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The Role of Tripartite Motif Family Proteins in TGF-β Signaling Pathway and Cancer

REVIEW

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TGF-β signaling plays a tumor suppressive role in normal and premalignant cells but promotes tumor progression during the late stages of tumor development. The TGF-β signaling pathway is tightly regulated at various levels, including transcriptional and post-translational mechanisms. Ubiquitination of signaling components, such as receptors and Smad proteins is one of the key regulatory mechanisms of TGF-β signaling. Tripartite motif (TRIM) family of proteins is a highly conserved group of E3 ubiquitin ligase proteins that have been implicated in a variety of cellular functions, including cell growth, differentiation, immune response, and carcinogenesis. Recent emerging studies have shown that some TRIM family proteins function as important regulators in tumor initiation and progression. This review summarizes current knowledge of TRIM family proteins regulating the TGF-β signaling pathway with relevance to cancer.
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Key Words: Tripartite motif proteins, Transforming growth factor beta, Neoplasms

INTRODUCTION

TGF-β is a pleiotropic cytokine that involved in a variety of cellular functions. The TGF-β signaling pathway plays a pivotal role in regulating cellular responses including cell growth, apoptosis, differentiation, migration and metastasis in a context-dependent manner.[1] Dysregulation of TGF-β signaling pathway has been implicated in numerous human diseases, including cancer.[2] In particular, TGF-β signaling plays a crucial but paradoxical role in cancer. In early stages of tumor development, TGF-β acts as a tumor suppressor, whereas in later stages, cancer cells become resistant to the growth inhibitory effect of TGF-β, TGF-β can switch to tumor promoter.[3] In later stages of cancer progression, TGF-β promotes epithelial-mesenchymal transition (EMT), angiogenesis and suppression of immune surveillance.[4,5] The TGF-β signaling pathway is strictly regulated at various levels including the processing and availability of extracellular ligands, transcriptional control by coactivator and corepressor, and the post-translational modification of signaling components.[6-8] TGF-β receptors and Smads are well known to be downregulated via ubiquitination by E3 ubiquitin ligases.[9]

Tripartite motif (TRIM) family proteins are evolutionarily conserved proteins that are implicated in a number of cellular processes including proliferation, transcriptional regulation, differentiation, and cancer.[10,11] The most typical feature of TRIM family is the highly conserved order of domains in the N-terminal RBCC motif, which contains a really interesting new gene (RING) domain, one or two B-box motifs, and a coiled-coil (CC) region.[12] TRIM family proteins contain a RING domain, which can confer E3 ubiquitin ligase activity[13] that mediates post-translational modifications of various cancer-associated proteins. In fact, some TRIM proteins are implicated in various aspects of tumorigenesis, including proliferation, apoptosis, transcriptional regulation, chromatin remodeling, invasion, and metastasis.[14,15]

Recent studies have shown that several members of TRIM proteins are implicated in the regulation of TGF-β signaling

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pathway. This review focuses on the regulatory role of TRIM proteins in TGF-β pathway identified so far and further discusses how the TRIM protein-associated TGF-β signaling pathway affects cancer progression.

TRIPARTITE MOTIF FAMILY PROTEINS

TRIM family comprises more than 80 members in human that is characterized by the presence of a TRIM, which consists of a RING domain, followed by one or two zinc-finger domains named B-boxes (B1 and B2), and a CC region in the N-terminal region.[12] TRIM family proteins are implicated in a broad range of cellular processes, including intracellular signaling, protein quality control, innate immunity, inflammation, and carcinogenesis.[14]

1. Structure of tripartite motif proteins

The N-terminal RBCC domains are aligned in the same order, as shown in Figure 1, implying a modular function of the TRIM. The RING domain, a zinc finger motif, has been found in many functionally diverse proteins and shown to play an important role in ubiquitination of target proteins.[13] The B-box domains are also zinc-binding motifs which are supposed to act as protein-protein interaction domains and thereby determine the substrate specificity of RING-finger E3 ubiquitin ligase. The CC region that spans approximately 100 residues is thought to mediate homo- and hetero-interactions between TRIMs and other proteins.[11]

The N-terminal TRIM domain is usually followed by one or two C-terminal domains of variable length and composition. There are 10 different types of C-terminal domain, and the TRIM family has been classified into 11 subgroups according to their different C-terminal domains alone or in combination (Fig. 1).[12]

