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The role of tribbles homolog 2 in cell proliferation

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Abstract
Tribbles homolog 2 (TRIB2), a pseudoserine/threonine kinase, is a member of the TRIB family. TRIB2 primarily regulates cell proliferation through its scaffold or adaptor effect on promoting the degradation of target proteins by E3 ligase-dependent ubiquitination and regulating mitogen-activated protein kinase (MAPK) and protein kinase B (AKT) signaling pathways. TRIB2 is not only involved in the physiological proliferation of cells (granulosa cells, myoblasts, naive T cells, and thymocytes) during normal development but also in the pathological proliferation of vascular smooth muscle cells and a variety of cancer cells (lung cancer cells, liver cancer cells, leukemia cells, pancreatic cancer cells, gastric cancer cells, prostate cancer cells, thyroid cancer cells, cervical cancer cells, melanoma cells, colorectal cancer cells, ovarian cancer cells and osteosarcoma cells) under disease conditions. Its expression level and functional role predominantly hinge on the specific tissue and cell type it targets. This review elucidates the specific mechanisms of TRIB2 in physiological and pathological cell proliferation from the perspective of different kinds of cells.

Keywords TRIB2, Cell proliferation, Pseudokinase, Ubiquitin, Signaling

Background

In the human genome, tribbles homolog 2 (TRIB2) and two other homologs, TRIB1 and TRIB3, collectively form the TRIB protein family, playing crucial roles in various physiological and pathological processes [1, 2]. TRIB2 is considered the evolutionary ancestor of TRIB1 and TRIB3. The amino acid homology of TRIB1 and TRIB2 is 71%, TRIB2 and TRIB3 is 53%, and TRIB1 and TRIB3 is 53.7% [2]. The human kinase group encodes over 500 kinases, with approximately 10% belonging to pseudokinases [3]. TRIB2 is classified as a pseudo serine/threonine kinase because its pseudokinase domain lacks the aspartate-phenylalanine-glycine tripeptide motif that can chelate Mg^{2+} regulating adenosine triphosphate (ATP) binding in conventional kinase domains. Therefore, TRIB2 cannot efficiently bind ATP and transfer phosphate groups to target proteins to catalyze phosphorylation like an actual protein kinase [4–6].

TRIB2 is involved in various diseases, including cardiovascular and metabolic diseases [7–9], immune and inflammatory diseases [10–12], neurological diseases [13], and cancers [14]. As a scaffold or adaptor protein, TRIB2 plays an essential role in regulating cell proliferation, apoptosis, survival, and differentiation by promoting the degradation of target proteins through E3 ligase-dependent ubiquitination and regulating mitogen-activated protein kinase (MAPK) and protein kinase B (AKT) signaling pathways [15]. The expression level and functional role of TRIB2 in cell proliferation predominantly hinges on the specific tissue and cell type it

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targets [16, 17]. This review aims to elucidate the exact mechanisms of TRIB2 in physiological and pathological cell proliferation from the perspective of different kinds of cells.

TRIB2 structure and function

TRIB2 contains three structural domains: N-terminus (70–100 residues), C-terminus (approximately 25 residues), and serine/threonine protein kinase-like pseudokinase. The N-terminal PEST sequence and the five terminal amino acids (TRIB2 degradation domain) are implicated in TRIB2 degradation. The pseudokinase domain N-lobe Ser83 can be phosphorylated by the p70 ribosomal protein S6 kinase (p70S6K) to participate in TRIB2 homeostasis. The nuclear factor κB (NF-κB) and the substrate of the ubiquitin (Ub) proteasome system (UPS) can interact with TRIB2 in the C-lobe of the pseudokinase domain, and the ESLED motif of the C lobe is related to ATP binding and hydrolysis. At the C-terminus, the ILDHPWF motif can interact with MAPK, while the DQLVPD motif can interact with E3 Ub ligase and poly (rC) binding protein 2 (PCBP2), leading to the ubiquitination of the substrates attached to the pseudokinase domain and a reduction in the overall ubiquitination level, respectively. Furthermore, the C-terminal domain can directly interact with the non-phosphorylated Thr308 of AKT, promoting the phosphorylation of Ser473 in AKT and enhancing its activation [14]. (Fig. 1) (Table 1).

TRIB2 in physiological cell proliferation

The proliferation of normal cells under physiological conditions is a strictly controlled process essential for the proper development and maintenance of tissues [18]. TRIB2 plays a pivotal role in the physiological proliferation of granulosa cells, myoblasts, naive T cells, and thymocytes [19–22].

Granulosa cell (GC)

The regulation of GC proliferation and function is crucial for normal follicular development, necessitating precise regulation of specific target gene transcription. TRIB2 plays a vital role in this process [23]. Utilizing gene chip technology, Kulus et al. identified that TRIB2, regulated by exosomes, is involved in the adhesion, migration, and proliferation of porcine GC [24]. Warma et al. found that the mRNA level of TRIB2 in the GCs of dominant follicles from collected bovine follicles at different developmental stages is higher than that of ovulation cells induced by human chorionic gonadotropin (HCG) [19]. Moreover, HCG inhibits the expression level of TRIB2 protein. Inhibiting TRIB2 through CRISPR/Cas9 gene editing technology leads to a significant increase in proliferating cell nuclear antigen (PCNA) expression in GC while reducing the phosphorylation levels of extracellular regulated protein kinase (ERK) 1/2 and p38 MAPK [19]. This suggests that TRIB2 may influence GC proliferation by regulating the MAPK signaling pathway. Furthermore, TRIB1 or TRIB3 may not be able to compensate for the TRIB2 deficiency caused by TRIB2 knockdown in GC. While TRIB2 seems to exert a negative regulatory effect on GC proliferation, it may positively or negatively regulate GC proliferation based on the status of follicles, stimulating GC proliferation in small follicles and inhibiting preovulatory follicle proliferation in large follicles [19].

On the other hand, the seven binding partners screened from the GC-cDNA library of dominant follicles that interact with TRIB2 in GC, including calmodulin 1 (CALM1) and inhibin subunit beta A (INHBA), inositol polyphosphate phosphatase like 1 (INPPL1), ecto-5'-nucleotidase (NT5E), stearyl CoA depletion (SCD), successive dehydrogenase complex iron sulfur subunit B (SDHB), and Ras-associated protein 14 (RAB14), are all expressed in the GC of dominant follicles but are differentially regulated at different stages of follicular development [25]. Although no research has elucidated the specific mechanism by which TRIB2 regulates the expression of binding partners, these findings further expand the signal transduction pathway by which TRIB2 regulates GC proliferation. (Fig. 2A)

Myoblast

During myogenesis, myoblasts exit the cell cycle and initiate the differentiation process. Therefore, proliferation and differentiation are typically opposing processes [26]. TRIB2 is localized in the nucleus and cytoplasm of differentiated myoblasts, and its expression gradually increases as myoblasts differentiate. Silencing TRIB2 expression in myoblasts significantly enhances their proliferation while suppressing differentiation. The activation of the mammalian target of rapamycin (mTOR) signaling pathway is crucial for muscle differentiation, and miR-100-5p can directly target TRIB2, inactivating the mTOR/p70S6k1 signaling pathway and impeding myoblast differentiation. In addition, miR-100-5p can promote myoblast proliferation by targeting TRIB2 [20]. These represent a primary discovery regarding TRIB2-mediated growth and development of skeletal muscle, contributing to the broader comprehension of the mechanisms involved in skeletal muscle differentiation and development. (Fig. 2B)

Naive T cell

T cell generation has multiple mechanisms and significant changes throughout life. With increasing age, there is a decrease in the frequency of naive T cells [26]. Moreover, a notable discrepancy can be observed in the extent of reduction in the population of naive $CD4^+$T and $CD8^+$T cells [27]. Although the naive $CD4^+$T cell count

