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REVIEW

Transforming growth factor-β1 in carcinogenesis, progression, and therapy in cervical cancer

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Abstract Transforming growth factor β1 (TGF-β1) is a multifunctional cytokine that plays important roles in cervical tumor formation, invasion, progression, and metastasis. TGF-β1 functions as a tumor inhibitor in precancerous lesions and early stage cancers of cervix whereas as a tumor promoter in later stage. This switch from a tumor inhibitor to a tumor promoter might be due to various alterations in TGF-β signaling pathway, such as mutations or loss of expression of TGF-β receptors and SMAD proteins. Additionally, the oncoproteins of human papillomaviruses have been shown to stimulate TGF-β1 expression, which in turn suppresses host immune surveillance. Thus, in addition to driving tumor cell migration and metastasis, TGF-β1 is believed to play a key role in promoting human papillomavirus infection by weakening host immune defense. In this article, we will discuss the role of TGF-β1 in the expression, carcinogenesis, progression, and therapy in cervical cancers. A better understanding of this cytokine in cervical carcinogenesis is essential for critical evaluation of this cytokine as a potential prognostic marker and therapeutic target.

Keywords TGF-β1 · Cervical cancers · Tumor promotion · Tumor suppression

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Introduction

Cervical cancer, the third most frequent cancer and the fourth leading cause of cancer death among women worldwide, accounts for nearly 10 % of the total newly diagnosed cancer cases and 8 % of the total cancer deaths [1]. Although high risk human papillomavirus (HPV) is considered as a major etiologic agent for cervical cancer, only a small number of women exposed to this virus develop cancer, implying that other risk factors should be considered [2]. Molecular alterations of tumor suppressor genes and/or oncogenes play a pivotal role in the development of cervical cancer. Since its discovery in the early 1980s, transforming growth factor β (TGF-β) has emerged as a family of growth factors involved in essential physiological processes, including cell proliferation, apoptosis, differentiation, cell motility, angiogenesis, extracellular matrix turnover, immunosuppression, embryonic development, and wound healing [3]. Also, TGF-β1 has been implicated in the pathogenesis of human diseases, such as cancer. It may function as either a tumor suppressor or a tumor promoter depending on the stage of the tumor [4, 5]. TGF-β1 acts as a potent tumor suppressor during early stages of carcinogenesis because of its ability to induce cell cycle arrest and apoptotic reactions [4, 5]. However, during disease progression, tumor cells escape the inhibitory effects of TGF-β and at later stages of carcinogenesis TGF-β1 exert tumor promoter activities [4, 5]. In this article, we will discuss the expression and the role of TGF-β1 in the carcinogenesis, progression, and therapy in cervical lesions. A better understanding of this cytokine in cervical carcinogenesis is essential for critical

evaluation of this cytokine as a potential prognostic marker and therapeutic target.

Biology of TGF-β1

TGF-β belongs to a family of dimeric peptide growth factors including bone morphogenetic proteins, activins, and inhibins [3]. There are three mammalian isoforms of TGF-β ligand, named TGF-β1, TGF-β2, and TGF-β3 with significant homology and similarities in function [3]. TGF-β1 is expressed in epithelial, endothelial, hematopoietic, and connective tissue cells, and TGF-β2 is expressed in epithelial and neuronal cells. While TGF-β3 is expressed primarily in mesenchymal cells [6]. All three isoforms are secreted in a latent form and activated via various mechanisms [3, 4]. Active TGF-β binds to three different cell surface receptors called type I (TβRI), type II (TβRII), and type III (TβR III) receptors. TβRI and TβRII are serine/threonine kinase receptors. TGF-β ligand signals through TβRII, which recruits and phosphorylates the TβRI kinase domain. Recruitment and phosphorylation of TβRI phosphorylate intracellular SMAD2 and SMAD3, which then interact with SMAD4 protein to regulate gene expression in the nucleus [3, 4]. There are several positive and negative feedback mechanisms that control the strength of TGF-β signaling. For example, SMAD7 is stimulated by TGF-β but acts as a negative regulator of this signaling pathway through inhibition of SMAD2 and SMAD3 phosphorylation [4]. TGF-β mediates growth inhibition mainly through this SMAD-dependent pathway. In addition to this canonical signaling pathway, TGF-β binding to its receptors also activates noncanonical signaling pathways such as mitogen-activated protein kinases and the phosphoinositol-3 kinase, as well as small guanosine triphosphatase pathways. These pathways are implicated in epithelial-mesenchymal transition (EMT), tumor cell motility, and migration [4].

