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Review Article

Unveiling the multifaceted functions of TRIM proteins in glioma pathogenesis

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ABSTRACT

Gliomas, the most prevalent malignant primary brain tumors in adults, represent a heterogeneous group of neoplasms characterized by poor prognosis and limited therapeutic options, particularly in high-grade cases. Understanding the molecular mechanisms underlying glioma pathogenesis is crucial for developing novel and effective treatment strategies. In recent years, increasing attention has been directed toward the tripartite motif (TRIM) family of proteins, a class of E3 ubiquitin ligases, due to their significant roles in glioma development and progression. This review comprehensively explores the diverse functions of TRIM proteins in gliomas, including their expression patterns, prognostic significance, and mechanisms of action that are both ubiquitination-dependent and -independent. By synthesizing current knowledge, we aim to elucidate the role of TRIM proteins in glioma pathogenesis and identify potential therapeutic targets within this protein family.

Introduction

The tripartite motif (TRIM) proteins are a group of subordinate members of the RING-type E3 ubiquitin ligases. In humans, more than 70 TRIM proteins have been identified, most of which are characterized by a unique structure consisting of one RING-finger domain, one or two B boxes domains, and an associated coiled-coil region [1] (Fig. 1). Recent studies have demonstrated that many TRIM proteins play pivotal roles in multiple physiological and pathophysiological processes, including viral infections, carcinogenesis, inflammatory and neuropsychiatric disorders [2–6].

Gliomas, the most prevalent malignant primary brain tumors in adults, are classified into grades 1–4 according to the world Health Organization (WHO) criteria [7]. The overall 5-year survival rate for patients with gliomas is approximately 35 %, whereas for glioblastoma (WHO Grade 4), the five-year survival rate is only about 5 % [8–10]. Despite continuous advancements in the treatment of glioblastoma in recent years, including traditional methods such as surgical intervention, radiation therapy, and chemotherapy, as well as newly proposed treatments like immunotherapy and electric field therapy, the survival rates for patients with glioblastoma have not seen significant improvement [11–13]. This underscores the critical need for a deeper understanding of glioma pathogenesis and the development of novel therapeutic strategies to improve patient outcomes. Emerging evidence has implicated TRIM proteins in multiple aspects of glioma pathobiology, including tumorigenesis, invasiveness, proliferation, stemness maintenance, therapy resistance, and tumor recurrence [14–18]. Moreover, targeting TRIM proteins has garnered considerable attention as a therapeutic strategy, with some pre-clinical experiments showing promising results [19–21]. This review provides a comprehensive analysis of the multifaceted roles of TRIM proteins in glioma, encompassing both their ubiquitin ligase functions and non-ubiquitination activities. Furthermore, we discuss recent developments and future prospects in targeting TRIM proteins as an innovative therapeutic approach for glioma treatment.

A survey of the structural and functional features of TRIM proteins

Structure and function of the N-terminal region

The nomenclature of the tripartite motif (TRIM) protein family stems from the presence of a RING domain, one or two B-box domains and a coiled-coil region situated at the N-terminus. The TRIM proteins are commonly classified as E3 ubiquitin ligases due to the presence of their RING domain. In detail, the RING finger domain typically consists of

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10–20 amino acid residues located in the N-terminal region, organized by an arrangement of cysteine and histidine [21,22]. Specifically, the N-terminal region contains a pair of cysteine residues, while the C-terminal region contains a pair of histidine residues, which combine to form a cavity that can bind two zinc atoms [21,23]. This binding event is crucial for mediating ubiquitination reactions of either the protein itself or various substrates. Consequently, the RING finger domain has become a hallmark of many E3 ubiquitin ligases. However, TRIM proteins belonging to the UC subfamily lack a RING domain, which implies the absence of E3 ubiquitin ligase activity [21,24].

The B-box domains, which are categorized into two types (B-box1 and B-box2) based on the presence of one or two distinct zinc-binding motifs, can either enhance the catalytic activity of the RING domain or facilitate substrate ubiquitination independently [25]. In detail, the B-box1 and B-box2 domains exhibit limited sequence similarity, with the exception of conserved cysteine and histidine residues, which are present in eight and seven residues, respectively, across most B-box1 and B-box2 domains [25]. Moreover, the B-box1 domain, spanning from Val117 to Pro164, is composed of a three-turn alpha-helix, two short beta-strands, and three beta-turns [25,26]. This domain is known to bind two zinc atoms, with one being coordinated by cysteine residues 119, 122, 142, and 145, while the other is coordinated by cysteine 134, 137, and histidine 150 and 159. On the other hand, the B-box2 domain consists of a short alpha-helix and a structured loop that contains two short anti-parallel beta-strands [25,26]. Despite the lack of primary sequence similarity with the B-box1 and RING structures, the B-box2 domain adopts a tertiary structure similar to them. In addition, the B-box2 domain coordinates two zinc atoms in a 'cross-brace' pattern, with one being coordinated by Cys175, His178, Cys195, and Cys198 and the other being coordinated by Cys187, Asp190, His204, and His207[26].

