

Role and clinical significance of TGF- β 1 and TGF- β R1 in malignant tumors (Review)

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Abstract. The appearance and growth of malignant tumors is a complicated process that is regulated by a number of genes. In recent years, studies have revealed that the transforming growth factor- β (TGF- β) signaling pathway serves an important role in cell cycle regulation, growth and development, differentiation, extracellular matrix synthesis and immune response. Notably, two members of the TGF- β signaling pathway, TGF- β 1 and TGF- β receptor 1 (TGF- β R1), are highly expressed in a variety of tumors, such as breast cancer, colon cancer, gastric cancer and hepatocellular carcinoma. Moreover, an increasing number of studies have demonstrated that TGF- β 1 and TGF- β R1 promote proliferation, migration and epithelial-mesenchymal transition of tumor cells by activating other signaling pathways, signaling molecules or microRNAs (miRs), such as the NF- κ B signaling pathway and miR-133b. In addition, some inhibitors targeting TGF- β 1 and TGF- β R1 have exhibited positive effects in *in vitro* experiments. The present review discusses the association between TGF- β 1 or TGF- β R1 and tumors, and the development of some inhibitors, hoping to provide more approaches to help identify novel tumor markers to restrain and cure tumors.

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1. Introduction

Transforming growth factor- β (TGF- β) is a complicated polypeptide that exerts essential effects on cell cycle regulation, growth and development, differentiation, extracellular matrix (ECM) synthesis, hematopoiesis, chemotaxis and the immune response (1-3). TGF- β 1 and TGF- β receptor 1 (TGF- β R1) serve important roles in the TGF- β family, and have irreplaceable effects on cell reproductive capacity, growth, wound regeneration and immunological reactions (4,5). Almost all cells in the body, not only the epithelium and lymphocytes, but also the stroma, cellular immunity and endotheliocytes, are associated with tumor occurrence and development (6,7). Furthermore, most tumor cells express TGF- β 1 and TGF- β R1 (8-10). Previous studies have found that cancer cells create an environment that hinders the immune response by producing factors, such as TGF- β 1, to evade T-cell surveillance (11,12). Other studies have revealed that TGF- β 1 can cause epithelial-mesenchymal transformation (EMT), resulting in increased migration of cancer cells (13,14). TGF- β R1 is an irreplaceable downstream molecule of TGF- β 1 that participates in the entire life cycle of cells, including cell movement, differentiation, adsorption, fission and death (4,15). Mutant cells that lack TGF- β R1 do not respond to TGF- β 1, which further affects the transduction of the TGF- β signaling pathway (16,17). Additionally, the activation or overexpression of TGF- β R1 is observed in different types of tumor and can serve an important role in tumor cell proliferation and migration to other tissues by taking part in EMT (18), such as in colon (19) and gastric cancer (20). Previous studies (20-22) have revealed that TGF- β R1 is observed in different types of tumor and serves an important role in tumor metastasis by participating in cancer development, cell migration and blood vessel regeneration, leading to unsatisfactory responses to treatment.

The present review primarily discusses the impact of TGF- β 1 and TGF- β R1 on malignant tumors, to offer different strategies to restrain and cure these tumors.

Methods. Literature searches of PubMed/MEDLINE (<https://pubmed.ncbi.nlm.nih.gov/>) for relevant articles published between January 1995 and October 2020 were performed using the key term combinations of 'TGF- β 1', 'TGF- β R1', 'transforming growth factor- β 1', 'transforming growth factor- β receptor1', 'ALK5', 'TGF- β 1' with 'tumor',

'TGF- β R1' with 'tumor', 'TGF- β 1' with 'cancer', 'TGF- β R1' with 'cancer', 'TGF- β 1' with 'inhibitor', 'TGF- β R1' with 'inhibitor' or 'ALK5' with 'inhibitor'. Studies associated with breast cancer, gastric cancer, colon cancer, hepatocellular carcinoma, thyroid cancer, leukemia, cervical cancer, ovarian cancer, lung cancer and inhibitors of TGF- β 1 and TGF- β R1 were selected from the search results. Moreover, to identify clinical progress on inhibitor research, the terms 'LY2382770', 'LY2157299', 'TEW-7197' or 'LY3200882' were searched for at <https://clinicaltrials.gov/>.

2. TGF- β family and its signaling pathway

The TGF- β superfamily is a class of structural and functional polypeptide growth factor subfamilies, including bone morphogenetic protein, growth differentiation factor, anti-Müllerian tube hormone, activin Nodal and TGF- β (4,23). Since TGF- β was first isolated from serum-free culture medium of mouse sarcoma virus-transformed embryonic fibroblasts in 1978, five subtypes of TGF- β have been identified, namely TGF- β 1-5. However, only TGF- β 1/2/3 exist in mammals (24). These three growth factors have 70-82% homology at the amino acid level, but their functions are distinct, with TGF- β 1 being the most important (25). TGF- β R exists on the cell surface and has high affinity for TGF- β (26). According to the features and roles of the receptor, it can be divided into TGF- β R1 (or ALK-5), TGF- β R2 and TGF- β R3 (27,28). At present, seven types of TGF- β R1 and five types of TGF- β R2 have been identified in humans (29). TGF- β signaling positively influences early embryonic growth and tissue and organ formation, immune supervision, tissue repair and adult cell homeostasis (30). Abnormal TGF- β cell signaling transduction pathways are finely regulated at different levels, including ligands, receptors, Smad and nuclear transcription. In the classical Smad signaling pathway (Fig. 1), TGF- β family cytokines first induce serine/threonine kinase receptors on the cell membrane to form functional complexes: two TGF- β R2 and two TGF- β R1 (31,32). Subsequently, TGF- β R2 phosphorylates the domains of glycine and serine in TGF- β R1, activating the kinase activity of TGF- β R1, which then phosphorylates Smad2 and Smad3, binding them to Smad4 and resulting in the synthesis of Smad compounds, nuclear transport and Smad-DNA binding (30). Next, Smad mediates the transcription of target gene DNA to RNA, together with the general transcription factor, other transcription factors or helper proteins (2,33). Additionally, TGF- β can exert signal transduction through non-Smad pathways (Fig. 1). To date, these pathways primarily include the RhoA-Rock1, RAS, ShcA, ERK1/2 and MAPK signaling pathways (34,35).

3. Function and structure of TGF- β 1 and TGF- β R1

In mammals, the TGF- β family uses 33 genes to encode a polypeptide, a predomain of 250 residues and a structural domain of growth factors composed of 110 residues (24). TGF- β 1 is an important member of the cytokine TGF- β superfamily and is located on chromosome 19q3 (30). Mature TGF- β 1 is composed of 112 amino acids and contains nine highly conserved cysteine residues at the C-terminus, which form the rigid structure of cysteine through disulfide linkages (36).

