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The paradoxical role of transforming growth factor-β in controlling oral squamous cell carcinoma development

Ruiting Peng[a], Yun Huang[a], Ping Huang[a], Linyi Liu[b], Lei Cheng[c] and Xian Peng[d,*]
[a]*Department of Stomatology, The General Hospital of Western Theater Command PLA, Chengdu, China*
[b]*Maine Health Institute for Research, Scarborough, ME, USA*
[c]*State Key Laboratory of Oral Diseases & National Center for Stomatology & National Clinical Research Center for Oral Diseases & Department of Operative Dentistry and Endodontic, West China Hospital of Stomatology, Sichuan University, Chengdu, China*
[d]*State Key Laboratory of Oral Diseases & National Center for Stomatology & National Clinical Research Center for Oral Diseases, West China Hospital of Stomatology, Sichuan University, Chengdu, China*

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Abstract. Transforming growth factor-β (TGF-β) is a multifunctional cytokine that plays a vital role in regulating cell growth, differentiation and survival in various tissues. It participates in a variety of cellular processes, including cell apoptosis, cell migration and evasion, and plays a paradoxical role in tumor genesis and development. In the early stage of tumor, TGF-β inhibits the occurrence of tumor by inhibiting cell proliferation and regulating cell apoptosis. In the advanced stage of tumor, TGF-β promotes tumor development and affects prognosis by promoting cell survival and proliferation, cell migration and invasion, participates in immune escape, etc. In this article, we will review the paradoxical role of TGF-β on the occurrence and development of oral squamous cell carcinoma.

Keywords: TGF-β, OSCC, signal transduction, cell proliferation, cell apoptosis, cell migration, cell invasion, EMT

1. Introduction

Oral cancer is the most common malignant tumor in the head and neck region, and its incidence has been on the rise. According to the latest data from the International Agency for Research on Cancer, there were approximately 377,713 new cases and 177,757 deaths worldwide [1]. Oral squamous cell carcinoma (OSCC) accounts for 90% of all oral cancer cases. Despite the effectiveness of surgical treatment combined with postoperative radiotherapy and chemotherapy, the 5-year survival rate of oral cancer patients is still around 50∼60% due to tumor metastasis, recurrence, drug resistance, and other factors [2]. The survival rate of advanced-stage patients is even lower. Oral cancer can affect patients' eating, swallowing, breathing, speaking, as well as their physical and mental health, causing significant health and economic burdens [3]. The etiology of oral cancer is not clear, with the most common risk factors being smoking, alcohol consumption, and other risk factors including systemic diseases such as diabetes, metabolic syndrome, chronic inflammation, and HPV virus infection [4,5,6]. Identifying the key molecules and pathways driving OSCC progression and elucidating the pathogenesis and regulatory mechanisms of oral cancer are important and urgent tasks.

The transforming growth factor-β (TGF-β) signaling pathway is an important transmembrane signal-

*Corresponding author: Xian Peng, State Key Laboratory of Oral Diseases & National Center for Stomatology & National Clinical Research Center for Oral Diseases, West China Hospital of Stomatology, Sichuan University, Chengdu 610041, Sichuan, China. Tel.: +86 2885501787; E-mail: pengx07@hotmail.com.