The coiled-coil domain, which is highly conserved across all TRIM proteins and frequently positioned downstream of the B-Box2 domain,

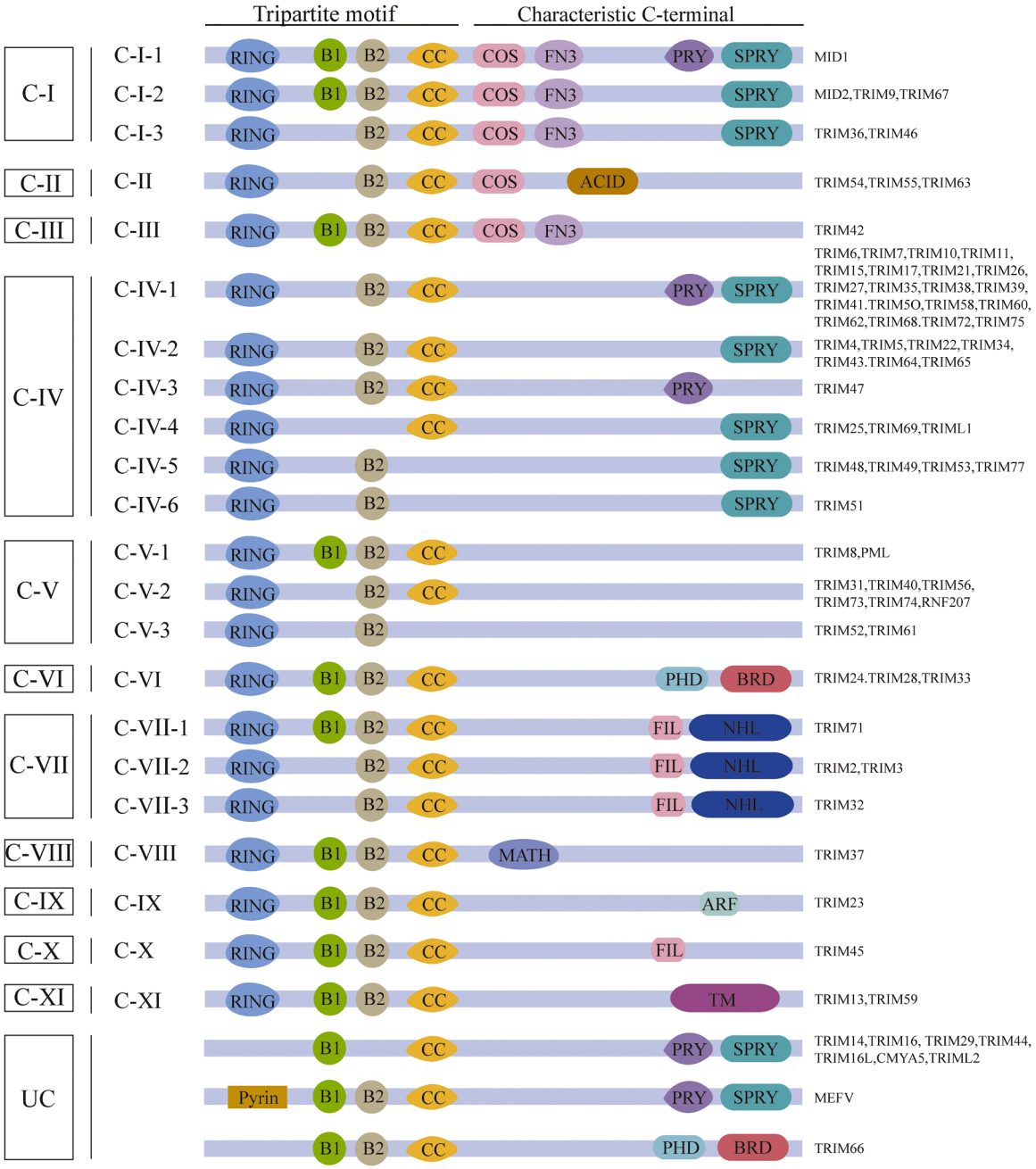

Fig. 1. Schematic representation of TRIM protein domain structures.

acts as a conserved structural scaffold that facilitates the formation of anti-parallel homodimers or heterodimers [27,28]. Previous research has identified a pattern of conserved hydrophobic amino acids, with leucine being the most frequently represented residue, within a contiguous helical structure of approximately 110 amino acids in the coiled-coil region of most TRIM proteins, indicating the conservation of the unique arrangement of heptad and hendecad repeats throughout the entire TRIM protein family [28].

Structure and function of the C-terminal region

While the N-terminal domains exhibit similarity across subtypes, the C-terminal domains of TRIM proteins differ among subfamilies, leading to classification into C-I to C-XI subtypes based on their unique C-terminal domains [29,30]. The C-terminal domains of TRIM proteins comprise various distinct domains, such as the Fibronectin type-III domain (FN3), COS domain, B30.2/SPRY domain (SPRY), PRY domain, acid-rich region (ACID), filamin-type I domain (FIL), NHL domain, PHD domain, Meprin and TRAF-homology domain (MATH), transmembrane region (TM), ADP-ribosylation factor family domain (ARF), and bromodomain (BRD) [27]. In detail, the PHD domain and the adjacent bromodomain contribute to DNA-binding properties and confer transcriptional regulation [31]. The COS domain is essential for microtubule binding, while the ARF domain regulates intracellular trafficking through GTP hydrolysis activity [29,31]. Prior studies have identified the prevalence of the fibronectin type III motif among cell surface proteins, suggesting its potential role in mediating molecular recognition processes [31]. The filamin-type I domain, characterized by its immunoglobulin-like structure, binds to several scaffolding, signaling, and transmembrane proteins, thus playing essential roles in regulating various cellular processes, including cell morphology, adhesion, migration, differentiation, and mechanosensing [32]. The PRY-SPRY domain has been identified as a critical component of innate immune responses and the recognition of certain proteins, while also playing a crucial role in subcellular localization of specific TRIM proteins [33]. For example, the interaction between the C-terminal SPRY domain of TRIM25 and the N-terminal CARDs of RIG-I facilitates the transfer of Lys 63-linked ubiquitin moiety to the N-terminal CARDs of RIG-I, leading to a significant enhancement in the downstream signaling activity of RIG-I [34]. Lastly, the Meprin and TRAF-homology domain, functioning to facilitate receptor binding and oligomerization, is capable of participating in various modular arrangements as an independent folding unit, determined by multimerization domains that are linked to it [31,35].

