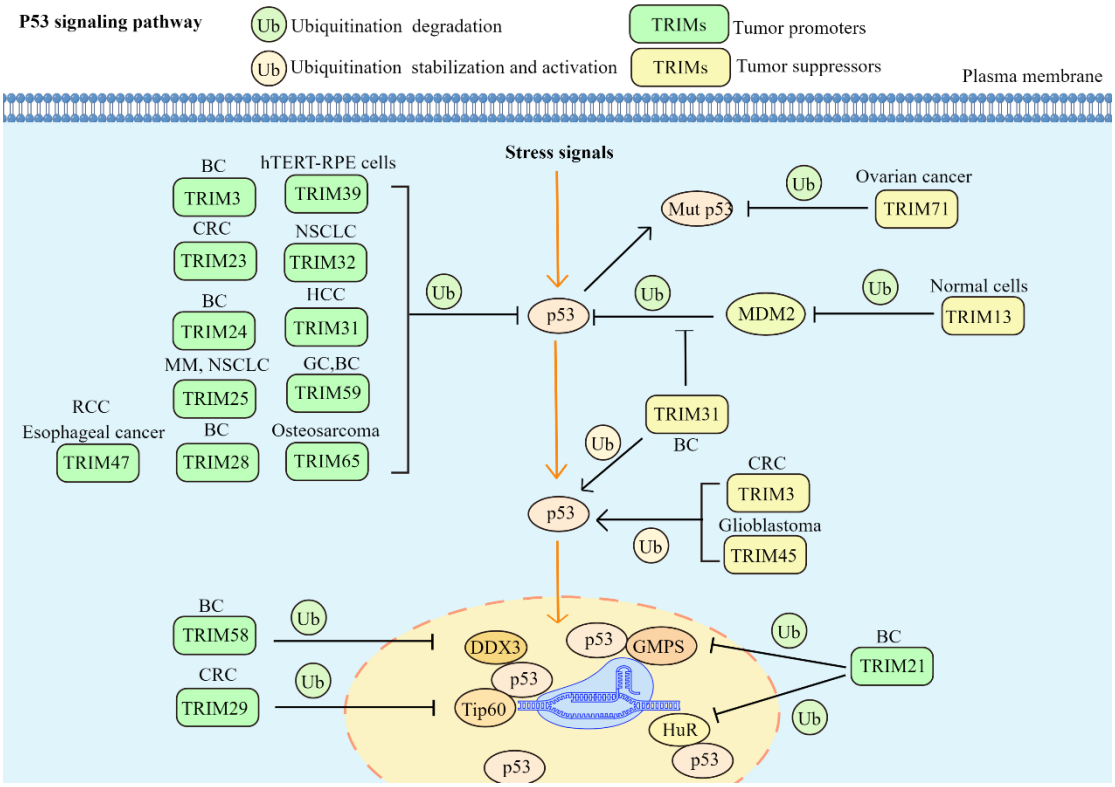

Figure 5. TRIMs as E3 ligase in regulating the p53 signaling pathway of cancer cells.

3.5 TRIMs as E3 ligase in regulating the ERK signaling pathway

TRIMs, including TRIM7, 9s, 11, 21, 37, and 59, play an important role as E3 ligases in regulating the ERK

signaling pathway (Figure 6). For instance, TRIM59 promotes ovarian cancer cell proliferation by ubiquitinating MAP kinase phosphatase 3 (MKP3) that dephosphorylates and inactivates ERK, ultimately leading to ERK activation and an increase in glycolysis [108]. In NSCLC cells, activated TRIM7 mediates Lys63-linked ubiquitination and stabilization of the AP-1 co-activator RACO-1 protein, which promotes tumor cell growth both in vitro and in vivo. This activation of TIRM7 is induced by Ras-Raf-MEK-ERK-MSK1 cascades-mediated TRIM7 phosphorylation [109]. Moreover, TRIM7 and TRIM37 activate p38 or ERK1/2 signaling, respectively, by facilitating polyubiquitination-mediated degradation of DUSP6, leading to subsequent growth and cell cycle progression of HCC and GC cells [42, 110]. Similar to TRIM7 and TRIM37, TRIM11 activates the ERK1/2 signaling by ubiquitinating DUSP6, which promotes glucose metabolism and NSCLC development in vitro and in vivo [111]. TRIM21 activates the ERK pathway by inducing polyubiquitination and degradation of small G protein signaling modulator 1 (SGSM1), and acts as a positive regulator of nasopharyngeal carcinoma (NPC) cell metastasis in vitro and in vivo [112]. In contrast, the TRIM9 short isoform (TRIM9s) suppresses the progression of glioblastoma by promoting K63-linked ubiquitination and stabilization of mitogen-activated protein kinase kinase 6 (MKK6), thereby enhancing p38 signaling that suppresses glioblastoma progression [113]. Furthermore, a positive feedback loop generates since MKK6 can also stabilize TRIM9s by facilitating p38-mediated TRIM9s Ser76/80 phosphorylation [113].

Targeting the ERK signaling pathway can be an effective cancer treatment strategy. This can involve inhibiting upstream regulators like RAF and MEK, or downstream effectors. The ERK pathway may have different roles at various stages of tumorigenesis, making precise intervention attractive. Given above mentioned researches, TRIM protein, as an E3 ligase, primarily promotes the activation of the ERK signaling pathway. Thus, screening small molecule drugs or peptide synthetics that inhibit their interaction could be a promising therapeutic strategy.

3.6 TRIMs as E3 ligase in regulating the STAT3 signaling pathway

TRIM8, 14, and 52 positively regulate the STAT3 signaling pathway by ubiquitinating and degrading specific inhibitors of STAT3 (Figure 6). For example, TRIM8 amplifies tumorigenesis in NIH3T3 cells and maintains stemness of glioblastoma stem-like cells (GSCs) by interacting with, ubiquitinating and degrading protein inhibitor of activated STAT3 (PIAS3), an inhibitor of STAT3 activation [114, 115]. Similarly, TRIM14, TRIM6 and TRIM52 interact with, ubiquitinate and degrade suppressor of cytokine-signaling-1 (SOCS1), SOCS2 and Src homology 2 domain-containing protein tyrosine phosphatase 2 (SHP2), respectively, three negative regulators of STAT3 activation. This leads to the activation of STAT3 signaling and ultimately promotes cell proliferation or metastasis of human papillary thyroid carcinoma and CRC, respectively [116-118].

Abnormal STAT3 activation can promote tumor cell growth and metastasis, making it a promising target for cancer treatment. Current efforts to develop more effective and specific inhibitors and explore combination therapies, such as combining STAT3 inhibitors with chemotherapeutic agents or immune checkpoint inhibitors, offer hope for improved outcomes in cancer patients. The inhibitory effect of TRIMs on the STAT3 pathway mentioned above suggests that reducing their interaction with small molecule drugs would effectively deactivate STAT3 signaling and benefit cancer treatment.