Expression of TGF-β1 in cervical lesions

Although there are controversial reports indicating variations in TGF-β1 expression levels among cervical intraepithelial neoplasia (CIN) [7–9], cervical cancer [7, 10], and normal tissue specimens, most studies showed decreased TGF-β1 expression in cervical intraepithelial neoplasia and increased TGF-β1 expression in cervical cancer in comparison to normal cervical tissue [7, 8, 10]. These data suggests TGF-β1 functions as a tumor inhibitor in precancerous cervical lesions and early stage cervical cancers whereas a tumor promoter in later stage tumors.

Decreased expression of TGF-β1 in cervical intraepithelial neoplasia

Decreased expression of TGF-β1 protein was observed commonly in cervical intraepithelial neoplasia [11]. Lower concentrations of plasma TGF-β1 were detected in the patients with cervical intraepithelial neoplasia than that in normal cervical tissues [7]. Similarly, the mRNA levels of TGF-β1 also decreased in cervical intraepithelial neoplasia [12]. Furthermore, Torng et al. [13] indicated that expression of TGF-β1 decreased as tumor cells progressed from cervical intraepithelial neoplasia 1, cervical intraepithelial neoplasia 2, cervical intraepithelial neoplasia 3, to microinvasive carcinoma.

Increased expression of TGF-β1 in cervical cancer

TGF-β1 expression was detected immunohistochemically in about 71.21 % of cervical carcinoma [10], and higher TGF-β1 plasma levels were found in cervical cancer patients compared to healthy control groups [8, 9, 14] and were shown to decrease in patients who underwent surgical resection of their tumors [15]. Additionally, compared with normal cervical tissues, RT-PCR analysis demonstrated an abnormal overexpression of TGF-β1 mRNA in cervical cancer tissues [16].

In some advanced cervical cancers, levels of TGF-β1 are positively associated with clinicopathological features such as tumor size, invasiveness, and dedifferentiation. Interestingly, Farley et al. [17] reported an increase of TGF-β1 and its receptor protein expression during malignant transformation from endocervical epithelium to adenocarcinoma, which was in contrast to findings in squamous cell carcinogenesis and raises the question whether TGF-β1 plays a different role in adenocarcinoma and in squamous cell carcinoma. However, studies comparing TGF-β expression in these two types of cancer have yielded different observations. Santin et al. [18] reported differential TGF-β secretion in adenocarcinoma and squamous cell carcinoma of the uterine cervix in vitro, which was supported by the study by Hazelbag et al. [19]. In contrast, Dickson et al. [20] found no significant difference of TGF-β-1 levels between squamous cell carcinoma and adenocarcinoma.

TGF-β1 polymorphisms with cervical cancer

Although genetic alterations of TGF-β signaling components are common in various types of cancer, mutation of TGF-β1 is uncommon in cancers including cervical cancer. Ramos-Flores et al. [21] found that the frequency of the allele A of the polymorphism G-800A was significantly elevated in cervical cancer patients compared with healthy subjects. In

another study, although none of the TGF-β1−509C>T genotypes were found to be associated with increased risk of cervical cancer, TGF-β1−509T allele was found to be significantly associated with reduced risk of early stage cervical cancer, as well as the progression of late-stage cervical cancer [22] . However, no significant difference was found in the frequencies of TGF-β1 codon 10 and 25 gene polymorphisms between patients with cervical cancer and healthy women both in a Chinese and a Zimbabwe population [23, 24]. Thus, TGF-β1 polymorphism G-800A and TGF-β1−509T allele may present important genetic determinants that together contribute to risk of cervical cancer.