The most common C-terminal domain that expressed by TRIM proteins is PRY or SPRY sequence. The SPRY domain is often linked to the PRY domain to form the PRY-SPRY domain. The PRY-SPRY domain, also known as B30. The 2 domain, has been

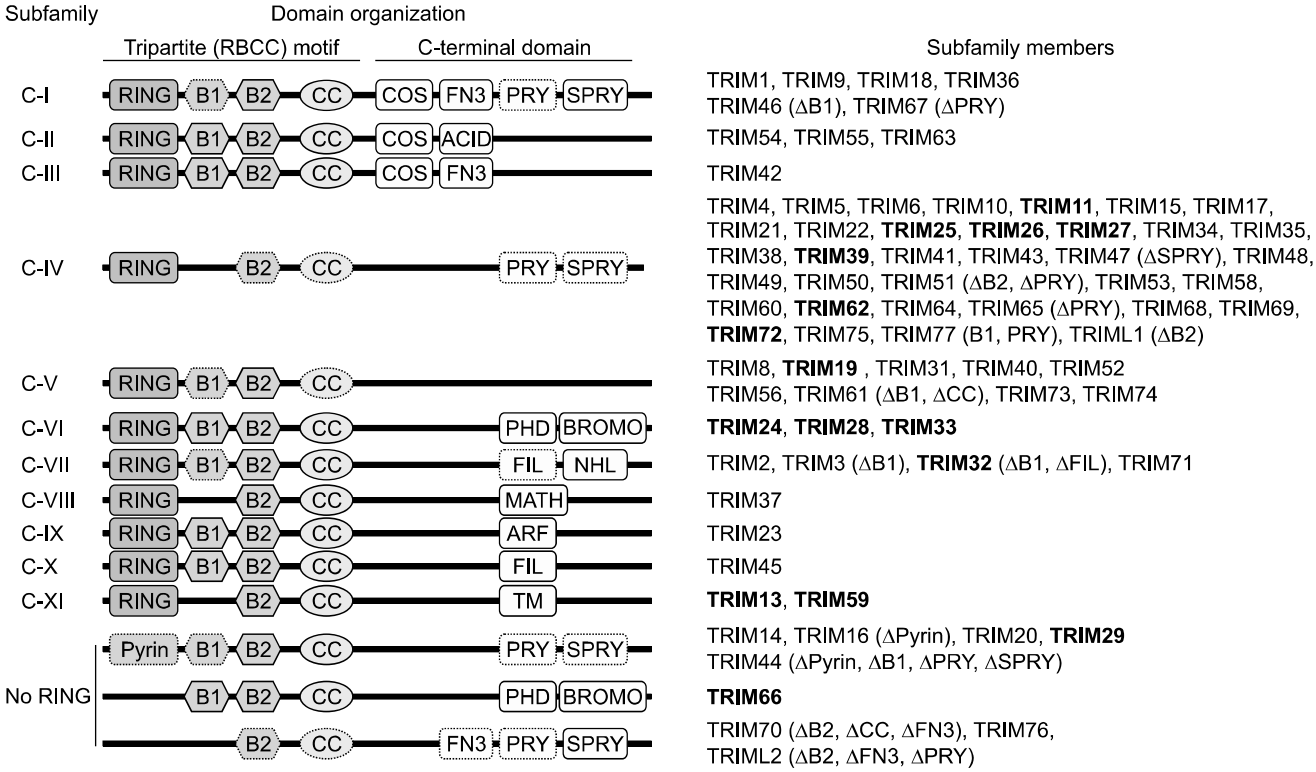

Figure 1. The structural classification of tripartite motif (TRIM) family proteins. Most of TRIM proteins contain a really interesting new gene (RING) finger domain, one or two B-box domain (B1 and B2) and a coiled-coil (CC) domain in N-terminal region. TRIM proteins are classified into 11 subfamilies (C-I to C-XI) based on a variable C-terminal domain. There is an additional unclassified group lacking a RING finger domain (No RING). Some TRIM family members lack one or more domain as denoted in brackets and by a dashed outline. TRIM proteins described in this review are in bold. Pyrin, Pyrin domain; COS, cos-box; FN3, fibronectin type III repeat; PRY, PRY domain; SPRY, SPRY domain; ACID, acid-rich region; PHD, PHD domain; BROMO, bromodomain; FIL, filamin-type immunoglobulin domain; NHL, NCL1, HT2A and LIN41 domain; MATH, meprin and TRAF-homology domain; ARF, ADP-ribosylation factor family domain; TM, transmembrane region.