ing pathway that is closely associated with various human diseases, including tissue fibrosis, cardiovascular disease, skeletal disease, and cancer [7]. Aberrant TGF-β signaling is considered one of the pathways leading to OSCC carcinogenesis. Studies have shown that TGF-β is significantly expressed in oral cancer tumor samples, especially in the tumor center and invasive front, and is associated with cancer invasion, metastasis, and poor prognosis [8,9]. The TGF-β signaling pathway is mainly composed of TGF-β signaling molecules, transmembrane receptors (TβRs), intracellular transcription factors, and corresponding target genes. TGF-β has three highly homologous subtypes, namely TGF-β1, TGF-β2, and TGF-β3, which are located on chromosomes 19q13, 1q41, and 14q24, respectively [10]. The transmembrane receptors are also divided into three types: TβRI, TβRII, and TβRIII. The TGF-β signaling molecule first forms a complex with TβRII on the cell membrane surface, and then recruits and phosphorylates TβRI (ALK5). The activated TβRI continues to activate and phosphorylate downstream Smads proteins (Smad1/2/3/5/8 is receptor related Smads also named R-Smads, Smad4 is common Smads also named Co-Smads, and Smad6/7 is inhibitory Smads also named I-Smads). The activated R-Smads and Co-Smads form a polymer, enter the cell nucleus, interact with intracellular transcription factors, and achieve DNA binding and selective transcription, translation, and protein synthesis of target genes, thereby activating the typical TGF-β signaling pathway [11]. In addition, TGF-β can phosphorylate the linker region between the N-terminal MH1 (Madhomology 1) and C-terminal MH2 of the Smad2/3 protein, activating the non-typical TGF-β signaling pathway [12] (Fig. 1). For example, TGF-β can activate the MAPK kinases TAK1 and downstream JNK, p38 MAPK signaling, and NF-κB signaling through the specific Smad E3 ligase (TRAF6) [13,14], or promote the formation of TβRI and p85α complex through the polyubiquitination of p85α by TRAF6, leading to the activation of downstream PI3K and AKT signals [15]. TGF-β can also activate the STAT3 signal through the interaction between JAK1 and TβRI [16], and activate the RAS pathway through TβRI binding and phosphorylating adaptor protein ShcA, recruiting GRB2 and SOS to form the ShcA-GRB2-SOS complex, leading to the activation of downstream ERK1/2 [17]. At the same time, the TGF-β signaling pathway is closely related to other signaling pathways, including the Wnt/β-catenin, Hippo/YAP signaling pathways, which can also regulate the transmission of TGF-β/Smad signaling pathway in various situations [18,19].

TGF-β was initially discovered in the 1980s to promote the proliferation of fibroblasts and anchorage-independent cell growth in vitro [20]. Subsequently, TGF-β has been shown to inhibit the proliferation of various types of cells, including epithelial cells, endothelial cells, and hematopoietic cells [21]. Therefore, TGF-β is considered to play a paradoxical role in cell proliferation and growth [22]. In the tumor microenvironment, TGF-β can act as a tumor suppressor, maintaining cellular homeostasis and preventing early tumor deterioration. However, long-term abnormal activation can transform its function into promoting cell proliferation, migration, invasion, and immune evasion, thereby promoting tumor development [23,24]. The seemingly opposite roles of TGF-β in tumors are referred to as the "TGF-β paradox". There have been some reviews that mainly summarize the activation of the TGF pathway and its general mechanisms in systemic tumors or squamous cell carcinoma. However, there is no in-depth summary of its mechanisms in oral squamous cell carcinoma. This article summarized new research and the progress of TGF-β in promoting and inhibiting OSCC development, providing a review and theoretical basis for exploring the occurrence and regulation mechanisms of oral cancer.

2. TGF-β inhibits OSCC development

TGF-β is a typical anti-proliferative cytokine for many epithelial cells, including oral epithelial cells. TGF-β can interfere with the normal cell cycle and inhibit cell proliferation, also mediate apoptosis and senescence, thereby inhibiting tumor development (Fig. 1). Among them, the effect of TGF-β on inhibiting cell proliferation has been extensively studied, and its function is worthy of recognition. However, more research is needed to reveal the role of TGF-β in regulating cell apoptosis and senescence.

2.1. TGF-β can mediate cell cycle arrest in multiple ways

Firstly, TGF-β can induce the expression of cyclin-dependent kinase inhibitors (CDKIs) in epithelial cells, such as $p15^{Ink4b}$, $p21^{Cip1}$, $p57^{Kip2}$, etc. $p15^{Ink4b}$ belongs to the inhibitor of cyclin-dependent kinase 4 (INK4) family protein, which can specifically bind to CDK4 and CDK6 proteins, inhibiting the binding of cell cycle protein D and CDK4/6, thereby inhibiting cell cycle progression from G1 to S phase [25]. $p21^{Cip1}$ and