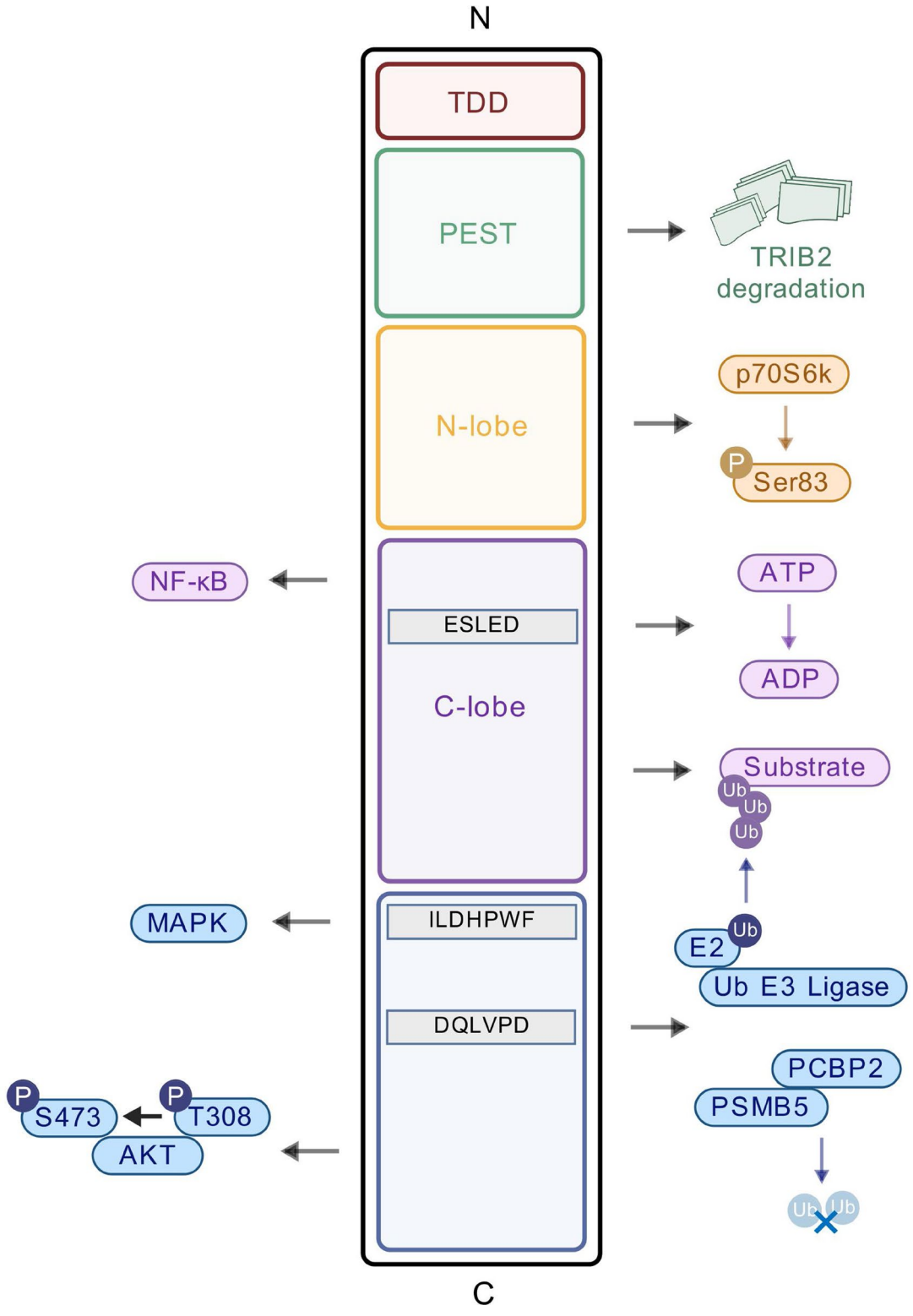

Fig. 1 The structure and function of TRIB2. TRIB2 is composed of N-terminal, C-terminal, and pseudokinase domains. The N-terminus region plays a role in TRIB2 degradation, while the pseudokinase domain is crucial for maintaining TRIB2 homeostasis and mediating interactions with NF-κB and ubiquitinated substrates. The C-terminus region interacts with MAPK, E3 Ub ligase, PCBP2, and AKT to regulate ubiquitination levels and AKT activity. Created with BioGDP.com. TRIB2, tribbles homolog 2; p70S6K, p70 ribosomal protein S6 kinase; NF-κB, nuclear factor κB; ATP, adenosine triphosphate; ADP, adenosine diphosphate; MAPK, mitogen-activated protein kinase; Ub, ubiquitin; AKT, protein kinase B; PCBP2, poly (rC) binding protein 2; PSMB5, proteasome 20S subunit beta 5

Table 1 The structure and function of TRIB2

Structure		Interaction protein	Function
N-terminal domain	PEST sequence		Degradation of TRIB2
	Terminal 5 amino acids		
Pseudokinase domain	N-lobe	p70S6K	Phosphorylation of Ser83 to participate in TRIB2 homeostasis
	C-lobe	NF- κB and UPS substrates (TCF4, β-Catenin, C/EBPα, and CDC25B/C)	
	C-lobe ESLED motif		Binding and hydrolysis of ATP
C-terminal domain	ILDHPWF motif	p38 MAPK, MEK1, and MMK7	
	DQLVPD motif	E3 Ub ligases (Smurf1, β-TrCP, COP1, and TRIM21)	Ubiquitinating substrates on the pseudokinase domain
		PCBP2	Reducing the overall ubiquitination level
		Nonphosphorylating Thr308 of AKT	Promoting phosphorylation of Ser473 of AKT and enhancing its activation

TRIB2, tribbles homolog 2; p70S6K, p70 ribosomal protein S6 kinase; NF-κB, nuclear factor κB; UPS, ubiquitin proteasome system; TCF4, T cell factor 4; C/EBPα, CCAAT enhancer-binding protein α; CDC25B/C, Cyclin 25B/C; ATP, adenosine triphosphate; MAPK, mitogen-activated protein kinase; MEK1, MAPK kinase 1; MMK7, MAPK kinase 7; Ub, ubiquitin; Smurf1, Smad ubiquitination regulatory factor 1; β-TrCP, β-transducin repeat containing protein; COP1, constitutive photomorphogenic 1; TRIM21, tripartite motif containing 21; PCBP2, poly (rC) binding protein 2; PSMB5, proteasome 20S subunit beta 5; AKT, protein kinase B

decreases in older people, it remains relatively high, while the naive $CD8^+$T cell count experiences a more pronounced decrease [28]. Cao et al. discovered that TRIB2 is more highly expressed in immature $CD4^+$T cells compared to immature $CD8^+$T cells, and this expression difference is regulated by the transcription factors Th inducing POZ-Kruppel factor (ThPOK) and runx-related transcription factor 3 (RUNX3) specific to the $CD4^+$ and $CD8^+$ lineages. Specifically, ThPOK promotes TRIB2 transcription, while RUNX3 inhibits TRIB2 transcription. Due to the low expression of TRIB2, AKT activity increases in naive $CD8^+$T cells in response to homeostatic cytokines. Consequently, naive $CD8^+$T cells exhibit heightened T cell activation and proliferation. In addition, in ThPOK/Cbfb double knockout mice, the differential expression of TRIB2 between naive $CD4^+$ and $CD8^+$T cells was eliminated, almost equalizing the lymphocyte reduction-induced proliferation in these two subgroups [21]. These findings underscore the critical role of TRIB2 in naive T cell proliferation, particularly in age-related immune changes. (Fig. 2C)

Thymocyte

During T-cell development, TRIB2 stands out as the first-discovered thymocyte proliferation regulator in the mammalian TRIB family. It governs the cell division dynamics of developing thymocytes by regulating the entry or exit of the cell cycle [22]. Knockout of TRIB2 increases the proliferation of developing thymocytes but has no significant effect on their terminal maturation, Tcrb rearrangement (a key event in early T cell differentiation), or the proportion of peripheral T cells caused by cell proliferation [22]. In stress hematopoiesis, TRIB2-deficient developing thymocytes undergo accelerated proliferation and demonstrate hypersensitivity to cell death induced by 5-fluorouracil (5-FU). Thymocyte death significantly increased after 24 h of 5-FU intervention in vivo, and proliferative $DN3_L$ and DP_{bl} subgroups were reduced considerably. However, TRIB2 deficiency accelerates the recovery of thymogenesis due to the enhanced cell division dynamics of the developing thymocytes. On the 4th and 14th days after the 5-FU intervention, TRIB2-deficient mice had more thymocytes, and the thymus on the 14th day was relatively larger. These may be attributed to the expansion of c-Kit^- DN1 progenitor cells promoting recovery progress [22]. (Fig. 2D)

TRIB2 in pathological cell proliferation

The proliferation of cancer cells is a critical biological process contributing to the malignant phenotype of cancer, primarily driven by gene mutations that disrupt normal cell cycle regulation and uncontrolled cell growth [29]. Furthermore, pathological factors may also affect the proliferation process of normal cells, resulting in abnormal cell growth [30]. TRIB2, as a critical regulatory molecule, not only participates in the physiological proliferation of normal cells, but also the proliferation of cancer cells, promoting cancer growth and spread, and the proliferation of non-cancer cells under certain pathological conditions [14, 30].

Vascular smooth muscle cell (VSMC)

The proliferation of VSMC is closely related to proliferative diseases such as neointima formation after vascular injury [30], in-stent restenosis [31], and atherosclerosis [32]. Takaguri et al. found that TRIB2 exhibits heightened expression levels in the early stage following carotid artery injury in mice and platelet-derived growth factor-BB (PDGF-BB)-induced rat VSMCs [33]. Previous studies have shown that TRIB2 can enhance the phosphorylation of AKT through the constitutive photomorphogenic 1 (COP1) domain [34]. Interestingly, the phosphorylation