shown to play an important role in immune regulation.[16] Other domains present in C-terminal region include the cos-box, fibronectin type 3 domain, plant homeodomain (PHD) zinc finger and bromodomain. The PHD zinc finger and bromodomain are commonly found in nuclear proteins and associated with chromatin remodeling and chromatin-mediated transcriptional regulation.[17] The divergent C-terminal domains might contribute to the functional diversity of TRIM family proteins.

2. Role of tripartite motif family proteins in cancer

TRIM family proteins are involved in a wide range of biological processes, and their altered expression or aberrant function leads to various pathological conditions, such as developmental diseases, infectious diseases, and neurodegenerative diseases.[18,19] Recently, a number of studies have shown that some TRIM family members are implicated in carcinogenesis and tumor progression.[15]

It has been known for many years that four TRIM family genes, *TRIM19, TRIM24, TRIM27,* and *TRIM33,* are frequently translocated to the loci of known oncogenes in different types of tumors and are involved in cancer initiation and progression.[20] Among these, the most famous is TRIM19, also known as promyelocytic leukemia, which is fused to retinoic acid receptor α (RARα) in acute promyelocytic leukemia.[20] TRIM24, also known as transcriptional intermediary factor 1α (TIF1-α) belongs to the TIF1 subgroup of TRIM family members which includes, TRIM28 (TIF1β), TRIM33 (TIF1γ), and TRIM66 (TIF1δ).[21] TRIM24 can be fused to BRAF in hepatocellular carcinoma and Ret receptor tyrosine kinase in papillary thyroid carcinoma.[22,23] Furthermore, TRIM24 has been shown to play a role as either promoting or suppressing tumor development depending on the cell type or context. The expression of TRIM24 is upregulated in breast cancer tissues and directly correlated with poor prognosis in both estrogen receptor-positive and -negative breast cancers.[24] However, TRIM24 can suppress the RARα-mediated transcriptional activity, and thereby preventing hepatic tumor growth.[25] TRIM24 deficiency resulted in a high incidence of spontaneous hepatic tumor formation and lung metastasis.

The highly conserved RING domain confers E3 ubiquitin ligase activity to most members of the TRIM family, and ubiquitination of substrate proteins appears to be one of the key mechanisms by which TRIM proteins exert their biological functions.[17] Ubiquitination is one of the most prevalent post-translational modifications that regulate various signaling pathways and cellular functions. The ubiquitin-mediated proteolytic pathway has a pivotal role in quality control of proteins or elimination of short-lived regulatory proteins including those that participate in cell cycle, cellular signaling, and transcriptional regulation.[20]

Some members of TRIM family can control carcinogenesis by modulating the stability or functional activity of p53, which is one of the most important tumor suppressor proteins. Joo et al.[26] demonstrated that TRIM13 increases ubiquitination and proteasomal degradation of mouse double minute 2 (Mdm2), which targets p53 for degradation. It has been reported that TRIM19 enhances the stabilization of p53 by binding and sequestering Mdm2 protein to the nucleus.[27] These results imply that TRIM13 and TRIM19 can function as tumor suppressors by positively regulating p53 activity.

On the other hand, other TRIM proteins including TRIM24, TRIM28, TRIM29, and TRIM39 act as negative regulators of p53. TRIM24, as an E3 ubiquitin ligase, has also been identified as a p53-binding protein by mass spectrometry.[28] TRIM24 directly ubiquitinates p53 via RING domain and negatively regulates p53 function, indicating that TRIM24 is a therapeutic target to restore tumor suppression by p53. TRIM28, also known as TIF1β and Krüppel-associated box (KRAB)-associated protein 1 (KAP1) was identified as a Mdm2-interacting protein and targets the p53 for proteasomal degradation via interaction with Mdm2.[29] Another TRIM protein, TRIM29, which lacks a RING domain and has no E3 ubiquitin ligase activity, associates with p53 and sequestrates it in the cytoplasm thus inhibiting p53-dependent transcriptional activation.[30] In addition, Sho et al.[31] demonstrated that TRIM29 promotes degradation of Tat-interactive protein 60 (Tip60), which has histone acetyltransferase activity, resulting in the abrogation of p53 acetylation mediated by Tip60. By suppressing p53 activity, TRIM29 enhances cell growth and transforming activity. These findings suggested that TRIM29 may act as an oncogene that promotes tumor growth. TRIM39 can also directly bind and ubiquitinate p53 and targets it for degradation in a RING-dependent manner, indicating that TRIM39 acts as a negative regulator of p53.[32]