Expression pattern and prognostic value of TRIM proteins in glioma

Modulation of TRIM proteins in glioma

The expression of TRIM proteins in glioma is often altered through various mechanisms, including genetic alterations, DNA methylation and abnormal transcriptional activities at the gene level, regulation by non-coding RNAs such as mi-RNA, circRNAs, and lncRNA at the mRNA level, and post-translational modifications like ubiquitylation at the protein level.

Firstly, to investigate the genetic alterations of TRIM proteins in glioma, we utilized Cbioportal to analyze the occurrence of such alterations in the TCGA-LGG (Lower-grade glioma/514 patients) and TCGA-GBM (Glioblastoma/390 patients) cohorts, respectively [36,37]. The results show that the incidence of genetic modifications in patients diagnosed with LGG or GBM exhibits a similar pattern, with TRIM genes being altered in approximately 33 % of LGG patients (168 events among 514 patients) and 32 % of GBM patients (126 events among 390 patients). Among the TRIM genes examined, namely TRIM3(4 %), TRIM5 (4 %), TRIM6(4 %), TRIM21(4 %), TRIM22(4 %), TRIM28(4 %), TRIM34(4 %), TRIM68(4 %), TRIML1(4 %), and TRIML2(4 %), the mutation rates were relatively higher in LGG patients **(Figure S1)**, while in GBM patients, relatively higher mutation rates were observed in TRIM76(2.8 %), TRIM50(2.6 %), and TRIML1(2.6 %) **(Figure S2)**. Notably, TRIM3 gene is located within the chromosomal locus 11p15.5, and approximately 20 % of human glioblastoma samples demonstrate loss of heterozygosity in this region [38,39]. Despite the presence of an intact 11p15.5 locus in many GBM samples, analysis has revealed a lower than anticipated expression of TRIM3, indicating the potential involvement of other mechanisms in the regulation of TRIM3 expression [40]. Given that the 11p15 region is also prone to frequent dysregulated DNA methylation and loss of imprinting [41], it is possible that DNA methylation may play a role in the low expression of TRIM3. Interestingly, The TRIM8 gene is located on chromosome 10q24.3, which also is a region that exhibits frequent deletion or loss of heterozygosity in GBM [42]. Despite its frequent hemizygous deletion in GBM, TRIM8 demonstrates similar expression levels in GBM samples as in normal brain tissue [43]. A plausible mechanism for this phenomenon is the activation of STAT3, which upregulates TRIM8 and thus enables the normalization of TRIM8 expression in the context of hemizygous gene deletion [43]. In addition, certain transcription factors linked to the aberrantly activated signaling pathways in glioma have the potential to regulate the expression of TRIM proteins. For instance, TRIM19 (PML) transcription is suppressed by transcription factor SOX2 in GBM cells [44]. Additionally, in EGFR/EGFRvIII-driven gliomas, the activation of STAT3 by EGFR/EGFRvIII enhances the transcription of TRIM24[14]. TRIM59 transcription is activated by EGFR/EGFRvIII through transcription factor SOX9 in GBM cells [45]. Similarly, our previous work has demonstrated that the transcription factor SP1 can directly bind to the −91 to −82 region of the TRIM56 promoter, resulting in the activation of TRIM56 transcription [46].

Secondly, microRNA (miRNA) has the ability to modulate the expression of TRIM proteins through various mechanisms, including inhibition of mRNA translation and induction of mRNA decay. For instance, the expression of TRIM8 is regulated by miR-17 through direct binding to the 3′-untranslated region (3′-UTR) of TRIM8 [47]. The miR-491 functions as a tumor suppressor by binding to the 3′-UTR of TRIM28 and subsequently downregulating TRIM28 protein levels [48]. Similarly, miR-101–3p [49] and miR-623 [50] directly inhibits TRIM44 translation by binding to its 3′-UTR. In addition, both circular RNAs and long non-coding RNAs (lncRNAs) have the ability to function as miRNA sponges, leading to the inhibition of miRNA activity. For example, circular RNA Circ_0000741 functions as a competitive endogenous RNA by sequestering miR-379–5p, thereby relieving its inhibitory effect on TRIM14 expression [51]. Circ_0005198 acts as a sponge for miR-198, which binds to the 3′UTR of TRIM14, thus elevating TRIM14 expression [52]. In addition, TRIM14 was reported to be directly regulated by miR-6893–3p, whereas the lncRNA CHASERR can act as a sponge for miR-6893–3p thus indirectly affecting TRIM14[53]. Interestingly, TRIM24 has been reported as a downstream target of both miR-137 [54] and miR-138–2–3p [55], with lncRNA NCK1-AS1 upregulating TRIM24 expression by repressing miR-137 and miR-138–2–3p. TRIM44 is a target of miR-194–5p, and circ_0030018 upregulates TRIM44 by sequestering miR-194–5p [56]. Similarly, LINC01857 functions as a putative competing endogenous RNA that sequesters miR-1281, thereby reducing its expression levels and ultimately upregulating TRIM65 expression [57].

Thirdly, expression of TRIM proteins can be altered directly at protein level in gliomas. For example, MAPKK6 exerts a stabilizing effect on TRIM9 protein through the promotion of phosphorylation at Ser76/80 residues via the p38 pathway, thereby impeding degradation via the ubiquitin-proteasome pathway [58]. In addition, USP11 can stabilize and upregulate TRIM19 level by serving as a deubiquitinating enzyme for TRIM19 [59]. The SP140 inhibitor GSK761 was reported to inhibit the mRNA and protein level of TRIM22 [60]. LncRNA PVT1 increases the protein level of TRIM24 by deubiquitinating TRIM24 through COPS5 and interacting directly with TRIM24 [61]. The abnormal

upregulation of MAGED4B has been shown to promote glioma progression by enhancing the ubiquitination and subsequent degradation of TRIM27 [62].

