TGF-β signaling: A complex role in tumorigenesis (Review)

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Abstract. Tumor progression can be affected by various cellular components of tumor cells and/or by tumor microenvironmental factors. The tumor microenvironment comprises a variety of nonmalignant stromal cells and inflammatory cytokines, which are pivotal in tumor promotion and progression. The transforming growth factor-β (TGF-β) ligands (TGF-β1, 2 and 3) are secreted inflammatory cytokines, which are known to be involved in various aspects of tumor development through two transmembrane serine-threonine kinase receptors, TGFβR1 and TGFβR2. TGF-β promotes or inhibits tumorigenesis depending on the concurrent gene mutations and tissue microenvironment present through the small mothers against decapentaplegic (Smad) and non-Smad pathways. This review aims to provide a comprehensive overview of the role of the TGF-β pathway in tumor initiation and progression.

Contents

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Abbreviations: TGF-β, transforming growth factor-β; EMT, epithelial-mesenchymal transition; CDKIs, cyclin-dependent kinase inhibitors; PI3K, phosphoinositide 3-kinase; MAPK, mitogen-activated protein kinase; CSCs, cancer stem cells; TAMs, tumor-associated macrophages; ROS, reactive oxygen species; MMP, matrix metalloproteinase

Key words: transforming growth factor-β, epithelial-mesenchymal transition, cancer stem cells, inflammation, metastasis

1. Introduction

Transforming growth factor-β (TGF-β) signaling forms a complex web in the progression of cancer. There is substantial evidence indicating that downregulated TGF-β signaling in tumor initiation. However, in certain tumors, TGF-β appears to have the ability to exert a tumor-promoting effect depending on cellular context (1-3). Accordingly, TGF-β signaling has been considered as a tumor suppressor and a promoter of tumor progression (4,5). It acts as a tumor suppressor by inhibiting cell proliferation through repressing the expression of c-Myc and certain cyclin-depenent kinase inhibitors (CDKIs) and through the secretion of anti-angiogenic factors (6,7). It functions as a tumor promoter through the stimulation of matrix deposition, perturbation of immune function and induction of epithelial-mesenchymal transition (EMT) (8). The TGF-β super-family is a large group of structurally associated proteins including TGF-β, nodal, activin, lefty, bone morphogenetic proteins and growth and differentiation factor. There are numerous cellular context-dependent factors tightly implicated in the balance of TGF-β signaling, thus TGF-β signaling forms a complicated network in cancer cells (5).

2. TGF-β signaling pathways

TGF-β signaling is transduced through Smad and non-Smad pathways. These pathways are mediated by TGF-β ligands, type1 and type2 receptors and Smad or non-Smad proteins, including Akt, extracellular signal-regulated kinase (ERK)1/2 and p38 mitogen-activated protein kinase (MAPK; Fig. 1). In mammals, there are three types of TGF-β (TGF-β1, 2 and 3), which are encoded by different genes and which function through the same receptor signaling systems (9). Of these, TGF-β1 is most frequently upregulated in tumor cells (10,11). However, the fate of cells following TGF-β1 treatment is often determined by cellular context and experimental conditions (12-14).

The TGF-β protein is produced as an inactive 'latent' high weight complex (14) and can be activated through the activity of plasminogen, which preferentially degrades the TGF-β prosegments (15,16) and through its conformational change

by the metalloproteinases, matrix metalloproteinase (MMP)-9 and MMP-2 (17). There are other activation mechanisms. For example, the extracellular matrix protein, thrombospondin (18,19) and αvβ6 integrin can regulate the activity of TGF-β through a conformational change (20). Taken together, tumor cells are well equipped to activate TGF-β locally.

The effects of TGF-β signaling are mediated by three TGF-β ligands (TGF-β1-3) through TGF-β type1 (TGFβR1) and type2 receptors TGFβR2 (21-23). TGFβR1 recruits and phosphorylates receptor-regulated Smads (R-Smads) when phosphorylated. TGF-β ligands can bind to TGFβR2 with high affinity once activated by metalloproteinases. Binding of the ligands causes the formation of a heterotetrameric active receptor complex, which results in the phosphorylation of TGFβR1 by TGFβR2. The phosphorylation of R-Smads by TGFβR1 form heteromeric complexes with the common partner Smad (co-Smad; Smad4 in mammals) (17) and these R-Smads-co-Smad complexes translocate into the nucleus to regulate the expression of target genes with other DNA-binding transcription factors.

TGF-β can also activate non-canonical signaling pathways, also termed non-Smad pathways. For example, TGF-β1 is known to activate the Erk/MAPK (24,25) pathway and the phosphoinositide 3-kinase (PI3K)/Akt (26-28) pathway. These non-Smad pathways work independently or together with Smad complexes to regulate the functions of TGF-β. For example, the activation of Akt signaling by TGF-β1 has been shown to promote cell proliferation (28). TGF-β receptors activate MMPs, p38MAPK and Zinc finger E-box-binding homeobox 1 (ZEB1), ZEB2, Snail and Slug, leading to EMT, which is required for cancer cell invasion and metastasis. TGF-β can also regulate target gene expression through the MAPK signaling pathway (29,30).