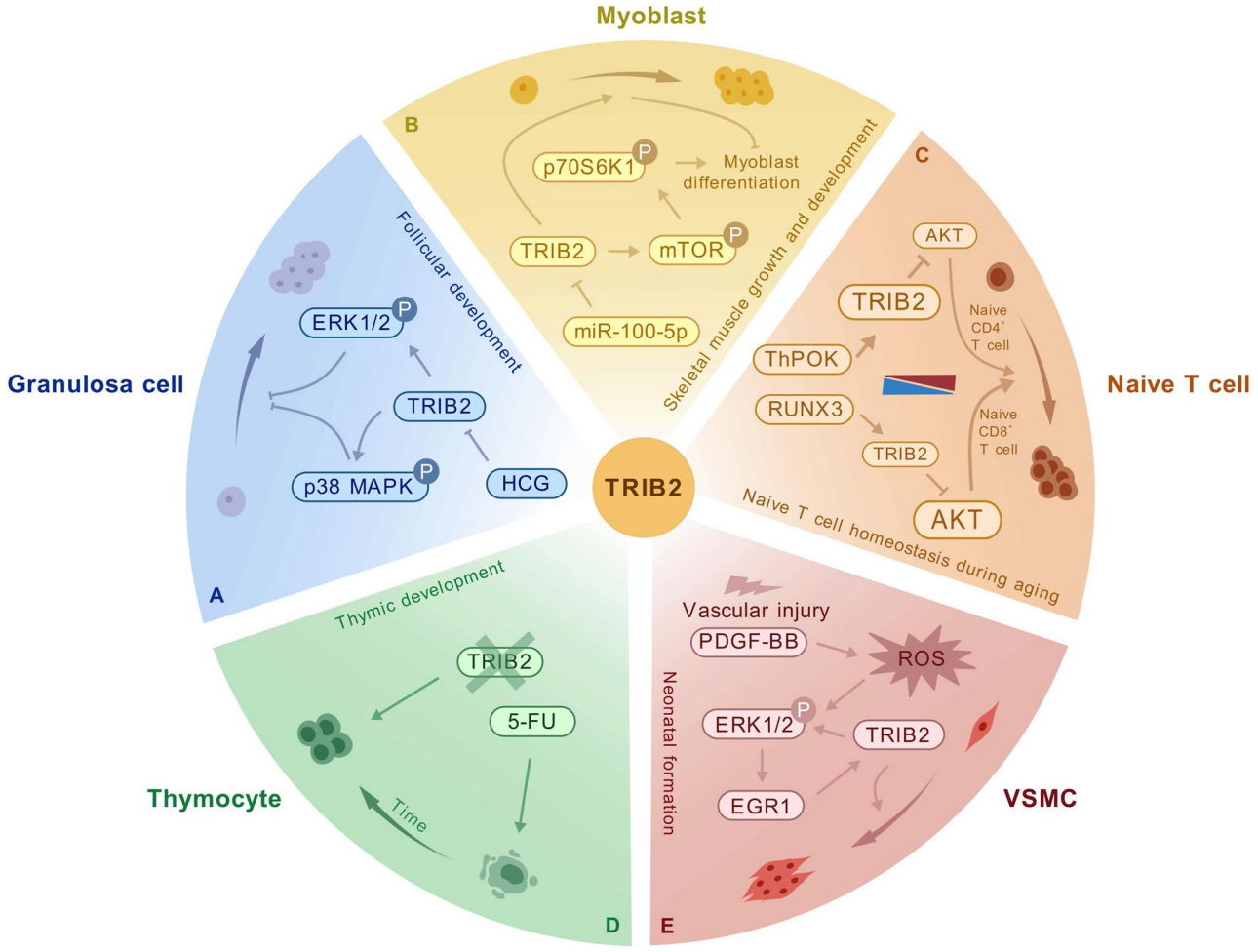

Fig. 2 The role of TRIB2 in the physiological proliferation of granulosa cells, myoblasts, naive T cells, and thymocytes, and pathological proliferation of VSMCs. (**A**) HCG promotes granulosa cell proliferation by reducing the phosphorylation of ERK1/2 and p38MAPK by inhibiting TRIB2. (**B**) MiR-100-5p enhances myoblast proliferation by targeting TRIB2 and inhibits differentiation by the TRIB2/mTOR/p70S6K1 signaling pathway. (**C**) ThPOK and RUNX3 respectively upregulate and downregulate TRIB2 expression, with TRIB2 inhibiting AKT activity in $CD4^+$T cells, while its absence promotes cell proliferation in $CD8^+$T cells. (**D**) Knockout of TRIB2 increases the proliferation of developing thymocytes, and after the 5-FU intervention, the cells gradually regain and enhance their proliferative capacity over time. (**E**) PDGF-BB induces TRIB2 expression through the ROS/ERK/EGR1 signaling pathway, subsequently promoting VSMC proliferation. Created with BioGDP.com. TRIB2, tribbles homolog 2; HCG, human chorionic gonadotropin; p38 MAPK, p38 mitogen-activated protein kinase; ERK, extracellular regulated protein kinase; mTOR, mammalian target of rapamycin; p70S6K1, p70 ribosomal protein S6 kinase 1; ThPOK, Th inducing POZ-Kruppel factor; RUNX3, runx-related transcription factor 3; AKT, protein kinase B; PDGF-BB, platelet-derived growth factor-BB; ROS, reactive oxygen species; EGR1, early growth responsive gene 1; VSMC, vascular smooth muscle cell

level of AKT remains unchanged when TRIB2 is knocked down in VSMCs, and the underlying mechanism is currently unclear [33]. Nonetheless, TRIB2 knockdown reduces PDGF-BB-induced ERK phosphorylation in VSMCs [33], consistent with previous reports that TRIB2 knockdown inhibits ERK activity in KG-1 cells [35]. In VSMCs, the reactive oxygen species (ROS) induced by PDGF-BB can react with the MAPK family member ERK, thereby promoting TRIB2 expression. Heightened TRIB2 expression can enhance ERK phosphorylation via positive feedback [33]. In addition, the transcription factor early growth responsive gene 1 (EGR1) is associated with vascular proliferative diseases [36]. Knockdown of EGR1 can inhibit the expression level of TRIB2, and the ROS/ERK/EGR1 signaling is involved in PDGF-BB-induced TRIB2 expression in VSMC. However, it remains unclear whether EGR1 directly interacts with the TRIB2 promoter [33]. Although the study did not use VSMC-specific TRIB2 knockout mouse models to investigate further whether TRIB2 affects neointimal formation and its specific mechanisms, the potential role of TRIB2 in VSMC proliferative vascular diseases cannot be underestimated. (Fig. 2E)

Cancer cells

Lung cancer cell

TRIB2 is upregulated in lung cancer tissue, and a high level of TRIB2 expression is associated with poor patient

survival [37]. Previous research has found that overexpression of TRIB2 enhances the proliferation and migration of lung cancer cells, which is closely related to COP1. The interaction between TRIB2 and COP1 participates in regulating COP1 substrate inhibitory κB-α (IκB-α) phosphorylation, leading it into the ubiquitination degradation pathway, while IκB-α can also directly interact with COP1 and TRIB2 to form ternary complexes [38]. In addition, knocking down TRIB2 leads to an increase in the expression and activity of the CCAAT enhancer-binding protein α (C/EBPα), thereby promoting the proliferation of lung cancer cells. The interaction between TRIB2 and tripartite motif-containing protein 21 (TRIM21) plays a crucial role in C/EBPα degradation, and TRIB2 or TRIM21 alone has little or no degradation effect on it [39].

Multiple miRNAs are associated with regulating TRIB2 expression levels in lung cancer cells. MiR-206 and miR-140 regulate TRIB2 promoter activity through p-small mothers against decapentaplegic 3 (Smad3) binding to CAGACA, leading to lung cancer cell death and suppressed cell proliferation [40]. Let-7c (tumor suppressive miRNA), miR-511, and miR-1297 can elevate the expression of C/EBPα by targeting TRIB2 to inhibit the proliferation of lung cancer cells [41, 42].In terms of radiation therapy, TRIB2 is overexpressed in radiation-resistant A549/R cells. MiR-511 elevates B cell lymphoma-2 (Bcl-2) associated X protein (Bax) expression by suppressing TRIB2 and arrests the cell cycle in the G1-S transition phase, effectively regulating the growth of radiation-resistant A549/R cells and offering a potential therapeutic approach for treating radiation-resistant lung adenocarcinoma [43].

Pyruvate kinase M2 (PKM2) is a critical enzyme in glycolysis and participates in metabolic reprogramming, pivotal in the proliferation and migration of tumor cells [44]. In lung cancer cells, TRIB2 phosphorylates PKM2 at Ser37 via central pseudokinase domain and interacts with it, causing PKM2 translocation to the nucleus, which subsequently promotes the expression of aerobic glycolysis-related genes glucose transporter 1 (GLUT1) and lactate dehydrogenase A (LDHA), as well as cell proliferation-related genes Cyclin D1 and cellular-myelocytomatosis viral oncogene (c-Myc), thereby regulating aerobic glycolysis, proliferation, and migration of lung cancer cells [37]. These findings not only reveal the new kinase activity of TRIB2, posing a challenge to it as a pseudokinase, but also underscore the significant role of TRIB2 in lung cancer cell proliferation through metabolic reprogramming. (Fig. 3A)

Liver cancer cell

TRIB2 is pivotal in liver cancer cells' viability and oncogenic conversion. Wang et al. demonstrated that suppression of TRIB2 expression attenuates both the population density and proliferative capacity of liver cancer cells while having no discernible impact on the proliferation and apoptosis of normal liver cells [45]. The canonical Wnt signaling pathway governs the cytoplasmic abundance of β-Catenin. When β-Catenin stabilizes in the cytoplasm, it translocates to the nucleus, where it interacts with the T cell factor (TCF) family of transcription factors, thereby instigating the transcriptional activation of downstream target genes [46]. In liver cancer cells, TRIB2 emerges as a downstream target gene of the Wnt/TCF pathway, and forkhead box A (FOXA) and TCF synergistically regulate TRIB2 transcriptional activation. TRIB2 exerts its oncogenic influence by fostering the protein stabilization of the Yes-associated protein (YAP) via an interaction with the Ub ligase β-transducin repeats-containing protein (β-TrCP) and alleviating the cancer suppressor protein C/EBPα-mediated repression of YAP/transcriptional enhanced associate domain (TEAD) transcriptional activation within liver cancer cells [45]. Moreover, TRIB2 assumes an upstream modulatory role in the Wnt pathway. Xu et al. identified that within liver cancer cells, TRIB2 serves to downregulate the expression and stability of TCF4 and β-Catenin through a complex formed by TRIB2 and E3 Ub protein ligases β-TrCP, COP1, and Smad ubiquitination regulatory factor 1 (Smurf1), thus exerting a suppressive effect on Wnt signaling. The absence of the E3 ligase binding region in TRIB2 protein mitigates the nuclear accumulation of E3 ligases and prevents the ubiquitination of TCF4 and β-Catenin. Intriguingly, TRIB2 overexpression paradoxically attenuates the proliferation of liver cancer cells, underscoring a dualistic role for TRIB2 in the tumorigenic processes of liver cancer cells [47].