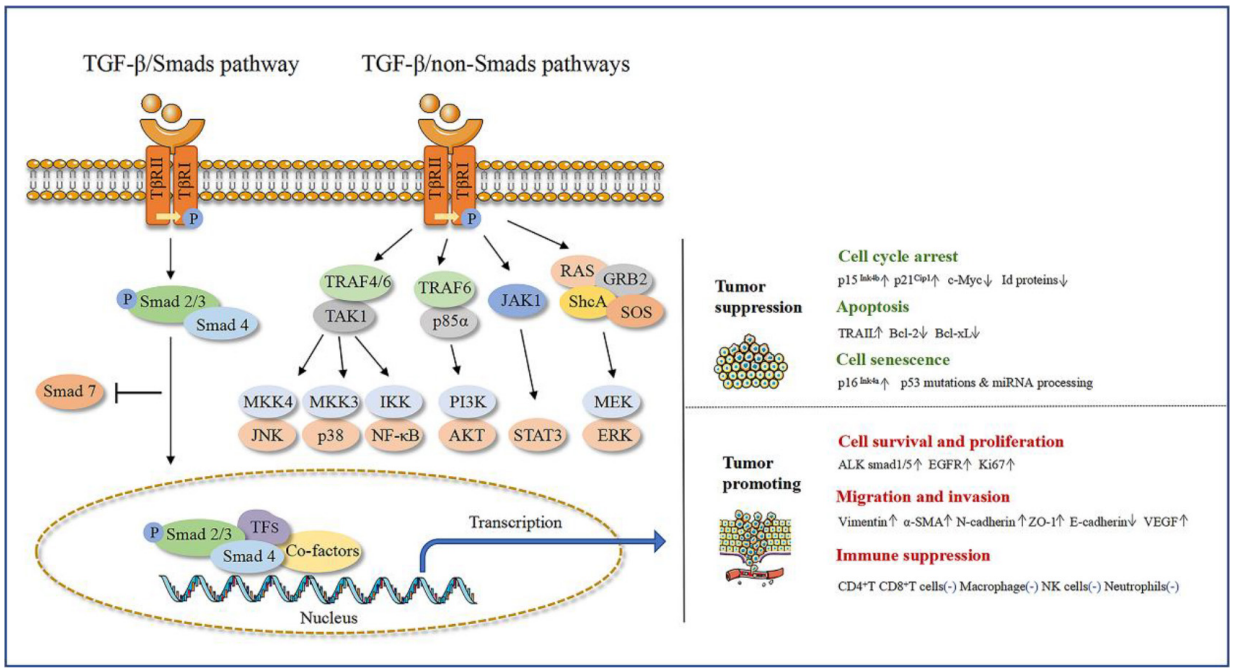

Fig. 1. The double role of TGF-β signaling in OSCC development. Figure note: TGF-β signaling pathway can be activated through typical and non-typical TGF-β signaling pathway. TGF-β plays a double role on the development of oral squamous cell carcinoma. TGF-β can inhibit the proliferation of OSCC cells and inhibit tumor occurrence by interfering with cell cycle, mediating cell apoptosis and cellular senescence effects, etc. TGF-β also can promote the development of OSCC by promoting cell survival and proliferation, promoting cell migration and invasion, and participating in immune escape, etc. The figure is created by Adobe AI software.

$p57^{Kip2}$ belong to the CIP/KIP family protein, among which $p21^{Cip1}$ can block the binding between cyclin E and CDK2, leading to cell cycle arrest in G1 phase [26]. The study by Nakamura et al. showed that TGF-β can mediate cell cycle arrest by inducing the expression of $p21^{Cip1}$ and $p15^{Ink4b}$, thereby inhibiting the proliferation and differentiation of tongue epithelial cells [27]. There are also studies showing that TGF-β requires the activation of the Notch signaling pathway to inhibit epithelial cell proliferation, and the two pathways synergistically regulate the cell cycle inhibitor $p21^{Cip1}$ to inhibit epithelial cell proliferation [28]. Zhang et al. found that low concentrations of TGF-β (0.5 ng/mL) can inhibit the proliferation of dental epithelial cells by activating typical TGF-β signaling pathway through activating ALK5 receptor and the downstream Smad2/3 [22]. Liu et al. found that Smad7 deficiency can lead to upregulation of Smad2/3, resulting in excessive activation of the TGF-β pathway, upregulation of $p21^{Cip1}$ expression, and downregulation of Cyclin D1 expression, leading to the inhibition of dental epithelial cell proliferation [29]. Another study showed that tongue squamous cell carcinoma cells (Ts-Smad4 cells) with high expression of Smad4 can upregulate $p21^{Cip1}$ and MMP-2 expression under TGF-β stimulation, thereby inhibiting the proliferation and reducing the metastasis of tongue squamous cell carcinoma cells [30].

TGF-β can also induce cell cycle arrest through downregulating growth-stimulating proteins, especially the proliferative transcription factor c-Myc and inhibitors of differentiation (Id proteins). The downregulation of c-Myc expression is mediated by the TGF-β-induced repressor complex, which includes the Smad3-Smad4 complex, transcription factor p107, E2F4/5, and C/EBPβ (CCAAT/enhancer binding protein β). Under TGF-β stimulation, the repressor complex translocates to the nucleus and binds to the transcriptional inhibitory element on the c-Myc promoter, thereby inhibiting c-Myc transcription [31]. The reduction of c-Myc expression not only directly prevents cells from entering the proliferative state but also activates several important CDKIs promoter inhibitory genes, such as $p21^{Cip1}$ and $p15^{Ink4b}$, leading to cell cycle arrest [32]. Members of the Id proteins, including Id1, Id2, and Id3, can inhibit the process of cell differentiation and promote cell proliferation. The transcriptional inhibition of Id1, Id2, and Id3 is mediated by Smad signaling [33]. In epithelial cells, TGF-β can directly promote the expression of the stress response factor ATF3 by activating Smad3, which directly inhibits the expression of Id1 [33]. Id2 can

antagonize the anti-proliferative effect of $p21^{Cip1}$, and TGF-β can inhibit Id2 expression and induce $p21^{Cip1}$ expression, mediating epithelial cell growth arrest [34].

In summary, the inhibition of oral squamous cell carcinoma cell proliferation by TGF-β is mainly related to the upregulation of $p21^{Cip1}$ and downregulation of c-Myc and Id proteins, but the specific mechanism still needs to be explored.

2.2. TGF-β can induce cell apoptosis and senescence

Apoptosis is a genetically controlled autonomous and orderly death process that eliminates excessive or damaged cells during embryonic organogenesis and adult organ homeostasis, maintaining stable internal environment [35]. TGF-β can induce apoptosis in liver cancer cells through the death receptor pathway (extrinsic pathway) or the mitochondrial pathway (intrinsic pathway) [36,37]. The extrinsic apoptosis pathway is usually recognized by death receptors for tumor necrosis factor (TNF)-related ligands, including TNF-α, FasL, and TNF-related apoptosis-inducing ligand (TRAIL), which activate caspase-3/7/8 to execute the apoptosis process [36]. The intrinsic apoptosis pathway is usually activated by intracellular cues such as p53 protein activation, and is regulated by the Bcl-2 (B-cell lymphoma 2) protein family. Its characteristic is the release of cytochrome c from mitochondria and the formation of apoptotic bodies, leading to the activation of caspase-3/7/8 to execute the apoptosis process [36,38]. However, it's still unknown TGF-β inhibits cell apoptosis in oral squamous cell carcinoma through which mechanismMoreover, it is imperative to investigate the impact of TGF-β on alternative forms of programmed cell death, such as pyroptosis and ferroptosis.To our knowledge,on the effect of TGF-β on pyroptosis and ferroptosis is rarely related to squamous cell carcinoma cells but is mainly related to acute renal injury or attenuated cardiac fibrosis, lung cancer, etc. Perhaps TGF-β has a similar effect on pyroptosis and ferroptosis in oral squamous cell carcinoma.Therefore, more research is needed to fill the gap in this area.

Cellular senescence is a stress response program that limits cell proliferation by inducing persistent and irreversible cell cycle arrest [39]. Cellular senescence can be triggered by telomere shortening (referred to as replicative senescence) or various cell stresses, such as activation of oncogenes, mitochondrial dysfunction, inactivation of tumor suppressor genes, endoplasmic reticulum stress, DNA damage, etc [40]. The cell cycle arrest associated with cellular senescence is one of the key mechanisms that limit the proliferation of epithelial tumor cells. Loss of genes such as p53 and $p16^{Ink4a}$ in late-stage malignant tumors leads to the occurrence of genetically unstable OSCC (GU-OSCC) [41]. Hassona et al. found that fibroblasts extracted from GU-OSCC showed high levels of cellular senescence, with an increased activity of senescence-associated β-galactosidase (SAβ-Gal) and overexpression of $p16^{Ink4a}$, which was induced by GU-OSCC-related tumor cells through ROS and TGF-β-dependent mechanisms [42]. The p53 tumor suppressor is also one of the most studied mediators of cellular senescence, and p53 gene mutations can promote tumor development. The p53 pathway and TGF-β signaling intersect at multiple levels, such as direct interaction of p53 with Smad2 and Smad3, leading to transcriptional activation of genes containing p53 binding elements and TGF-β response elements, mediating cell cycle arrest and senescence [43]. In addition, p53 and Smads can co-regulate miRNA expression, among which anti-proliferative miR-34a, miR-215, and miR-192 can regulate tumor cell senescence [44]. Although there is some evidence to suggest the role of TGF-β in cell senescence, its specific mechanism remains to be studied.