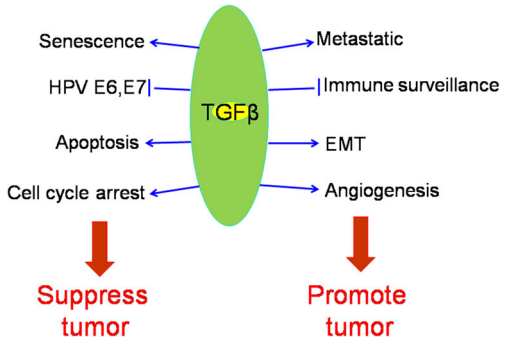

Fig. 1 Overview of the roles of TGF-β1 in cervical cancer. TGF-β1 acts as a potent tumor suppressor during early stages of carcinogenesis because of its ability to induce cell cycle arrest, apoptotic reactions, senescence, and downregulate HPV oncogene E6 and E7 levels. At later stages of carcinogenesis, TGF-β1 exerts tumor promoter activities by promoting epithelial-mesenchymal transition, cell motility, invasion, and inducing angiogenesis, as well as escaping from host immune surveillance in cervical carcinogenesis

Roles of TGF-β1 in cervical lesions

TGF-β1 as a tumor inhibitor in early stage of cervical cancer

Markedly decreased TGF-β1 expression in cervical intraepithelial neoplasia suggested that an early event in the neoplastic transformation of cervical epithelial cells may involve the loss of TGF-β1 [11]. TGF-β1 has major tumor-suppressive properties as its primary function. It inhibits proliferation of epithelial, normal stromal, and hematopoietic cells by promoting cell cycle arrest, inducing apoptosis, autophagy, and senescence [3, 6]. Mechanisms by which TGF-β1 inhibits the growth of cervical carcinoma are complex and may include downregulation of proliferative drivers such as c-Myc and upregulation of p27Kip1 protein [25]. In vitro, TGF-β1 downregulated human papillomavirus-16 oncogene E6 and E7 levels, rescued p53 expression and Rb response pathway, and induced cellular senescence in Caski cells [26], while in Rb mutant HT-3 cells, p130, instead of Rb, mediated TGF-β-induced growth inhibition [27]. More recently, in HeLa cell, TGF-β-activated SMAD3 signaling was shown to inhibit telomerase reverse transcriptase (TERT) gene expression and induced G1/S phase cell cycle arrest and apoptosis [28] (Fig. 1).

TGF-β1 as a tumor promoter in later stage of cervical cancer

TGF-β1 is associated with and promotes metastatic properties

Accumulating evidence showed that TGF-β1 could promote invasion and node metastasis of cervical cancer [5]. Hagemann et al. [29] compared differential gene expression profiles between lymph node micrometastases or recurrent tumors and matched primary cervical cancers by Taqman low-density arrays and found that TGF-β1 was upregulated in lymph node micrometastases, which was further confirmed by immunohistochemistry. A recent study in cervical adenocarcinoma patients with stage Ib~IIa [10] strengthened the evidence that TGF-β1 expression was associated with depth of infiltration and lymphatic metastasis. It can induce remodeling of intratumoral stroma [30] and enhance the interaction between cervical squamous cell carcinoma cells and stromal cells such as cancer-associated fibroblasts [31]. In addition, TGF-β1 promotes tumor invasiveness through matrix metalloproteinase (MMP) induction. For example, MMP-2 and MMP-9 were upregulated in vitro by TGF-β1 [32]. Similarly, in vitro, TGF-β1 treatment significantly increased the invasive behavior of cervical cancer cells [31].

TGF-β1 promotes epithelial-mesenchymal transition

TGF-β1 is a major regulator of the epithelial-mesenchymal transition process, a well-known transdifferentiation program that enables epithelial cells to generate a mesenchymal phenotype [3]. It has been demonstrated that TGF-β1 stimulated epithelial-mesenchymal transition in SiHa and HeLa cells, allowing cancer cells to lose polarity and cell-cell contacts and acquiring fibroblast-like properties, which allow the cells to invade surrounding tissues and eventually metastasize [33, 34].

TGF-β1 induces angiogenesis

TGF-β1 plays a pro-tumorigenic role in cervical cancer also by promoting angiogenesis. TGF-β1 can induce angiogenic factors such as vascular endothelial growth factor in cervical epithelial cells. Moon et al. [35] showed that the serum TGF-β1 levels were positively related to the serum vascular endothelial growth factor levels in the cervical cancer patients.

Similarly, research by Baritaki et al. [36] revealed a co-expression pattern for vascular endothelial growth factor and TGF-β1 mRNAs in Pap smears in normal cervix and low-grade squamous cervical intraepithelial lesions. In addition, TGF-β1 was shown to facilitate the proliferation of human umbilical vein endothelial cells induced by human papillomavirus-positive epithelial cells [37].

TGF-β1 induces the escape from immune surveillance

A growing number of studies suggest immunoregulation may play an important role in cervical cancer carcinogenesis. TGF-β1 is a potent immunosuppressor and plays a crucial role in the escape of cancer cells from immune surveillance [38]. TGF-β1 inhibited T cell proliferation and CD3zeta expression, which was found essential in T cell activation in cervical cancer patients [39]. TGF-β secreted in vitro by cervical cancer cells inhibited the proliferation of CD4+ lymphocytes and induced them to undergo apoptosis [40]. It also drove the upregulation of CD94+/NKG2A+ cells within the CD8+ CTLs and thus diminished their antitumor effect in the cancer milieu [41]. In addition to impairing T cell effector function, TGF-β is also a potent inducer of regulatory T cells (Tregs), which inhibits the functions of effector T cell [14]. Overall, TGF-β1 generates an immunosuppressive state in the microenvironment of the cervix, especially infected with human papillomavirus, and TGF-β1 inhibition may contribute to restoring anti-tumoral cytotoxic immune response.

Together, these data suggest that TGF-β1 promotes tumor progression by promoting epithelial-mesenchymal transition, cell motility, invasion, and inducing angiogenesis, as well as escaping from host immune surveillance in cervical carcinogenesis (Fig. 1).

Alteration of TGF-β1 pathways in cervical cancer

As alluded above, TGF-β1 can inhibit tumor cell growth in early stage of cervical cancer, but it promotes tumor cell growth and progression at late stages. The molecular mechanism of this TGF-β1 paradox remains largely unexplained. In addition to increasing amounts of TGF-β1 secreted by tumor cells, which itself serves as a pro-malignant factor by suppressing immune surveillance in the cancer host and by augmenting angiogenesis, the loss of responsiveness to TGF-β1-mediated growth inhibition in tumor cells can also contribute to tumor growth. De Gees et al. [42] compared the cells sensitivity to TGF-β1 and found that the cervical carcinoma cell lines were resistant to the growth inhibitory effects of TGF-β1, while the cervical intraepithelial neoplasia cell lines were significantly more sensitive than the carcinoma cell lines but less sensitive than normal cervical cells. Mechanisms related to TGF-β1 responsiveness are thought to be due to alterations of the core elements in TGF-β signaling pathway, the receptors, and the SMADs.

Expression and mutation of TGF-β receptor in cervical carcinogenesis

TGF-β type I receptor (TβRI) gene expression levels were decreased in cervical cancer samples in contrast with cervical intraepithelial neoplasia samples [43]. Furthermore, mutations in TβRI were described in cervical cancer. Chen et al. [44] studied 16 paraffin-embedded primary invasive cervical carcinoma specimens by polymerase chain reaction-single-strand conformation polymorphism (PCR-SSCP) and found that 7 of 16 cases were heterozygous for a G=A polymorphism in intron 7 of TβRI, 6 of 16 cases carried del (GGC) 3 TβRI variant allele, also, in one tumor, a silent A=C transversion mutation that might affect mRNA splicing was present in exon 6 of TβRI.

Mutations or loss of expression of TGF-β type II receptor (TβRII) are the most common mechanism of loss of TGF-β signaling in cervical cancer. A decreased expression of TβRII mRNA was demonstrated not only in several cervical cancer cells [45] but in human cervical cancer tissues as well [16]. Kang et al. [45] examined the expression and structural integrity of TβRII gene in a series of human cervical cancer cell lines and reported ME-180 and C-33 cell failed to express TβRII -specific RNA, which in ME-180 was due to a homozygous deletion of the entire TβRII gene. In addition, in a K14-E7 transgenic mice model, diminished expression of TβRII mRNA and protein levels in cervical cancer was also demonstrated and these levels were further decreased after estrogen treatment [46]. Furthermore, research by Chen et al. [44] found a novel G=T transversion in exon 3 of TβRII that introduced a premature stop codon (E142Stop) and presumably resulted in the synthesis of a truncated soluble exoreceptor.