In liver cancer cells, the steady-state regulation of the UPS holds significant implications for hepatocarcinogenesis [48]. TRIB2 primarily reduces Ub levels by stimulating the proteasomal degradation of Ub. In the proteasome, the proteasome 20S subunit beta 5 (PSMB5) does not directly interact with TRIB2, but it serves as a pivotal mediator for the function of TRIB2. PCBP2 emerges as a putative downstream effector of TRIB2, significantly correlating with TRIB2. More importantly, PCBP2 interacts with both TRIB2 and PSMB5, with the interaction between PCBP2 and TRIB2 specifically dependent on the DQLVPD motif of TRIB2 and the KH3 domain of PCBP2. Notably, PCBP2 is a prerequisite for TRIB2-mediated induction of PSMB5 activity and subsequent reduction of Ub levels. TRIB2 upregulates PCBP2 predominantly by inhibiting the K48 ubiquitination of PCBP2, culminating in the diminution of the overall K48 Ub level through PSMB5. TRIB2-PCBP2 axis further alleviates the K48 ubiquitination of the terminal effector glutathione peroxidase 4 (GPX4). It maintains its

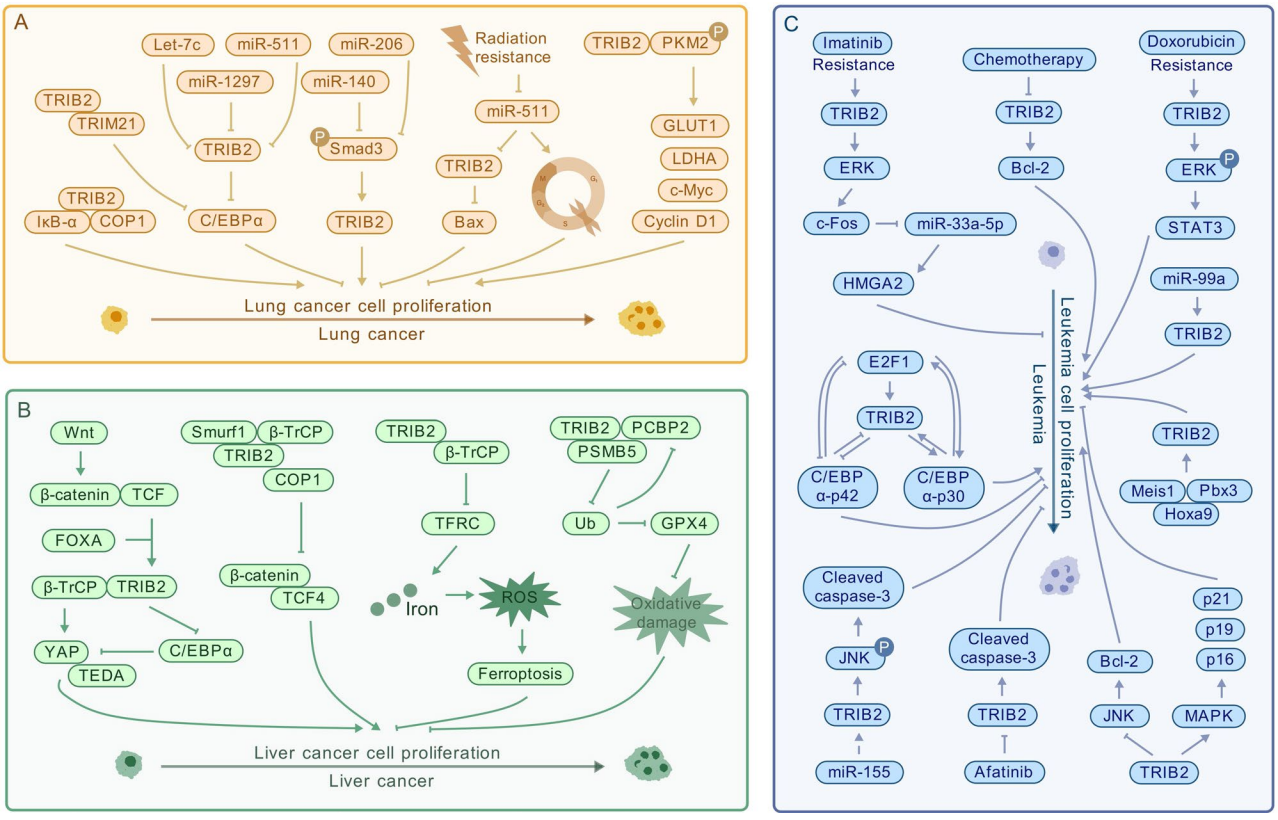

Fig. 3 The role of TRIB2 in the lung cancer cell, liver cancer cell, and leukemia cell proliferation. (**A**) TRIB2 promotes lung cancer cell proliferation by mediating the ubiquitination and degradation of IκB-α and C/EBPα via COP1 and TRIM21, respectively, and enhancing glucose metabolism via phosphorylating PKM2. MiR-206, miR-140, Let-7c, miR-511, and miR-1297 inhibit lung cancer cell proliferation by inhibiting TRIB2. Notably, miR-511 suppresses TRIB2 and inhibits the proliferation of radiation-resistant A549/R cells. (**B**) TRIB2 can be activated by the Wnt/TCF pathway through FOXA transcription and promote liver cancer cell proliferation by stabilizing YAP protein through β-TrCP. Additionally, TRIB2 negatively regulates Wnt activity and inhibits liver cancer cell proliferation by reducing TCF4 and β-Catenin expression through β-TrCP, COP1, and Smurf1. TRIB2 also maintains GPX4 expression through its interactions with PCBP2 and PSMB5, protecting cells from oxidative stress and promoting liver cancer cell proliferation. Furthermore, it reduces intracellular iron levels and ROS production by degrading TFRC through β-TrCP, mitigating ferroptosis-related cell death. (**C**) In Imatinib and Doxorubicin-resistant CML cells, TRIB2 respectively acts on the c-Fos/miR-33a-5p/HMGA2 axis through the ERK signaling pathway and downstream product STAT3 by regulating ERK phosphorylation to promote cell proliferation. Afatinib inhibits AML cell proliferation by inhibiting TRIB2 and inducing caspase-3 cleavage. In drug-resistant AML cells, TRIB2 promotes cell proliferation through Bcl2. E2F1 acts on C/EBPα by activating TRIB2 transcription and forms a feedback loop to promote the proliferation of AML cells. MiR-99a and miR-155 may promote leukemia cell proliferation through TRIB2. Hoxa9/Pbx3/Meis1 complex may promote AML cell proliferation through TRIB2. TRIB2 modulates p16, p19, and p21 through the MAPK signaling pathway, facilitating sustained leukemia cell proliferation after stress. Moreover, TRIB2 increases Cleaved caspase-3 by phosphorylating JNK, inhibiting AML cell proliferation. Created with BioGDP.com. TRIB2, tribbles homolog 2; COP1, constitutively photomorphogenic 1; IκB-α, inhibitory κB-α; TRIM21, tripartite motif-containing protein 21; C/EBPα, CCAAT enhancer-binding protein α; Smad3, small mothers against decapentaplegic 3; Bax, Bcl-2 associated X protein; PKM2, pyruvate kinase M2; GLUT1, glucose transporter 1; LDHA, lactate dehydrogenase A; c-Myc, cellular-myelocytomatosis viral oncogene; TCF, T cell factor; FOXA, forkhead box A; β-TrCP, β-transducin repeats-containing protein; YAP, Yes-associated protein; TEAD; transcriptional enhanced associate domain; Smurf1, Smad ubiquitination regulatory factor 1; TFRC, transferrin receptor; ROS, reactive oxygen species; PCBP2, Poly (rC) binding protein 2; PSMB5, proteasome 20S subunit beta 5; Ub, ubiquitin; GPX4, glutathione peroxidase 4; ERK, extracellular regulated protein kinase; c-Fos, oncogene Fos; HMGA2, high mobility group protein A2; JNK, c-Jun N-terminal kinase; Bcl-2, B cell lymphoma-2; MAPK, mitogen-activated protein kinase; STAT3, signal transducer and activator of transcription 3; E2F1, E2F transcription factor 1; Hoxa, Homeobox a

expression through this mechanism so that liver cancer cells are protected from oxidative stress damage, thereby fostering excessive cell proliferation and promoting the initiation and progression of liver cancer [49].

Guo et al. revealed that TRIB2 exerts an additional role in diminishing the transferrin receptor (TFRC) level mediated by β-TrCP, culminating in reduced labile iron content within liver cancer cells. Consequently, this downregulation impedes the generation of reactive oxygen species, thus desensitizing cells to ferroptosis and ultimately mitigating ferroptosis-associated cell death [50]. (Fig. 3B)

Leukemia cell

TRIB2 is markedly overexpressed in Imatinib-resistant chronic myeloid leukemia (CML) patients. TRIB2 suppresses miR-33a-5p transcription via the ERK/oncogene Fos (c-Fos) signaling pathway, leading to reduced

expression of high mobility group protein A2 (HMGA2), thereby promoting CML cell proliferation and resistance to imatinib [51]. Moreover, TRIB2 knockout in Doxorubicin-resistant CML cells inhibits cell proliferation and enhances intracellular drug accumulation, with reduced expression of multidrug resistance protein 1 (MDR1) and MDR-associated protein 1 (MRP1). Furthermore, TRIB2 modulates drug resistance in CML cells by regulating phosphorylated ERK and its downstream effector signal transducer and activator of transcription 3 (STAT3) [52].

In acute myeloid leukemia (AML), the cell cycle regulator E2F transcription factor 1 (E2F1) binds to and activates the TRIB2 promoter, resulting in the degradation of C/EBPα-p42 and upregulation of the oncogenic C/EBPα-p30 isoform [35, 53, 54]. C/EBPα-mediated inhibition of E2F1 is essential for granulocytic differentiation, and the expression levels of C/EBPα-p42 and -p30 regulate E2F1-driven TRIB2 promoter activation, suggesting a feedback loop involving E2F1 and C/EBPα in the regulation of TRIB2. Meanwhile, E2F1 is critical in regulating TRIB2 expression through C/EBPα-p42 and -p30 [35]. Pharmacological inhibition of the cell cycle or TRIB2 knockdown induces cell cycle arrest and reduces proliferation in AML cells, concomitant with decreased expression of E2F1 and TRIB2. Clinically, the upregulation of TRIB2 levels positively correlates with the E2F1 expression and negatively correlates with C/EBPα expression in AML patients [35]. Afatinib, a covalent inhibitor of the epidermal growth factor receptor (EGFR) family protein kinases, rapidly destabilizes endogenous TRIB2 at low concentrations, inducing caspase-3 cleavage and enhancing cytotoxicity, ultimately prompting AML cell apoptosis [34]. Additionally, TRIB2 overexpression contributes to drug resistance by upregulating Bcl-2, thus mitigating chemotherapy-induced AML cell death [55]. MiR-99a, implicated in the progression of childhood myeloid leukemia, may also promote AML and CML cell proliferation by targeting TRIB2 [56].