3. TGF-β promotes OSCC development

TGF-β can promote the development of oral cancer by promoting cancer cell survival and proliferation, promoting epithelial-mesenchymal transition, stimulating tumor angiogenesis, and promoting immune escape, etc (Fig. 1). Among them, the research progress in promoting epithelial-mesenchymal transition and promoting immune escape is the most significant.

3.1. TGF-β can promote cell survival and proliferation

TGF-β can stimulate the activation of both pro-apoptotic and pro-survival signals in normal or malignant tumor cells, and the balance between the two will determine the cell's fate. TGF-β can promote the activation of various survival pathways, such as PI3K/Akt, Ras/ERK, NF-κB, and JAK/STAT3, to counteract TGF-β-induced cell death [21]. A comprehensive cohort study integrating genomic and transcriptomic data from 9,125 tumor samples of 33 cancer types in The Cancer Genome Atlas (TCGA) database showed that 39% of tumors had alterations in TGF-β-related genes [45]. High expression of TGF-β is associated with the sur-

vival, proliferation, migration, and invasion of oral cancer cells, as well as a significantly increased risk of lymph node metastasis, disease recurrence, and shortened survival in patients with pathological stage III-IV oral cancer, which can serve as a diagnostic or prognostic biomarker [8]. Zhang et al. showed that high concentrations of TGF-β1 (5 ng/mL) can promote the proliferation of odontogenic epithelial cells through the activation of downstream noncanonical Smad1/5 signaling pathways by the ALK1/2-ALK5 receptor [22]. Activation of the TGF-β pathway can also promote the in vitro proliferation of oral squamous cell carcinoma cells and the growth of tumors in mice, upregulate Ki67 expression, and promote the development of oral cancer [46]. In addition, a novel TβRII mutation of TGF-β (I227T/N236D) can promote the survival of oral squamous cell carcinoma by enhancing epidermal growth factor receptor(EGFR) signaling pathway, as well as cell migration and invasion [47].

TGF-β can also promote the survival of OSCC cells by inducing autophagy [48]. Autophagy is a fundamental cellular process that degrades damaged organelles and dysfunctional proteins within cells, and recycles intracellular material for survival, thereby maintaining cellular and tissue homeostasis, especially under stress conditions (such as nutrient deprivation) to enable cell survival [49]. Autophagy is believed to protect OSCC cells from apoptosis, allowing them to survive under stressful conditions and avoid death caused by chemotherapy drugs [50]. In vitro studies have shown that TGF-β can induce autophagy in normal fibroblasts, acting prior to cellular senescence, and can induce the transformation of normal fibroblasts into cancer-associated fibroblasts (CAFs), which then secrete growth factors that promote OSCC proliferation and invasion, promoting OSCC cell survival and invasion [51]. Another study suggests that TGF-β can induce normal fibroblasts to convert into CAFs, which in turn secrete growth factors that lead to OSCC proliferation and invasion [52]. Studies have also shown that CAFs can promote the migration and invasion of oral squamous cell carcinoma cells by activating the TGF-β/SOX9 pathway [53].

In summary, researchers have found that TGF-β can promote the survival and proliferation of oral squamous cell carcinoma cells by activating noncanonical Smad1/5 signaling pathways or the EGFR signaling pathway. However, the study of TGF-β and autophagy is still in its early stages, but given the important role of autophagy in maintaining cellular energy homeostasis and altering cellular signal output, exploring the interaction between TGF-β signaling and autophagy in the tumor microenvironment would be highly meaningful.