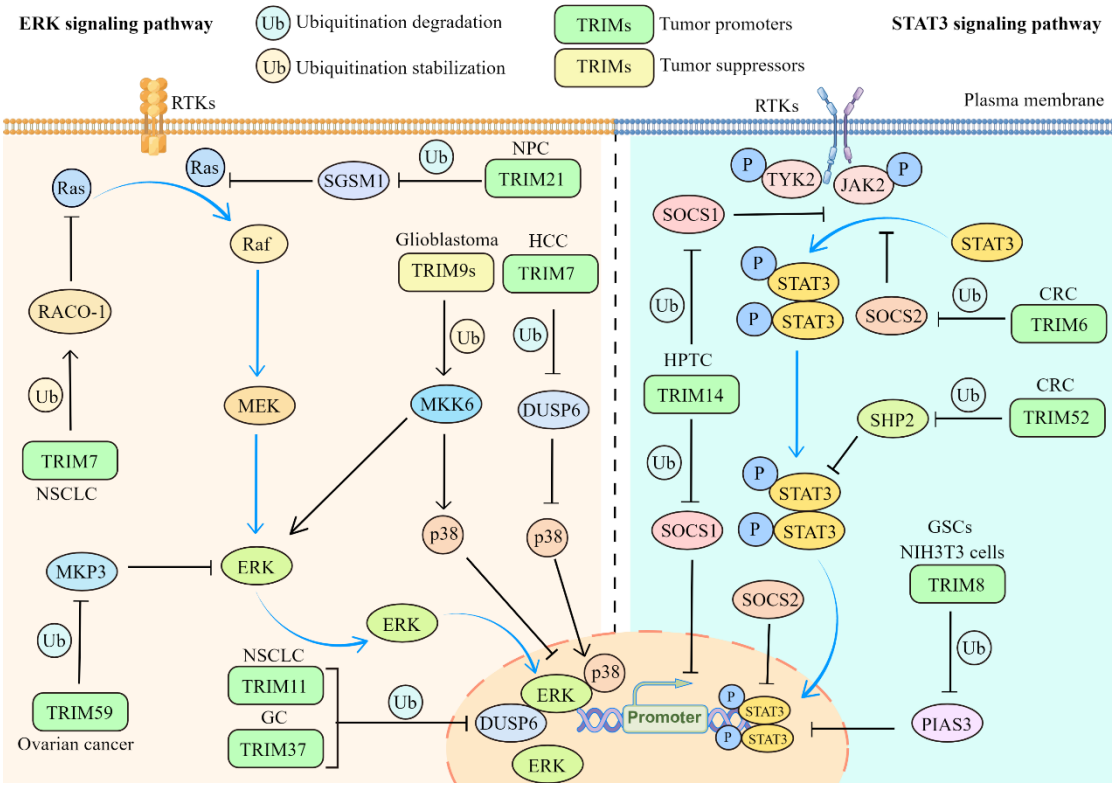

Figure 6. TRIMs as E3 ligase in regulating ERK and STAT3 signaling pathways of cancer cells.

3.7 TRIMs as E3 ligase in regulating the Wnt/β-catenin signaling pathway

Currently, only a few TRIM proteins, including TRIM11, 27, 29, 33, 36, 50, 58, and 65, have been identified as E3 ligases in cancer development by regulating the Wnt/β-catenin signaling pathway (Figure 7). The activation of this pathway plays a crucial role in the oncogenic process of tumor initiation and development [119]. TRIM11, TRIM27, and TRIM65, regulate this pathway through promoting ubiquitination and degradation of its inhibitors. For instance, TRIM11 and TRIM65 act as oncogenes to promote proliferation and metastasis in lymphomas and GC, or in HCC, respectively, by binding to and promoting ubiquitination degradation of axis inhibition protein 1 (Axin1), a negative regulator of the Wnt/β-catenin signaling, which leads to the increased expression of β-catenin, Cyclin D1 or c-Myc[120-122]. Additionally, TRIM11 interacts with and ubiquitinates another negative regulator of the Wnt/β-catenin signaling, dishevelled-associating protein with a high frequency of leucine residues (Daple), to promote p62-selective autophagic degradation of Daple, eventually increasing DDP chemoresistance in nasopharyngeal carcinoma [123]. Similarly, TRIM27 ubiquitinates and degrades a suppressor of the Wnt/β-catenin pathway, transcriptional factor SIX homeobox 3 (SIX3), to promote cell proliferation and metastasis in NSCLC [124].

Ataxia-telangiectasia group D complementing gene (ATDC), also named TRIM29, promotes cellular proliferation in vitro and PC growth and metastasis in vivo [125]. Mechanically, ATDC uses its coiled-coil domain, including amino acids 260-348, to interact with and stabilize Disheveled-2 (Dvl-2), a negative regulator of glycogen synthase kinase 3β in the Wnt/β-catenin pathway. It also binds to components destructing β-catenin to stabilize β-catenin [125]. In contrast to the promotive role of other TRIMs in cell growth, TRIM33, TRIM36, TRIM50, and TRIM58 inhibit cell proliferation of brain cancer, ESCC, and GC, respectively, by interacting with, ubiquitylating and degrading β-catenin [126-129]. For TRIM33, its degradation of β-catenin is dependent on β-catenin phosphorylation at Ser715 by protein kinase Cδ [126].

In brief, a few TRIM E3 ligases bind to and degrade inhibitors of the Wnt/β-catenin pathway to promote cancer

development. In light of this, a possible avenue of research would be to screen for small molecule drugs that can inhibit this interaction, thereby inhibiting the β-catenin pathway and reducing tumor progression.

3.8 TRIMs as E3 ligase in regulating the TGF-β1/SMAD2/3/4 signaling pathway

TRIM37, 47, 52, and 62 are E3 ligases that play a role in regulating cancer cell proliferation and metastasis through the TGF-β1/SMAD2/3/4 signaling pathway (Figure 7). TRIM37 is critical for promoting metastatic potential and EMT process of RCC cells by binding to and ubiquitinating histone H2A, leading to the activation of TGF-β1/SMAD2/3 signaling pathway [130]. TRIM47 interacts with SMAD4 and promotes its ubiquitination and degradation to accelerate CRC proliferation and metastasis both in vitro and in vivo, as well as 5-FU chemoresistance [131]. TRIM52 enhances cell proliferation, migration and invasion of HCC cells through interacting with and ubiquitinating Mg^{2+}/Mn^{2+} dependent 1A (PPM1A), thereby upregulating the expression of matrix metalloproteinase 2 (MMP2) and phosphorylated SMAD2/3 [132]. In contrast, TRIM62, also called DEAR1, blocks TGF-β/SMAD3 signaling through binding to and ubiquitinating SMAD3, suppressing the process of EMT driven by TGFβ in BC [133, 134].

The TGF-β/SMAD signaling pathway has been found to have both positive and negative effects on cancers, highlighting its complex role in regulating cancer progression. The impact of TRIMs on cancer development can vary depending on the regulatory mechanism and specific cancer cell type. Thus, additional research is necessary to determine the association of TRIMs with this pathway in carcinogenesis.

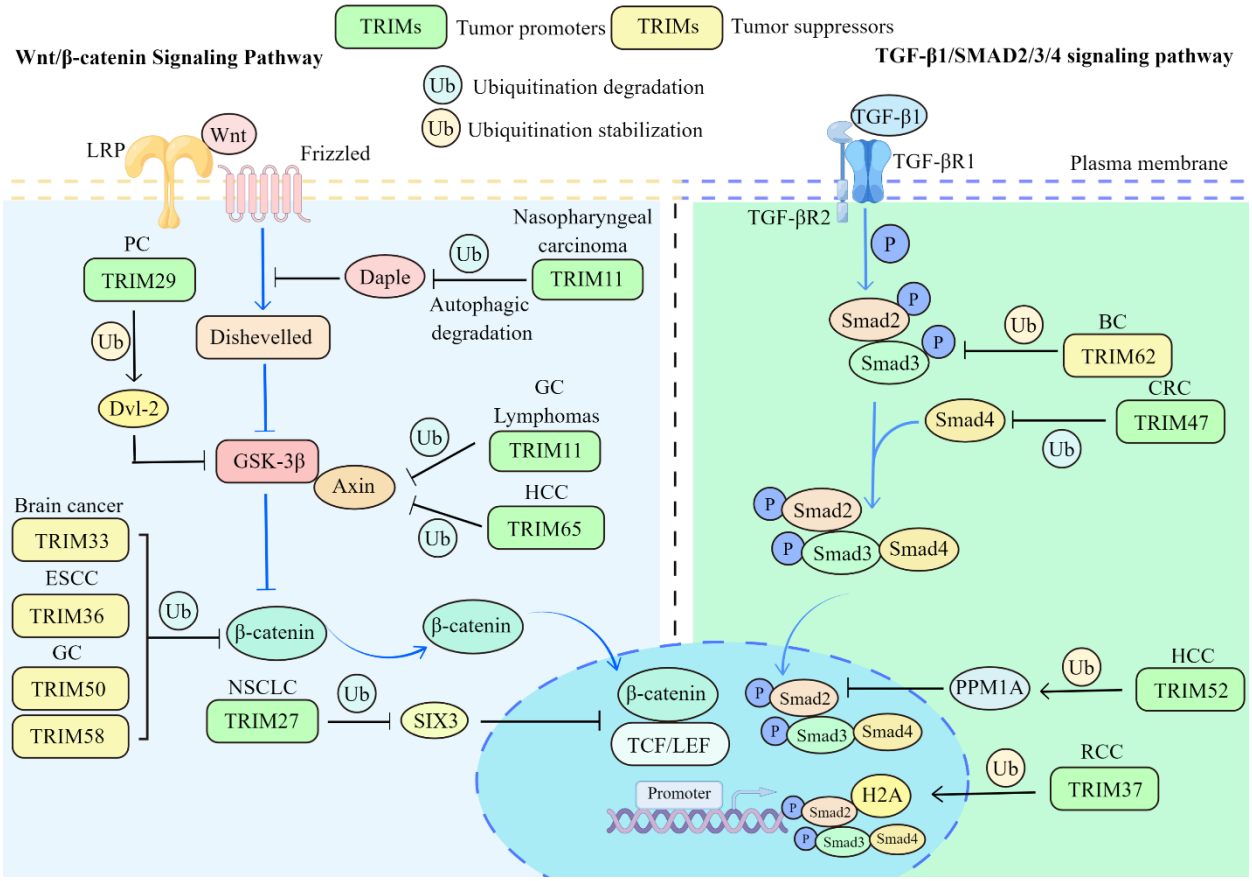

Figure 7. TRIMs as E3 ligase in regulating the Wnt/β-catenin and TGF-β1/SMAD2/3/4 signaling pathways of cancer cells.

3.9 TRIMs as E3 ligase in regulating metabolic reprogramming

Researches have provided increasing evidences that cancer cells undergo metabolic reprogramming, particularly in terms of glucose metabolism. The "Warburg effect" is a well-known phenomenon in which cancer cells increase their glucose uptake and prefer glycolysis over oxidative phosphorylation, even when oxygen is present [12]. Several TRIMs, including TRIM21, 22, 27, 28, 29, 36,38, and 47, play a crucial role as E3 ligases in regulating metabolic reprogramming (Figure 8). For instance, TRIM21 suppresses glycolysis, tumorigenesis and metastasis of RCC by promoting ubiquitination and degradation of hypoxia-inducible factor 1-α (HIF-1α) [135]. In BC cells, TRIM21 inhibits de novo fatty acid synthesis by triggering ubiquitination and degradation of fatty acid synthase (FASN), thereby inhibiting cell proliferation, which can be reversed by the nuclear neddylated PTEN [136]. TRIM22 inhibits the Warburg effect by interacting with nuclear factor erythroid-derived 2-related factor 2 (Nrf2) and promoting ubiquitination and degradation of Nrf2, a redox regulator, leading to the inhibition of proliferation and metastasis of osteosarcoma cells in vitro and in vivo [137]. TRIM36 blocks glycolysis of neuroendocrine prostate cancer (NEPC) by binding to hexokinase 2 (HK2), inducing lys48-mediated ubiquitination and degradation of HK2, which results in the downregulation of glutathione peroxidase 4 (GPx4) and an increase in ferroptosis [138]. TRIM38 inhibits glucose uptake by interacting with glucose transporter type 1 (GLUT1) and promoting its ubiquitous degradation, leading to the suppression of bladder cancer malignant features such as proliferation, migration and stemness [139].

On the other hand, TRIM27 can accelerate glucose uptake through mediating the polyubiquitination of PTEN and subsequently activating the AKT signaling in ESCC cells [54]. TRIM28 and TRIM47 promoted aerobic glycolysis and cell growth of HCC and PC, respectively, by direct binding and promotion of ubiquitination and degradation of fructose-1,6-biphosphatase (FBP1), a tumor suppressor [140, 141]. Interestingly, the MAGE-A3/6-TRIM28 complex maintains tumor cell growth by ubiquitinating and degrading AMP-activated protein kinase α1 (AMPKα1). This is because the AMPK pathway, which restricts growth, promotes catabolic processes and suppresses anabolic processes to regain energy homeostasis upon metabolic stress [142]. TRIM29 enhances PKM2-mediated aerobic glycolysis by directly targeting pyruvate kinase isozymes M1 (PKM1) to promote its ubiquitination and degradation, leading to a reduction in the PKM1/PKM2 ratio and an increase in the malignant phenotype of CRC in vitro and in vivo [143].

To conclude, TRIM E3 ligases can either exert a positive or negative impact on reprogramming cancer cell metabolism by ubiquitinating and degrading several key regulators. Utilizing small molecule drugs to regulate their interactions or adopting the PROTACs technique could potentially serve as a promising treatment option. Furthermore, more research is needed to fully comprehend how TRIMs function as E3 ligases in controlling glycolysis in cancer.

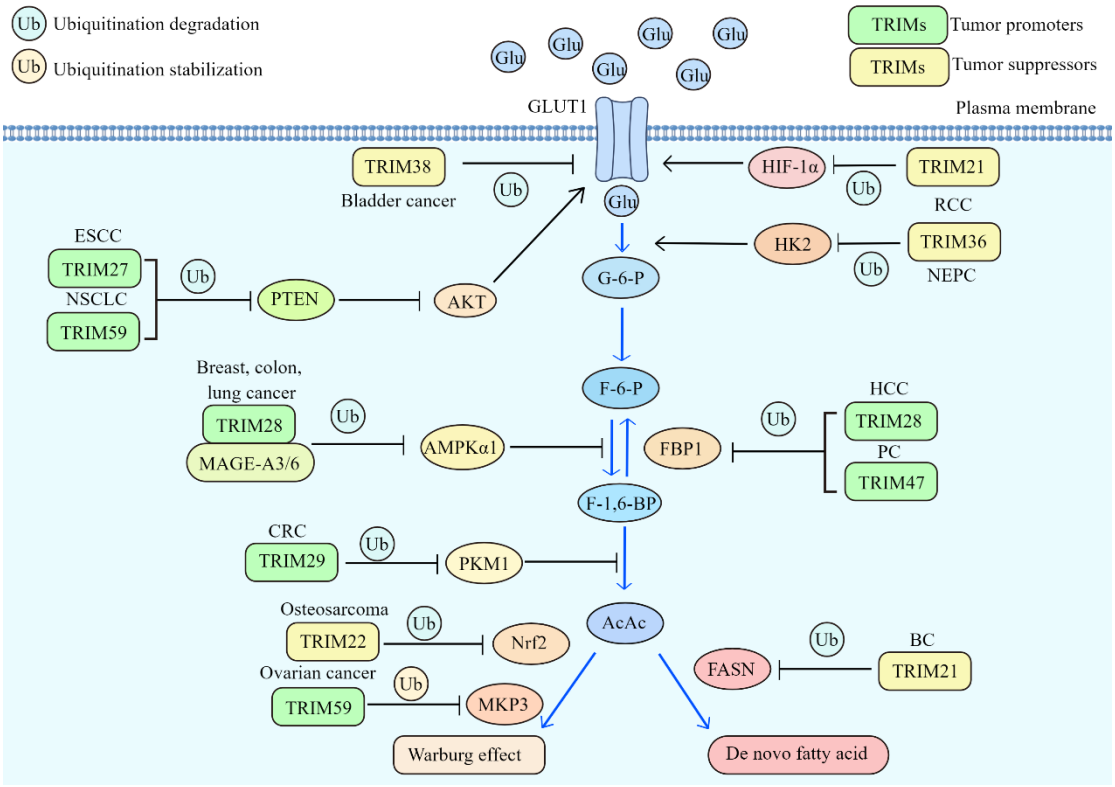

Figure 8. TRIMs as E3 ligase in regulating metabolic reprogramming of cancer cells.

3.10 TRIMs as E3 ligase in regulating other various pathways.

Certain TRIMs are essential E3 ligases in regulating various pathways that contribute to cancer development (Table 1). For example, TRIM11 interacts with estrogen receptor α (ERα) through its RING domain to facilitate mono-ubiquitination and stability of ERα, ultimately accelerating BC cell proliferation and migration [144]. TRIM29 and TRIM32 also control protein stabilization by binding to and stabilizing yes-associated protein 1 (YAP1) or retinoic acid receptorα (RARα), via regulating their ubiquitination, ultimately leading to promotion or inhibition of cancer development, respectively [145-147].

TRIM16 mediates proteasomal degradation of glioma-associated oncogene homolog 1 (Gli-1) protein, a crucial molecule in the sonic hedgehog (SHH) pathway, to inhibit BC stem cell properties [148]. Similarly, TRIM16 can bind to zinc finger E-box binding homeobox 2 (ZEB2) or snail family transcriptional repressor (Snail) to promote their ubiquitination and proteasomal degradation, leading to suppression of metastases of HCC cells or CRC cells [149, 150].

TRIM21 facilitates ubiquitination and degradation of several modulators including POU class 2 homeobox 1 (OCT1), Snail, Zinc finger and homeobox 3 (ZHX3), Src, or zeste homolog 1 (EZH1), to suppress the growth or metastasis of cancer cells [151-155]. On the other hand, TRIM21 acts as E3 ubiquitin ligase for p62 to positively regulate HCC progression [156].

TRIM25 exhibits both positive or negative role in carcinogenesis. On the one hand, TRIM25 facilitates the ubiquitination and degradation of non-phosphorylated glycogen synthase kinase-3β (GSK3β) or Kelch-like ECH-associated protein 1 (Keap1), which eventually promotes cancer development [157, 158]. On the other hand, TRIM25 promotes the ubiquitination and degradation of insulin-like growth factor 2 mRNA-binding protein (IGF2BPs), Ets related gene (ERG), specificity protein 1 (SP1), DEAD-box helicase 5 (DDX5), or metastasis associated

1 protein (MTA1), leading to the inhibition of growth and metastatic capacity of tumor cells [159-163].

TRIM50 represses proliferation and metastasis of cancers through directly binding to Snail or Src and promoting K48-mediated polyubiquitination and degradation of them [164, 165]. In contrast, TRIM65 enhances metastasis of cancers by binding to and facilitating the ubiquitination and degradation of Rho GTPase-activating protein 35 (ARHGAP35) and annexin A2 (ANXA2), respectively [166, 167]. The impacts of other TRIM E3 ligases on proliferation, metastasis and cell death of cancer cells are documented in Table 1.

Table 1. TRIM E3 ligases involved in cancer proliferation by regulating other various pathways

TRIM E3 ligases	Cancer type	Mechanism of TRIMs on their targets	Effect of TRIMs on cancer development
TRIM2	Epithelial ovarian cancer	Ubiquitination and degradation of Bim	Promoter [168, 169]
TRIM2	BC	Ubiquitination and degradation of Bim	Promoter [170]
TRIM2	Lung adenocarcinoma	Deubiquitination and stabilization of Snail1	Promoter [171]
TRIM2	LSCC	Ubiquitination of Vimentin (supposed)	Suppressor (supposed) [172]
TRIM6	BC	Ubiquitination and degradation of STUB1	Promoter [173]
TRIM11	BC	Mono-ubiquitination and stabilization of ERα	Promoter [144]
TRIM11	Inflammation-associated colon cancer	Ubiquitination and autophagy-driven degradation of RIPK3	Promoter [174]
TRIM13	BC	Ubiquitination and degradation of Nur77	Promoter [175]
TRIM13	NSCLC	Ubiquitination and degradation of p62	Suppressor [176]
TRIM15	NSCLC	Ubiquitination and degradation of Keap1	Promoter [177]
TRIM15	PC	Polyubiquitination and degradation of APOA1	Promoter [178]
TRIM16	BC	Ubiquitination and degradation of Gli-1	Suppressor [148]
TRIM16	HCC	Ubiquitination and degradation of ZEB2	Suppressor [149]
TRIM16	CRC	Ubiquitination and degradation of Snail	Suppressor [150]
TRIM17	BC	Ubiquitination and degradation of ZWINT	Suppressor [179]
TRIM17	NSCLC	Ubiquitination and degradation of RBM38	Promoter [180]
TRIM21	CRC	Ubiquitination and degradation of OCT1	Suppressor [151]
TRIM21	BC	Ubiquitination and degradation of Snail	Suppressor [152]
TRIM21	UCB	Ubiquitination and degradation of ZHX3	Suppressor [153]
TRIM21	CTCs	Ubiquitination and degradation of Src	Suppressor [154]
TRIM21	GC	Ubiquitination and degradation of EZH1	Suppressor [155]
TRIM21	HCC	Ubiquitinating p62	Promoter [156]
TRIM23	CRC	Ubiquitination and degradation of PES1	Promoter [181]
TRIM25	HCC	Ubiquitination and degradation of Keap1	Promoter [158]
TRIM25	Triple-negative BC	Proteasomal degradation of non-phosphorylated GSK3β	Promoter [157]
TRIM25	NSCLC	Ubiquitination and degradation of IGF2BPs	Suppressor [159]

TRIM25	Prostate cancer	Polyubiquitinating and degrading Ets related gene (ERG)	Suppressor [160]
TRIM25	GC	Ubiquitination and degradation of SP1	Suppressor [161]
TRIM25	Thyroid cancer	Ubiquitination and degradation of DDX5	Suppressor [163]
TRIM25	HCC	Ubiquitination and degradation of MTA1	Suppressor [162]
TRIM25	GBM	Ubiquitination of keap1	Promoter [182]
TRIM27	Non-TNBC cells	Ubiquitination and degradation of p21	Promoter [183]
TRIM28	Melanoma cells	Ubiquitination and degradation of BCL2A1	Suppressor [184]
TRIM29	PC	Ubiquitination and stabilization of YAP1	Promoter [145]
TRIM32	Leukemia, neuroblastoma, embryonal carcinoma	Ubiquitination and stabilization of RARα	Suppressor [146,147]
TRIM32	Squamous cell carcinoma	Ubiquitination and degradation of ABI2	Promoter [185,186]
TRIM32	HEK293T cells	Ubiquitination and degradation of XIAP	Suppressor [187]
TRIM35	diffuse large B-cell lymphoma (DLBCL)	Ubiquitination and degradation of CLOCK	Suppressor [188]
TRIM36	Lung adenocarcinoma	Ubiquitination and degradation of RAD51	Suppressor [189]
TRIM37	TP53-mutant TNBC	Mono-ubiquitination of histone H2A	Promoter [190]
TRIM44	Multiple myeloma	Deubiquitination and stabilization of HIF-1α	Promoter [191]
TRIM48	NSCLC and HEK293A cells	Polyubiquitination and degradation of PRMT1	Suppressor [192]
TRIM50	HCC	K-48 linked polyubiquitination and degradation of Snail	Suppressor [164]
TRIM50	Ovarian cancer	K48-mediated polyubiquitination and degradation of Src	Suppressor [165]
TRIM50	PC	Ubiquitination and degradation of Snail1	Suppressor [193]
TRIM54	GC	K63-linked ubiquitination and degradation of filamin C (FLNC)	Promoter [194]
TRIM55	CRC	Ubiquitination and degradation of c-Myc	Suppressor [195]
TRIM56	Ovarian cancer	Ubiquitination and degradation of Vimentin	Suppressor [196]
TRIM56	GBM	Deubiquitination and stabilization of cIAP1	Promoter [197]
TRIM59	NSCLC	Ubiquitination and degradation of ABHD5	Promoter [198]
TRIM65	CRC	Ubiquitination and degradation of ARHGAP35	Promoter [166]
TRIM65	Bladder cancer	Ubiquitination and degradation of ANXA2	Promoter [166]
TRIM71	Human embryonal carcinoma cells	Ubiquitination and degradation of Lin28B	Suppressor [199]
TRIM72	Uveal melanoma	Ubiquitination and degradation of O6-methylguanine DNA methyl transferase (MGMT)	Suppressor [200]

4. Discussion

In this review, we provide a summary of recent progress made in understanding the role of TRIMs as E3 ligases in cancer cell proliferation, metastasis, and death. In many types of cancers, specific TRIMs have been found to ubiquitinate and degrade important regulators of various signaling pathways to control the cell growth, cell death, and metastasis. These controlled signaling pathways include Wnt/β-catenin, PI3K/AKT, NF-κB, p53 signaling, ERK signaling, as well as STAT3 signaling, and many others. Additionally, TRIM-mediated ubiquitination modification can also activate, inactivate, or stabilize target proteins. These findings lay a foundation for the development of E3 ligase-based treatment strategy, such as the PROTACs technique.

Multiple TRIMs have been identified as E3 ligases that participate in the same signaling pathway by ubiquitinating either the same or different nodes, partly depending on the cellular context. It is possible that some studies have only identified one TRIM protein in heterodimers or multimers of TRIMs, while other research has identified different subtypes of TRIM complexes. Additionally, TRIMs may have the ability to sensitively sense the internal and external environments of cells, forming diverse groups of TRIMs that regulate protein expression equilibrium in response to stress or stimuli by selectively ubiquitinating specific substrate proteins. Therefore, identifying individual members of these diverse TRIM groups can help us to better understand the pathological mechanisms of cancer progression and potentially identify combined markers. One possible method of grouping members of TRIM proteins could be through bioinformatics analysis.

Although a large body of literature has reported the association of TRIM family members with cancers, only a small part has examined the specific molecular mechanisms involved. Thus, conducting more in-depth studies on other members of the TRIM family is imperative to enhance the application of TRIM family-related research in tumor diagnosis and prevention. To better determine the specific substrate of TRIM E3 ligases, immunoprecipitation/GST pull-down combined with mass spectrometry analysis is a highly effective technique for identifying substrate pools. Furthermore, it is also important to identify upstream regulators of the E3 ligases TRIMs, including transcription factors, miRNAs, lncRNAs, circRNAs, and other regulators that activate or deactivate them. This knowledge could potentially provide new ideas for cancer treatments targeting both TRIMs and their upstream regulators.

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Conflict of interest

All authors declare that there are no conflicts of interest.

Author contributions

Investigation: Gui Zhang, Yunfang Zhang, Luxuan Chen; Writing-original draft: Gui Zhang, Xuejuan Gao; Writing – review & editing: Yunfang Zhang, Langxia Liu, Xuejuan Gao.

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