Interestingly, Salomé et al. first elucidated the cancer suppressor function of TRIB2 in myeloid leukemia. TRIB2 deficiency impairs MAPK signaling pathway activation, subsequently disrupting cell cycle regulatory factors p21, p16, and p19, leading to sustained proliferation of leukemia cells under stress conditions. Moreover, TRIB2-deficient leukemia cells exhibit enhanced chemotherapy resistance, reduced apoptosis, and continuous proliferation, whereas re-expression of TRIB2 or pharmacological activation of p38 sensitizes these cells to chemotherapy-induced apoptosis [57]. Additionally, miR-155 may enhance c-Jun N-terminal kinase (JNK) phosphorylation by upregulating TRIB2, promoting caspase-3 cleavage, and inducing cell apoptosis [58]. Gilby et al. demonstrated that knockdown of TRIB2 promotes the proliferation of Me-1 cells but has no impact on the growth rate of Kasumi-6, U937, HEL, and K562 cells. Elevated TRIB2 expression in Me-1 cells leads to decreased JNK phosphorylation and triggers cell apoptosis via subsequent dephosphorylation of Bcl-2 at Ser70 [59].

In the experimental setting, the overexpression of most Homeobox a (Hoxa) gene cluster genes is adequate to block the differentiation of primary hematopoietic stem cells and precursor cells in vitro, although Hoxa gene transformation alone sporadically develops leukemia [60]. However, leukemia induction can be effectively propelled under the influence of the cofactor Pbx (homologous to Drosophila) and the bone marrow viral integration site Meis (homologous to Fly) proteins within the three-loop amino-acid-loop extension (TALE) homeobox family [61, 62]. In a mouse bone marrow transplant model, Meis1 overexpression synergizes with various natural and nucleoporin 98 (NUP98)-Hox fusion genes to expedite the onset of AML [63]. As a target gene of Meis1, TRIB2 exhibits expression dependence on the dimerization of Pbx3/Meis1 while inhibiting this dimerization attenuates the proliferation of Hoxa9-transformed primary cells [64]. Similarly, TRIB2 exerts a proliferative effect akin to Meis1 in bone marrow cells mediated by the NUP98-HOXD13 fusion [65]. Moreover, C/EBPα is pivotal in sustaining Hoxa9/Meis1-mediated leukemia cell proliferation. Hoxa9 and C/EBPα act synergistically to inhibit cyclin-dependent kinase inhibitors, thus alleviating arrest in the G1 phase of the cell cycle [66]. Despite the synergistic pathogenic effects between TRIB2 and Hoxa9 on AML [67] and the interaction between C/EBPα and TRIB2 in leukemia cells [35], it is still inconclusive whether TRIB2 is regulated by Hoxa9 and C/EBPα to participate in the proliferation of leukemia cells by affecting the cell cycle. (Fig. 3C)

Pancreatic cancer cell

TRIB2 exhibits heightened expression levels in pancreatic cancer, with its upregulation correlating with poor prognosis among pancreatic cancer patients. Bioinformatics analysis revealed that there is a binding sequence between TRIB2 and miR-505, and lncRNA ZEB1-AS1 is a promoter of proliferation, migration, and invasion in pancreatic cancer cells by regulating the miR-505-3p/TRIB2 axis [68]. These findings indicate that TRIB2 may be an essential regulatory factor in pancreatic cancer development, highlighting a complex regulatory network involving TRIB2 and other non-coding RNAs. (Fig. 4A)

Gastric cancer cell

In chromosomal instability gastric cancer, low TRIB2 mRNA expression correlates with advanced cancer stage [69]. Foscarini et al. found TRIB2 overexpression reduced the proliferation and colony formation ability of MKN45 gastric cancer cells (diffuse histotype) and induced G2/M

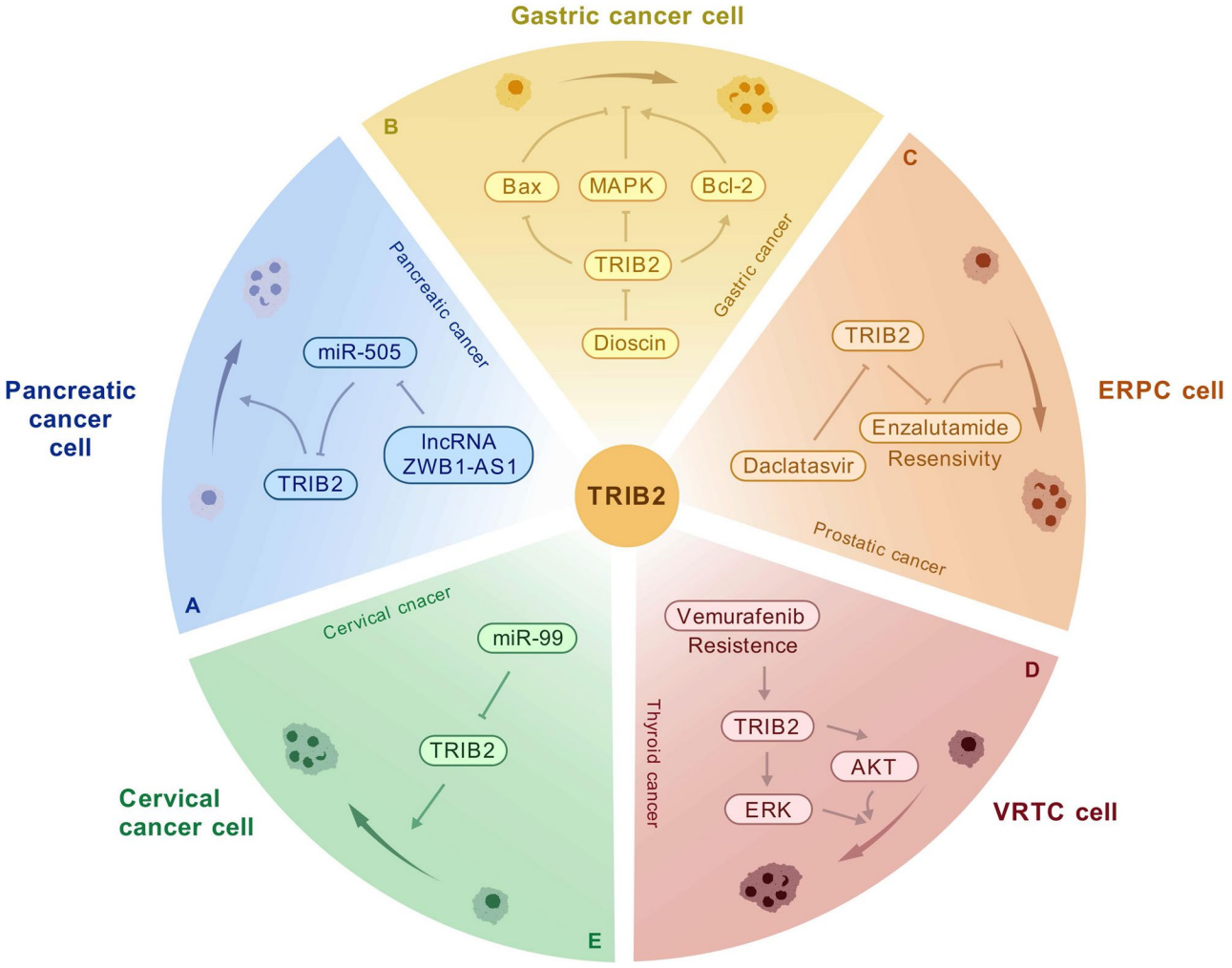

Fig. 4 The role of TRIB2 in pancreatic cancer cell, gastric cancer cell, ERPC cell, VRTC cell, and cervical cancer cell proliferation. (**A**) LncRNA ZEB1-AS1 promotes pancreatic cancer cell proliferation by regulating the miR-505-3p/TRIB2 axis. (**B**) Dioscin activates the MAPK pathway and the Bcl-2 family by inhibiting TRIB2, ultimately suppressing gastric cancer cell proliferation. (**C**) DCV promotes TRIB2 degradation to restore ERPC cell sensitivity to Enzalutamide, thereby inhibiting proliferation. (**D**) TRIB2 promotes VRTC cell proliferation by activating ERK and AKT pathways. (**E**) MiR-99 inhibits cervical cancer cell proliferation by downregulating TRIB2. Created with BioGDP.com. TRIB2, tribbles homolog 2; Bcl-2, B cell lymphoma-2; Bax, Bcl-2 associated X protein; MAPK, mitogen-activated protein kinase; ERPC, Enzalutamide-resistant prostate cancer; VRTC, Vemurafenib-resistant thyroid cancer; ERK, extracellular regulated protein kinase; AKT, protein kinase B

cell cycle arrest without affecting their migration. In contrast, it reduced the proliferation and migration of NCI-N87 cells (intrinsic histotype) without influencing their cell cycle, indicating that TRIB2 inhibits cancer cell proliferation in gastric cancer with chromosomal instability phenotype. The MAPK pathway, closely related to TRIB2, was not implicated in mediating these effects, which may be related to other unexplored mechanisms. In addition, TRIB2 did not affect the survival rate of either gastric cancer cell line following treatment with 5-FU, a commonly used chemotherapeutic agent for gastric cancer [69].