On the other hand, in regard to cervical intraepithelial neoplasia (CIN), levels of TβRI and TβRII stayed the same in CIN1, CIN2, CIN3, and microinvasive carcinoma [13].

Expression and mutation of SMADs in cervical carcinogenesis

SMAD2 gene expression levels were reduced in cervical cancers [16, 43]. Also, research by Maliekal et al. [47] identified a missense mutation in the MH1 domain of SMAD2 in a cervical cancer sample and reported C-terminal of SMAD2 was deleted in human cervical cancer.

The levels of phosphorylated SMAD3 (P-SMAD3) was thought as an indicator of TGF-β signaling activity. Interestingly, Nagura et al. [31], in their study on evaluation of the expression status of TGF-β signaling-associated molecules in 67 cervical cancers, revealed that cases with tumor

boundary P-SMAD3 expression were more likely to have node metastasis and stromal expression of thrombospondin-1, which were a noteworthy poor prognostic factor and an activator of TGF-β signaling, respectively. Thus, P-SMAD3 boundary staining could be an indicator not only of active TGF-β signaling but may also serve as a biomarker to predict progression of cervical cancer.

SMAD4 inactivation is one of the most common alterations in cervical cancer, caused by deletion [16, 47], mutation [47], or epigenetic modification [48]. Many studies showed that loss of SMAD4 expression correlated with a worse prognosis [48]. For instance, in a study by Kloth et al., absent nuclear SMAD4 expression was significantly associated with poor disease-free and 5-year overall survival [48]. Also, SMAD4 was negatively correlated with lymph node metastasis and infiltration depth [49]. In vitro, loss of expression and SMAD4 mutations also were found in cervical cancer cell lines [50]. Baldus et al. [51] performed an analysis of SMAD4 in 13 individual cervical cancer cell lines and detected functional inactivation of SMAD4 in four of the 13 cell lines and was due to homozygous loss of 30 exons in two of them and presumably to insertional inactivation in intron 3 in the other two. SMAD4-mediated tumor suppression in cervical cancer cells may be due to tumor cell extracellular matrix interactions [52].

SMAD7 is an important member of the SMAD family that functions as a negative feedback regulator of TGF-β responses [3]. Overexpression of SMAD7 and suppression of TGF-β signaling have been reported in endometrial carcinomas and thyroid follicular tumors [3]. However, a recent study on mutational analysis of SMAD7 exon 4 has shown no mutations or aberrations could be detected in any of the 60 cervical cancer samples [53]. Therefore, mutations of SMAD7 are unlikely to be of etiological significance as far as human cervical cancer is concerned.

Roles of TGF-β1 in human papillomavirus infection

Multiple studies have reported a higher tendency of TGF-β1 expression in human papillomavirus-positive women than human papillomavirus-negative controls [9, 43, 54]. In addition, the expression of TGF-β1 was positively correlated with human papillomavirus oncogenes expression, such as E2 and E7 [13, 55]. Blocking human papillomavirus type 16 oncogene E7 expression could lower the expression of TGF-β1 and induce cells to enter apoptosis [55]. Decreasing TGF-β expression was also observed in HeLa-sphere-forming cells when silencing the human papillomavirus oncogene E6/E7 [56]. The effects of human papillomavirus type 16 oncogenes E6 and E7 on the promoter activity of the human TGF-β1 gene in cervical tumor cell lines may be due to E6 and E7 action on one specific Sp1-binding site (Sp1e) located at positions −108 to −102 in the TGF-β1 core promoter [54].

