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Dichotomous Roles of TGF-β in Human Cancer

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Abstract

Transforming growth factor-β (TGF-β) mediates/regulates numerous biological processes including embryonic development and maintenance of cellular homeostasis in a context dependent manner. Consistent with its central role in maintaining cellular homeostasis, inhibition of TGF-β signaling results in disruption of normal homeostatic processes and subsequent carcinogenesis, defining the TGF-β signaling pathway as a tumor suppressor. However, once carcinogenesis is initiated, the TGF-β signaling pathway functions to promote cancer progression. This dichotomous function of the TGF-β signaling pathway is mediated both through altered effects on the cancer cells, including via inducing epithelial to mesenchymal transition, as well as through effects on the tumor microenvironment, including via effects on angiogenesis and immunosurveillance. Current studies support inhibition of TGF-β signaling either alone, or in conjunction with anti-angiogenic therapy or immunotherapy as a promising of strategy for the treatment of human cancers.

Transforming growth factor-β (TGF-β) is a ubiquitously-expressed cytokine that mediates or regulates a wide spectrum of biological processes including embryonic development, maintenance of cellular homeostasis, angiogenesis and immune regulation in a context dependent manner. Consistent with its pervasive and central role in maintaining cellular homeostasis, inhibition of TGF-β signaling results in disruption of normal homeostatic processes and subsequent carcinogenesis, defining the TGF-β signaling pathway as a tumor suppressor. However, once carcinogenesis is initiated, the TGF-β signaling pathway functions to promote cancer progression (Figure 1). This dichotomous function of the TGF-β signaling pathway during cancer initiation and progression presents a tremendous challenge, both in terms of understanding how the same pathway mediates these divergent effects, and in confounding efforts to target this pathway for therapeutic purposes. Here we review potential mechanisms though which TGF-β mediates its dichotomous functions during cancer progression and establish a framework for rationale targeting of the pathway in human patients.

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Mechanism of TGF-β Signaling

TGF-β initiates downstream signaling when the dimerized TGF-β ligand binds to the type III TGF-β receptor (TβRIII), which then presents ligand to the type II TGF-β receptor (TβRII) [1, 2]. TβRII then recruits and phosphorylates the type I TGF-β receptor (TβRI) to active its kinase activity [3, 4]. In canonical TGF-β signaling, activated TβRI phosphorylates the intracellular proteins Smad2 or Smad3, which then complex with Smad4 before translocating into and accumulating in the nucleus where they act with co-activators or co-repressors to initiate transcriptional changes [5–8]. TGF-β can also signal through non-canonical pathways including p38, JNK, Erk1/2 and PI3K [9] and has also been reported to signal through Smad1/5/8 [10, 11]. The TGF-β signaling pathway is regulated at many levels. At the extracellular level, TGF-β ligand bioactivity is regulated by activation steps, which release it from a latent complex [12], as well as by interaction with antagonists, including the soluble type III TGF-b receptor [13, 14]. At the intracellular level, negative feedback is provided both by the inhibitory Smad6 and Smad7, which are upregulated by TGF-β and antagonize signaling at the receptor/Smad level [15–17], and by transcriptional repressors, including Ski and SnoN, which are upregulated by TGF-β and antagonize signaling at the Smad/promoter level [18]. Perturbations to TGF-β signaling can occur at each of these multiple levels of regulation, including increased ligand availability due to loss of shed TβRIII [13, 14], loss or mutation of cell surface receptors [19–25] or of downstream mediators [26–30].

TGF-β as a Tumor Suppressor

Dysregulation of TGF-β signaling pathway is a frequent event in human cancers. Disruption can occur either through deletion or inactivating mutations of the TGF-β receptors or their downstream effectors. TβRII deletions or mutations are often seen in colon, gastric, bladder and ovarian cancers [19–23], and TβRI receptor altercations are also commonly seen in ovarian, head and neck, breast, bladder, and prostate cancers, among others [21, 23–25]. Over 50% of pancreatic cancers and 15% of colon cancers harbor altercations to the downstream effector Smad4 [26–28]. Additionally, Smad4 mutations are a known cause juvenile polyposis, an inherited autosomal dominant disease that predisposes patients to hamartomatous polyp formation and colorectal cancer [29]. Other mediators of TGF-β signal transduction, including Smad2 and Smad3, are mutated in colorectal cancer [28], hepatocellular carcinoma [31] and gastric cancer [30]. Contrary to the loss of function of TGF-β mediators, antagonists of the TGF-β pathway including Smad7, Ski, and SnoN are often overexpressed in colorectal cancer, melanoma and breast cancer, among others [32–36]. The tumor suppressive role of TGF-β is largely thought to be due to TGF-β's roles in limiting proliferation, promoting apoptosis and inducing senescence in normal cells.