Overall, in the context of glioma, multiple lines of evidence indicate that the expression levels of TRIM3 [63], TRIM8 [47], TRIM9s [58], TRIM17 [64], TRIM33 [65], TRIM45 [66], and TRIM48 [67] are down-regulated in comparison to normal brain tissue, while up-regulation is observed for TRIM6 [68–70], TRIM7 [71], TRIM11 [72], TRIM14 [53,73], TRIM19 [74], TRIM21 [75], TRIM22 [76], TRIM24 [77], TRIM25 [78,79], TRIM27 [80], TRIM28 [81], TRIM31 [82,83], TRIM37 [84,85], TRIM44 [86], TRIM47 [87,88], TRIM56 [89], TRIM65 [57], TRIM66 [90], and TRIM67 [91]. Notably, the expression of TRIM8 in glioma remains controversial, as two separate studies have reported conflicting findings. Specifically, one study found that TRIM8 expression in glioblastoma is similar to that in normal brain tissue, while the other study reported a decrease in TRIM8 expression in high-grade glioma [43,47].

Prognostic significance of TRIM proteins in glioma

The search for biomarkers has been a hot issue in tumor research [92–94]. To assess the prognostic significance of TRIM proteins in gliomas, we conducted a univariate Cox analysis within the TCGA-LGG, TCGA-GBM, and Pan-glioma cohorts. Our analysis revealed that numerous TRIM proteins demonstrated significant prognostic value in the LGG cohort **(Figure S3)**. However, in the GBM cohort, only TRIM4, TRIM13, and TRIM56 exhibited significant prognostic associations **(Figure S4)**. Notably, TRIM13 and TRIM56 showed consistent prognostic significance across all three cohorts examined **(Figure S5)**. The limited prognostic impact of individual TRIM proteins in GBM may be attributed to the highly aggressive nature of this malignancy and the generally poor prognosis associated with it. In such an aggressive disease context, alterations in the expression of individual TRIM proteins may have less pronounced effects on patient outcomes. Additionally, prognostic signatures developed in several studies by combining TRIM genes

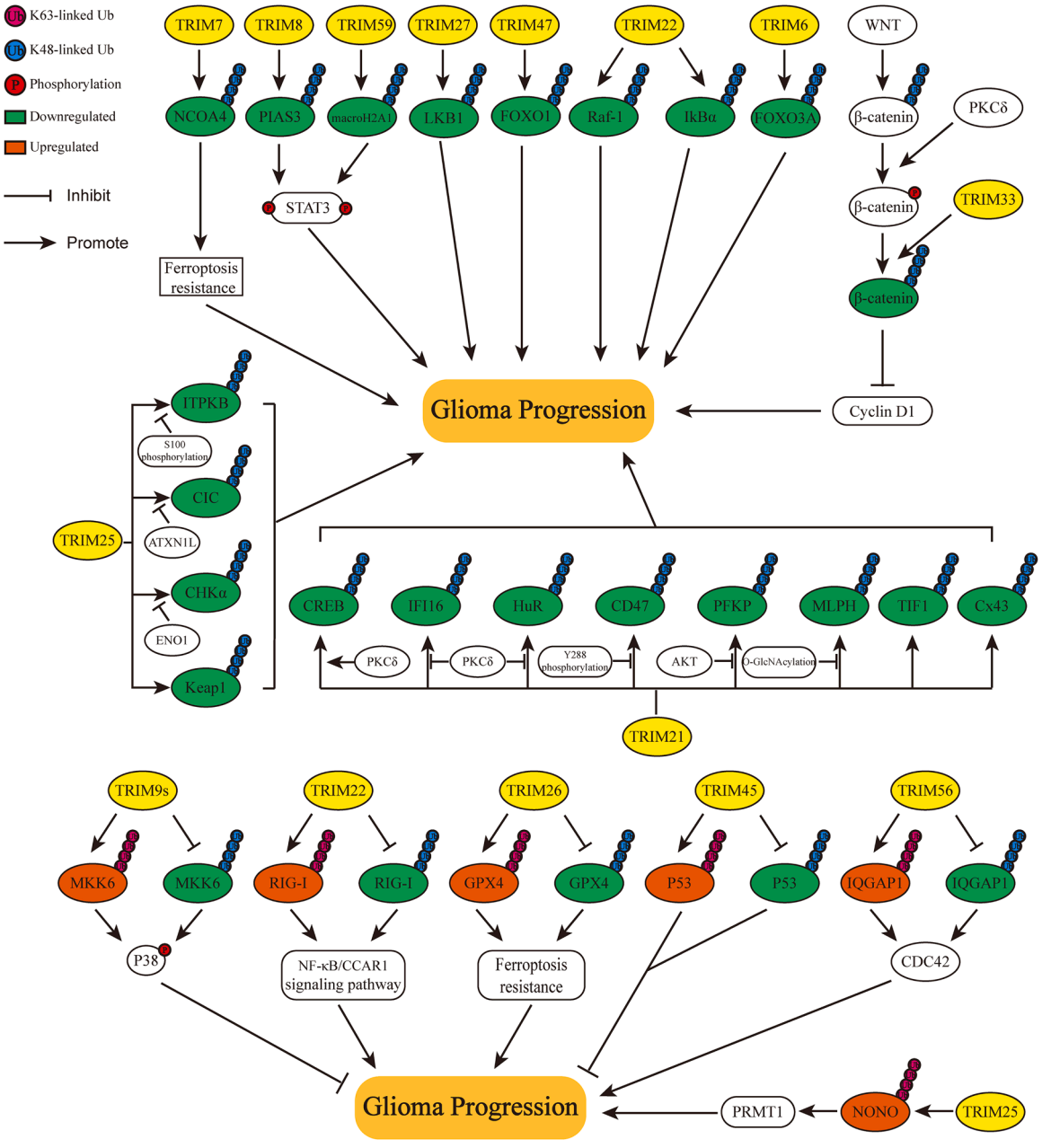

Fig. 2. TRIM proteins mediate ubiquitination of downstream molecules via K48- or K63-linked chains.

with other molecular markers have demonstrated strong predictive power [64,95–98].

An overview of various roles of TRIM proteins in glioma

TRIM proteins act as E3 ubiquitin ligases in glioma

Most TRIM proteins function as E3 ubiquitin ligases due to the RING-finger structural domain. Ubiquitination is a post-translational modification that involves the attachment of ubiquitin molecules to target proteins. This process is classified into seven main types based on the specific lysine residues involved: K6, K11, K27, K29, K33, K48, and K63 [99,100]. Among these, K48- and K63- linked ubiquitination are two of the most studied types. K48-linked ubiquitination is typically associated with the proteasomal degradation of target proteins, while K63-linked ubiquitination is extensively involved in other cellular functions such as signal transduction and DNA damage response [99–101]. In glioma, many TRIM proteins have been reported to mediate K48 or K63 ubiquitination of substrate proteins, subsequently influencing tumor biological behavior (Fig. 2).

TRIM proteins: molecular maestros orchestrating ubiquitin-mediated protein degradation

TRIM6 inhibits FOXO3A protein levels by promoting FOXO3A ubiquitination and subsequent degradation, promoting glioma cell proliferation, invasion, and migration [68]. TRIM7 facilitates K48-linked ubiquitination and subsequent degradation of NCOA4, resulting in decreased NCOA4-mediated ferritinophagy and ferroptosis in glioblastoma cells [71]. TRIM8 facilitates the ubiquitination of PIAS3, resulting in its subsequent degradation by the ubiquitin-proteasome system [43]. This process activates STAT3 signaling, thereby preserving the stemness and self-renewal properties of glioblastoma stem-like cells (GSCs) [43]. However, an additional study has reported that TRIM8 functions as a tumor suppressor in glioblastoma by impeding the proliferation of glioblastoma cells [47]. TRIM21 has been reported to promote the ubiquitination and degradation of several proteins, including CREB [102], IFI16 [103], HuR [103], CD47 [104], TIF1γ [105], MLPH [106], PFKP [107], and Cx43 [108]. These processes are modulated by various factors: CUEDC2 enhances CREB ubiquitination [102]; ARPC1B inhibits the ubiquitination of IFI16 and HuR [103]; CD47 Y288 phosphorylation impedes CD47 ubiquitination [104]; O-GlcNAcylation hinders MLPH ubiquitination [106]; and S386 phosphorylation of PFKP restricts its ubiquitination [107]. The dysregulation of these ubiquitination processes results in either reduced degradation of oncogenic proteins or enhanced degradation of tumor suppressors, ultimately contributing to the malignant phenotype of glioma. TRIM22 promotes K48-linked ubiquitination and protein degradation of IκBα [76] and Raf-1 [109], leading to activation of NF-κB and MAPK signaling pathways and tumor progression. TRIM25 plays a crucial role in mediating the ubiquitination and subsequent degradation of proteins such as ITPKB [110], CIC [111], CHKα [112], and Keap1 [113]. Similarly, this process is influenced by various factors: TRIM25 S100 phosphorylation inhibits the ubiquitination of ITPKB [110], ATXN1L blocks the ubiquitination of CIC [111], and ENO1 impedes the ubiquitination of CHKα [112]. These disruptions in the ubiquitination process contribute to tumor progression and resistance to treatment. TRIM27 directly binds to LKB1 and promotes K-48 ubiquitination and degradation of LKB1, which enhances glycolysis and promotes malignant progression of GBM cells by regulating the LKB1/AMPK/mTOR pathway [80]. TRIM33 acts as a tumor suppressor by promoting ubiquitination and degradation of β-catenin [65]. TRIM47 promotes ubiquitination and degradation of FOXO1, leading to glioma progression [88]. TRIM59 promotes the ubiquitination and degradation of the tumor suppressor histone variant macroH2A1, thereby enhancing the activation of the STAT3 signaling pathway and driving tumorigenesis [114].

TRIM proteins: versatile regulators driving ubiquitination beyond protein degradation

TRIM9s promotes K63-linked ubiquitination at the Lys82 site of MKK6 while inhibiting K48-linked ubiquitination at the same lysine residue [58]. This dual regulation prevents MKK6 protein degradation and thereby enhances p38 signaling. TRIM21 facilitates the transport of β-catenin from the cytoplasm to the nucleus by mediating its K63 ubiquitination [105]. TRIM22 enhances K63-linked ubiquitination of RIG-I while attenuating K48-linked ubiquitination, thereby activating the RIG-I/NF-κB/CCAR1 signaling axis and promoting glioma proliferation [115]. TRIM25 maintains K63-linked ubiquitination of NONO and ensures the normal splicing function of NONO, which further leads to activation of the PRMT1/c-MYC pathway and progression of GBM [78]. TRIM26 directly interacts with GPX4 through its RING domain, catalyzing the ubiquitination of GPX4 at K107 and K117 sites, promoting the switch from K48 to K63 ubiquitination, thereby enhancing the stability of the GPX4 protein and inhibiting ferroptosis [116]. Similarly, TRIM45 interacts with and stabilizes p53 by attaching K63-linked polyubiquitin chains to the C-terminal six lysine residues of the protein, which hinders the availability of these lysine residues for K48-linked polyubiquitination, a process that typically results in the degradation of p53 [66]. Our previous research has demonstrated that TRIM56 interacts with IQGAP1 to enhance K63-linked ubiquitination while inhibiting K48-linked ubiquitination at Lys-1230, ultimately activating CDC42 and promoting glioma cell migration and invasion [46].