Besides the p53 regulation, several other TRIM proteins are implicated in a variety of cancer signaling pathways. For example, TRIM32 expression is upregulated in breast tumor tissues and increases cell growth through activation of the NF-κB signaling pathway.[33] TRIM32 also promotes cell proliferation and invasion of gastric or lung cancer cells by activating β-catenin or JAK2/STAT3-signaling pathway, respectively.[34,35] Also, some TRIM family proteins have been reported to play roles in the regulation of the TGF-β signaling pathway.

INVOLVEMENT OF TRIPARTITE MOTIF FAMILY PROTEINS IN TGF-β SIGNALING

TGF-β signaling is regulated in both positive and negative manners, and is tightly controlled temporally and spatially by various mechanisms.[36] Positive regulation can contribute to the amplification and sustaining of the TGF-β signaling. Negative regulation plays a critical role in restriction and termination of TGF-β signaling primarily through a negative feedback loop. TRIM family proteins have been shown to both positively and negatively regulate TGF-β signaling (Table 1).

1. Negative regulation by tripartite motif family proteins

The core TGF-β signaling components, TGF-β receptors and Smads, are shown to be downregulated by protein ubiquitination and subsequent degradation in proteasome.[37-39] Ectodermin, the *Xenopus* ortholog of mammalian TRIM33, also denominated as TIF1-γ, was one of the first proposed TRIM family members to function as a negative regulator of TGF-β signaling. The RING-type E3 ubiquitin ligase TRIM33 was shown to restrict the mesoderm-inducing activity of TGF-β and favor the specification of ectoderm.[40] This activity was demonstrated to be dependent on the ubiquitination of Smad4 by TRIM33, which leads to degradation of Smad4 and inhibits TGF-β signaling. TRIM33 also monoubiquitinates Smad4 at lysine 519 in its Mad homology (MH) 2 domain, which promotes nuclear export of Smad4, thus destabilizes the functional nuclear Smad complex formation.[41] The functional inactivation of Smad4 has been closely linked to human cancers including pancreatic and colorectal carcinoma.[42] Vincent et al.[43] showed that TRIM33 works with Smad as a complementary agonist molecule during pancreatic carcinogenesis. Although the relationship between TRIM33 and Smad4 in cancer is unclear, TRIM33 may act as a negative regulator of TGF-β signaling through antagonizing the transcription coactivator role of Smad4.

Beside the inhibitory effect of TRIM33 on TGF-β signaling, TRIM33 also has been identified as a binding partner of Smad2 and Smad3 in response to TGF-β, and promoting Smad4-independent signaling pathway.[44] Interaction of Smad2/3 with TRIM33 stimulates erythroid differentiation of hematopoietic stem cells, whereas interaction of Smad2/3 with Smad4 inhibits the proliferation of these cells in response to TGF-β. TRIM33 (TIF1-γ) and other TIF family members are characterized by the presence of a PHD zinc finger and a bromodomain in the C-terminal region of the protein. The PHD and bromodomain are known to recognize post-translational modifications on histone.[45] Agricola et al.[46] demonstrated that TRIM33 is recruited to chromatin upon TGF-β stimulation and the E3 ubiquitin ligase activity of TRIM33 is induced by binding of TRIM33 to histones via its PHD zinc finger-bromodomain to modified histones. The monoubiquitination of Smad4 disrupts chromatin-bound Smad complexes, and TRIM33 is responsible for dictating the residence time of Smad complexes at TGF-β-regulated enhancers.[47] Xi et al.[48] demonstrated that TRIM33 activates nodal signaling by complexing of TRIM33 with receptor-activated Smads and binding to poised chromatin to displace the chromatin-compacting factor, chromobox protein homolog 3. These results