Tumor Suppressive Role of TGF-β in proliferation

In normal epithelial and hematopoietic cells, TGF-β inhibits cell growth by targeting cell-dependent kinases (CDKs) and their inhibitors (CDK-Is) that are responsible for controlling progression past the G1 phase of the cell cycle during proliferation. TGF-β promotes the expression of the CDK-Is $p15^{INK4B}$, $p21^{CIP1}$ and $p27^{KIP1}$, which inhibit cyclin-CDK

complexes, leading to G1 phase cell cycle arrest [37–40]. In addition, TGF-β inhibits CDK4, which is required for exit from the G1 phase and progression into the S phase of the cell cycle, directly mediating growth suppression. [41, 42]. TGF-β also suppresses c-Myc, leading to suppression of $p15^{INK4B}$ and $p21^{CIP1}$, and thus, loss of cell proliferation [43–45]. Id family proteins including Id1, Id2 and Id3, which help mediate differentiation and cytostasis, are also repressed by TGF-β, resulting in decreased proliferation [46, 47].

When TGF-β signaling is disrupted by mutation, deletion or altered expression of critical components, this anti-proliferative signaling is lost, leading to sustained proliferation due to lack of G1 cell cycle arrest. The critical role for loss of TGF-β signaling in mediating sustained proliferation in human cancers is supported by the ability of restoration of TGF-β signaling to rescue TGF-β responsiveness and control of proliferative signaling. Thus, restoration of TβRII in the human breast cancer cell line, MCF-7, or of Smad3 in the gastric cancer cell line, SNU-484, rescues TGF-β sensitivity while TGF-β stimulation once again initiates growth arrest [30, 48]. In a reciprocal manner, loss of negative regulators of TGF-β signaling, including SnoN and SKI, can inhibit proliferation of breast, lung and pancreatic cancer cells [49, 50].

Tumor Suppressive Role of TGF-β in apoptosis

TGF-β triggers apoptosis in a wide range of cell types acting through both Smad-dependent and independent pathways. The Smad-dependent pathway involves the induction of pro-apoptotic proteins including TGF-β inducible early response gene (TIEG1) [51], death-associated protein kinase (DAPK) [52, 53], and inositol-5-phophatase (SHIP) [53]. TIEG1 induces oxidative stress [54] while DAPK induces mitochondrial cytochrome c release to trigger apoptosis [52]. SHIP inhibits the pro-survival PI3K-Akt pathway to instigate cell death [53]. TGF-β also works through Smad4 to induce SAPK/JNK pathway signaling to induce the expression of pro-apoptotic genes including BIM, BMF, and BAX and caspase 9 [55–57]. Independent of the SAPK/JNK pathway, TGF-β can also promote the expression of pro-apoptotic genes, including BIK and caspase 3 and 8, while suppressing anti-apoptotic genes, including Bcl-X_L, XIAP, and Bcl-2 [58–61]. TGF-β is also linked to the Fas-mediated apoptosis pathway through DAXX, an adaptor protein that mediates Fas receptor signaling. DAXX stabilizes TβRII, leading to JNK activation and potentiation of Fas apoptosis signaling [62]. Interestingly, cells that are resistant to TGF-β induced growth inhibition can still respond to TGF-β induced apoptosis through inducing the translocation of the mitochondrial protein ARTS to the nucleus. This translocation then stimulates caspase 3 activation and suppresses the anti-apoptotic proteins Bcl-X_L and XIAP to induce apoptosis [63–65]. Apoptosis can also be induced after malignant epithelial-to-mesenchymal transition (EMT) if cells are TGF-β responsive. In Smad4-expressing TGF-β responsive pancreatic cancer, TGF-β can stimulate cells to undergo EMT while simultaneously suppressing Klf5 signaling. Without Klf5 cooperation, Sox4 induces apoptosis [66].