TRIM proteins as transcriptional regulators

In addition to their ubiquitination-related functions, TRIM proteins have been implicated in transcriptional regulation in glioma, including roles in histone modification, acting as transcription factors, and modulating mRNA stability (Fig. 3). Previous study reported that TRIM3 exerts a suppressive effect on c-Myc transcriptional activity, resulting in the downregulation of c-Myc levels, and consequently, playing a tumor-suppressive role in glioma [63]. TRIM19 promotes SOX9 transcription and establishes a SOX9-STAT3-TRIM19 regulatory loop that is essential for maintaining glioma stem cell stemness [117]. Additionally, another study reported that TRIM19 modulates the level and distribution of H3K27me3 in GBM cells, which subsequently alters the gene expression network, exacerbating the malignant phenotype of GBM [118]. TRIM22 may function as a transcription factor for CCAR1, upregulating its expression and thereby promoting glioma progression [115]. TRIM24 functions as a transcription factor by binding to the promoter regions of SOX2 [119] and PIK3CA [77], thereby promoting their transcription and ultimately contributing to malignant progression and treatment resistance in GBM. Additionally, TRIM24 binds to H3K23ac and acts as a transcriptional co-activator, recruiting STAT3 and enhancing its chromatin binding, thereby reinforcing oncogenic signaling from EGFR-STAT3 [14]. Another study found that TRIM24 elevates H3K27ac level, which enhances ATF3 transcription, leading to epigenomic and transcription factor network remodeling and driving Ep-GBM-like transformation [120]. Moreover, TRIM24 acts as a transcriptional activator to upregulate PIK3CA expression, leading to activation of PI3K/AKT signaling [121]. TRIM28 has been demonstrated to decrease the stability of E-cadherin mRNA, thereby repressing its expression [81].

TRIM proteins directly interact with targets

In addition to their role as E3 ubiquitin ligases, TRIM proteins can directly interact with substrate proteins and modulate their functions through alternative mechanisms (Fig. 4). For example, the tumor suppressor TRIM3 is capable of directly binding to p21, thereby inhibiting its ability to promote the accumulation of cyclin D1-cdk4 and resulting in a reduction of glioma cell proliferation [40]. Another study reported that TRIM3 can bind to the importin nuclear transport complex, sequestering it in the cytoplasm and consequently inhibiting the nuclear

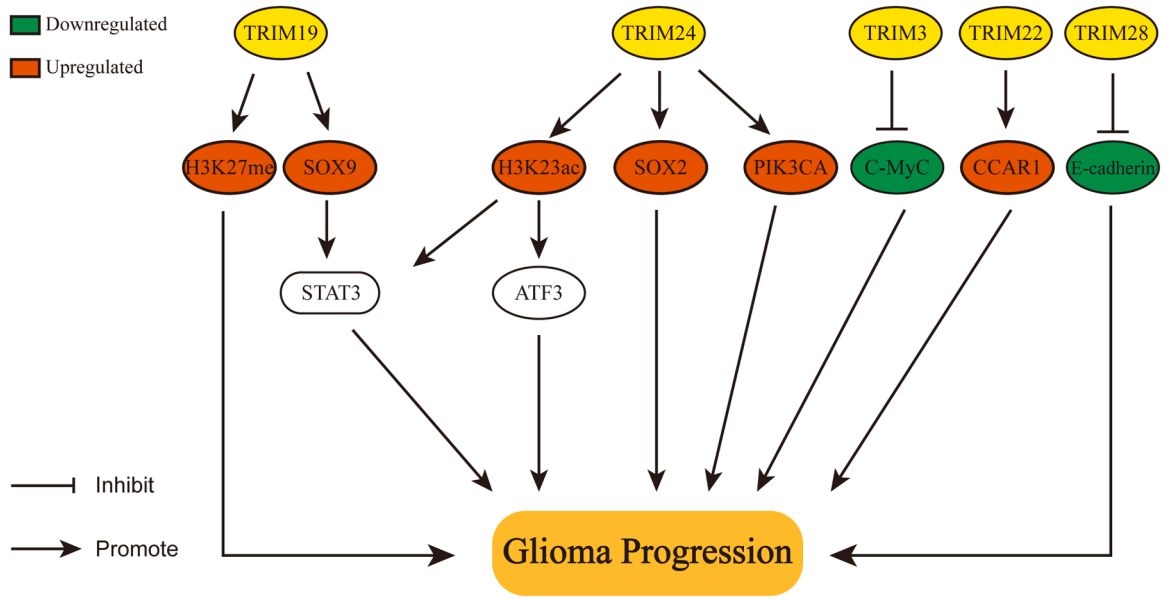

Fig. 3. TRIM proteins regulate the transcription of downstream target genes.

translocation of NICD, thereby suppressing the activation of NOTCH1 signaling [122]. TRIM14 directly interacts with Dvl2 through its PRY/SPRY domain, enhancing Dvl2 stability [73]. This interaction strengthens the Wnt/β-catenin signaling pathway and promotes the expression of MGMT, ultimately contributing to treatment resistance in glioma [73]. TRIM19, also known as PML, serves as a primary substrate for SUMO1 SUMOylation in glioma stem cells (GSCs) [123]. SUMO1 SUMOylation of TRIM19 increases its affinity for c-Myc, leading to augmented stability of c-Myc and an overall enhancement of the tumorigenic potential of GSCs [123]. In addition, the TRIM26 protein, through its C-terminal PRYSPRY domain, exhibits the capability to enhance the stability of SOX2 protein, independent of the RING domain which usually mediate ubiquitination function in TRIM proteins [16]. This stabilization is achieved by the direct inhibition of the interaction between SOX2 and WWP2, which is recognized as a genuine E3 ligase for SOX2 in glioblastoma stem cells [16]. TRIM37 directly interacts with EZH2 in glioma stem cells, which in turn leads to PTCH1 inhibition and enhanced glioma stem cell stemness [124]. TRIM56 enhances the stability of cIAP1 [15] and FOXM1 [125] by directly inhibiting their ubiquitination-mediated degradation, thereby promoting the malignant behavior of glioma cells. TRIM59 inhibits p-STAT3 dephosphorylation by disrupting the STAT3-TC45 complex, thereby enhancing the STAT3 signaling pathway [45]. These mechanisms suggest that, beyond their ubiquitination-related functions, TRIM proteins can directly interact with key oncogenic or oncostatic proteins, thereby broadly regulating glioma cell function.

Impact of TRIM proteins on glioma phenotypes through unspecified mechanisms

In the preceding sections, we investigated the roles of TRIM proteins in gliomas, focusing on specific molecular mechanisms, including ubiquitination-related functions and non-ubiquitination-regulated activities. Although a definitive mechanism through which TRIM proteins exert their functions has not been identified, numerous studies have confirmed their influence on the malignant phenotype of gliomas, which we summarize in this section. In summary, TRIM6 [70], TRIM14 [52,126], TRIM28 [81,127,128], TRIM31 [82,83,129], TRIM37 [84,85], TRIM44 [86], TRIM47 [87,130], TRIM52 [131], TRIM65 [57], TRIM66 [90], and TRIM67 [91] have been reported to promote malignant behaviors in glioma cells, including proliferation, migration, invasion, angiogenesis, and treatment resistance. In contrast, TRIM3 [63] and TRIM48 [67] have been identified as tumor suppressors, playing inhibitory roles in the malignant behavior of glioma cells. Interestingly, previous studies have reported that TRIM19 overexpression inhibits GBM cell proliferation while preserving their invasive capacity [132]. Specifically, TRIM3 regulates the Musashi-Numb-Notch signaling axis and inhibits stemness of glioma stem cells by restoring asymmetric cell division [63]. The existing literature on TRIM19 is contradictory. Some studies suggest that TRIM19 functions as a tumor suppressor in glioma by inhibiting the malignant phenotype of tumor cells [44,59,133], whereas others report that elevated TRIM19 levels contribute to drug resistance and sustain the tumorigenic potential of glioma stem cells [74,134]. Additionally, it has been reported that TRIM31 promotes proliferation and invasion of glioma cells by activating the NF-κB pathway [83]. TRIM33 and TRIM47 have been reported to play crucial roles in the regulation of the Wnt/β-catenin signaling pathway [87,135]. TRIM31, TRIM37, and TRIM44 were reported to promote the PI3K/Akt signaling pathway in glioma [82,85,86,129]. TRIM56 was reported to mediate M2 polarization of macrophages in the glioma microenvironment [89]. TRIM67 was reported to affect the expression and distribution of cytoskeletal proteins, and regulate the Rho GTPase/ROCK-mediated signaling pathway which in turn induced cell rounding and the appearance of a bubble morphology [91].

Targeting TRIM proteins in glioma: current progress and future perspectives

As previously noted, TRIM proteins exert significant influence on glioma through diverse mechanisms, including oncogenic and tumor-suppressive effects **(Table S1)**. Therefore, targeting specific TRIM proteins could potentially represent a novel therapeutic approach for glioma patients, with considerable implications for the treatment of this malignant disease. Here, we present the latest advancements in the development of targeting TRIM proteins in glioma.

Currently, the majority of experiments aimed at targeting TRIM proteins in glioma are performed at the cellular level. For example, regulating the MKK6/p38 signaling pathway, T9sP, a novel antitumor peptide derived from TRIM9s, inhibits glioma cell proliferation and migration while promoting apoptosis [136]. Through the activation of the p38/MAPK pathway, Piperlongumine (PL) is capable of markedly reducing TRIM14 expression, which effectively inhibits glioma cell

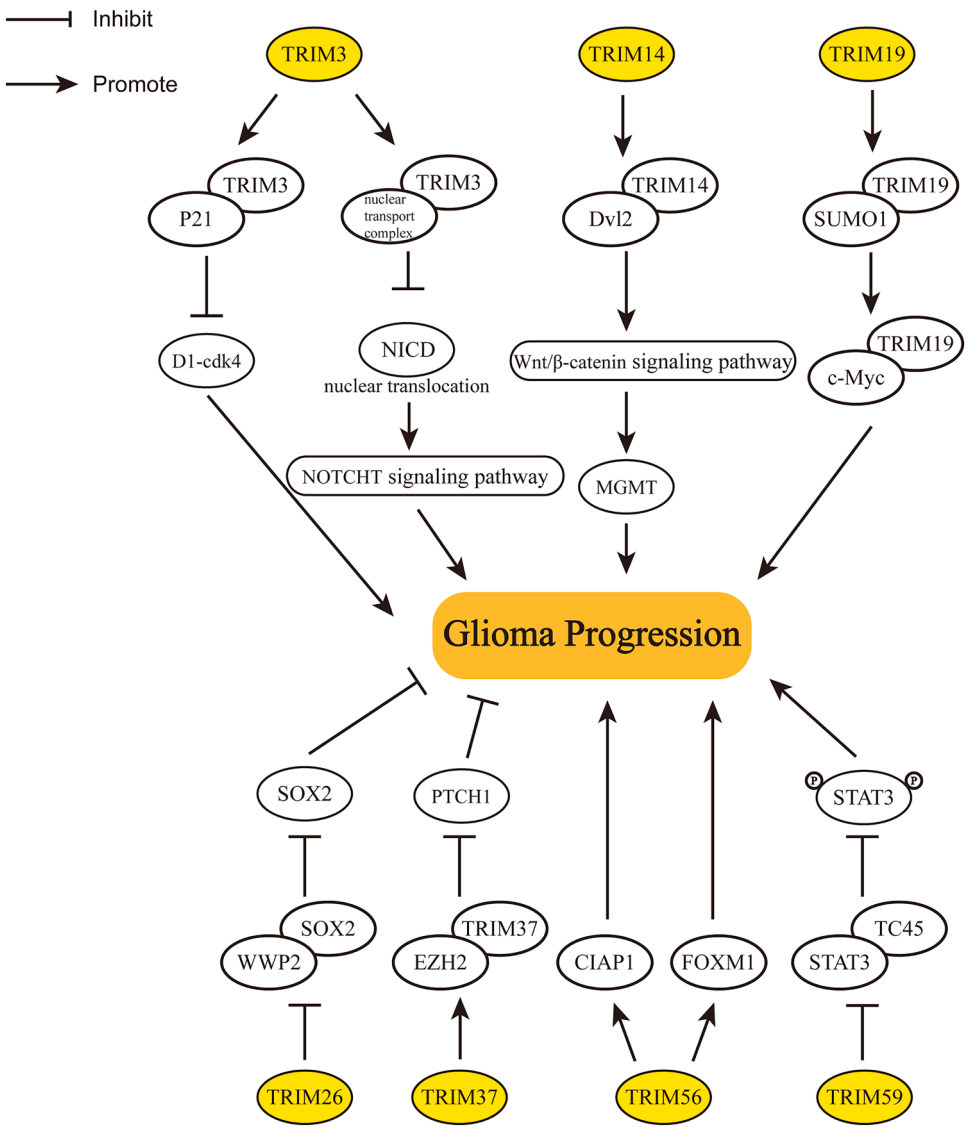

Fig. 4. TRIM proteins directly interact with and modulate target molecules.

invasion, colony generation, and sphere formation [126]. Furthermore, it enhances the cytotoxic effects of temozolomide [126]. The inhibitory effects of the compound arsenic trioxide (As2O3) on TRIM19 expression led to a significant reduction in tumor growth in orthotopic xenografts derived from glioblastoma stem cells [134]. Intriguingly, H3.3 point mutations in pediatric gliomas have been shown to disrupt the formation of promyelocytic leukemia (TRIM19) nuclear bodies, a phenomenon analogous to that observed in leukemias driven by PML mutations [137]. This disruption potentially sensitizes these glioma cells to therapeutic agents targeting PML bodies. Two novel selective TRIM24 antagonists, namely dTRIM24 and IACS-9571, can inhibit proliferation and invasion of several patient-derived GBM stem cells partially through suppressing the TRIM24-SOX2 axis [19]. An anti-TRIM28 selective nanobody, namely NB237, can significantly inhibit invasiveness of glioma cells both in vitro and in vivo [138]. A novel glucose transporter 1 (GLUT1)-targeting curcumin derivative, designated DMC-GF, has been demonstrated to induce TRIM33-mediated ubiquitination and subsequent degradation of the mitochondrial citrate carrier SLC25A1, thereby inhibiting the proliferation and self-renewal capacity of glioma stem cells [139]. Although these therapies directly targeting TRIM proteins have shown promising results in tumor cells, their role within the complex tumor microenvironment still requires further investigation.

Although substantial evidence suggests that targeting TRIM proteins could be an effective glioma treatment, no clinical trials have yet been reported in this area. Several challenges hinder the clinical translation of TRIM proteins, including their functional diversity. TRIM proteins play multiple roles in tumor progression, often exhibiting both tumor-promoting and tumor-suppressing functions, as seen with TRIM8 in gliomas [18]. Another challenge is the incomplete characterization of TRIM protein conformations and the potential off-target effects that may arise in therapeutic applications [140]. Additionally, the presence of complex compensatory mechanisms in glioma cells further complicates treatment strategies. For instance, ubiquitination-mediated degradation of specific TRIM proteins may be counteracted by other E3 ubiquitin ligases, reducing therapeutic efficacy. Finally, the intricate tumor microenvironment presents another hurdle. Modulating TRIM proteins may not only impact tumor cells but also influence immune and stromal cells, necessitating a deeper understanding of their broader effects within the glioma microenvironment [1141–143]. Despite these challenges, emerging preclinical data have identified several promising targets within TRIM proteins. Notably, TRIM25 has been associated with temozolomide resistance in glioma; its inhibition could potentially restore chemosensitivity in GBM. In parallel, TRIM3, which is frequently deleted in GBM, functions as a tumor suppressor, suggesting that

therapeutic strategies aimed at restoring its expression—or mimicking its function—could provide possible clinical benefit. These findings underscore the potential of TRIM25 and TRIM3 as priority candidates for future drug development and clinical investigation in glioma.

Conclusion

The dysregulation of multiple critical signaling pathways plays a pivotal role in glioma pathogenesis [144–147]. TRIM proteins are frequently involved as mediators in these pathways, exerting their effects through several mechanisms: facilitating ubiquitination that leads to the degradation or functional modulation of target proteins, regulating the transcription of target molecules, and directly interacting with target proteins. These actions collectively contribute to the regulation of glioma cell malignancy. Consequently, targeting TRIM proteins to restore normal signaling pathways represents a promising therapeutic strategy for glioma.

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Consent for publication

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Wenjie Wu: Writing – review & editing, Writing – original draft, Project administration, Data curation, Conceptualization. **Youxi Xie:** Writing – original draft, Visualization, Project administration, Data curation. **Cheng Jiang:** Writing – review & editing, Writing – original draft, Supervision. **Xiaobing Jiang:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

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