Table 1. TRIM family proteins associated with TGF-β signaling pathway

TRIM	Involvement in TGF-β signaling pathway	Reference No.
TRIM11	Suppression of TGF-β-mediated MED15 function	59
TRIM25 (EFP)	Smad activation and promotion of migration	65
TRIM26	Transcriptional induction of TRIM26 by TGF-β	67
TRIM28 (TIF1β)	Promotion of TGF-β-induced EMT and migration	68
TRIM33 (TIF1γ)	Ubiquitination and degradation of Smad4	40
	Monoubiquitination of Smad4	41
	Stimulation of TGF-β-induced erythroid differentiation by TRIM33/Smad2/3 complex	44
	Ubiquitination of Smad4 requires histone modification	46
	Activation of nodal signaling by TRIM33/Smad2/3 complex	48
TRIM59 (MRF1)	Depletion of TRIM59 reduces TGF-β and Smad activation	75, 76
TRIM62 (DEAR1)	Ubiquitination and degradation of Smad3	56
TRIM66 (TIF1δ)	Promotion of TGF-β-induced EMT	71
TRIM72 (MG53)	Depletion of TRIM72 reduces TGF-β and type I receptor	78
	Inhibition of TGF-β-induced myofibroblast differentiation	79

TRIM, tripartite motif; EFP, estrogen-responsive finger protein; TIF1, transcriptional intermediary factor 1; MRF1, mouse ring finger 1; DEAR1, ductal epithelium-associated RING Chromosome 1; MG53, mitsugumin 53; MED15, mediator of RNA polymerase II transcription subunit 15; EMT, epithelial mesenchymal transition.

implied that the transcription factors Smads can regulate gene expression by initially detecting histone marks as a platform to switch master regulators of cell differentiation from the poised to the active state.

TRIM62, also known as ductal epithelium-associated RING Chromosome 1, is a tumor suppressor gene which maps to chromosome 1p35, a region that frequently deleted in a broad range of human cancers.[49] TRIM62 is expressed in the ductal and glandular epithelium of normal mammary and other tissues and functioned as a dominant regulator of acinar morphogenesis in the mammary glands.[50] The TGF-β signaling is one of the most frequently deregulated pathways in breast cancer and also associated with tumor malignancy.[51] TRIM62 is a member of the TRIM/RBCC family and has a RING finger E3 ubiquitin ligase activity.[52] TRIM62 gene has been found mutated in breast and other epithelial cancers and its low expression is correlated with poor clinical prognosis.[53-55] Chen et al.[56] demonstrated that TRIM62 acts as chromosome 1p35 tumor suppressor and negative regulator of TGF-β/Smad signaling. TRIM62 specifically binds to the linker and MH2 domains of Smad3 and promotes the ubiquitination and degradation of Smad3. These resulted in a decrease in TGF-β/Smad3 target genes, including Snail1 and Snail2, which act as master transcriptional regulators of EMT. These data implied that TRIM62 acts as an important regulator of TGF-β-induced EMT and might be a potential biomarker for clinical strategies that target the TGF-β/Smad3 signaling pathway.

2. Positive regulation by tripartite motif family proteins

TRIM11 is shown to be highly expressed in glioma and lung cancer tissues and correlated with poor prognosis.[57,58] Ishikawa et al.[59] showed that TRIM11 suppresses TGF-β-induced transcription of transcriptional cofactor mediator of RNA polymerase II transcription subunit 15 (MED15). MED15, also known as ARC105, is a component of activator-recruited cofactor complex that mediates chromatin-directed transcriptional activation.[60,61] MED15 has been shown to play a key role in TGF-β/activin/nodal signaling in *Xenopus laevis* axis formation and mesendoderm differentiation.[62] MED15 also interacts with Smad2/3 and Smad4 in response to TGF-β stimulation. TRIM11 interacts and destabilizes MED15 through the ubiquitin-proteasome dependent degradation pathway. Recently, Zhao et al.[63] showed that MED15 deficiency attenuates the TGF-β-targeted gene expression and inhibits TGF-β-induced EMT, through the inhibition of receptor-activated Smad activation.