These TGF-β-induced apoptotic homeostatic mechanisms are also disrupted when intact TGF-β signaling is lost. In many cases, TGF-β's apoptotic signaling is Smad dependent, with overexpression of Smad4 inducing apoptosis in MDA-MB-468 breast cancer cells [67]. Meanwhile, use of a dominant-negative Smad3 prevented apoptosis in the Hep3B

hepatocarcinoma cell line [68]. TβRII's role in mediating apoptosis is also critical for regenerating epithelial tissue, where apoptosis helps prevent hyperproliferation. When TβRII is lost in skin epithelial cells, the loss of apoptosis disrupts this balance between apoptosis and hyperproliferation, leading oncogenic progression and invasive squamous cell carcinoma [69]. Similarly, knock-down of Smad2 or expression of a dominant negative TβRII in NRP-152 cells, a non-tumorigenic prostate epithelial cell line, greatly reduced sensitivity to TGF-β-induced apoptosis, subsequently leading to malignant transformation and the newfound ability to form tumors when injected into nude mice [70, 71],. On the other hand, in TGF-β non-responsive Smad4 null pancreatic cancer cells, Klf5 signaling is induced, inhibiting apoptosis, leading to cell immortalization and subsequent tumorigenesis [66].

TGF-β as a Tumor Promoter

While TGF-β may suppress cancer initiation, in cancers that do form, increased expression of TGF-β ligands has been broadly reported, including in breast [72, 73], esophageal [74], colorectal [75], gastric [76], lung [77] and pancreatic cancers [78]. In these cancers, increases in TGF-β ligand levels have been demonstrated both locally and systemically, with elevated circulating levels. Higher levels of TGF-β have been demonstrated in lymph node metastasis compared to primary tumors or in tumors that eventually metastasize. High levels of TGF-β also correlate with increased invasiveness, disease progression and a poorer prognosis [72, 75–80]. TGF-β can be produced by the tumor cell itself or other cells in the tumor microenvironment including stromal cells, macrophages and platelets [81–83]. Additionally, secreted TGF-β that is stored in the extracellular matrix can be release by the tumor-associated increase in matrix degradation factors [84–86]. Although the increase in TGF-β may enhance the cell autonomous tumor suppressive effects, many tumorigenic cells have already lost their TGF-β responsiveness and thus, its homeostatic effects. Instead, this increase in TGF-β may act in the tumor microenvironment to promote changes that encourage tumor progression. Along those lines, TGF-β has roles in promoting angiogenesis, inducing EMT, modifying the extracellular matrix, and suppressing immune surveillance.

Tumor Promoter Role of TGF-β in EMT and Metastasis

TGF-β induces EMT during normal growth and development. It is essential for embryonic tissue differentiation [87] and normal heart and lung development [88, 89]. EMT is also accompanied by changes in tight junction and cell adhesion molecules, including decreasing E-cadherin, claudin and occludin expression while upregulating vimentin and N-cadherin [90, 91]. The EMT gene signature involves the Smad-mediated induction of HMGA2 to mediate Snail, Slug, ZEB2 and Twist expression [92] as well as the Smad-independent upregulation of the polarity protein Par6 [93] which lead to loss of cell polarity, E-cadherin downregulation and increased invasion and metastasis [94]. TGF-β also induces cytoskeleton re-organization by inducing focal adhesion kinase signaling, smooth muscle actin expression and stress fiber formation [95]. These EMT-associated changes allow cells to change to lose connections to other epithelial cells, acquire a fibroblast phenotype and migrate away from their initial location. This EMT process can be hijacked by cancer cells

to lead to decrease cell adhesion and encourage migration and invasion to promote to cancer metastasis.

TGF-β signaling is essential to EMT in cancer cells. In squamous cell carcinoma and breast cancer, use of a dominant negative TβRII abrogated their ability to undergo EMT and migration and metastasize to distant sites [96–98]. Meanwhile, restoration of TβRII activity in the typically TβRII-null and non-invasive hereditary nonpolyposis colorectal cancer cells promoted invasive behavior [99]. Transgenic mice with activated TGF-β1 expression in keratinocytes demonstrated an increased propensity to form spindle cell carcinomas, suggesting that TGF-β1 is involved in this keratinocyte-to-spindle cell transition [100]. In breast cancer, TGF-β also has been demonstrated to induce MDM2, destabilizing p53, leading to EMT and tumor progression [101]. In addition, in cancers where p53 is mutated, TGF-β induces the formation of a mutant p53, Smad and p63 complex. In this complex, p63 loses its tumor suppressive function, allowing both TGF-β and mutant p53 to initiate EMT and metastasis [102]. Moreover, high levels of TGF-β are often seen at the invasive front, suggesting that TGF-β is involved in the EMT, migration and invasion of tumor cells [96].

TGF-β can also increase migration, invasion and the metastasis of cancer cells, including mediating the balance between single-cell versus group migration of cancer cells. In TGF-β responsive breast cancer cells, single cell migration occurs through a Smad-mediated pathway involving downstream activation of EGFR, Jun and Rho signaling pathways and CTGF. However, collective migratory behavior and increased lymph node metastasis is seen in when TGF-β signaling is inhibited [103]. TGF-β has been demonstrated to promote migration in prostate cancer by inducing cytoskeletal rearrangement in a Cdc42 and RhoA dependent fashion, increasing formation of stress fibers and lamellipodia [104] while TGF-β-mediated induction of DOCK4 in lung cancer also leads to increased cell protrusion, motility and metastasis [105]. Breast cancer migration and invasion can also be inhibited by ectodomain shedding of TβRIII, which generates a soluble form of the receptor that can act as a ligand sink. Abrogation of soluble receptor generation increases migration and invasion [14]. Meanwhile, the cytoplasmic domain of TβRIII signals through GIPC to suppress cancer progression and loss of the receptor increases migratory and invasive behavior [106]. TGF-β is also able to down-regulate tumor-suppressive microRNAs that including miR-124 and miR-187, enhancing EMT and metastasis. miR-124 also contributes to a positive feedback loop that further upregulates TGF-β expression leading increased metastasis [107, 108].

In addition to promoting EMT and metastasis, TGF-β can also promote colonization of metastatic cells through mesenchymal-to-epithelial transition (MET) and upregulation of metastatic niche genes. TGF-β promotes MET in breast cancer cells that metastasize to the lung through an Id1-Twist1 signaling axis, leading to lung colonization [109]. Furthermore, TGF-β is critical for the establishment of bone metastasis in breast cancer by inducing growth factors, including PTHrP, RANKL, IL-11 and CTGF, which encourage bone colonization [98, 110–112]. TGF-β is also released from the bone itself, further promoting bone metastasis, bone destruction, muscle weakness and loss of muscle mass [113].

Tumor Promoter Role of TGF-β in the Tumor Microenvironment

The stroma in the tumor microenvironment consists of many cells and structures that are important for normal tissue physiology but also can influence tumor progression. These cells and structures include myofibroblasts, blood vessels and immune cells which reside in the extracellular matrix (ECM), which is comprised of collagen, elastin, fibronectin and laminin scaffolding proteins [114]. Together with its cell autonomous effects, TGF-β can influence these complex stromal components to support tumor growth and progression.

Tumor Promoter Role of TGF-β on the Extracellular Matrix

Differentiation of fibroblasts, stellate cells or smooth muscle cells into myofibroblasts occurs normally in response to tissue injury and TGF-β, and these myofibroblasts secrete extracellular matrix (ECM) components and help remodel the ECM to aid with wound healing. Once repair is completed, they undergo apoptosis, suggesting that myofibroblasts are a transient rather than permanent cell population [115]. In cancer, TGF-β helps differentiate fibroblast into myofibroblasts, which then become a persistent and important component of the tumor microenvironment, where they secrete pro-tumor growth factors [116–118]. This progression from fibroblastic to myofibroblastic characteristics correlates with tumor progression in colon and breast cancer [119, 120]. Myofibroblasts also acquire autocrine and paracrine signaling that promote a pro-tumorigenic phenotype by stimulating the expression of proteins including MMPs, cytokines and chemokines to promote proliferation, EMT, invasion and angiogenesis. These proteins lead to further increase in TGF-β levels and also stimulate tumor cells to further promote progression [116, 121–124]. Loss of TGF-β signal by deletion of TβRII in fibroblasts resulted in prostate and gastric cancer due to the dysregulation of HGF, MST1 and TGF-α in surrounding tissue, further suggesting that fibroblasts are involved in both autocrine and paracrine signaling in the tumor microenvironment. Further, co-injecting TβRII null fibroblasts with renal cell carcinoma cells promoted tumor invasion, angiogenesis and proliferation [121, 122]. Stromal TGF-β signaling also helped establish a metastatic niche for colorectal cancer cells, promoting colonization, while use of a TβRI inhibitor prevented metastasis. A TGF-β induced gene signature in fibroblasts is also predictive of disease recurrence while low stromal signaling correlated with improved survival [125].

TGF-β is also involved in ECM remodeling through increasing the expression of matrix metalloproteinases (MMPs), including MMP1, MMP2, MMP7, MMP9, MMP13 and MMP14. These MMPs degrade the ECM, providing a pathway for tumor migration and invasion and activates the TGF-β sequestered in the ECM, feeding a positive feedback loop. ECM remodeling also stimulates angiogenesis, further supporting tumor growth [126, 127]. Meanwhile, MMP13 induced by TGF-β promoted tumor extravasation from the tumor microenvironment to support metastatic growth [128, 129]. Changing the ECM force mechanics also influence tumor progression: decreasing the ECM rigidity increased the sensitivity of cells to TGF-β-induced apoptosis while increasing rigidity promoted TGF-β-mediated EMT [130].

Tumor Promoter Role of TGF-β in Angiogenesis

Endothelial cells are the major cell type regulated during angiogenesis and exhibit increased permeability, proliferation, migration and invasion during the formation of new blood vessels [131]. The TGF-β signaling pathway has an important role in endothelial biology and normal angiogenesis. Mice deficient in TGF-β signaling in endothelial cells due to the loss of ALK-1, a type I TGF-β receptor [132]; TβRII [133, 134]; endoglin, a TGF-β co-receptor [135, 136]; or TGF-β1 [137] exhibit dysregulated angiogenesis and embryonic lethality [132, 135, 136]. TGF-β also induces the production pro-angiogenic growth factors, including VEGF and CTGF by epithelial cells and fibroblasts [138, 139] and directly stimulates endothelial cells to form capillaries. Meanwhile, TGF-β-induced VEGF and CTGF induces endothelial migration that is necessary for angiogenesis [133, 140].

During tumor growth the tumor quickly outgrows the existing vasculature and induces angiogenesis to provide nutrients and oxygen to the cancer cells [141]. TGF-β has an important role for inducing and sustaining tumor angiogenesis, which in turn supports cancer progression and metastasis. Higher levels of TGF-β in the tumor microenvironment correlates with increased vascular density, tumor progression and worse prognosis in a non-small cell lung cancer cohort [77]. High circulating levels of TGF-β1 in plasma also correlated with increased tumor angiogenesis and poor prognosis in prostate cancer, renal cell carcinoma and hepatocellular carcinoma [80, 142–144]. TGF-β can also induce the endothelial microRNA miR-29a, leading to PTEN/AKT pathway activation and increased angiogenesis [145]. In xenografts, Chinese hamster ovary cells transfected to overexpress TGF-β1 resulted in increased angiogenesis while a TGF-β neutralizing antibody inhibited angiogenesis, further demonstrating the importance of TGF-β in angiogenesis and tumor progression [146]. In addition to TGF-β ligand effects, TGF-β receptors are also critical for angiogenesis. Treating mice xenografted with TβRII null 786-O renal carcinoma cells with a TGF-β neutralizing antibody also decreased angiogenesis [147]. Endoglin also works in concert with VEGF to induce tumor angiogenesis. Suppression of both endoglin and VEGF led to decreased endothelial tube formation and subsequent angiogenesis [148, 149].

TGF-β can also generate an environment more conducive to endothelial cell migration, which is essential for angiogenesis, by inducing MMP activity to modify the ECM. TGF-β can act through one of its type I receptors, ALK5, to enhance MMP9 expression, and promote the formation of new blood vessels. Use of dominant negative ALK5 or knock-down of MMP9 enhanced angiogenesis and tumor progression in breast and prostate cancer cell lines [150, 151].

Tumor Promoter Role of TGF-β in Immune Surveillance

TGF-β is generally immunosuppressive and exerts these suppressive effects on all the components of the immune system. It suppresses the activity of cytotoxic T-cells, natural killer cells and dendritic cells and creates a pro-inflammatory environment, which recruits macrophages and neutrophils. These effectors secrete tumor promoting cytokines and chemokines including TGF-β, initiating a positive feedback loop that further promotes tumor progression [152, 153]. Since TGF-β is often upregulated in the tumor

microenvironment, tumors are able to evade immune destruction through both immunosuppression and decreased immune surveillance.

Cytotoxic $CD8^+$ T-cells can produce cytokines including perforins, granzymes and IFN-γ to induce apoptosis of any cancer cell that the encounter. However, TGF-β can inhibit their activity through transcriptional repression of these mediators by Smads and ATF1. Moreover, preventing TGF-β signaling through generating cytotoxic T-cells that express dominant-negative TβRII restored the cytotoxic T-cell activity and prolonged survival [154]. In addition to suppressing cytotoxic T-cell activity, TGF-β can also induce regulatory T-cell (Treg) differentiation [155, 156], leading to immunosuppression and loss of immune surveillance. Tregs then respond to TGF-β by preventing cytotoxic $CD8^+$ T-cell proliferation and induction, inhibiting the release of cytotoxic cytokines and chemokines and further dampening anti-tumor immune responses [157].

Natural killer (NK) cells also play an important role in immune surveillance by recognizing tumor cells and initiating a cytotoxic response [158]. TGF-β can suppress NK cell activation by inhibiting IL-15 production and downregulating its activating receptor NKG2D [159, 160]. In addition, TGF-β also can induce miR-183 expression to destabilize DAP12, a receptor that is required for NK cell cytotoxicity [161]. Treating NK cells with TGF-β decreased their ability to release cytokines including perforin to induce tumor cell apoptosis while TGF-β neutralizing antibodies reversed this phenotype by promoting IL-15 production and NKG2D and DAP12 expression, which promoted NK cell survival and activation and allowed them to regain their effector function [159–161].

Dendritic cells (DC) are antigen presenting cells that responsible to inducing the adaptive T-cell response and their activity is important for anti-tumor immunity [162, 163]. TGF-β prevents the differentiation of DCs from its myeloid precursors and instead shifts differentiation toward the anti-tumorigenic myeloid-derived suppressor cells through the upregulation of the TGF-β responsive gene ID1 [164]. Specifically deleting TβRII in myeloid cells to abolish TGF-β signaling in dendritic cells increased their ability to activate T-cells, leading to decreased tumor growth. On the other hand, treating myeloid precursor cells with TGF-β inhibited their ability to activate T cells [165]. In addition, TGF-β inhibition alone has been shown to subdue DC-mediated Treg activation, and when combined with anti-CTLA-4 immunotherapy, synergistically decreased melanoma growth and metastasis though neither alone prevented progression [166].

TGF-β has been shown to drive polarization of neutrophils from an anti-tumor phenotype (N1) to a tumorigenic phenotype (N2). In the presence of TGF-β, neutrophils develop into a pro-tumorigenic phenotype and showed a decreased ability to activate cytotoxic T-cells and secrete anti-tumorigenic cytokines and chemokines. Furthermore, depletion of these neutrophils lead to a decrease in tumor size. However, treating mice with SM16, an Alk4/Alk5 TβRI kinase inhibitor, allowed tumor suppressive neutrophils to hone to the tumor, leading to cytotoxic T-cells activation and secretion of cytokines and chemokines to promote immune surveillance. When these neutrophils were then systemically depleted, tumors exhibited rapid growth, suggesting that without TGF-β stimulation, neutrophils retain their tumor suppressive phenotype [167].

Macrophages can also be divided into two groups, with the classically activated M1 phenotype regarded as tumor suppressive and the alternatively activated M2 phenotype as tumor promoting. TGF-β is a critical driver for macrophages adopting the M2 phenotype [168], which produce cytokines and chemokines including MMP9, CXCL8, CXCL12, VEGF, and IL-10 that induce tumor growth and invasion, modify the ECM and promote angiogenesis. Moreover, macrophages also suppress the adaptive arm of the immune system, further preventing immune responses [169].

Conclusion

Though much work has been done on TGF-β's role as a tumor suppressor and tumor promoter, the mechanism by which this switch occurs has yet to be elucidated (Figure 1). As with most aspects of tumor progression, there are likely to be multiple mechanisms for this switch, including both cell autonomous (i.e. EMT) and non-cell autonomous (i.e. angiogenesis, immune system) mechanisms. Recent studies support the involvement of 14-3-3ζ, which is able to simultaneously induce cytostasis by downregulating 14-3-3σ, p53 and $p21^{CIP1}$ and promote bone metastasis by upregulating PTHrP and other bone metastasis gene signatures [170], as well as the anti-oxidative stress transcription factor Nrf2 [171–173].

Early trials using TGF-β inhibitors have demonstrated that they can promote anti-tumorigenic effects even in Smad4 defective tumors, suggesting that they may function to inhibit TGF-β function in the tumor microenvironment, including angiogenesis and immune surveillance [174]. Indeed, agents targeting endoglin (e.g.TRC-105) and ALK1 (e.g. ACE-041, PF-03446962) have demonstrated single agent efficacy in Phase I studies [175–177]. In addition, with the emerging role of immunotherapy in cancer treatment and the effects of TGF-β on inhibiting the immune system, combination of TGF-β inhibition with immunotherapy appears promising. Supporting this premise, in the context of breast cancer, TGF-β inhibition was able to increase the effectiveness of a HER2 vaccine [178], and in the context of melanoma, TGF-β inhibition restored sensitivity to anti-CTLA-4 therapy [166]. Better understanding of the influence of TGF-β on the different components of the tumor microenvironment will be critical to fully harnessing anti-TGF-β targeted therapy and rational combinations with other targeted approaches.

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References

1. Lopez-Casillas F, Wrana JL, Massague J. Betaglycan presents ligand to the TGF beta signaling receptor. Cell. 1993; 73(7):1435–44. [PubMed: 8391934]
2. Sankar S, et al. Expression of transforming growth factor type III receptor in vascular endothelial cells increases their responsiveness to transforming growth factor beta 2. J Biol Chem. 1995; 270(22):13567–72. [PubMed: 7768960]
3. Attisano L, et al. Identification of human activin and TGF beta type I receptors that form heteromeric kinase complexes with type II receptors. Cell. 1993; 75(4):671–80. [PubMed: 8242742]

4. Franzen P, et al. Cloning of a TGF beta type I receptor that forms a heteromeric complex with the TGF beta type II receptor. Cell. 1993; 75(4):681–92. [PubMed: 8242743]
5. Eppert K, et al. MADR2 maps to 18q21 and encodes a TGFbeta-regulated MAD-related protein that is functionally mutated in colorectal carcinoma. Cell. 1996; 86(4):543–52. [PubMed: 8752209]
6. Chen Y, Lebrun JJ, Vale W. Regulation of transforming growth factor beta- and activin-induced transcription by mammalian Mad proteins. Proc Natl Acad Sci U S A. 1996; 93(23):12992–7. [PubMed: 8917532]
7. Zhang Y, et al. Receptor-associated Mad homologues synergize as effectors of the TGF-beta response. Nature. 1996; 383(6596):168–72. [PubMed: 8774881]
8. Lagna G, et al. Partnership between DPC4 and SMAD proteins in TGF-beta signalling pathways. Nature. 1996; 383(6603):832–6. [PubMed: 8893010]
9. Mu Y, Gudey SK, Landstrom M. Non-Smad signaling pathways. Cell Tissue Res. 2012; 347(1):11–20. [PubMed: 21701805]
10. Daly AC, Randall RA, Hill CS. Transforming growth factor beta-induced Smad1/5 phosphorylation in epithelial cells is mediated by novel receptor complexes and is essential for anchorage-independent growth. Mol Cell Biol. 2008; 28(22):6889–902. [PubMed: 18794361]
11. Liu IM, et al. TGFbeta-stimulated Smad1/5 phosphorylation requires the ALK5 L45 loop and mediates the pro-migratory TGFbeta switch. EMBO J. 2009; 28(2):88–98. [PubMed: 19096363]
12. Annes JP, Munger JS, Rifkin DB. Making sense of latent TGFbeta activation. J Cell Sci. 2003; 116(Pt 2):217–24. [PubMed: 12482908]
13. Lopez-Casillas F, et al. Betaglycan can act as a dual modulator of TGF-beta access to signaling receptors: mapping of ligand binding and GAG attachment sites. J Cell Biol. 1994; 124(4):557–68. [PubMed: 8106553]
14. Elderbroom JL, et al. Ectodomain shedding of TbetaRIII is required for TbetaRIII-mediated suppression of TGF-beta signaling and breast cancer migration and invasion. Mol Biol Cell. 2014; 25(16):2320–32. [PubMed: 24966170]
15. Hayashi H, et al. The MAD-related protein Smad7 associates with the TGFbeta receptor and functions as an antagonist of TGFbeta signaling. Cell. 1997; 89(7):1165–73. [PubMed: 9215638]
16. Nakao A, et al. Identification of Smad7, a TGFbeta-inducible antagonist of TGF-beta signalling. Nature. 1997; 389(6651):631–5. [PubMed: 9335507]
17. Imamura T, et al. Smad6 inhibits signalling by the TGF-beta superfamily. Nature. 1997; 389(6651): 622–6. [PubMed: 9335505]
18. Deheuninck J, Luo K. Ski and SnoN, potent negative regulators of TGF-beta signaling. Cell Res. 2009; 19(1):47–57. [PubMed: 19114989]
19. Markowitz S, et al. Inactivation of the type II TGF-beta receptor in colon cancer cells with microsatellite instability. Science. 1995; 268(5215):1336–8. [PubMed: 7761852]
20. Myeroff LL, et al. A transforming growth factor beta receptor type II gene mutation common in colon and gastric but rare in endometrial cancers with microsatellite instability. Cancer Res. 1995; 55(23):5545–7. [PubMed: 7585631]
21. Tokunaga H, et al. Decreased expression of transforming growth factor beta receptor type I is associated with poor prognosis in bladder transitional cell carcinoma patients. Clin Cancer Res. 1999; 5(9):2520–5. [PubMed: 10499628]
22. Lynch MA, et al. Mutational analysis of the transforming growth factor beta receptor type II gene in human ovarian carcinoma. Cancer Res. 1998; 58(19):4227–32. [PubMed: 9766642]
23. Levy L, Hill CS. Alterations in components of the TGF-beta superfamily signaling pathways in human cancer. Cytokine Growth Factor Rev. 2006; 17(1–2):41–58. [PubMed: 16310402]
24. Chen T, et al. Transforming growth factor-beta receptor type I gene is frequently mutated in ovarian carcinomas. Cancer Res. 2001; 61(12):4679–82. [PubMed: 11406536]
25. Chen T, et al. Transforming growth factor beta type I receptor kinase mutant associated with metastatic breast cancer. Cancer Res. 1998; 58(21):4805–10. [PubMed: 9809982]
26. Bartsch D, et al. Higher frequency of DPC4/Smad4 alterations in pancreatic cancer cell lines than in primary pancreatic adenocarcinomas. Cancer Lett. 1999; 139(1):43–9. [PubMed: 10408907]

27. Thiagalingam S, et al. Evaluation of candidate tumour suppressor genes on chromosome 18 in colorectal cancers. Nat Genet. 1996; 13(3):343–6. [PubMed: 8673134]
28. Ohtaki N, et al. Somatic alterations of the DPC4 and Madr2 genes in colorectal cancers and relationship to metastasis. Int J Oncol. 2001; 18(2):265–70. [PubMed: 11172591]
29. Howe JR, et al. Mutations in the SMAD4/DPC4 gene in juvenile polyposis. Science. 1998; 280(5366):1086–8. [PubMed: 9582123]
30. Han SU, et al. Loss of the Smad3 expression increases susceptibility to tumorigenicity in human gastric cancer. Oncogene. 2004; 23(7):1333–41. [PubMed: 14647420]
31. Dumont E, et al. Evidence for a role of Smad3 and Smad2 in stabilization of the tumor-derived mutant Smad2.Q407R. J Biol Chem. 2003; 278(27):24881–7. [PubMed: 12700238]
32. Boulay JL, et al. Combined copy status of 18q21 genes in colorectal cancer shows frequent retention of SMAD7. Genes Chromosomes Cancer. 2001; 31(3):240–7. [PubMed: 11391794]
33. Boulay JL, et al. SMAD7 is a prognostic marker in patients with colorectal cancer. Int J Cancer. 2003; 104(4):446–9. [PubMed: 12584741]
34. Buess M, et al. Amplification of SKI is a prognostic marker in early colorectal cancer. Neoplasia. 2004; 6(3):207–12. [PubMed: 15153332]
35. Reed JA, et al. Cytoplasmic localization of the oncogenic protein Ski in human cutaneous melanomas in vivo: functional implications for transforming growth factor beta signaling. Cancer Res. 2001; 61(22):8074–8. [PubMed: 11719430]
36. Zhang F, et al. Ski-related novel protein N (SnoN), a negative controller of transforming growth factor-beta signaling, is a prognostic marker in estrogen receptor-positive breast carcinomas. Cancer Res. 2003; 63(16):5005–10. [PubMed: 12941827]
37. Li JM, et al. Transforming growth factor beta activates the promoter of cyclin-dependent kinase inhibitor p15INK4B through an Sp1 consensus site. J Biol Chem. 1995; 270(45):26750–3. [PubMed: 7592908]
38. Datto MB, et al. Transforming growth factor beta induces the cyclin-dependent kinase inhibitor p21 through a p53-independent mechanism. Proc Natl Acad Sci U S A. 1995; 92(12):5545–9. [PubMed: 7777546]
39. Hannon GJ, Beach D. p15INK4B is a potential effector of TGF-beta-induced cell cycle arrest. Nature. 1994; 371(6494):257–61. [PubMed: 8078588]
40. Polyak K, et al. p27Kip1, a cyclin-Cdk inhibitor, links transforming growth factor-beta and contact inhibition to cell cycle arrest. Genes Dev. 1994; 8(1):9–22. [PubMed: 8288131]
41. Ewen ME, et al. TGF beta inhibition of Cdk4 synthesis is linked to cell cycle arrest. Cell. 1993; 74(6):1009–20. [PubMed: 8402878]
42. Geng Y, Weinberg RA. