Review Article

A narrative review of the relationship between TGF-β signaling and gynecological malignant tumor

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Objective: This paper reviews the association between transforming growth factor-β (TGF-β) and its receptor and tumor, focusing on gynecological malignant tumors. we hope to provide more methods to help increase the potential of TGF-β signaling targeted treatment of specific cancers.

Background: The occurrence of a malignant tumor is a complex process of multi-step, multi-gene regulation, and its progression is affected by various components of the tumor cells and/or tumor microenvironment. The occurrence of gynecological diseases not only affect women's health, but also bring some troubles to their normal life. Especially when gynecological malignant tumors occur, the situation is more serious, which will endanger the lives of patients. Due to differences in environmental and economic conditions, not all women have access to assistance and treatment specifically meeting their needs. TGF-β is a multi-potent growth factor that maintains homeostasis in mammals by inhibiting cell growth and promoting apoptosis *in vivo*. TGF-β signaling is fundamental to inflammatory disease and favors the emergence of tumors, and it also plays an important role in immunosuppression in the tumor microenvironment. In the early stages of the tumor, TGF-β acts as a tumor inhibitor, whereas in advanced tumors, mutations or deletion of the TGF-β signaling core component initiate neogenesis.

Methods: Literatures about TGF-β and gynecological malignant tumor were extensively reviewed to analyze and discuss.

Conclusions: We discussed the role of TGF-β signaling in different types of gynecological tumor cells, thus demonstrating that targeted TGF-β signaling may be an effective tumor treatment strategy.

Keywords: Malignant tumor; signal transduction; transforming growth factor-β (TGF-β); SMAD; gynecology

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Introduction

Malignant tumors are a public health problem that seriously threatens the lives and health of people. For female patients, the total incidence rate of malignant tumors has increased slightly in recent years (1). Gynecological malignancies, such as cervical cancer (CC), endometrial carcinoma (EC),

ovarian cancer (OC), vaginal cancer, and choriocarcinoma, are the main causes of cancer-related death in women (2). In particular, CC, has a high incidence in developing countries, accounting for over 85% of confirmed cases (3). Clinically, the treatment of gynecological malignancies remains challenging, as many cases are not diagnosed until the advanced stage. Transforming growth factor-β (TGF-β) is a cytokine that is involved in the regulation of most cell and molecular processes during development and disease. Extensive studies have shown that TGF-β plays a dynamic role in inhibition and promotion during cancer change (4,5), and TGF-β signaling is a key regulator of tumor initiation and progression. On the one hand, in the early stage, TGF-β signaling can induce cell cycle arrest, apoptosis, and differentiation, thereby inhibiting the abnormal growth of cancer cells and preventing uncontrollable tumor progression (6,7). On the other hand, in advanced tumors, TGF-β secreted by tumor cells can stimulate the formation of matrix and immune evasion of tumor cells. Pathological TGF-β can alter immune and tumor microenvironments, promote epithelial-mesenchymal cell transformation (EMT), cause cancer cell growth, and increase invasion and immune response suppression (8,9). With increasing understanding of molecular details, the function of TGF-β signaling and the extensive role of the TGF-β family in development, immunity, and cancer have been reviewed in detail (5,6,10,11). This review summarizes the impact of TGF-β signaling on gynecological malignancies and provides molecular insights into the development of new anti-cancer strategies.

We present the following article in accordance with the Narrative Review reporting checklist (available at https://dx.doi.org/10.21037/atm-21-4879).

TGF-β superfamily

The TGF-β superfamily is composed of more than 40 cytokines that are classified into TGF-β and bone morphogenetic protein (BMP) subtypes based on their sequence similarity and functional characteristics, which are jointly involved in various biological processes *in vivo* (7,12,13). Currently, three different highly conservative TGF-β subtypes (TGF-β1, TGF-β2, and TGF-β3) have been identified, which show similar sequence homology, and are expressed in mammals (13,14). Among them, TGF-β1 (44 kDa) was the earliest discovered and most studied isoform, and it was expressed in all tissues (15). TGF-β1 activity is multi-potent and can be synthesized by almost all cells. It plays an important role in cell growth and differentiation, apoptosis, extracellular matrix (ECM) formation, angiogenesis, intracellular homeostasis, immune modulation, and tumorigenesis (14,16-19).

TGF-β is secreted in an inactive form, including a signal sequence, a N-terminal region [latency-associated peptide (LAP)], and a mature C-terminal encoding region (20). After the removal of the signal sequence, the active TGF-β dimer is connected to the LAP in non-covalent bonds, forming a small complex, which hinders the key contact sites of the cytokines and their homologous receptors. In a variety of cells, the complex is covalent cross-linked to a latent TGF-β binding protein (LTBP) via a disulfide bond (21), forming a large potential complex (LLC) of 240 kDa. LLC is secreted into the ECM, and active TGF-β is released from LAP by proteases and non-enzyme substances (integrin, pH, or reactive oxygen, etc.) (20,22,23), mediating its biological function.

Regulation of TGF-β signal transduction

TGF-β signaling is a very conservative pathway during development and cell processes, with positive effects on early embryonic growth, cell differentiation, immune regulation, and histohomeostasis (24). The activated TGF-β ligands bind to 7 type I and 5 type II transmembrane TGF-β-receptors (TGFβR) with extracellular serine/threonine kinase activity, thus changing the expression of protein-coding and non-coding target genes (25). TGF-β binds to a single TGFβR-II, promoting the combination of two TGFβR-I and two TGFβR-II into an heterotetrametric complex (26,27). Subsequently, TGFβR-II phosphorylates the kinase activity of TGFβR-I. The activated heterotetramer functional complex activates the downstream SMAD-dependent and SMAD-independent signaling pathways through its serine/threonine activity (28,29).

Canonical TGF-β/SMAD signaling pathway

TGF-β signaling from the receptor to the nucleus depends on the SMAD protein family, which was the first downstream signal sensor of TGF-β to be discovered (30). The active TGFβR-I on the cell surface conducts signals through recruitment and phosphorylation of the SMAD protein. These proteins are divided into different functional groups (12,31): receptor-regulated SMAD (R-SMAD 2 and 3), common mediator SMAD (co-SMAD4), and inhibitory SMAD (I-SMAD 6 and 7). The activated TGFβR-I simultaneously phosphorylates SMAD2 and SMAD3 on the serine/