TGF- β 1 exerts a critical effect on cellular development with respect to cell proliferation, differentiation, adsorption and programmed cell death (37).

The generation and secretion of TGF- β 1 is based on latency-associated peptide (LAP), which is a potentially inactive compound with a large predomain and a dimeric non-covalent binding TGF- β 1 growth factor domain (36). Latent TGF- β 1 is activated through coordination with its binding protein. Latent TGF- β binding proteins (LTBPs) consist of four subtypes (LTBP-1, LTBP-2, LTBP-3 and LTBP-4), which covalently bind to LAP through disulfide bonds to form a potential complex with pre-TGF- β 1 (38). Once hydrolyzed by proteases or LAP interactions with integrin α v β 3, α v β 5 or α v β 8, TGF- β 1 can combine with downstream receptors (15).

At present, seven types of TGF- β 1 receptors and five types of TGF- β 2 receptors have been identified in humans (29). The TGF- β 1 receptor contains seven protein activin receptor-like kinases (ALK1-ALK7), and ALK5 is also known as TGF- β R1 (39). TGF- β R1, an essential molecule in the TGF- β signaling pathway with a weight of 53 kDa, phosphorylates serine or threonine in downstream signaling proteins; it consists of a signal peptide, a hydrophilic extracellular region, a transmembrane domain and an intracellular region (27,30). The extracellular region contains multiple cysteines and has a glycosyl slip site; the intracellular region near the membrane contains a region rich in glycine and serine that is associated with its autophosphorylation (40). On the other hand, there is a segment rich in serine/threonine in the intracellular region of TGF- β R2 that can phosphorylate TGF- β R1 during signal transduction, activating the TGF- β R1 kinase region, further phosphorylating downstream substrates and transferring the TGF- β signal into cells (2) (Fig. 2).

4. TGF- β , TGF- β R1 and malignant tumors

In vivo, the development of malignant tumors is a complicated process that is regulated by a variety of genes. Numerous tumor suppressor genes serve a role through TGF- β 1 signaling (41), while TGF- β 1 acts through different pathways, such as ERK1/2, NF- κ B, PUMA and p21WAF1 (42-44). TGF- β 1 regulates the cell cycle, induces apoptosis and inhibits cell proliferation to inhibit the progression of tumors in healthy and precancerous epithelial cells (3); however, this does not always prevent cancer cells from surviving and successfully spreading to other tissues, since in some cases, when the TGF- β 1 signaling pathway is altered, it can affect other signaling pathways or cell signaling molecules (1,45).

Some studies have demonstrated that TGF- β 1 expression is increased in prostate cancer (46), ovarian cancer (47), hepatocellular carcinoma (12), bladder cancer (48), breast cancer (49) and cholangiocarcinoma (50), suggesting that abnormal TGF- β 1 expression can influence tumor invasiveness and result in a poor prognosis. Regarding TGF- β R1, a previous study has found that it promotes tumor angiogenesis by upregulating matrix metalloproteinase 9 in metastatic human melanoma cells (51). Moreover, changes in TGF- β R have been observed in numerous types of human tumors, such as breast (52,53), colon (54) and gastric cancer (20), and are characterized by gene mutations, decreased levels or inactivation of TGF- β R. TGF- β R1 mutations have been

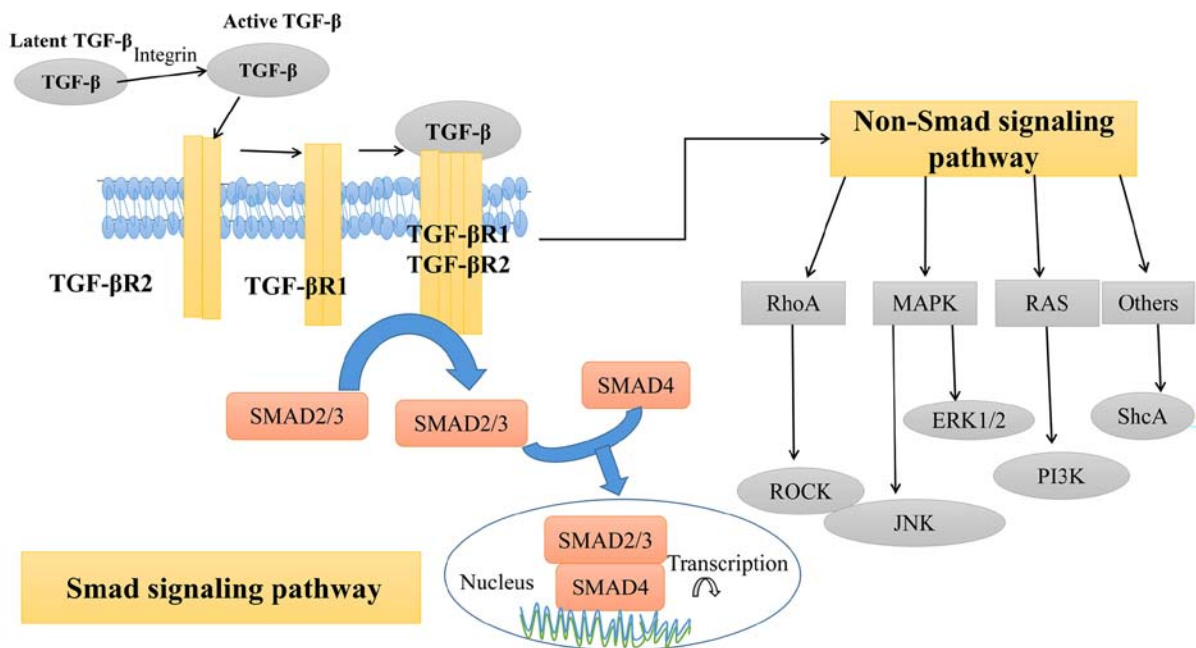


Figure 1. TGF- β signaling pathway. In the Smad signaling pathway, the latent TGF- β is activated by integrins and becomes active TGF- β . TGF- β promotes TGF- β R2 to phosphorylate the domains of glycine and serine in TGF- β R1, activating the kinase activity of TGF- β R1, which then phosphorylates Smad2 and Smad3, binding them to Smad4 and resulting in the synthesis of Smad compounds, nuclear transport and Smad-DNA binding. Next, Smad mediates the transcription of target genes. The TGF- β signaling pathway can also act through non-Smad signaling pathways, which include the RhoA-Rock1, RAS-PI3K, ShcA, MAPK-ERK1/2 and MAPK-JNK signaling pathways. TGF- β 1, transforming growth factor- β 1; TGF- β R1/2, TGF- β receptor 1/2; RhoA, member A of Ras homolog gene family; ROCK, rho-associated kinase; ShcA, Src homology 2/ α -collagen.