3. TGF-β and cell proliferation

TGF-β can regulate cell growth, apoptosis, differentiation and fibrosis (1). There is substantial evidence suggesting that TGF-β can inhibit the proliferation of normal epithelial cells (31,32). TGF-β signaling has been reported to mediate cell-cycle progression inpancreatic β-cells by regulating the nuclear localization of CDKI, p27 (31). TGF-β signaling has also been reported to inhibit the proliferation of tumor cells in certain cases. The findings of a study by Senturk *et al* suggested that TGF-β induced p53-independent and p16 (Ink4a)-independent and reactive oxygen species (ROS)-dependent, senescence in hepatocellular carcinoma (HCC) cells and inhibited tumor growth (32). TGF-β was also reported to mediate galangin-induced autophagy. The induction of autophagy reflected the anti-proliferation effect of TGF-β signaling on HCC cells (33). Certain drugs, including Akbu-LAAO, an L-amino acid oxidase with apparent antibacterial activities, inhibits the growth and induces the apoptosis of HepG2 cells via the TGF-β signaling pathway (34). By contrast, TGF-β signaling may have a completely different role in cell growth. A previous study demonstrated that TGF-β1 induced the activation of Akt to promote β-catenin nuclear accumulation, which then regulated cyclin D1/c-myc gene transcription to eventually promote mouse precartilaginous stem cell proliferation (35).

4. TGF-β signaling is involved in the regulation of epithelial-mesenchymal transition

EMT is a key step in the progression of cancer invasion and metastasis, characterized by reduced epithelial marker and elevated mesenchymal marker expression (36,37). The EMT process is often associated with upregulation of TGF-β signaling and TGF-β drives EMT through the Smad-mediated or non-Smad-mediated reprogramming of gene expression (Fig. 2) (38). TGF-β receptors can induce the expression of ZEB1, ZEB2, Snail and Slug through the Smad pathway and mediate MMPs and p38MAPK through non-Smad pathways, which both lead to EMT (39). ROS are also important in TGF-β-induced EMT, primarily through the activation of MAPK and through subsequent ERK-directed activation of the Smad pathway in proximal tubular epithelial cells (40). TGF-β signaling not only mediates EMT, but it is also required for distant metastases. A previous study demonstrated that TGF-β in the breast cancer microenvironment promoted pulmonary metastases of breast cancer cells (41).

5. TGF-β and cancer stem cells

Advances in cancer stem cell (CSC) research have indicated that the TGF-β signaling pathway is essential for the maintenance of CSCs. CSCs have been reported to be responsible for the recurrence of disease following anticancer therapy (42). Certain extracellular and intracellular signals allow cancer progenitors to dynamically revert to a stem cell state. Evidence has shown that TGF-β induced the expression of CD133, a CSC marker, in liver cancer cell lines and increased tumor initiating ability in mice, compared with the milder and transient effect of interleukin-6 (43). Chanmee *et al* found that the over production of hyaluronan allowed cancer progenitors to revert to stem cell states via Twist and the TGF-β-Snail signaling axis (44). Furthermore, tumor-associated macrophages (TAMs) in the tumor microenvironment promoted CSC-like properties via TGF-β1-induced EMT in HCC (45). MicroRNA (miR)-106b is significantly upregulated in CD44(+) cells and the inhibition of miR-106b shows suppression of the TGF-β/Smad signaling pathway and decreases self-renewal capacity and cell invasiveness (46). These findings suggest that TGF-β signaling is associated with cancer cell stemness.

There are epigenetic differences in TGF-β signaling-related genes between cancer stem-like cells and differentiated cancer cells. It was previously reported that the methylation levels of genes coding TGF-β signaling-related proteins can regulate breast cancer stem cell differentiation (47). Evidence suggests that several members of the TGF-β pathway are targeted by long non-coding RNAs, key epigenetic mediators and this may, at least in part, explain the association between cancer cell stemness and TGF-β signaling (48). These findings may assist in the development of novel agents, which can specifically control increases and decreases in the TGF-β signaling pathway in CSCs and thereby provide a novel avenue for the prevention and treatment of malignant cancer (48).