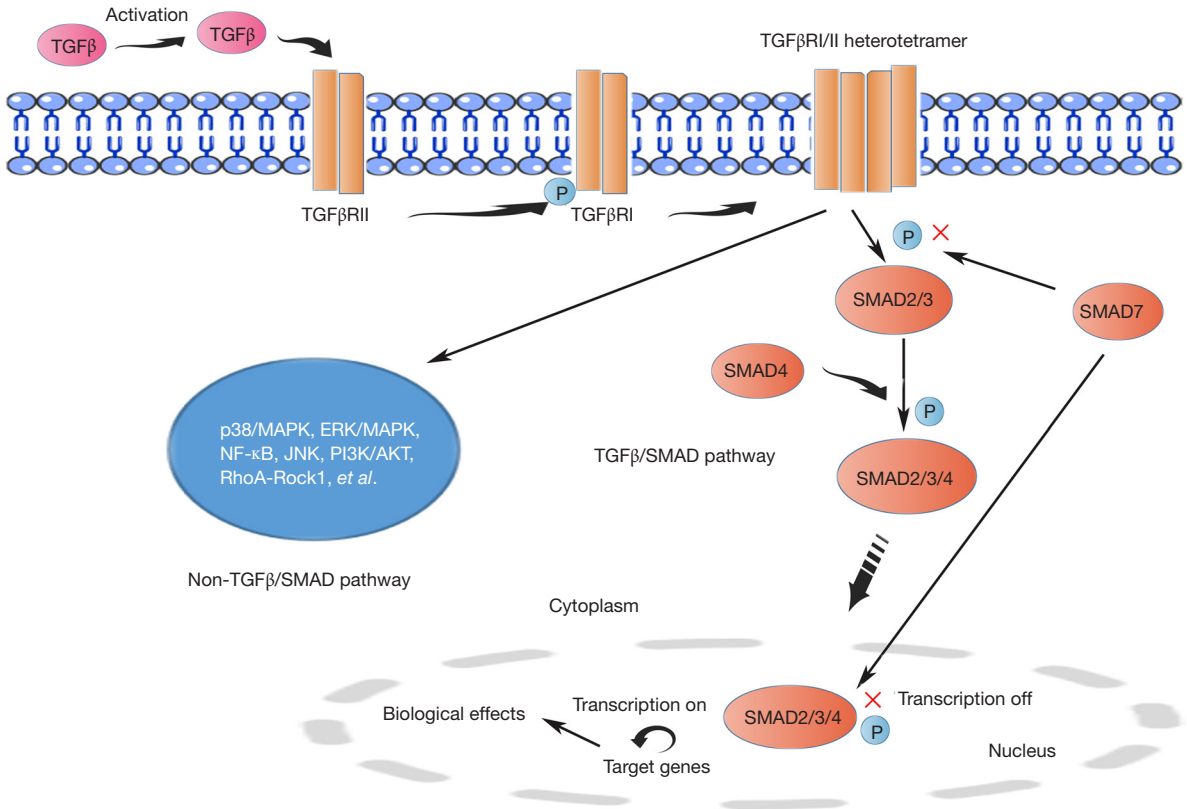

Figure 1 The role of TGF-β signaling pathway in cancer. In the SMAD-dependent pathway (right), TGF-β binds to TGFβR-II and phosphorylates TGFβR-I, which activates SMAD2 and SMAD3. The activated SMAD2/3 forms a complex with SMAD4, which enters the nucleus in the early and advanced stages of tumorigenesis, interacts with various transcription factors and transcription co-activators, and regulates the transcription of the target gene. SMAD7 antagonizes TGF-β-delivery signals by blocking SMAD2/3 activation and interfering with the formation of the SMAD2/3/4 complex. In the SMAD-independent pathway (left), TGF-β signaling can also regulate cellular responses through non-SMAD signaling pathways, such as p38/MAPK, ERK/MAPK, NF-κB, JNK, PI3K/AKT, and RhoA-Rock1, etc. TGF-β, transforming growth factor-β.

threonine kinase residues, resulting in the release of SMAD2 and SMAD3 from the receptor-activated protein, and their C-terminal MH2 domain with SMAD4 oligomization to form the SMAD2/3/4 complex. This complex is translocated to the nucleus mediated by nucleoporins and interacts with various transcription factors to stimulate or inhibit the transcription of its target genes (32,33). It has been observed that SMAD7 is overexpressed in the endometrial cancer cell line (34). Compared with SMAD6, SMAD7 can effectively inhibit the excessive activation of TGF-β signaling. SMAD7 promotes the ubiquitination degradation of the TGFβR-I receptor by recruiting the E3-ubiquitin ligase (35,36). Furthermore, SMAD7 can antagonize the binding of SMAD2/3 and TGFβR-I receptor through its MH2 domain and interfere with SMAD2/3/4 complex (37,38), thereby preventing TGF-β-mediated signal propagation (*Figure 1*).

Non-TGF-β/SMAD signaling pathway

TGF-β is a pleiotropic cytokine from the tumor microenvironment that is thought to mainly primarily regulate the transcription of SMAD-dependent signals, and can also couple with SMAD-independent target genes (12,39) to activate the NF-κB, JNK, p38-MAPK, ERK-MAPK, Rho-GTPase, and PI3K-AKT pathways (*Figure 1*). The mechanisms involved in the non-TGF-β/SMAD pathway remain to be elucidated, perhaps mediating signaling activity alone, or co-regulating TGF-β signaling with the SMAD-

dependent pathway (40,41). Activated SMAD-independent signaling pathways play an important role in cell proliferation, differentiation, apoptosis, metastasis, and ECM protein synthesis. For example, TGF-β can activate RhoA/Rho1-related protein kinases, induce actin polymerization, and then participate in cancer cell movement and EMT (42). The activated TGF-β receptor recognizes TRAF6-TAK1, activates the JNK/p38 channel, and promotes the invasion of a variety of tumor cells *in vitro* (43-45). The autocrine TGF-β of breast cancer cells activates the ERK-MAPK signaling pathway through the phosphorylation of tyrosine and serine residues by TGFβR-I to induce their motility and invasiveness (46,47). In particular, cross crosstalk between the SMAD-dependent and -independent signaling pathways are not mutually exclusive. Studies have found that the two pathways jointly mediate growth arrest of breast cancer cells (48). Although TGF-β also activates other signaling pathways, the SMADs-mediated effects fully reflect the context-dependence of TGF-β action, and novel mechanisms of non-TGF-β/SMAD signaling are likely to be discovered in the near future.