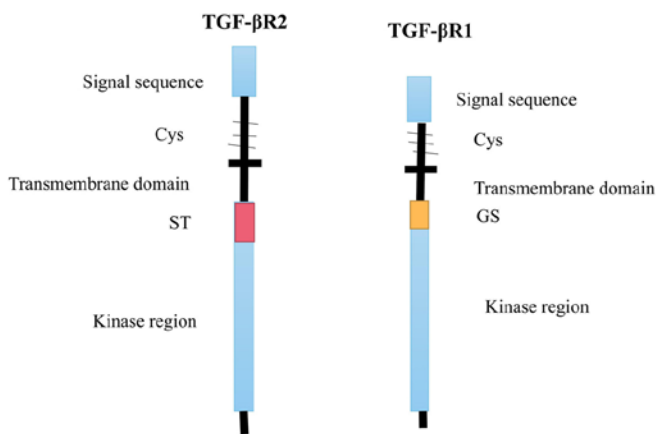


Figure 2. Structure of TGF- β R1 and TGF- β R2. TGF- β R1 and TGF- β R2 contain multiple cysteines and a signal sequence in the extracellular region. In the intracellular region near the membrane, TGF- β R1 contains a region rich in glycine and serine that is associated with its autophosphorylation, and TGF- β R2 contains a region rich in serine and threonine that can phosphorylate TGF- β R1 during signal transduction, activating the TGF- β R1 kinase region. TGF- β R1/2, TGF- β receptor 1/2; Cys, cysteine; GS, glycine and serine domain; ST, serine and threonine domain.

reported in malignant tumors of the ovary, breast and pancreas, as well as in colon cancer (16,52-56). These findings all suggest that TGF- β R mutations serve an important role in the genesis and progression of tumors (57). The functions of TGF- β and TGF- β R1 can be either direct or indirect in the pathogenesis of some tumors (Table I).

Breast cancer (BC). Worldwide, BC is one of the most common types of cancer in women, with high mortality and recurrence

rates (58,59). Although numerous efforts have been made to increase the quality of treatment for BC, the 5-year survival rate of patients after metastasis is 27% (60).

TGF- β 1 is well known to regulate the development, differentiation, carcinogenesis and tumor progression of breast epithelial cells. TGF- β 1 was first identified as a regulatory factor of BC >20 years ago (49). Previous studies have revealed that TGF- β 1 promotes BC metastasis by promoting EMT in tumor cells (61,62). These cells lose epithelial characteristics during EMT, as well as cell polarity and adhesion, developing migratory and invasive capacities (63). It has been demonstrated that microRNAs (miRNAs/miRs) are key factors in the growth and metastasis of numerous invasive tumors (64), and TGF- β 1 signaling is associated with miRNAs (65-67). Compared with benign proliferative breast diseases, TGF- β 1 upregulates miR-21 expression, but it down-regulates miR-196A-3p expression (66,68). miR-21 expression is significantly upregulated in BC (66). A series of steps to promote tumor development through miR-21 occur via mutual interaction with tumor suppressor genes, such as PTEN (66). Thus, the process of TGF- β 1 upregulating miR-21 expression and miR-21 interacting with tumor suppressor genes promotes the progression and therapy resistance of BC (66). The down-regulation of miR-196A-3p by TGF- β 1 is associated with the progression of BC and is a biomarker for predicting BC metastasis and patient survival (68). However, Wang *et al* (63) revealed that overexpression of miR-133b markedly restrained the function of TGF- β R1 in TGF- β 1/Smad signal transduction and inhibited TGF- β induced endometrial stromal transformation and BC cell invasion *in vitro*.

In addition, a previous study has demonstrated that TGF- β 1 can regulate the expression of C-X-C motif chemokine

Table I. Roles of TGF- β 1 and TGF- β R1 in malignant types of cancer.

Type of cancer	Mechanism	Effect	(Refs.)
Breast cancer	TGF- β 1 increases EMT, miR-21, CXCR4 and SMA expression and decreases miR-196A-3p expression; HIF-1 α induces TGF- β 1/Smad3 pathway; Leptin interacts with TGF- β 1; TGF- β R1*6A induces TGF- β , RhoA, ERK1 signaling pathway	Promote	(52,61-63,66,68,69,74)
Colon cancer	miR-133b decreases TGF- β R1 expression	Inhibit	(63)
	TGF- β 1 increases ECM remodeling and growth factors expression; TGF- β 1 increases GPx-1 expression by promoting TGF- β R1/Smad2/ERK1/2/HIF-1 α ; TGF- β 1 increases EMT by promoting NF- κ B pathway; BAG-1 increases TGF- β 1 expression; TGF- β R1 increases EMT by interacting with Neuropilin-2; TGF- β R1*6A promotes MAPK signaling pathway activation	Promote	(19,80,86-88,90-93)
Gastric cancer	Upregulation of lncRNA MORT decreases TGF- β 1 expression	Inhibit	(85)
	TGF- β 1 promotes basement membrane barrier, Tregs expression, ERK signaling pathway activation; TGF- β 1 decreases uPA expression by decreasing miR-193b expression; miR-331-3p promotes EMT by increasing TGF- β R1 expression	Promote	(22,98,102-104,107-109)
Hepatocellular carcinoma	TGF- β 1 promotes angiogenesis, cell adhesion and immunosuppression; TGF- β 1 promotes EMT by JAK/STAT3/Twist signaling pathway; TGF- β 1-miR-140-5p axis promotes EMT; TGF- β 1 promotes HCC-StCs and Ld-MEC proliferation by decreasing NCAM expression; TGF- β 1 decreases KLF4 expression by miR-135a-5p	Promote	(67,111,115-117,119)
	TGF- β 1 inhibits EMT by inhibiting HIPPO signaling pathway; miR-4458 inhibits EMT by decreasing TGF- β R1 expression	Inhibit	(120,121)
Thyroid cancer	TGF- β 1 increases HMGA1 expression by PI3K/Akt signaling pathway; TGF- β 1 promotes cell proliferation, migration and invasion by increasing lncRNA-ATB expression; SLC35F2 induces MAPK signaling pathway by increasing TGF- β R1 and p-ASK-1 expression; miR-483-3p promotes cell migration, invasion and EMT by TGF- β 1	Promote	(125,126,128,129,131)
	TGF- β 1 increases apoptosis by TGF- β /ERK1/2/NF- κ B/PUMA pathway; EGCG promotes EMT, TGF- β /Smad signaling pathway	Inhibit	(127,130)
Leukemia	Fibroblasts decreases NK cells by TGF- β /Smad pathway; Megakaryocytes increases EGR3 expression by increasing TGF- β 1 expression; LRRC33 increases GF- β 1 expression by interacting with Pro-TGF- β 1	Promote	(5,138-142)
Lung cancer	HnRNP K, MAP1B-LC1 promotes EMT by increasing TGF- β 1 expression; TFAP2C promotes cell migration by increasing TGF- β R1 expression; AWPPH increases TGF- β 1 expression	Promote	(21,146,150-152)
	HPIP silencing TGF- β 1; miR-144-3p decreases TGF- β 1 expression by Src-Akt-Erk signaling pathway; miR-98-5p decreases TGF- β R1 expression and EMT; miR-195 and miR-497 decreases TGF- β R1 expression by SMURF2	Inhibit	(18,147,149,153)
Cervical cancer	P68 promotes EMT by increasing TGF- β 1 expression; miR-106b increases TGF- β 1 expression	Promote	(156,158)
	miR-27a decreases TGF- β R1 expression; Sema4C decreases EMT by decreasing TGF- β 1 expression; CDKN2B-AS1 increases miR-181a-5p/TGF- β 1 axis expression; Let-7a decreases TGF- β /Smad signaling pathway expression	Inhibit	(154,157,159,164-168)