6. Crosstalk between TGF-β signaling and inflammation

Acute inflammation is an essential component of the wound-healing response to stimuli. However, chronic

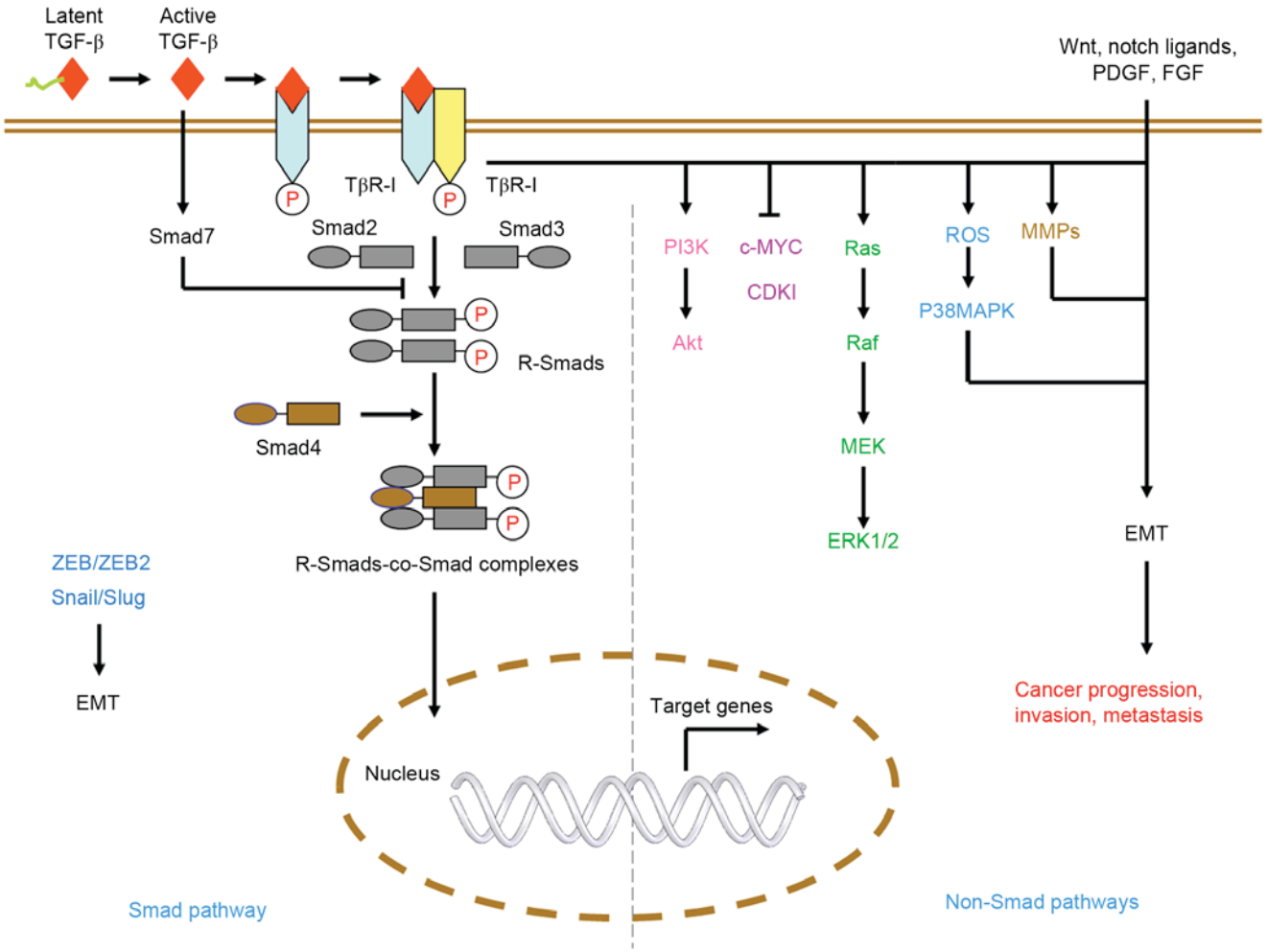

Figure 1. TGF-β transduces signaling through the Smad and non-Smad signaling pathways. In the Smad pathway (left), TGF-β binds to TβRII, which phosphorylates TβRI, which activates Smad2 and Smad3 (R-Smads). Activated Smad2/3 forms R-Smads-co-Smad complexes with Smad4 (co-Smad), which interact with various transcription factors and transcriptional co-activators and regulates the transcription of target genes. TGF-β induces EMT through non-Smad proteins, including ZEB1/ZEB2 and Snail/Slug through the Smad pathway. In the non-Smad pathway (right), TGF-β can mediate EMT through non-Smad pathways. EMT is also mediated by extracellular signaling proteins, including Wnt, Notch ligands and PDGF. TGF-β can regulate other cellular responses with the exception of EMT, through non-Smad pathways, for example the PI3K-Akt signaling pathway and MAPK signaling. TGF-β, transforming growth factor-β; TβR, TGF-β receptor; Smad, small mothers against decapentaplegic; EMT, epithelial-mesenchymal transition; ZEB1, Zinc finger E-box-binding homeobox 1; ZEB2 Zinc finger E-box-binding homeobox 2; PDGF, platelet-derived growth factor; FGF, fibroblast growth factor; PI3K, phosphoinositide 3-kinase; MAPK, mitogen-activated protein kinase; ROS, reactive oxygen species; MMPs, matrix metalloproteinases.

inflammation favors the accumulation of mutations and epigenetic aberrations in normal cells, thereby promoting malignant transformation (49,50). This process is mediated by chemokines, cytokines and growth factors secreted by stromal components of the tumor microenvironment. Among those secreted factors, the TGF-β subfamily has been shown to generate a favorable immune microenvironment for tumor growth. TGF-β can impair anticancer immune responses in several ways, including immune cell inhibition and the elimination of major histocompatibility complex class I and II (51). It can also induce TAMs and generate ROS with genotoxic activity (52-54). TAMs are primarily a macrophage subpopulation with an M2 phenotype. TAM-derived factors may enhance the invasiveness of tumor cells by enhancing their adhesion to extracellular matrix in the tumor stroma (55,56). Evidence from clinical and epidemiological studies has shown that TAM density is positively associated with poor survival rates in several types of cancer (56,57). The involvement of ROS signaling in tumor progression has also been

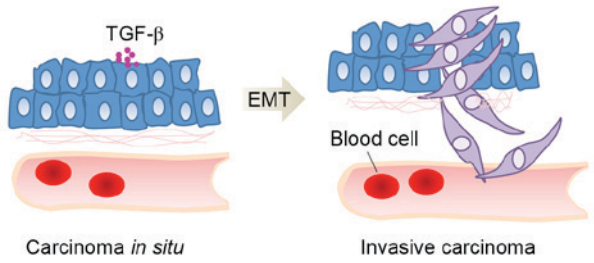

Figure 2. TGF-β drives EMT phenotype. Exposure of tumor cells to TGF-β *in situ* causes certain cells to become motile and invade into neighboring blood vessels and tissues. This is accompanied by morphogenetic changes. TGF-β, transforming growth factor-β; EMT, epithelial-mesenchymal transition.

recognized (58,59). Previous studies have suggested that the increased generation of ROS in tumor cells may affect certain redox-sensitive molecules, leading to mutations and genetic instability, cellular proliferation and metastasis (60,61).

7. TGF-β signaling in the regulation of tumor angiogenesis

The ability of tumor cells to induce the formation of blood vessels is crucial for tumor growth, invasion and metastasis. TGF-β is a key mediator of angiogenesis in the tumor microenvironment, contributing to angiogenesis by inducing proangiogenic factors (62).

TGF-β can induce a proangiogenic environment and stimulate tumor-associated angiogenesis. Elevated expression levels of TGF-β have been linked to increased microvessel density in certain tumor types (63). The mechanism of angiogenesis stimulated by TGF-β signaling includes the induction of key angiogenic factors, including connective tissue growth factor, vascular endothelial growth factor and insulin-like growth factor-binding protein 7, in epithelial cells and fibroblasts (64,65). In addition, TGF-β can induce the expression, secretion and activation of matrix metalloproteinase 2 (MMP2) and MMP9 and down regulate the expression of tissue inhibitor of metalloproteinase in tumor and endothelial cells (66-68).

However, TGF-β also has angiostatic functions. For example, in pancreatic cancer and diffuse-type gastric cancer, TGF-β induces the production of thrombospondin1, a potent angiogenic inhibitor, whereas perturbations of TGF-β signaling resulted in accelerated angiogenesis and growth of tumors (69). Whether TGF-β is angiogenic or angiostaticis is dependent on the cellular context of tumor cells, epithelial cells and the tumor microenvironment.

8. Conclusion

Several lines of evidence suggest that the TGF-β family is involved in tumor initiation and progression, including cell proliferation, angiogenesis, cancer cell stemness, EMT, invasion and inflammation. TGF-β signaling is complex and mediates pro- and anti-tumoral activities in cancer cells depending on their context in space and time and their microenvironment (52). It is generally accepted that TGF-β is primarily a tumor suppressor in premalignant cells but functions as a promoter of metastasis in cancer cells (70,71). However, the mechanisms underlying the contextual changes in the role of TGF-β remain to be elucidated. Xu *et al* provided molecular insight into how TGF-β converts from a tumor suppressor to a tumor promoter. It was found that 14-3-3ζ turned off the tumor suppression function of TGF-β by destabilizing p53, a Smad partner in premalignant cells. By contrast, 14-3-3ζ promoted TGF-β-induced distant metastasis by stabilizing Gli family zinc finger 2 (Gli2) and inducing the partnering of Gli2 with Smads in malignant cells (70). Therefore, the 14-3-3ζ-driven contextual changes of Smad partners from p53 to Gli2 may provide therapeutic targets in TGF-β-mediated cancer progression.

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