In a feedback mechanism, TGF-β1 inhibited human papillomavirus type 16 RNA expression at the transcriptional level [57], which was mediated by a decrease in Ski levels and nuclear factor I activity [58], and exerted antiproliferative effects on these human papillomavirus-transformed cells by downregulating expression and function of different proliferation-enhancing molecules [59, 60]. Simultaneously, TGF-β1 downregulated human papillomavirus-16 oncogenes E6 and E7 levels [26], which resulted in a shifted balance (lowered activity of E6) in favor of increased p53 expression, resulting in activation of the cell cycle inhibitory gene, p21 (WAF1). This protein binds and inhibits the cyclin E/CDK2 complex that maintains Rb in a hyperphosphorylated state. Rb then shifts to a hypophosphorylated state, resulting in G1 arrest, presumably by binding E2F transcription factors [61]. Also, TGF-β1 promoted chromosomal instability in human papillomavirus type 16 oncogenes E6- and E7-infected cervical epithelial cells [62]. However, the human papillomavirus type 16 oncogenes E6 and E7 were shown to exhibit an inhibitory effect on TGF-β receptor promoter activity [63]; moreover, the human papillomavirus E7 oncoprotein inhibited TGF-β signaling in the infected cells by blocking binding of the SMAD complex to its target sequence [64]. As such, while TGF-β1 may inhibit the expression of the oncogenes of human papillomaviruses, this activity can be attenuated by the negative effects of the oncoproteins on TGF-β1 signaling pathway.

On the other hand, TGF-β1 plays an important role in generating an immunosuppressive state in the tumor microenvironment, which allows human papillomavirus to evade the host's immune response [38]. Thus, TGF-β1 plays a key role in promoting high risk human papillomavirus infection, which may be part of mechanism of TGF-β-mediated cervical carcinogenesis in human papillomavirus-infected patients.

Clinical utilities of TGF-β1

Predictive significance of TGF-β1 in radiosensitivity and radiation therapy toxicity

TGF-β1 has been demonstrated to be a key mediator of fibrogenesis in a number of pathologic conditions, including postradiation tissue reactions [65]. Several studies have evaluated the predictive significance of TGF-β1 levels and its polymorphisms in the radiation therapy for cervical cancer (Table 1). Two recent studies reported a negative correlation between pretreatment TGF-β1 levels and radiosensitivity in cervical carcinoma [20, 66], which suggest that lowering pretreatment TGF-β1 levels should increase tumor response to radiation. With respect to radiation therapy toxicity, however, published results are conflicting. Yang et al. [66] studied 42 patients with cervical carcinoma receiving cisplatin-based chemoradiation and reported that a sudden elevation of serum

Table 1 Overview of clinical utilities of TGF-β1 in cervical cancer

Clinical utilities	Patients and methods	Significances	Reference
Predictive significance in radiosensitivity	Plasma-TGF-β1 levels were analyzed by ELISA in 79 cervical cancer patients undergoing radiotherapy	Pretreatment TGF-β1 levels had a weak associated with radiosensitivity	Dickson et al. [20]
	Plasma-TGF-β1 levels were analyzed by ELISA in 42 cervical cancer patients undergoing chemoradiation	Lower pretreatment TGF-β1 levels were associated with tumor response to chemoradiation	Yang et al. [66]
Predictive significance in radiation therapy toxicity	Plasma-TGF-β1 levels were analyzed by ELISA in 42 cervical cancer patients undergoing chemoradiation	The sudden elevation of serum TGF-β1 after brachytherapy was accompanied with increased vaginal mucositis and proctitis	Yang et al. [66]
	Polymorphic sites in TGF-β1 were examined in 35 cervical cancer patients and 43 endometrial carcinoma	TGF-β1 −1552delAGG, −509C>T, and L10P polymorphisms were associated with the risk of developing severe radiotherapy reactions	De Ruyck et al. [67]
	TGF-β1 polymorphisms were analyzed in 55 patients with locally advanced cervical cancer treated by chemoradiotherapy	TGF-β1 compound homozygosity (−1552delAGG, −509C>T, L10P) was associated with radiotherapy toxicity; however, there was no association between single TGF-β1 polymorphism and late toxicity	Paulikova et al. [65]
	Plasma-TGF-β1 levels were analyzed by ELISA in 79 cervical cancer patients undergoing radiotherapy	Pretreatment TGF-β1 levels were not associated with radiotherapy toxicity	Dickson et al. [20]
Prognostic significance	Plasma-TGF-β1 levels were analyzed by ELISA in 79 cervical cancer patients undergoing radiotherapy	Pretreatment TGF-β1 levels were a significant prognostic factor for survival and local control	Dickson et al. [20]
	TGF-β1 protein expression was measured by immunohistochemistry in 66 cervical adenocarcinoma	TGF-β1 was an independent prognostic factor for cervical adenocarcinoma	Fan et al. [10]
	TGF-β1 protein expression was measured by immunohistochemistry in 51 cervical squamous cell carcinoma	TGF-β1 expression in the vaginal margin had a close association with vaginal recurrence and was an independent prognostic marker of cervical squamous cell carcinoma	Fan et al. [68]
	TGF-β1 mRNA in 108 paraffin-embedded cervical carcinomas was detected by mRNA in situ hybridization	TGF-β1 was not associated with worse survival	Hazelbag et al. [19]