Table I. Continued.

Type of cancer	Mechanism	Effect	(Refs.)
Ovarian cancer	TGF- β 1 promotes EMT by inducing TGF- β /Smad and NF- κ B signaling pathways; miR-29b promotes EMC by increasing TGF- β 1 expression; TGF- β 1 induces CD8 ⁺ Treg expression by P38MAPK pathway; miR-520h increases TGF- β 1 expression; carrying TGF- β R1*6A alleles	Promote	(111,169,171-174)

TGF- β 1, transforming growth factor- β 1; TGF- β R1, TGF- β receptor 1; EMT, epithelial-mesenchymal transition; CXCR4, C-X-C motif chemokine receptor 4; SMA, smooth muscle actin; HIF-1 α , hypoxia inducible factor-1 α ; RhoA, member A of Ras homolog gene family; ECM, extracellular matrix; GPx-1, glutathione peroxidase-1; lncRNA MORT, long non-coding RNA mortal obligate RNA transcript; uPA, urokinase-like plasminogen activator; NCAM, neural cell adhesion molecule; HCC-StCs, HCC-derived stromal cells; Ld-MEC, liver-derived microvascular endothelial cells; KLF4, Krüppel-like factor 4; SLC35F2, solute carrier family 35 member F2; EGCG, epigallocatechin-3-gallate; EGR3, epigallocatechin-3-gallate; HnRNP K, heterogeneous ribonucleoprotein k; MAP1B-LC1, microtubule-associated protein 1B-light chain 1; TFAP2C, transcription factor activation enhancer binding protein 2c; HPIP, hematopoietic pre-B-cell leukemia transcription factor-interacting protein; SMURF2, SMAD-specific E3 ubiquitin protein ligase 2; Sema4C, semaphorin 4C; HMGA1, high mobility group A1; p-ASK-1, phosphorylated apoptosis signal-regulating kinase 1; miR, microRNA; Treg, regulatory T cell; NK, natural killer; LRRRC33, leucine-rich repeat containing protein 33.

receptor 4 (CXCR4) in MCF-7 BC cells, which has a critical effect on the metastasis of BC (69). Moreover, the upstream regulator of the TGF- β 1/Smad3 signaling pathway in BC is hypoxia-inducible factor-1 (HIF-1), which regulates the proliferation and apoptosis of BC cells (70). Furthermore, another study has revealed that leptin mediates the metastatic invasiveness and cancer stem cell behavior of BC cells via binding TGF- β 1 and its receptor (71), which may explain why women with BC who are obese or overweight have a poor prognosis according to epidemiological studies (72,73).

Catteau *et al* (74) performed CD34, smooth muscle actin (SMA), TGF- β 1 and TGF- β 1 immunohistochemical experiments on 155 cases of invasive BC and 10 cases of normal breast tissue, and treated breast fibroblast cell lines with TGF- β 1. The results showed that TGF- β 1 was highly expressed in tumor cells and that TGF- β R1 was highly expressed in tumor stroma compared with in normal breast tissue (74). TGF- β 1 can induce the transformation of breast fibroblasts to SMA-positive fibroblasts, and this transformation process is associated with the invasion of BC cells (74). From a genetic point of view, Moore-Smith and Pasche (52) have demonstrated that TGF- β R1*6A is a common low-deformation variant of TGF- β R1, which is associated with the risk of numerous types of cancer, especially BC. Patients with the TGF- β R1*6A allele have a higher risk of BC; in addition, functional analysis revealed that the aforementioned mutation changes the TGF- β signaling pathway and promotes tumorigenesis (52,53,75). Rosman *et al* (53) demonstrated that TGF- β R1*6A enhanced MCF-7 cell migration and invasion by activating the RhoA and ERK signaling pathways.

Colon cancer (CC). CC is a common type of cancer of the digestive system (76). Colorectal cancer is the third most common cause of cancer-associated death in both men and women in the United States according to the American Cancer Society, with ~147,950 individuals diagnosed with CRC and 53,200 who died from the disease in 2020 (77). In previous years, some studies have revealed that TGF- β 1 and TGF- β R1

are significantly associated with the risk of developing human colorectal cancer and may have great importance in tumor metastasis (19,78,79). It is generally believed that TGF- β 1 can restrain the proliferation of tumor cells since it suppresses the proliferation of epithelial cells *in vitro*; additionally, TGF- β 1 promotes ECM remodeling, which may regulate the mutual effect between tumor cells and the matrix/epithelial cell differentiation (80). Furthermore, TGF- β 1 is an effective regulator of immune and inflammatory cells (81). By regulating the function of immune cells, TGF- β 1 is thought to decrease the production of local growth factors and relieve tissue damage caused by free radicals (82,83). Therefore, controlling the proliferation and differentiation of epithelial cells and cell-matrix mutual effects, and keeping organisms away from genetic damage caused by inflammatory cells may serve a large role in the occurrence, acceleration or formation of CC (80-83). The long non-coding (lnc)RNA mortal obligate RNA transcript (MORT) is inhibited in numerous types of human cancer (84), such as ovarian, gastric and colon cancer, indicating its role as a tumor suppressor. Zhou *et al* (85) has revealed that TGF- β 1 increases the invasiveness and mobility of CC cells, while lncRNA MORT stops CC cells from invading and migrating by inactivating TGF- β 1.