Dioscin, a natural compound derived from certain medicinal plants, exhibits anticancer properties against various types of cancer [70]. Zhao et al. discovered that Dioscin prominently diminishes TRIB2 levels to initiate the MAPK pathway and activate the Bcl-2 family, ultimately triggering apoptosis in MGC803 gastric cancer cells. Intriguingly, while silencing TRIB2 in gastric cancer cells induces apoptosis, the concurrent administration of dioscin intervention only moderates the apoptotic effect observed with TRIB2 silencing alone [71]. The different responses induced by TRIB2 in MKN45, NCI-N87, and MGC803 gastric cancer cells are likely attributable to distinctions in their genetic backgrounds, including somatic mutations and histopathological characteristics of their originating cancers. (Fig. 4B)

Prostate cancer cell

For the treatment of advanced prostate cancer, the commonly used antiandrogenic drug enzalutamide is resistant in some patients. Enzalutamide-resistant prostate cancer (ERPC) cells are not only challenging to be effectively killed but also more likely to invade the bones, leading to a poor prognosis for patients. Monga et al. discovered that TRIB2 expression level is higher in ERPC cells [72]. Overexpression of TRIB2 enhances the growth of prostate cancer cells and makes them resistant to physiological doses of enzalutamide. Screening the TRIB2 fusion protein detection system labeled with luciferase revealed that the antiviral drug Daclatasvir (DCV) can effectively inhibit TRIB2 luciferase activity. Moreover, DCV directly binds to TRIB2 and promotes its degradation, making ERPC cells re-sensitive to enzalutamide. Furthermore, the synergistic effect of lower sublethal doses of DCV and enzalutamide can reduce the viability of prostate cancer cells and induce cell apoptosis [72]. These findings provide new ideas for overcoming enzalutamide resistance, and DCV may become a potential adjuvant therapy drug. (Fig. 4C)

Thyroid cancer cell

$BRAF^{V600E}$ mutation serves as a pivotal driver in cancer and is closely related to cancer invasiveness and prognosis in thyroid cancer patients [73]. Despite the application of Vemurafenib in treating thyroid cancer harboring the $BRAF^{V600E}$ mutation, the issue of drug resistance remains a significant challenge [74]. TRIB2 exhibits upregulation in Vemurafenib-resistant thyroid cancer cells and facilitates the activation of ERK and AKT to enhance cell invasion and proliferation capability and epithelial-mesenchymal transition (EMT). Conversely, TRIB2 knockdown impedes the activation of ERK and AKT, mitigates the invasion and EMT, and induces cell apoptosis [75]. These findings underscore the critical regulatory role of TRIB2 in Vemurafenib-resistant thyroid cancer, positioning it as a potential therapeutic target in this context. (Fig. 4D)

Cervical cancer cell

MiR-99 regulates cell apoptosis, proliferation, and angiogenesis, commonly exerting inhibitory effects in cancers [76]. TRIB2, identified as a targeted gene of miR-99, experiences reduced expression levels upon miR-99 overexpression in cervical cancer cells, consequently impeding cell proliferation [77]. (Fig. 4E)

Melanoma cell

The cancer analysis arrays showed that TRIB2 is overexpressed explicitly in melanoma but not in other types of skin cancer [78]. Chen et al. found that TRIB2 expression is upregulated in human melanoma tissue. The silencing of TRIB2 in melanoma cells leads to a decrease in proliferation and an increase in apoptosis, a decrease in Bcl-2 levels, and an increase in Bax and Cleaved caspase-3 levels [78, 79]. In addition, knocking out circ_0084043 in melanoma cells may inhibit cell proliferation and the Wnt/β-Catenin pathway by upregulating miR-429 and downregulating TRIB2 [79].

The transcription factor forkhead transcription factor O (FOXO) plays a pivotal role in regulating the expression of various genes involved in cell cycle progression, proliferation, and apoptosis, ultimately exerting cancer-suppressive effects [80]. Zanella et al. observed a correlation between the transcription level of TRIB2 and the extent of cytoplasmic localization of FOXO3a. TRIB2 confers growth and survival advantages to melanoma cells by impeding FOXO function [78]. (Fig. 5A)

Colorectal cancer cell

TRIB2 expression is markedly upregulated in colorectal cancer tissue, with a notable association observed between TRIB2 expression levels and cancer grading. High expression of TRIB2 correlates significantly with shortened overall survival in patients, establishing TRIB2 as an independent prognostic indicator for colorectal cancer patients [81, 82].

Liu et al. found that the downregulation of TRIB2 exerts inhibitory effects on the proliferation, migration, invasion, and induced apoptosis in colorectal cancer cells [81]. Taurine upregulated gene 1 (TUG1), a member of the lncRNA family, has been implicated in various cancers [83]. Overexpression of TRIB2 is found to counteract the effects of TUG1 silencing mediated repression on proliferation, migration, invasion, and promotion of apoptosis in colorectal cancer cells. Moreover, TUG1 is shown to interact with miR-542-3p and modulate downstream target TRIB2. Knockdown of miR-542-3p or overexpression of TRIB2 partially reverses the inhibitory effects of TUG1 deficiency on the Wnt/β-Catenin pathway [81].

Hou et al. uncovered that the knockdown of TRIB2 markedly decelerates the growth of colorectal cancer cells, manifested by an augmented proportion of the G0/G1 phase and a reduced proportion of the S phase in the cell cycle [82]. Cellular aging is typified by diminished proliferative capacity and cell cycle arrest [84]. Silencing of TRIB2 significantly increases the expression of senescence-related gene p21 and the population of senescence-associated β-galactosidase (SA-β-gal) positive cells, indicating that TRIB2-mediated growth inhibition in colorectal cancer cells is mediated through induction of cellular senescence [82]. Moreover, p53, a pivotal transcription factor implicated in cell cycle inhibition, directly modulates the promoter of p21 [85]. However, no notable alterations in p53 expression levels are observed

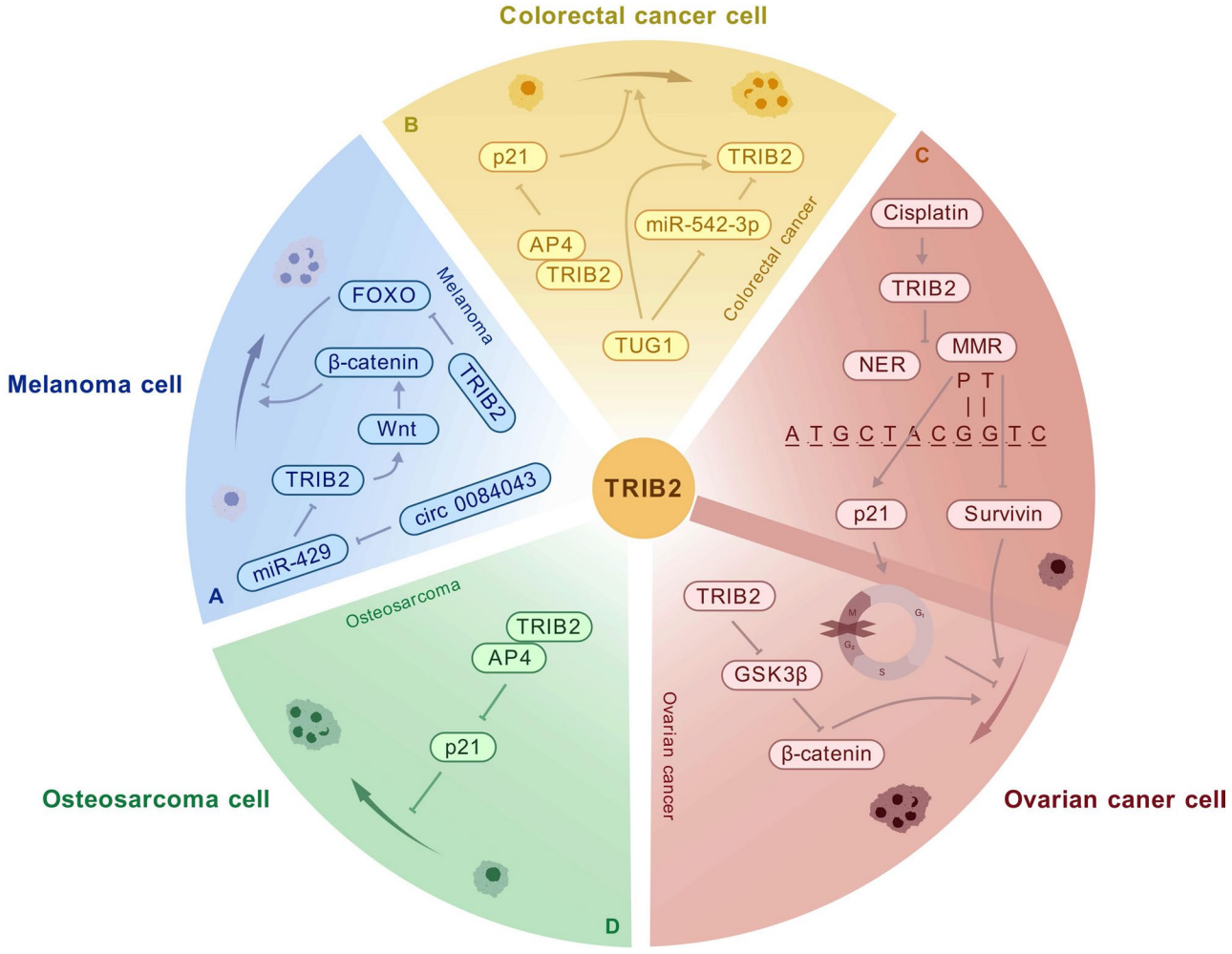

Fig. 5 The role of TRIB2 in melanoma cell, colorectal cancer cell, ovarian cancer cell, and osteosarcoma cell proliferation. (**A**) Circ_0084043 inhibits melanoma cell proliferation by targeting the Wnt/β-Catenin pathway through the miR-429/TRIB2 axis, while TRIB2 promotes melanoma cell proliferation by inhibiting FOXO. (**B**) TUG1 interacts with miR-542-3p to target TRIB2, and TRIB2 inhibits the expression of p21 through AP4 to promote the proliferation of colorectal cancer cells. (**C**) TRIB2 promotes ovarian cancer cell proliferation by regulating the GSK3β/β-Catenin signaling pathway. Cisplatin promotes the transition from NER to MMR through TRIB2, thereby inhibiting Survivor and inducing p21 expression, leading to the arrest of ovarian cancer cells in the G2/M phase and inhibiting their proliferation. (**D**) TRIB2 interacts with AP4 to inhibit the transcription of p21, thereby promoting the proliferation of osteosarcoma cells. Created with BioGDP.com. TRIB2, tribbles homolog 2; FOXO, forkhead transcription factor O; AP4, activating enhancer-binding protein 4; TUG1, taurine upregulated gene 1; NER, nucleotide excision repair; MMR, mismatch-mediated-DNA repair; GSK3β, glycogen synthase kinase 3β

following TRIB2 knockdown or overexpression. Remarkably, even upon silencing TRIB2 in p53-deficient colorectal cancer cells, TRIB2 still exerts inhibitory effects on cell growth and induced cellular senescence by upregulating p21 expression, indicating that the regulatory role of TRIB2 on p21 expression operates independently of p53. Subsequent investigations revealed that the kinase-like domain of TRIB2 enhances the transcriptional activity of activating enhancer-binding protein 4 (AP4) through direct interaction, thereby repressing p21 expression, forestalling senescence, and promoting proliferation in colorectal cancer cells [82]. (Fig. 5B)

Ovarian cancer cell

In ovarian cancer cells, the expression of TRIB2 at both mRNA and protein levels exhibits a significant time-dependent increase [86]. Following cisplatin treatment, TRIB2 leads to a shift from nucleotide excision repair (NER) to mismatch-mediated-DNA repair (MMR) pathway by modulating the stability of protein involved in the NER/MMR pathway. Although MMR cannot repair platin adducts, it can activate the expression of p21, resulting in cell cycle arrest at the G2/M phase and inhibition of Survivin. Ultimately, these events lead to cell growth arrest and apoptosis [87].