TGF-β and malignant tumors

The development of malignant tumors is a complex process of multi-gene regulation, and the dynamic change of TGF-β expression has been demonstrated in the progression of multiple cancers (4,5,7,12,49). In tumor progression and microenvironments, TGF-β is produced by tumor cells themselves or other cells (such as matrix cells, immune cells, and vascular cells), which plays the dual role of a tumor inhibitor and promoter during the tumorigenesis stage (4,5,50). In premalignant cells, TGF-β signaling can promote cell cycle arrest and apoptosis, thereby inhibiting the occurrence of tumors (51,52). In contrast, abnormal expression of TGF-β is associated with poor prognosis of patients with advanced tumors, and its activity is replaced by oncogenic mutations (53), resulting in the reduction or inactivation of TGFβRs or SMADs, thus promoting the continued proliferation and metastasis of cancer cells (53,54). These studies indicate that component mutations in TGF-β signals may be the main mechanism for TGF-β functional transition.

The inhibitory effect of TGF-β signaling in tumors

Under normal physiological conditions, TGF-β (especially TGF-β1) is an effective cell growth inhibitor, including tumor cells (55). Consistent with its core role in maintaining intracellular homeostasis, TGF-β prevents tumor growth by regulating its cell cycle and apoptosis. The cell cycle is regulated by the action of cyclin-dependent kinase (CDK); TGF-β1 reduces CDK activity by inducing expression of genes such as *p15INK4B*, *p16INK4A*, *p21CIP1*, and/or *p27Kip1* (CDK inhibitors), thereby blocking the cell cycle phase G1 into phase S (*Figure 2A*), which promotes tumor cell growth arrest and senescence (5,7,56). Furthermore, the cytostatic action of TGF-β1 involves transcription inhibition of the proto-oncogene, *c-Myc*. *C-Myc* can bind to the zinc finger protein MIZ1 to inhibit the transcription of *p15* and *p21* (*Figure 2A*), so TGF-β1 mediates the expression of c-Myc to hinder cell proliferation (5,7,55,56). Since TGF-β is not directly coupled to activated apoptosis, its potential regulatory mechanism is still poorly understood (*Figure 2B*). Yoo *et al.* suggested that the apoptosis pathway induced by TGF-β is related to the p38 MAPK signaling (57).

Surprisingly, cell proliferation still occurs, although the TGF-β1 receptor also exists on the tumor cell membrane. This seems to indicate that tumor cells require a higher concentration of TGF-β1 than normal cells to develop TGF-β1-anti-mitotic arrest (58). Boulanger *et al.* noted that an increase in TGF-β1 expression inhibits tumor cell growth in mice infected with breast tumor virus (59). Clinical and experimental studies have shown that the lack of intracellular TGF-β1-induced molecular background during malignant transformation is due to mutations in the TGFβR-II receptor and/or SMAD protein (53-56).

The promotion of TGF-β signaling in tumors

In the early stage of tumor progression, TGF-β signaling inhibits tumor growth. However, in the advanced stage, TGF-β signaling promotes tumor progression via the induction of angiogenesis, EMT, metastasis, and immune response (55,60,61). Currently, high expression TGF-β has been detected in various solid tumors, and it is positively associated with the degree of malignancy (62-65). Tumor cells can escape the inhibitory effect of TGF-β signaling (e.g., gene mutations, gene silencing, and inhibitory effect molecular mechanisms), and mutations or deletion of TGF-β receptors or SMADs can cause inactivation or disturbance of its downstream signal response, and loss of sensitivity to TGF-β (9,11). This strengthens the selective advantage over benign tumors to promote the progression of tumor cells. The most common gene mutations were found in TGFβR-II, which contains a 10-base pair polyadenylic acid repeat region in its coding sequence (66).