BAG-1 is a multifunctional protein associated with the heat shock response, cell signal transduction, cell survival and apoptosis (86). A previous study has found that BAG-1 expression is upregulated during the relatively early stages of colorectal tumorigenesis (87). Notably, BAG-1 is thought to promote the progression of colorectal tumors by inhibiting TGF- β 1 to allow more tumor cells to avoid death (87). Neuropilins were originally thought to be neuron receptors and were later found to be co-receptors for cancer-associated growth factors. The neuropilin family consists of two genes, neuropilin-1 and neuropilin-2 (88). Grandclement *et al* (19) revealed that neuropilin-2 was the receptor of TGF- β 1 through surface isomer resonance experiments. It was demonstrated that the synergistic action of neuropilin-2 and TGF- β R1 facilitated EMT in colorectal cancer cells (19). However, Huang *et al* (89) revealed

that TGF- β 1 induced glutathione peroxidase-1 (GPx-1), which is an antioxidant enzyme (90), expression and enzyme activity by activating TGF- β R1/Smad2/ERK1/2/HIF-1 α signaling cascades, and this GPx-1 upregulation protects human colon adenocarcinoma DLD-1 cells or colorectal cancer cells from oxidative damage. TGF- β 1 and TNF- α also induce EMT in CC cells through the NF- κ B signaling pathway (91).

Slattery *et al* (54) identified several high-risk alleles in the TGF- β signaling family, including in TGF- β 1 and TGF- β R1, in 1,553 patients with CC and 754 patients with rectal cancer, demonstrating that these high-risk alleles increase the possibility of death after a definite diagnosis of CC or rectal cancer. Moreover, a slight decrease in the expression of one allele (the TGF- β RA IVS7G+24A minor allele) of the TGF- β R1 gene is a risk factor for CC (92). Another study has shown that TGFBR1*6A, a subtype of TGF- β R1, enhances the propensity of SW48 cells for metastasis through the MAPK signaling pathway, which may participate in the development of colorectal cancer independently of TGF- β /Smad signaling (93). This indicates that TGF- β R1*6A exerts a carcinogenic function and has an important impact on the migration and invasion of CC cells (93).

Gastric cancer (GC). GC is a malignant neoplasm of the alimentary canal that derives from the gastric mucosal epithelium (94). GC accounted for 5.7% of global cancer cases, and its death rate (8.2%) ranked second among all cancer cases according to the GLOBOCAN 2018 estimates of cancer incidence and mortality produced by the International Agency for Research on Cancer (IARC) (95). At present, the pathogenesis of GC has not been entirely elucidated, and previous studies have demonstrated that multiple genes and regulatory factors are associated with the occurrence and progression of solid tumors, such as GC (96,97). Abnormalities in any part of the TGF- β /Smad signaling pathway may lead to signal transduction disorders, which lead to the development and progression of GC (98). Some studies have shown that TGF- β 1 and TGF- β R1 are highly expressed in GC and are associated with the initiation, development and metastasis of GC (20,99,100). Yanagihara and Tsumuraya (101) have demonstrated that TGF- β 1 restrains proliferation and leads to apoptosis of the GC cell lines HSC-39 and HSC-43 *in vitro*. It has been speculated that TGF- β 1 may regulate the metastatic ability of GC cells by facilitating the destruction and penetration of the basement membrane barrier, and the adhesion and activity of GC cells (102). Therefore, blocking the TGF- β 1 signaling pathway may inhibit the invasion and migration of GC cells. Furthermore, immunosuppression mediated by regulatory T cells (Tregs) is an important mechanism of tumor immune escape, as well as the primary obstacle to the success of tumor immunotherapy (103). A previous study has suggested that GC may gain strength by inducing Tregs under hypoxic conditions through the TGF- β signaling pathway, allowing tumor cells to escape immunosurveillance (104). In addition, increased Tregs in the tumor are critically associated with a poor prognosis in patients with GC (105). A previous study has demonstrated that TGF- β 1 can downregulate miR-193b expression in GC cell lines, and that miR-193b can downregulate urokinase-type plasminogen activator protein expression in GC cells to promote the invasion and peritoneal metastasis

of GC cells (106). In addition, some studies have revealed that the enhanced motility of tumor cells, tumor development and metastasis are associated with the ERK signaling pathway (107-109). TGF- β 1 mediates the ERK signaling pathway in GC with the participation of CD133 (107).

He *et al* (20) conducted a retrospective study of TGF- β R1 genotyping polymorphisms in 479 patients with GC and 483 healthy individuals. The results revealed that two polymorphisms (rs334348 and rs10512263) in TGF- β R1 were associated with a high risk of GC, while rs1927911 and rs10512263 were associated with decreased survival of patients with GC (20). Zhang *et al* (22) performed circular RNA expression profiling and cell culture experiments on GC tissue samples, revealing that TGF- β R1 was overexpressed in GC tissues and that circular RNAs promoted the proliferation, invasion, migration and EMT of GC cells through the regulation by miR-331-3p of TGF- β R1 mRNA and protein expression.

In addition to the aforementioned studies, an increasing number of studies have confirmed a significant impact of TGF- β 1 and TGF- β R1 expression on the biological behavior of malignant tumors, which is closely associated with prognosis (56,75,78).

Hepatocellular carcinoma (HCC). HCC is associated with more than half of the cases of primary liver cancer, ranking sixth among the most frequent types of cancer worldwide and third in cancer-associated deaths according to the GLOBOCAN 2018 estimates of cancer incidence and mortality produced by the IARC (95). The occurrence of liver cancer, like other malignant tumors, is a complex process of multistep, multifactorial and multilink interactions. In recent years, some studies have begun to focus their attention on the TGF- β signaling pathway in HCC (110-112). Numerous studies have demonstrated that TGF- β 1 and TGF- β R1 expression has critical impacts on the growth, metastasis, invasion and prognosis of liver cancer (32,111-114). Peng *et al* (12) analyzed the association between TGF- β 1 expression and clinicopathological characteristics in patients with HCC using The Cancer Genome Atlas, and assessed the impact of TGF- β 1 expression on the ability to recover after treatment. The results demonstrated that increased expression levels of TGF- β 1 promoted a poor prognosis in patients with HCC (12). TGF- β 1 expression is significantly upregulated in HCC tissues and regulates the tumor microenvironment by stimulating angiogenesis, increasing tumor cell adhesion and immunosuppression, or inducing Treg production to promote tumor invasion and metastasis (115). EMT has a critical effect on the development and metastasis of human cancer. TGF- β 1 induces EMT and promotes HepG2 cells to metastasize and invade other tissues through JAK/STAT3/Twist signal transduction (111). Moreover, the TGF- β 1/miR-140-5p axis promotes EMT in liver cell carcinoma by regulating the Flap endonuclease 1 (67). In addition, TGF- β 1 affects the interaction between HCC-derived stromal cells and liver-derived microvascular endothelial cells by downregulating the expression levels of neural cell adhesion molecule, in this way promoting vascular changes induced by HCC (116). Another study has reported that TGF- β 1 activates miR-135a-5p to downregulate Krüppel-like factor 4 (KLF4) to promote proliferation and metastasis of HCC cells (117). KLF4, a zinc finger transcription factor, can regulate the cell cycle,