In addition, TRIB2 exhibits heightened expression levels in ovarian cancer stem cells (CSCs). TRIB2 overexpression leads to an elevated expression of

stemness-related genes in CSCs, accompanied by augmented size and quantity of spheroids. Mechanistically, elevated TRIB2 expression triggers inactivation of glycogen synthase kinase 3β (GSK3β) inactivation via enhanced AKT-dependent phosphorylation at Ser9, bolstering β-Catenin level and stability through attenuation of GSK3β-mediated β-Catenin phosphorylation. This molecular cascade is pivotal in promoting the proliferation and migration of the spherical CSC population within ovarian cancer cells. Furthermore, in drug resistance, TRIB2 contributes to CSC resistance by regulating the transcription of ABC binding cassette transporter genes, notably ABCB1, ABCG2, and ABCC6. Silencing of TRIB2 enhances susceptibility to cell death in CSCs treated with paclitaxel or cisplatin, whereas TRIB2 overexpression significantly reduces cell death [86]. (Fig. 5C)

Osteosarcoma cell

Guo et al. found that TRIB2 expression was increased in osteosarcoma cells. Through its interaction with AP4, TRIB2 exerts a suppressive effect on the transcriptional activity of p21, consequently augmenting osteosarcoma cells' proliferation, migration, and invasion capacities. Thus, targeting TRIB2 holds promise as a potential therapeutic strategy for the management of osteosarcoma [88]. (Fig. 5D)

Therapeutic potential of targeting TRIB2

TRIB2 is a critical therapeutic target for diseases characterized by cell proliferation due to its pivotal role in regulating this process. Currently, most strategies targeting TRIB2 are based on pharmacological methods, indirectly manipulating the endogenous levels by manipulating its direct regulatory factors. These include downregulating its expression through miRNAs such as Let-7c, miR-511, miR-1297, miR-505, miR-429, miR-99, miR-542-3p, and miR-100-5p, or promoting its degradation by E3 ubiquitin ligase β-TRCP, thereby inhibiting cell proliferation [89]. Moreover, the unique cysteine residues in the pseudokinase domain of TRIB2 (deficiency in TRIB1 and TRIB3) can bind ATP and autophosphorylate in a metal-independent manner, providing potential for small molecule kinase inhibitors to target TRIB2 [90]. Dual human EGFR 2 (HER2) and EGFR inhibitors, such as Afatinib, Neratinib, and Osimertinib, can also interact with cysteine residues of TRIB2, leading to rapid TRIB2 protein degradation [34]. The antiviral drug DCV can effectively inhibit TRIB2 luciferase activity and promote TRIB2 degradation by directly binding to the protein, restoring enzalutamide sensitivity in ERPC cells [72]. Furthermore, two natural alkaloids, Harmine and Piperlongumine, have been proven to reverse TRIB2-dependent transcriptional signatures in osteosarcoma cells [91]. Dioscin, a compound derived from medicinal plants, can also suppress TRIB2 expression to inhibit gastric cancer cell proliferation [71]. Recent studies have found that the nanobody Nb4.103, which binds to TRIB2, not only stabilizes the specific conformation of TRIB2 but also affects the binding of TRIB2 to C/EBPα [92], providing a new possible direction for the development of inhibitors and therapeutic strategies targeting TRIB2.

Conclusions and perspectives

Cell proliferation is a fundamental physiological process essential for normal tissue development and maintenance throughout the life cycle, ensuring the growth, repair, and cellular renewal in response to changing physiological demands. However, under certain pathological conditions, the dysregulation of cell proliferation leads to uncontrolled growth, which may result in various diseases, most notably cancers and other non-cancer conditions such as atherosclerosis and fibrosis. Maintaining proper cell proliferation during normal development and inhibiting excessive proliferation under pathological conditions are pressing challenges. As a pseudokinase, TRIB2 plays a critical role in regulating the proliferation of both cancer and non-cancer cells and participating in various physiological and pathological processes. It exerts its effects primarily through its scaffold or adaptor functions, promoting the degradation of target proteins via E3 ligase-dependent ubiquitination and regulating multiple signaling pathways. These pathways are involved in cell proliferation and death, cell cycle, and metabolism processes, fully demonstrating the complexity of TRIB2 in regulating cell proliferation and its potential as a therapeutic target (Tables 2 and 3).

Although research on TRIB2 in cell proliferation has advanced our understanding of its potential mechanisms, a comprehensive understanding of its role remains incomplete. Future research should focus on the following aspects. Firstly, while TRIB2 mainly promotes cell proliferation and is primarily defined as an oncogene, it has also exhibited inhibitory effects in certain contexts. This dual regulatory function may depend on the specific tissue and cell type it targets. Therefore, we must give sufficient attention and conduct in-depth explorations to its inhibitory effect. Secondly, the impact of TRIB2 regulating intercellular interactions on cell proliferation should be further investigated. For instance, how TRIB2 regulates the interactions between stromal cells, immune cells, endothelial cells, and cancer cells within the cancer microenvironment, and how it modulates the interaction between endothelial cells, inflammatory cells, and VSMCs after vascular injury, promoting the proliferation of cancer cells and VSMCs, respectively. Additionally, research on the involvement of TRIB2 in non-cancer cell proliferation is still relatively limited, and

Table 2 The upstream regulations and downstream targets of TRIB2 and its effects on cell proliferation

Cells	Upstream regulations	TRIB2/E3 Ub ligase	Downstream targets	Effects	References
Granulosa cell	HCG	TRIB2	p-ERK1/2, p38 MAPK	↓	[19]
Myoblast	miR-100-5p	TRIB2		↑	[20]
Naive T cell	ThPOK, RUNX3	TRIB2		↓	[21]
Thymocyte		TRIB2		↓	[22]
VSMC	PDGF-BB/ROS/p-ERK1/2/EGR1	TRIB2		↑	[33]
Lung cancer cell		TRIB2/COP1	IκB-α	↑	[38]
		TRIB2/TRIM21	C/EBPα	↑	[39]
	miR-206/p-Smad3, miR-140/p-Smad3	TRIB2		↑	[40]
	Let-7c, miR-511, miR-1297	TRIB2	C/EBPα	↑	[41, 42]
	Radiation resistance/miR-511	TRIB2	Bax	↑	[43]
		TRIB2	p-PKM2/GLUT1, p-PKM2/LDHA, p-PKM2/Cyclin D1, p-PKM2/c-Myc	↑	[37]
Liver cancer cell	Wnt/β-Catenin/TCF/FOXA	TRIB2/β-TrCP	YAP/TEDA	↑	[45]
		TRIB2/Smurf1, TRIB2/β-TrCP, TRIB2/COP1	β-Catenin/TCF4	↓	[47]
		TRIB2	PCBP2/PSMB5/Ub/GPX4/Oxidative damage	↑	[49]
		TRIB2/β-TrCP	TFRC/ROS/Ferroptposis	↑	[50]
Leukemia cell	Imatinib resistance	TRIB2	ERK/c-Fos/miR-33a-5p/HMGA2	↑	[51]
	Doxorubicin resistance	TRIB2	p-ERK/STAT3	↑	[52]
	E2F1	TRIB2	C/EBPα	↑	[35]
	Afatinib	TRIB2	Cleaved caspase-3	↓	[34]
	Chemotherapy	TRIB2	Bcl-2	↑	[55]
	miR-99a	TRIB2		↑	[56]
		TRIB2	MAPK/p21, MAPK/p16, MAPK/p19	↓	[57]
	miR-155	TRIB2	p-JNK/Cleaved caspase-3	↓	[58]
		TRIB2	JNK/Bcl-2	↓	[59]
	Hoxa9/Meis1/Pbx3	TRIB2		↑	[64]
Pancreatic cancer cell	lncRNA ZWB1-AS1/miR-505	TRIB2	C/EBPα	↑	[68]
Gastric cancer cell		TRIB2		↓	[69]
	Dioscin	TRIB2	Bax, Bcl-2, MAPK	↑	[71]
Prostate cancer cell	Daclatasvir	TRIB2		↑	[72]
Thyroid cancer cell	Vemurafenib resistance	TRIB2	ERK, AKT	↑	[75]
Cervical cancer cell	miR-99	TRIB2		↑	[77]
Melanoma cell	circ_0084043/miR-429	TRIB2	Wnt/β-Catenin	↑	[79]
		TRIB2	FOXO	↑	[78]
Colorectal cancer cell	TUG1/miR-542-3p	TRIB2		↑	[81]
		TRIB2	AP4/p21	↑	[82]
Ovarian cancer cell	Cisplatin	TRIB2	p21, Survivin	↑	[87]
		TRIB2	GSK3β/β-Catenin	↑	[86]
Osteosarcoma cell		TRIB2	AP4/p21	↑	[88]

TRIB2, tribbles homolog 2; Ub, ubiquitin; HCG, human chorionic gonadotropin; ERK, extracellular regulated protein kinase; MAPK, mitogen-activated protein kinase; ThPOK, POZ-Kruppel factor; RUNX3, runx-related transcription factor 3; VSMC, vascular smooth muscle cell; PDGF-BB, platelet-derived growth factor-BB; ROS, reactive oxygen species; EGR1, early growth responsive gene 1; COP1, constitutive photomorphogenic 1; IκB-α, inhibitory κB-α; TRIM21, tripartite motif-containing protein 21; C/EBPα, CCAAT enhancer-binding protein α; Smad3,small mothers against decapentaplegic 3; Bax, Bcl-2 associated X protein; PKM2, pyruvate kinase M2; GLUT1, glucose transporter 1; LDHA, lactate dehydrogenase A; c-Myc, cellular-myelocytomatosis viral oncogene; TCF, T cell factor; FOXA, forkhead box A; β-TrCP, β-transducin repeats-containing protein; YAP, Yes-associated protein; TEAD, transcriptional enhanced associate domain; Smurf1, Smad ubiquitination regulatory factor 1; PCBP2, poly (rC) binding protein 2; PSMB5, proteasome 20S subunit beta 5; GPX4, glutathione peroxidase 4; TFRC, transferrin receptor; c-Fos, oncogene Fos; HMGA2, high mobility group protein A2; STAT3, signal transducer and activator of transcription 3; E2F1, E2F transcription factor 1; Bcl-2, B cell lymphoma-2; JNK, c-Jun N-terminal kinase; AKT, protein kinase B; FOXO, forkhead transcription factor O; AP4, activating enhancer-binding protein 4; TUG1, taurine upregulated gene 1; GSK3β, glycogen synthase kinase 3β

Table 3 The mechanisms of TRIB2 in cell proliferation

Mechanisms	Cells	Pathways/Axes	References
Cell proliferation-related signaling pathways	Granulosa cell	TRIB2/p-ERK1/2	[19]
		TRIB2/p38 MAPK	[19]
	Liver cancer cell	TRIB2/Smurf1/β-Catenin/TCF4	[47]
		TRIB2/β-TrCP/β-Catenin/TCF4	[47]
		TRIB2/COP1/β-Catenin/TCF4	[47]
	Leukemia cell	TRIB2/ERK/c-Fos/miR-33a-5p/HMGA2	[51]
		TRIB2/p-ERK/STAT3	[52]
	Gastric cancer cell	TRIB2/MAPK	[71]
	Thyroid cancer cell	TRIB2/AKT	[75]
		TRIB2/ERK	[75]
	Melanoma cell	TRIB2/Wnt/β-Catenin	[79]
	Ovarian cancer cell	TRIB2/GSK3β/β-Catenin	[86]
Cell death-related signaling pathways	Lung cancer cell	TRIB2/Bax	[43]
	Liver cancer cell	TRIB2/β-TrCP/TFRC/ROS	[50]
		TRIB2/PCBP2/PSMB5/Ub/GPX4	[49]
	Leukemia cell	TRIB2/Cleaved caspase-3	[34]
		TRIB2/Bcl-2	[55]
		TRIB2/p-JNK/Cleaved caspase-3	[58]
		TRIB2/JNK/Bcl-2	[59]
	Gastric cancer cell	TRIB2/Bax	[71]
		TRIB2/Bcl-2	[71]
	Ovarian cancer cell	TRIB2/Survivin	[87]
Cell cycle regulations	Lung cancer cell	TRIB2/p-PKM2/Cyclin D1	[37]
	Leukemia cell	TRIB2/MAPK/p21	[57]
		TRIB2/MAPK/p16	[57]
		TRIB2/MAPK/p19	[57]
	Colorectal cancer cell	TRIB2/AP4/p21	[82]
	Ovarian cancer cell	TRIB2/p21	[87]
	Osteosarcoma cell	TRIB2/AP4/p21	[88]
Cell metabolism regulations	Lung cancer cell	TRIB2/p-PKM2/GLUT1	[37]
		TRIB2/p-PKM2/LDHA	[37]
	Liver cancer cell	TRIB2/β-TrCP/TFRC/ROS	[50]
Others	Lung cancer cell	TRIB2/COP1/IκB-α	[38]
		TRIB2/TRIM21/C/EBPα	[39]
	Liver cancer cell	TRIB2/β-TrCP/YAP/TEDA	[45]
	Leukemia cell	E2F1/ TRIB2/C/EBPα	[35]
	Pancreatic cancer cell	TRIB2/C/EBPα	[68]
	Melanoma cell	TRIB2/FOXO	[78]

TRIB2, tribbles homolog 2; ERK, extracellular regulated protein kinase; MAPK, mitogen-activated protein kinase; Smurf1, Smad ubiquitination regulatory factor 1; TCF4, T cell factor 4; β-TrCP, β-transducin repeats-containing protein; COP1, constitutive photomorphogenic 1; c-Fos, oncogene Fos; HMGA2, high mobility group protein A2; STAT3, signal transducer and activator of transcription 3; AKT, protein kinase B; GSK3β, glycogen synthase kinase 3β; Bax, Bcl-2 associated X protein; TFRC, transferrin receptor; ROS, reactive oxygen species; PCBP2, poly (rC) binding protein 2; PSMB5, proteasome 20S subunit beta 5; Ub, ubiquitin; GPX4, glutathione peroxidase 4; Bcl-2, B cell lymphoma-2; JNK, c-Jun N-terminal kinase; PKM2, pyruvate kinase M2; AP4, activating enhancer-binding protein 4; GLUT1, glucose transporter 1; LDHA, lactate dehydrogenase A; IκB-α, inhibitory κB-α; TRIM21, tripartite motif-containing protein 21; C/EBPα, CCAAT enhancer-binding protein α; YAP, Yes-associated protein; TEAD, transcriptional enhanced associate domain; E2F1, E2F transcription factor 1; FOXO, forkhead transcription factor O

further exploration of its physiological and pathological functions in non-cancer cell proliferation needs to be strengthened.

While early progress has been made in developing small molecule inhibitors, natural products, and nanomaterials targeting TRIB2, this area remains in its infancy. Future efforts should leverage advanced biopharmaceutical technologies to suppress TRIB2 expression and function, promote its degradation, or block its involvement in cell proliferation-related pathways, offering new theoretical insights for maintaining physiological cell proliferation and treating diseases characterized by pathological cell proliferation.

Abbreviations

TRIB2	tribbles homolog 2
ATP	adenosine triphosphate
MAPK	mitogen-activated protein kinase
AKT	protein kinase B

p70S6K	p70 ribosomal protein S6 kinase
NF-κB	nuclear factor κB
Ub	ubiquitin
UPS	Ub proteasome system
PCBP2	poly (rC) binding protein 2
GC	granulosa cell
HCG	human chorionic gonadotropin
PCNA	proliferating cell nuclear antigen
ERK	extracellular regulated protein kinase
CALM1	calmodulin 1
INHBA	inhibin subunit beta A
INPPL1	inositol polyphosphate phosphatase like 1
NT5E	ecto-5′-nucleotidase
SCD	stearyl CoA depletion
SDHB	successive dehydrogenase complex iron sulfur subunit B
RAB14	Ras-associated protein 14
mTOR	mammalian target of rapamycin
ThPOK	POZ-Kruppel factor
RUNX3	runx-related transcription factor 3
5-FU	5-fluorouracil
VSMC	vascular smooth muscle cell
PDGF-BB	platelet-derived growth factor-BB
COP1	constitutive photomorphogenic 1
ROS	reactive oxygen species
EGR1	early growth responsive gene 1
IκB-α	inhibitory κB-α
C/EBPα	CCAAT enhancer-binding protein α
TRIM21	tripartite motif-containing protein 21
Smad3	small mothers against decapentaplegic 3
Bcl-2	B cell lymphoma-2
Bax	Bcl-2 associated X protein
PKM2	pyruvate kinase M2
GLUT1	glucose transporter 1
LDHA	lactate dehydrogenase A
c-Myc	cellular-myelocytomatosis viral oncogene
TCF	T cell factor
FOXA	forkhead box A
YAP	Yes-associated protein
β-TrCP	β-transducin repeats-containing protein
TEAD	transcriptional enhanced associate domain
Smurf1	Smad ubiquitination regulatory factor 1
PSMB5	proteasome 20S subunit beta 5
GPX4	glutathione peroxidase 4
TFRC	transferrin receptor
CML	chronic myeloid leukemia
c-Fos	oncogene Fos
HMGA2	high mobility group protein A2
MDR1	multidrug resistance protein 1
MRP1	MDR-associated protein 1
STAT3	signal transducer and activator of transcription 3
AML	acute myeloid leukemia
E2F1	E2F transcription factor 1
EGFR	epidermal growth factor receptor
JNK	c-Jun N-terminal kinase
Hoxa	Homeobox a
TALE	three-loop amino-acid-loop extension
NUP98	nucleoporin 98
ERPC	Enzalutamide-resistant prostate cancer
DCV	Daclatasvir
EMT	epithelial-mesenchymal transition
FOXO	forkhead transcription factor O
TUG1	taurine upregulated gene 1
SA-β-gal	senescence-associated β-galactosidase
NER	nucleotide excision repair
MMR	mismatch-mediated-DNA repair
CSCs	ovarian cancer stem cells
GSK3β	glycogen synthase kinase 3β
AP4	activating enhancer-binding protein 4
HER2	human EGFR 2

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Author contributions
Wenkang Zhang drafted the manuscript and created the diagrams. Mingkang Li revised the manuscript. Minhao Zhang revised the article format and added references. Gaoliang Yan and Chengchun Tang directed the writing of the manuscript and provided financial support. All authors approved the final version of the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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