3.2. TGF-β can promote cell migration

Epithelial to mesenchymal transition (EMT) plays a key driving role in tumor cell migration and invasion. When epithelial-mesenchymal-like cells lose adhesion to the extracellular matrix, they undergo mesenchymal-to-amoeboid transition (MAT), which enhances the contractile ability of actin and forms cell membrane protrusions, thereby enhancing the movement of deformed cells [54]. During the process of EMT, the expression of epithelial cell-cell adhesion proteins such as E-cadherin and zonula occludens-1(ZO-1) is downregulated, while the expression of mesenchymal markers such as N-cadherin, vimentin, and α-smooth muscle actin (α-SMA) is upregulated [55]. TGF-β can increase the expression of N-cadherin and vimentin and decrease the expression of E-cadherin by activating EMT transcription factors SNAIL, TWIST, and ZEB through downstream Smad proteins, thus promoting the EMT process [56]. Studies have also indicated that TGF-β can promote the EMT process of OSCC cells by activating the STAT3 and downstream Malat1/miR-30a signaling pathways, upregulating N-cadherin and downregulating E-cadherin [57]. Bu et al. have shown that, TGF-β can upregulate the expression of vimentin and downregulate the expression of E-cadherin in OSCC cells, inducing the EMT process and promoting the invasion and migration of OSCC cells [58]. Meng et al. have shown that the secretion of CXCL8 by OSCC cells binds to CXCR2 in bone mesenchymal stem cells (BMSCs), promoting their migration to OSCC, while TGF-β secreted by BMSCs induces the EMT process of OSCC through the activation of downstream Ras/Raf/Erk signaling pathways, promoting their proliferation, migration, and invasion [59]. In addition, fibroblasts extracted from genetically unstable GU-OSCC tumor samples secrete TGF-β, weakening the adhesion of tumor epithelial cells and promoting the EMT process of tumor cells [60].

Increasing evidence suggests that EMT is not a single, rigid process, but a multi-step process that passes through a partial EMT state (P-EMT), and the TGF-β-induced transition of epithelial cells to P-EMT is reversible [61]. Single-cell RNA-seq analysis shows that P-EMT plays an important role in head and neck cancer, and further in vitro analysis shows that TGF-β can dynamically control the transition of cells between P-EMT and non-P-EMT states [62]. EMT can promote tumor cell dissemination, followed by mesenchymal-epithelial transition (MET) to promote the formation of new tumors at the site of dissemination, during which

tumor cells undergo amoeboid-to-mesenchymal transition (AMT). Yokoyama et al. have shown that TGF-β1 can promote the AMT process of CD44high oral squamous cell carcinoma cells by activating Erk1/2 and Cofilin-1 phosphorylation, downregulating the expression of miR-422a, and upregulating the expression of N-cadherin, thereby promoting the settlement of tumor cells at the site of dissemination [63].

Angiogenesis provides the necessary nutrients and oxygen for tumors, and TGF-β promotes sustained angiogenesis, which is beneficial for tumor invasion and metastasis. TGF-β indirectly promotes angiogenesis by upregulating the expression and activity of vascular endothelial growth factor (VEGF), basic fibroblast growth factor (BFGF), connective tissue growth factor (CTGF), and proteases [64]. TGF-β can regulate VEGF expression not only through the canonical Smad2/3 pathway but also through the non-canonical AKT pathway [65]. Animal studies have found that TGF-β can stimulate VEGF expression around the tumor necrosis area by synergizing with hypoxia-inducible factor-1α (HIF-1α) through Smad3, promoting tumor invasion and metastasis [61]. In addition, under the synergistic action of TGF-β and sine oculis homeobox homolog 1(SIX1) molecules, VEGF-C expression can be increased, promoting tumor lymphangiogenesis and lymph node metastasis [66]. TGF-β1 can also activate the TβRII receptor and downstream Smad2/3 intracellular signaling, causing OSCC-associated tumor-associated macrophages (TAMs) to secrete more VEGF, promoting angiogenesis in the tumor tissue and affecting the prognosis of OSCC patients [67].

In summary, recent studies pointed out that TGF-β can promote EMT mainly by activating Smad proteins or the STAT3 signaling pathway. TGF-β can also promote AMT by activating Erk1/2 and Cofilin-1 phosphorylation. Moreover, TGF-β can regulate VEGF expression mainly through the Smad2/3 pathway, thus indirectly promoting tumor invasion and metastasis

3.3. TGF-β can promote cell immune escape

The tumor microenvironment (TME) is a complex system composed of various cell components, such as fibroblasts, endothelial cells, and various immune cells, including T cells and natural killer (NK) cells, which have natural cytotoxic effects on tumor cells [68]. Dendritic cells present tumor antigens to T cells, while macrophages and neutrophils clear cell debris through phagocytosis. TGF-β can affect the proliferation, differentiation, and survival of various immune cells (such as T cells, NK cells, macrophages, and neutrophils) in multiple ways, exerting anti-tumor immune effects [69].