proliferation and apoptosis (118), and inhibit tumor growth in HCC (119). In addition, Zhang *et al* (120) have demonstrated that TGF- β 1 targets the Hippo signaling pathway by regulating a series of key proteins, such as large tumor suppressor 1 and Yes-association protein 1; this process inhibits the proliferation of hepatoma cells.

Zhang *et al* (121) confirmed TGF- β R1 as a new target gene of miR-4458 through dual-luciferase reporter gene analysis and revealed that miR-4458 inhibited EMT in liver cancer cells by targeting TGF- β R1 to inhibit the TGF- β signaling pathway.

Thyroid cancer (TC). TC represents a group of malignant tumors that primarily originate from follicular cells, which are the main components of the thyroid unicellular epithelium. Anaplastic TC (ATC) is the main cause of death among all malignant thyroid tumors, and the median survival time of patients is ~6 months (122). The tolerance of ATC to routine treatment of TC, including surgery and radioiodine and thyrotropin inhibition, results in a very unsatisfactory therapeutic effect (123). At present, effective means to treat ATC have not been identified, and therefore the survival rate of patients has not improved for >60 years (124). In TC, it has been demonstrated that high expression levels of TGF- β 1 closely affect TC development (125,126). TGF- β 1 promotes apoptosis of ATC cells via TGF- β /ERK1/2/NF- κ B/PUMA signaling (127). Additionally, TGF- β 1 upregulates the expression levels of high mobility group A1 (128), which belongs to the superfamily of non-histone chromatin-binding proteins, serves an important role in multiple cellular biology processes through the PI3K/Akt signaling pathway and upregulates lncRNA-ATB expression to promote TC cell proliferation, migration and invasion (129). miRNAs are also critical factors in the occurrence and growth of numerous tumors. For example, Zhang *et al* (126) found that miR-483-3p targeting par-3 family cell polarity regulator induced TGF- β 1 to promote ATC cell migration, invasion and EMT. Notably, Li *et al* (130) found that epigallocatechin-3-gallate significantly inhibited the invasion and migration of ATC8505C cells *in vitro* by mediating EMT and the TGF- β /Smad signaling pathway.

For TGF- β R1, it has been found that solute carrier family 35 member F2 activates the MAPK signaling pathway by targeting the phosphorylation of TGF- β R1 and apoptosis signal-regulating kinase 1, accelerating the proliferation and migration of thyroid papillary carcinoma cells (131).

Leukemia. Leukemia is a type of malignant clonal disease of hematopoietic stem cells (132). Due to uncontrolled proliferation, impaired differentiation and inhibition of apoptosis, clonal leukemia cells proliferate and accumulate in the bone marrow and other hematopoietic tissues, leading to infiltration of other non-hematopoietic tissues and organs, and inhibition of normal hematopoietic functions (133). According to the degree of differentiation of leukemia, the natural course of disease can be divided into acute and chronic leukemia (134). Although the cure rate of acute lymphoblastic leukemia (ALL) in children is ~90%, the outcome and rescue rate of high-risk subgroups remain poor (135). TGF- β 1 protein has multiple effects on the entire process of hematopoiesis; it can have proliferative or anti-proliferative effects in different

types of cells over time (136,137). Therefore, TGF- β 1 and its downstream molecules have long provided new orientation for the treatment of blood cancers. TGF- β 1 is expressed in numerous human acute myeloid leukemia (AML) cell lines, such as OCI-AML-1, AML-193 and THP-1 cells, and TGF- β 1 affects their proliferation and differentiation through both autocrine and paracrine pathways (138). Natural killer (NK) cells serve a critical role in the inborn immunoreaction of malignant tumors, including leukemia (139). Tumor cells can destroy NK cells by regulating their surface receptors and releasing soluble immunosuppressive substances, including IL-10 and TGF- β (140). Rouse *et al* (141) found that ALL fibroblasts caused NK changes to help them escape innate immune system surveillance by mediating the TGF- β /Smad signaling pathway.

In the early stage of leukemia, megakaryocytes can produce excessive TGF- β 1 and directly upregulate early growth response 3 expression to interfere with the development of normal hematopoietic stem cells in patients with AML (142). This process may provide an effective therapeutic target for improving normal hematopoiesis in AML (142). Ma *et al* (5) found that leucine-rich repeat containing protein 33, a cell membrane-associated protein, formed complexes with pro-TGF- β 1 and regulated the function of TGF- β 1 in AML cells and other myeloid malignancies. However, to the best of our knowledge, no studies have investigated the mechanism of TGF- β R1 in leukemia.

Lung cancer. Lung cancer, including non-small cell lung cancer (NSCLC) and small cell lung cancer, is the dominant cause of cancer-associated death worldwide according to the GLOBOCAN 2018 estimates of cancer incidence and mortality produced by the IARC (95). Modern treatment primarily depends on radiotherapy and chemotherapy (143). NSCLC is the major type of lung cancer and is a severe public health issue in China and in numerous developing countries (144). More than half of patients with NSCLC experience tumor recurrence after surgical resection, and the survival rate of these patients is low (145). TGF- β 1 is closely associated with EMT in epithelial cancers, including NSCLC. Li *et al* (146) found that the interaction between heterogeneous ribonucleoprotein K (HnRNP K) and microtubule-associated protein 1B-light chain 1 promoted the transformation of lung cancer cells from epithelial to mesenchymal cells mediated by TGF- β 1. Shi *et al* (147) investigated the function of hematopoietic pre-B-cell leukemia transcription factor-interacting protein (HPIP) in the transformation of A549 lung cancer cells induced by TGF- β 1 *in vitro*, revealing that HPIP silencing significantly decreased the transformation, migration or invasion of A549 cells mediated by TGF- β 1, which makes HPIP a new potential target for lung cancer treatment.