TRIM25 was initially identified as estrogen-responsive finger protein that is essential for cell proliferation and organ development in response to estrogen.[64] It has recently been shown that TRIM25 is highly expressed in colorectal and gastric cancer tissues and promotes migration and invasion of cancer cells through activation of TGF-β signaling pathway.[65,66] The ectopic expression of TRIM25 in gastric and colorectal cancer cells increases Smad activation and cell migration.

Nakagawa et al.[67] demonstrated that TGF-β induces the expression of E3 ubiquitin ligase TRIM26, and the induction of TRIM26 is mediated by direct binding of TGF-β-activated Smad3 to Smad binding elements in the TRIM26 promoter. TGF-β-induced growth arrest in mammary epithelial cells is mediated by TRIM26-dependent degradation of a general transcription factor IID subunit TATA box binding protein-associate factor 7. These data suggested that TRIM26 is a direct target of Smad3, and is required for TGF-β-mediated growth inhibition.

Chen et al.[68] found that TRIM28 promotes TGF-β-induced EMT, cell migration and invasion of lung cancer cells. The expression of TRIM28 is induced by TGF-β and leads to modulate the expression of EMT marker genes, such as *Cdh1* and *Cdh2* through modification of histones of target gene promoters. TRIM28 has also been specifically implicated in the EMT process in cancer cells via different mechanisms.[69,70]

TRIM66 (TIF1δ) contains two B-boxes and a CC domain and does not have a RING-finger domain in the N-terminal region[21] Chen et al.[71] found that TRIM66 is significantly increased in osteosarcoma tissues and the high expression level of TRIM66 is associated with lung metastasis and poor survival rate in patients with osteosarcoma. Gene Expression Omnibus database analysis indicated that EMT and TGF-β signaling pathway-related genes are enriched in patients with high TRIM66 expression. These data suggested that TRIM66 acts as an oncogene through promoting TGF-β signaling and TGF-β-induced EMT.

TRIM59, also known as mouse ring finger 1, belongs to the TRIM family, which has been implicated in the carcinogenesis of several human cancers, such as gastric, lung, and breast cancer.[72-74] TRIM59 is highly expressed in bladder and breast cancer tissues and promotes migration and invasion through the TGF-β/Smad2/3 signaling pathway.[75,76] The downregulation of TRIM59 expression contributes to the inhibition of TGF-β signaling pathway, consequently reducing levels of TGF-β and Smad2/3 phosphorylation.

A muscle-specific TRIM family protein, TRIM72, also called mitsugumin 53, has been shown to be expressed specifically in the plasma membrane of skeletal muscle, and it has a critical role in membrane repair after acute muscle injury.[77] Zhao and Lei[78]

showed that TRIM72 promotes the proliferation and migration of cardiac fibroblasts. The gene expression analysis demonstrated that TRIM72 regulates the expression of TGF-β1 and TGF-β type I receptor. On the other hand, TRIM72 plays a negative regulatory role during wound healing and fibrotic processes. Recombinant human TRIM72 inhibits the activation of Smad2/3 and TGF-β-dependent activation of myofibroblast differentiation.[79] These results suggest that the differential regulation of TGF-β signaling by TRIM family proteins may have important implications in many physiological and pathological processes.

CONCLUSION AND PERSPECTIVE

As described in this review, many studies over the years have demonstrated that TRIM family proteins positively or negatively regulate the TGF-β signaling pathway in various types of cancer. Complex signaling by TGF-β regulates cancer initiation and progression through a cancer cell-autonomous mechanism or cancer-stroma interaction, and acts as either tumor suppressor or promoter in cell-type and context dependent manners. In line with the complex role of TGF-β in cancer, TRIM proteins also modulate the TGF-β signaling according to the cellular context by acting either positively or negatively. Most of TRIM family proteins have E3 ubiquitin ligase activity and contain different types of domains in the C-terminal region. Up to now, a few TRIM family proteins which interact with the signaling components of TGF-β have been identified to date. Therefore, further analyses are required to determine whether other TRIM family proteins are involved in the TGF-β signaling pathway. In addition, more detailed studies are needed to understand the role of TRIM protein-mediated regulation of TGF-β signaling pathway and its implications in cancer initiation and progression. It is also needed more detailed biochemical analyses and genetic approaches to identify the specific role of TRIM proteins in the TGF-β pathway and cancer. Achieving selectivity in targeting components will lead to potential strategies for treating cancers that result from deregulation of the TGF-β signaling pathway.

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CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

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