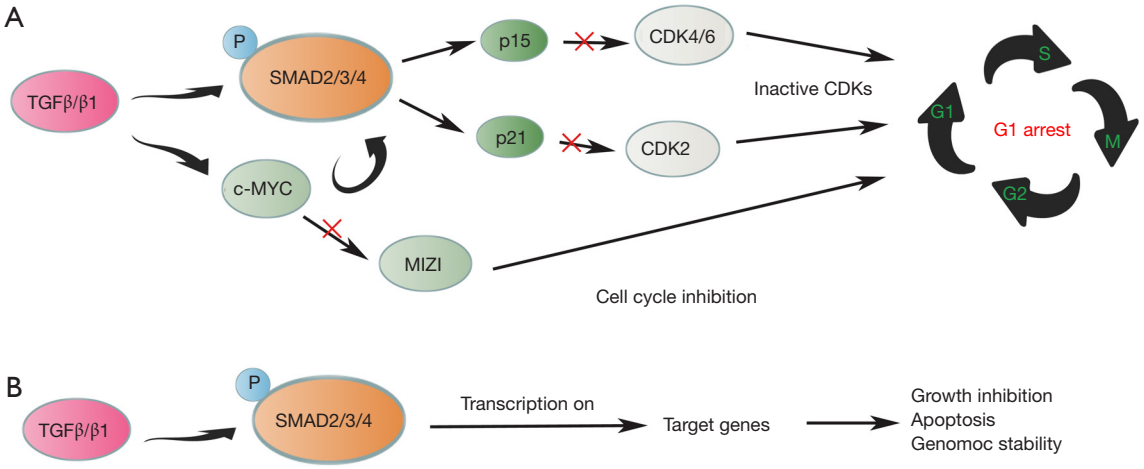

Figure 2 Tumor inhibitory function of TGF-β signaling. (A) TGF-β/β1 controls cell cycle progression by inhibiting oncogenic *c-Myc*, and this factor prevents the transcriptional activation of *CDK* inhibitors (p15 and p21) by interacting with MIZ1. TGF-β/β1 also directly activates *p15* (inactivates *CDK4/6*) and *p21* (inactivates *CDK2*) transcriptionally, which leads to cell cycle arrest at the G1-S boundary. (B) TGF-β/β1 regulates the growth, apoptosis, and genome stability of a variety of cells, however the exact molecular mechanism remains to be determined. TGF-β, transforming growth factor-β; CDK, cyclin-dependent kinase.

SMADs were involved in the anti-tumor process, however gene mutations in SMAD were observed in cases of breast, thyroid, ovarian, and colorectal cancer (55,67-69). In fact, invasive tumors retain the core components of TGF-β signaling, which they appear to give priority to obtaining gene mutations in the core components, thereby producing resistance to TGF-β signaling-mediated growth arrest.

TGF-β and gynecological malignancies

In this review, we focused on EC, OC and CC, which are currently the most common and intensively studied malignant gynecological tumors.

EC

EC is the fourth most common malignancy in women, occurring mainly in western developed countries (70). Early diagnosed EC is cured by surgery with a good prognosis and a reported 5-year survival rate of up to 81% (71). EC is mainly concentrated in women over 45 years of age, while extremely rare in women aged 15–44 (70). According to statistics, the incidence of EC has increased over time in the past 20 years. Unfortunately, approximately 30% of EC are distal invasive and metastasize to extrauterine tissue, placing patients at a higher risk of recurrence and poor prognosis (72,73). Genomic landscape mapping revealed that genetic mutations are related to EC progression.

TGF-β signaling was associated with tumor progression in EC, tumor transformation and tumor progression in the endometrium was accompanied by a significant increase in TGFβR-II protein expression (74). TGF-β signaling is upregulated in a dose-dependent manner in invasive EC colonies grown on a fibronectin matrix (75). Higher levels of TGF-β1, TGFβR-II, SMAD2, SMAD3 and SMAD4 proteins were found compared with normal endometrium (74,76). TGF-β signaling has tumor suppressive effect in normal endometrium, while *in vivo* studies have shown that inactivation of SMAD2/SMAD3 in the mouse uterus leads to endometrial tissue disorders, infertility, and uterine cancer (77). In particular, TGF-β promotes the progression and metastasis of advanced EC, in part by promoting EMT (78), which is supported by TGF-β1-induced low expression of E-cadherin and high expression of N-cadherin, Vimentin, and α-SMA (79). Notably, TGF-β1 induces cell migration in type II EC (80). Due to the important contribution of TGF-β signaling in EC metastasis, inhibition of TGF-β signaling may reduce EC metastasis diffusion.