Previous studies have demonstrated that miRNAs have critical effects on the early diagnosis and treatment of NSCLC. It has been demonstrated that overexpression of miR-29c inhibits the Sp1/TGF- β axis, which induces lung cancer endothelial cells to metastasize (148). miR-144-3p suppresses the metastasis and adhesion of lung carcinoma cells induced by TGF- β 1 by mediating the Src-Akt-Erk signaling pathway (149). AWPPH is a recently discovered lncRNA with carcinogenic effects in HCC and bladder cancer (150,151).

Tang *et al* (152) revealed that AWPPH upregulated TGF- β 1 expression, promoting long-term recurrence after NSCLC.

Kim *et al* (21) found that transcription factor activation enhancer binding protein 2c, which is part of the transcription factor AP-2 family, induced TGF- β R1 upregulation, promoted cell migration and led to malignant development of lung cancer. Jiang *et al* (18) recently discovered that a member of the let-7 miRNA family, miR-98-5p, decreased tumor development and transformation by inhibiting TGF- β R1 and EMT in NSCLC. Notably, SMAD-specific E3 ubiquitin protein ligase 2 (SMURF2) regulates the degradation of TGF- β R1, so that it can be used as a negative adjustment factor in TGF- β signaling (153). Chae *et al* (153) revealed that miR-195 and miR-497 inhibited tumor development by suppressing ubiquitination-mediated degradation of TGF- β R1 through SMURF2, and suggested that they may be used as latent effective targets for the treatment of lung cancer.

Cervical cancer. In recent years, with the improvements in screening and diagnostic techniques and the development of new vaccines, both the prevalence and mortality rates of cervical cancer have decreased; however, cervical cancer ranked fourth in morbidity (6.6%) and mortality (7.5%) rates among all female cancer cases according to the GLOBOCAN 2018 estimates of cancer incidence and mortality produced by the IARC (95). The pathogenesis of cervical cancer is complex and human papilloma virus (HPV) is considered one of the main risk factors (154). Development of EMT is a critical reason for the progression of primary cervical cancer, increased invasiveness and insensitivity to chemotherapy (155). TGF- β 1 can regulate the development of EMT and is considered to be the driving force of EMT in cervical cancer (156). Yang *et al* (157) reported that semaphorin 4C (Sema4C) downregulation inhibited cervical cancer cell EMT, invasion and metastasis, possibly by inhibiting TGF- β 1-induced activation of p38 MAPK in HeLa cells. However, Li *et al* (156) found that p68 promoted EMT in cervical cancer cells through transcriptional activation of the TGF- β 1 signaling pathway. Cheng *et al* (158) revealed that miR-106b was highly expressed in human cervical cancer tissues, and miR-106b targeting disabled-2 (DAB2) genes enhanced TGF- β 1-induced HeLa cell migration and promoted cervical cancer progression. DAB2 is a multimodular scaffold protein with signaling roles in cell proliferation and differentiation (159). Some studies have shown that TGF- β 1 promotes the development and metastasis of cervical cancer by regulating its role in the tumor microenvironment (160-162). Moreover, TGF- β 1 facilitates maspin expression in cervical cancer cells through Smad and non-Smad signaling pathways (163). Recently, miRNAs involved in cancer progression have come into focus. Studies have demonstrated that carcinogenic HPV infection influences the levels of multiple miRNAs in cervical cancer and cervical intraepithelial neoplasia (154,164,165). Cheng *et al* (158) demonstrated that high levels of miR-106b promoted cervical carcinoma cell metastasis by inducing TGF- β 1. Notably, it has been demonstrated that interference with the lncRNA CDKN2B-AS1 upregulates the miR-181a-5p/TGF- β 1 axis, inhibiting metastasis of cervical carcinoma cells and accelerating apoptosis and senescence (166). Additionally, let-7a

restrains cell proliferation in cervical carcinoma through the TGF- β /Smad signaling pathway (167).

Fang *et al* (168) indicated that miR-27a served an anti-cancer role in cervical carcinoma, especially adenocarcinoma, by suppressing the TGF- β R1 signaling pathway. Therefore, enhancement of miR-27a expression and function may be considered as a new therapeutic modality for cervical carcinoma.

Ovarian cancer (OC). OC ranked 8th in mortality (4.4%) among all female cancer cases in 2018 (95). At the time of diagnosis, 75-80% of patients with OC are at stage III/IV disease, since early disease is often asymptomatic (169). Studies have demonstrated that TGF- β 1 has carcinogenic activity in different types of cancer, including OC (48,128,169,170). It has been reported that ubiquitin-specific protease 22 (USP22) facilitates tumor cell proliferation and development of epithelial OC (EOC) by cooperating with TGF- β 1 (171). USP22 serves the role of an oncogene in EOC and may therefore represent a new treatment strategy for individualized EOC therapy. Additionally, it has been reported that ID-1, a member of the inhibitor of differentiation protein family, promotes the development of OC cells by promoting TGF- β 1-induced EMT in human OC cells (172). Notably, TGF- β 1 induces CD8⁺ Tregs in the OC microenvironment through the p38 MAPK signaling pathway; Tregs are highly enriched in the tumor microenvironment and contribute to cancer progression and immune escape (173). The increased CD8⁺ Tregs may help OC cells escape immune surveillance (169). Moreover, TGF- β 1 stimulation increases the expression levels of miR-520h in EOC cells by upregulating its transcription factor c-Myb (a DNA-binding transcription factor), and miR-520h promotes the progression of EOC by downregulating Smad7 and then activating the TGF- β signaling pathway (174).

For TGF- β R1, Baxter *et al* (16) found that carrying TGF- β R1*6A alleles increased the risk of OC in women in case-control studies, but the mechanism of this process remains unclear (16,175).

5. TGF- β 1 and TGF- β R1 inhibitors as treatment

TGF- β 1 and TGF- β R1 in the TGF- β signaling pathway exert multiple functions in regulating tumorigenesis, tumor growth and metastasis. Different inhibitors have been developed for potential anticancer treatments. Numerous inhibitors have been developed against TGF- β R1 or TGF- β 1 (Table II), such as LY2382770 (176), LY2157299 (galunisertib) (177-182), TEW-7197 (183,184) and LY3200882 (185), which have entered experimental clinical research.

LY2382770 is a TGF- β 1 inhibitor for the treatment of diabetic nephropathy and diabetic glomerulosclerosis currently in phase II clinical research (176). LY2157299 is a TGF- β R1 inhibitor currently in development as a drug for the treatment of myelodysplastic syndromes (MDS) in phase II/III (NCT0008318), HCC in phase II (NCT012246986), pancreatic cancer in phase I (NCT02154646) and NSCLC in phase I/II clinical studies (NCT02423343). LY2157299 is the only small molecule inhibitor of TGF- β R currently in a phase III clinical trial (177-182). TEW-7197 (vactosertib), an ALK5 kinase inhibitor developed by MedPacto, is currently undergoing

Table II. Inhibitors of TGF- β 1 and TGF- β R1.

A, TGF- β 1				
Name	Development phase	Indications in clinical trials	Company	(Refs.)
LY2382770	Clinical phase II	Diabetic kidney disease, diabetic nephropathy and diabetic glomerulosclerosis	Eli Lilly and Company	(176)
B, TGF- β R1/ALK5				
Name	Development phase	Indications in clinical trials	Company/First author, year	(Refs.)
LY2157299 (galunisertib)	Clinical phase II/III	Pancreatic carcinoma, glioblastoma, hepatocellular carcinoma, myelodysplastic syndrome	Eli Lilly and Company	(177-182)
TEW-7197	Clinical phase II and clinical phase I	Myelodysplastic syndrome and advanced solid tumor	MedPacto	(183,184)
LY3200882	Clinical phase I	Solid tumor	Eli Lilly and Company	(185)
SB-431542	Pre-clinical study	NA	GlaxoSmithKline	(186-188)
LY2109761	Pre-clinical study	NA	Eli Lilly and Company	(189,190)
SB505154	Pre-clinical study	NA	Araujo <i>et al</i> , 2020	(192)
GW6604	Pre-clinical study	NA	de Gouville <i>et al</i> , 2005	(193)
SD208	Pre-clinical study	NA	Johnson & Johnson	(191)
EW-7203	Pre-clinical study	NA	Park <i>et al</i> , 2011	(194)
Ki26894	Pre-clinical study	NA	Chugai Pharmaceutical Company	(195)
SM16	Pre-clinical study	NA	Suzuki <i>et al</i> , 2007	(196)

TGF- β 1, transforming growth factor- β 1; TGF- β R1, TGF- β receptor 1; NA, not applicable.

phase II clinical trials for MDS and phase I clinical trials for advanced solid tumors, such as melanoma, BC, HCC and prostate cancer (183,184). LY3200882 is another highly selective small molecule ALK5 inhibitor developed by Eli Lilly and Company that competitively binds to the ATP-binding site of the ALK5 kinase domain; a phase I clinical trial for healthy participants has been completed in 2019 (NCT03792139) and participants for a phase I clinical trial for solid tumors are currently being recruited (185).

However, some inhibitors are in the preclinical phase of experimental research, such as SB-431542 (186-188), LY2109761 (189,190), SD208 (191), SB505154 (192), GW6604 (193), EW-7203 (194), Ki26894 (195) and SM16 (196) (Table II). LY2109761 completely inhibits the phosphorylation of Smad2 mediated by TGF- β and has indicated antitumor effects in pancreatic cancer models (189,190). SM16 is a new oral bioavailable kinase inhibitor that combines with the ATP-binding pocket of ALK5, inhibiting its activation (196). SD-208 suppresses the proliferation and migration of mouse and human glioma cells, and enhances their immunogenicity by suppressing ALK-5 autophosphorylation (191). EW-7203 inhibits TGF- β R1 kinase activity, efficiently inhibiting TGF- β 1-induced Smad signaling, EMT and BC metastasis to the lung *in vivo* (194). Further inhibitors should be developed for the clinical treatment of malignant tumors in the future.

6. Conclusion and perspectives

The TGF- β signaling pathway serves an important role in cell cycle regulation, growth and development, differentiation, ECM synthesis, hematopoiesis, chemotaxis and immune response (1-3). In recent years, studies on malignant tumors have revealed that TGF- β 1 and TGF- β R1 may serve important roles in tumor occurrence and development, including in promoting tumor angiogenesis, invasion, EMT and immune escape (4,5,197). Increased expression levels of miR-331-3p (22), HnRNP K (146), Sema4C (157) and p68 (156), and the activation of the JAK/STAT3/ Twist (111), NF- κ B (127) and TGF- β signaling pathways in tumor cells can promote proliferation, migration and EMT through the action of TGF- β 1 or TGF- β R1. Increased levels of some molecules, such as miR-133b (63), miR-4458 and miR-27a (168), inhibit the progression of tumors by acting on TGF- β 1 or TGF- β R1. The increased levels of TGF- β 1 in the tumor itself lead to increases in miR-21, CXCR4, SMA and ECM remodeling, activation of ERK, TGF- β /Smad and NF- κ B signaling pathways, and a decrease of growth factors, miR-196A-3p, miR-193b and KLF4 expression, which promote tumor progression (66,68,69,117,198). On the other hand, self-mutation of TGF- β R1 is considered to promote tumor development through the MAPK signaling pathway (93). Some inhibitors have been developed for both TGF- β 1 and TGF- β R1, including LY2157299, TEW-7197 and

LY3200882 (177-185). LY2157299 specifically downregulates phosphorylation of Smad2 protein induced by TGF- β 1, and significantly inhibits the proliferation and migration of cancer cells (177-182). TEW-7197 (183,184) and LY3200882 (185) competitively bind to the ATP-binding site of the intracellular kinase domain of ALK5 to produce kinase inhibitory activity. These inhibitors are currently in clinical trials. Additionally, there are some inhibitors that can block the activity of ALK5, which are currently in preclinical research, such as SB-431542, LY2109761 and SD208 (186-191).

Therefore, TGF- β 1 and TGF- β R1 seem to have dual effects on tumors. With the development of molecular biology, the dual mechanism of TGF- β 1 inhibition and promotion in tumors is becoming increasingly clear, but the mechanism of TGF- β R1 in tumors remains unclear. At the same time, it has been difficult to clarify the mechanism of TGF- β 1 from tumor suppressor to tumor promoter. However, most studies have indicated that malignant tumors proliferate, metastasize, invade, undergo EMT and escape immune surveillance by acting on TGF- β 1 or TGF- β R1. With the development of clinical trials in the future, the understanding of TGF- β 1 and TGF- β R1 will become more comprehensive. Further exploration of the association between TGF- β 1 and TGF- β R1, and the mechanism of the occurrence and development of malignant tumors will provide useful information for the discovery of new therapeutic targets.

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Authors' contributions

JW wrote the manuscript. JW, YL, HX and TW investigated the roles of TGF- β 1 and TGF- β R1 in tumors. JW and TW are responsible for confirming the authenticity of the data. TW supervised and revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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