TGF-β has a significant inhibitory effect on T cell proliferation, activation, and effector function, and can directly suppress CD4+ and CD8+ T cells, and regulate the development and differentiation of immune inhibitory regulatory T cells (Treg cells) by regulating the Th1/Th2 balance of T helper cells [70,71]. TGF-β can inhibit CD4+ T cell differentiation by silencing the expression of two Th1-related transcription factors, T-BET and STAT-4 [72], and can also inhibit the proliferation of CD4+ T cells by suppressing interleukin-2 expression through Smad3, Smad4, and co-repressor TOB1 [73]. Another study showed that the TGF-β/SMAD3 pathway limits the growth and proliferation of CD4+ T cells by relieving the impact of CD28 co-stimulation and leads to a decrease in mTOR signaling [74]. TGF-β has also been shown to be an effective inhibitor of CD8+ T cells. TGF-β can inhibit the proliferation and function of CD8+ T cells through the TGF-β/Smad3 pathway [75]. Kondo et al. found that TGF-β can inhibit the proliferation and function of OSCC antigen-specific cytotoxic CD8+ T cells. TGF-β1 mRNA expression is significantly negatively correlated with the ratio of CD8+ T cells to Treg cells and is also significantly negatively correlated with Ki-67 expression in CD8+ T cells [76].

TGF-β can directly inhibit macrophage differentiation and function, such as inhibiting the expression of macrophage inflammatory protein 1α and 2 (MIP1α, MIP-2) and chemokine CXCL1, cytokine granulocyte-macrophage colony-stimulating factor (GM-CSF), as well as interleukins IL-1β, IL-8, and IL-10 [77]. TGF-β also has a widespread inhibitory effect on the development and function of NK cells. TGF-β suppresses the expression of surface activating receptors on NK cells, including NKG2D and NKp30 [78]. TGF-β can also inhibit the metabolic activity and proliferation of NK cells by inhibiting the mammalian target of rapamycin(mTOR) pathway [79]. Studies have also shown that TGF-β drives the conversion of NK cells to type 1 innate lymphoid cells (ILC1s), thereby promoting tumor immune escape [80]. In addition, TGF-β1 and IL-17A are significantly upregulated in OSCC patient tissue samples, and after co-infection with neutrophils, they can reduce the killing ability of neutrophils on tumor cells and promote immune escape [81].

In summary, recent studies have found that TGF-β can directly suppress CD4+ and CD8+ T cells through Smad3/4 proteins. TGF-β can also inhibit macrophage

and NK cell proliferation and function. However, the mechanisms involved in immune escape are complex, and further research is needed to explore the TGF-β effect on immune cells.

4. Conclusions and outlooks

Indeed, the dual role of TGF-β in cancer is a complex and multifaceted phenomenon that involves multiple mechanisms and pathways. One key mechanism by which TGF-β promotes tumor growth and metastasis is through its ability to induce EMT. TGF-β can induce EMT by activating various signaling pathways (including the SMAD pathway, PI3K-Akt pathway, and MAPK pathway) and regulating the expression of various EMT-related genes and transcription factors. Another way in which TGF-β promotes tumor growth and progression is through its regulation of the tumor microenvironment, such as inducing the expression of angiogenic factors, inhibiting T cells, macrophages, and other immune cells, and promoting immune escape. However, in the early stages of cancer, TGF-β can induce cell cycle arrest and apoptosis in normal and early cancer cells, exerting a tumor-suppressive effect. In some cases, TGF-β can also induce senescence in cancer cells, rendering them in an irreversible growth arrest state.

The dual role of TGF-β in cancer is highly dependent on the tumor microenvironment and can vary depending on the stage and type of cancer as well as other factors (such as the patient's genetic background and the presence of other signaling pathways or environmental factors). Therefore, developing effective TGF-β-targeted cancer therapies will require a deeper understanding of the underlying bidirectional regulatory mechanisms, which will help to better understand the impact on tumor metastasis and provide new treatment strategies for the prevention and treatment of cancer metastasis.

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Author contributions

PENG Ruiting: Contributed to conception, interpretation of data, preparation of the manuscript.

HUANG Yun & HUANG Ping & LIU Linyi: Contributed to conception, preparation of the manuscript.

CHENG Lei: Contributed to conception, revision for important intellectual content.

PENG Xian: Contributed to revision for important intellectual content, supervision.

All authors gave their final approval and agree to be accountable for all aspects of the work.

Conflict of interest

The authors declare no conflict of interest.

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