OC

OC is the seventh most common malignancy in women

worldwide and has the highest mortality among gynecological malignancies (1,2,81). Statistics show that there are more than 230,000 new cases of OC and more than 150,000 deaths globally every year (82). OC is divided into epithelial types, germ-type, or stromal types (cell sources), with epithelial neoplasms being the more common type (83). The early stage of OC is non-specific or atypical, and in addition to the lack of effective early detection, most patients are diagnosed at an advanced stage (III/IV stage) with peritoneal spread throughout the abdomen and pelvis (84). Although diagnosis and treatment strategies for OC have increased survival, the clinical prognosis remains poor, with a 5-year survival rate of less than 30% (85).

TGF-β is considered to be one of the most effective factors in inducing EMT (86), which is part of the oocyte release process (87). Immunohistochemical studies have shown that EMT in OC is significantly associated with peritoneal metastasis (88) and is associated with lower survival in patients (89). TGF-β induces global changes in DNA methylation during the EMT of OC cells (90). Mutations in p53 are the most common marker of high-grade serous OC (91). The tumor microenvironment stimulates the formation of the p53/SMAD/p300 complex, which requires increased transcription of TGF-β itself and may be critical in OC with strong p53 mutations (92). Ubiquitin specific protease 22 (USP22) cooperates with TGF-β to promote cell proliferation in OC (93). USP22 acts as an oncogene in epithelial OC (EOC), which provides a possible therapeutic strategy for individualized EOC. It has been reported that TGF-β increases the production of $CD8^+$ regulatory T cells (Tregs) in OC through the p38/MAPK pathway (94), and Tregs are highly enriched in the tumor microenvironment, which contributes to immune escape of OC cells (95). The fallopian tube is one of the sites of tumor origination and early metastasis of OC. In the fallopian tube, all TGF-β subtypes and their receptors are expressed. Compared with a normal ovary, the expression of all three subtypes (TGF-β1, 2, 3) of EOC is increased (96). Studies have shown that TGF-β is not only derived from tumor cells, but also from peritoneal mesothelial cells and tumor infiltrating cells in OC (97). However, the specific sources and mechanisms of TGF-β activation during OC metastasis remain elusive.

CC

CC is a malignant tumor of the gynecological reproductive system and one of the leading causes of death in women worldwide (1,2,81). Globally, the number of new cases of CC is increasing every year and is accompanied by younger cases (98), especially in developing countries (99). According to a 2018 international authoritative report, the incidence and mortality rates of CC among female related-cancers are 6.6% and 7.5%, respectively (82). Globally, 70% of CC is caused by infection with the human papillomavirus (HPV; two major HPV-16/18 subtypes), but only a small number of women exposed to the virus develop cancer (100), which suggests that other risk factors should also be considered [for example, mortality from CC is highest in countries where human immunodeficiency virus (HIV) is endemic]. In recent years, with the advancement of screening and diagnostic technology as well as the emergence of new vaccines, the prevalence and mortality of CC has exhibited a downward trend, but the treatment of patients with metastatic tumors and poor prognosis still needs to be improved. Therefore, CC remains a major public health problem for women worldwide.

Molecular alterations in TGF-β1 play a key role in the development of CC, which is located on chromosome 19q13.2 and is associated with CC susceptibility (101). Studies have shown that TGF-β1 regulates the metastasis and occurrence of CC in the tumor microenvironment (102,103). Serum TGF-β1 levels decrease during progression from cervical intraepithelial neoplasm to microinvasive carcinoma (104,105). Notably, it has also been shown that TGF-β1 expression is elevated in CC patients compared to normal cervical tissue (106). It was also reported that semaphorin 4c (Sema4c) in HeLa cells inhibit the EMT, invasion, and metastasis of CC cells by inactivating the TGF-β1-induced p38 MAPK pathway (107). Furthermore, TGF-β1 induces the expression of mammary serine protease inhibitor (maspin) in HeLa cells via the SMAD-dependent and SMAD-independent signaling pathways (108), which is an effective inhibitor of tumor cell invasion, metastasis, and angiogenesis. Another study observed a decrease in SMAD2 gene mutation and its expression in CC samples (109), which may impair the anti-tumor proliferative function of the TGF-β/SMAD pathway in CC.