TGF-β1 levels after the first brachytherapy was accompanied with increased vaginal mucositis and proctitis, suggesting that TGF-β1 may be an effective indicator of toxicity to brachytherapy. In addition, De Ruyck et al. [67] found possible associations between TGF-β1 −1552delAGG, −509C>T, and L10P polymorphisms and subsequent toxicity after radiotherapy in 78 patients treated for cervical or endometrial carcinoma. Interestingly, in a similar study, Paulikova et al. [65] found a significant association between TGF-β1 compound homozygosity (−1552delAGG, −509C>T, L10P) and subsequent toxicity after chemoradiotherapy, whereas no relationship in single TGF-β1 polymorphism in their study on 55 patients with FIGO stage IIB and higher without disease recurrence after a 6-year follow-up. However, Dickson et al. [20] suggested that pretreatment plasma TGF-β1 levels are not prognostic for the probability of developing late complications.

Taken together, these data suggest that pretreatment TGF-β1 levels in cervical cancer are a significant predictive factor for radiosensitivity but not for radiation therapy toxicity.

Prognostic significance of TGF-β1 in cervical cancer

Studies evaluating the potential of TGF-β1 for the prognosis and predictor of recurrence of patients with cervical cancer have yielded conflicting results (Table 1). Dickson et al. [20] indicated patients with elevated pretreatment plasma TGF-β1 levels had a significantly decreased local control rate and probability of survival in cervical cancer patients. Furthermore, Fan et al. [68] found that TGF-β1 expression in the vaginal margin had a close association with vaginal recurrence of stage Ib–IIa cervical cancer and was an independent prognostic marker of cervical squamous cell carcinoma. Accordingly, they also demonstrated that the expression of TGF-β1 was a significant prognostic factor for cervical adenocarcinoma and elevated TGF-β1 was associated with a short survival [10]. However, another retrospective study suggested that higher TGF-β1 expression in cervical cancer cells was not associated with worse survival and higher recurrent rates [19]. These apparently conflicting results may arise from the different techniques used to evaluate TGF-β1 alterations and differences in patient epidemiology and treatment history.

Potential role for TGF-β1 inhibitors in the treatment

Anti-TGF-β1-based therapy is being extensively evaluated as an attractive therapeutic target, especially for cancer treatment, due to its aberrant overexpression in tumors and its tumor-promoting activities. Novel drugs blocking the TGF-β pathway, including blocking production of TGF-β ligands with antisense molecules, small-molecule inhibitors of the kinase activity of TβRI and TβRII, monoclonal antibodies that block TGF-β signaling, and soluble forms of TβRII and TβRIII that function as ligand traps [6], have been developed and have shown efficacy in preclinical and clinical studies. Nonetheless, to date, none of these inhibitors have been tested in cervical cancer.

Conclusion

TGF-β1 exerts both anti-oncogenic and pro-oncogenic activities in cervical carcinogenesis. TGF-β1 functions as a tumor inhibitor in precancerous cervical lesions and early stage cervical cancers whereas a tumor promoter in later stage tumors. This switch from a tumor suppressor to a tumor promoter can be due to various alterations in TGF-β signaling pathway, such as mutations or loss of expression of TGF-β receptors and SMAD proteins. Furthermore, the metastasis-promoting activity of TGF-β1 is in part through its action in tumor microenvironment. Additionally, TGF-β1 facilitates the infection of high risk human papillomavirus, which may be part of the mechanisms of TGF-β1-driven carcinogenesis in human papillomavirus-positive cervical cancer. These tumor-promoting roles associated with TGF-β1 warrant future preclinical and clinical testing of anti-TGF-β1 therapy for the prevention and treatment of cervical cancer. Additionally, TGF-β1 may also be a mediator of radiosensitivity and a useful prognostic biomarker and predictor of recurrence after therapy.

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Compliance with ethical standards

Conflicts of interest None

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