Treatment of gynecological malignant tumor based on TGF-β

In the tumor microenvironment, the tumor inhibition effect of TGF-β is usually replaced by the promotion of tumor invasion in the advanced stage, and excessive secretion of TGF-β will further promote tumor progression and metastasis. Similarly, the high expression of TGF-β is

associated with poor prognosis, so TGF-β and its signaling pathway provide a promising target for the development of anti-tumor therapy. Currently, the basic strategies for blocking TGF-β signaling of human cancer are mainly focused on TGF-β, TGFβRs, or SMADs. Over the years, several approaches have hindered TGF-β signaling, such as small molecule therapies, monoclonal antibodies, or soluble TGF-β receptor and kinase inhibitors, which have been used in preclinical models (7,49,110). Based on two observable factors, research into the methods TGF-β signaling suppression has progressed slowly in clinic. On the one hand, the inhibitory effect of TGF-β signaling in some environments has raised concerns, including whether systematic inhibition of TGF-β signaling will suppress it. Also, it has been observed in experimental models that the initial generation of TGFβR1 inhibitors can cause significant cardiac side effects (111).

Different inhibitors have been successively developed, such as Galoncelib (LY21577299), Vaselteb (TEW-7197), LY2382770, and LY3200882, which have entered into experimental clinical studies as potential anti-cancer therapies. In contrast, the most extensively clinically evaluated is LY21577299, which is a small-molecule TGFβR1 inhibitor. Also, LY2157299 is a targeted drug for the treatment of stage II (112) hepatocellular carcinoma (HCC) and stage I/II (113) non-small cell lung cancer (NSCLC). The combination of LY2157299 and Gemcitatin has shown moderate and significant therapeutic activity in phase II clinical trials of pancreatic cancer (114). In addition, small molecule inhibitors that are more specific than LY2157299 are also being tested in patients. Of these, TEW-7197 has been used in phase I/II clinical trials in cancer (115). Notably, LY2157299 showed a safe profile in these clinical models, with no obvious cardiotoxicity.

While some molecules have shown promising clinical results, anti-TGF-β therapy still needs to overcome multiple challenges. In fact, so far, the results of clinical trials for the TGF-β pathway have not been conclusively tested in other gynecological malignancies (except for uterine and OCs) (116,117). However, from these encouraging clinical trials, there is reason to believe that the strategy of TGF-β based on malignant gynecological tumors has a bright future.

Concluding remarks

The complex mechanisms of TGF-β signaling have been studied over the past several decades. There is evidence that the pleiotropy of TGF-β signaling cascades results from the interaction of SMADs with different specific transcription factors. It is widely believed that TGF-β signaling in cancer cells is altered due to genetic and epigenetic changes, and that TGF-β is primarily an inhibitor of precancerous cells, but acts as a promoter in advanced cancer cells. With the development of molecular biology, the dynamic mechanisms of TGF-β in tumors have become increasingly clear, but we are still in the early stages of understanding the role TGF-β signaling in gynecological tumors. With the increasing understanding of clinical studies on TGF-β, the interest in therapeutic interventions targeting the TGF-β pathway is increasing. Existing studies have indicated that TGF-β plays an important role in the occurrence and metastasis of gynecological tumors at different stages, and the dysregulation of TGF-β signaling pathway is closely related to the occurrence and development of a variety of gynecological tumors. However, the role of TGF-β signaling transduction under normal conditions and its dysfunction in different types of gynecological cancers remains to be further investigated. Of course, there will be further clinical trials and a more complete understanding of TGF-β in the future. Further exploration of the mechanisms through which TGF-β, TGFβRs, and their downstream signals are associated with the occurrence and progression of malignancies will provide useful information for the development of new therapeutic targets and approaches to maximize the therapeutic effect and improve the prognosis of these deadly cancers.

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Footnote

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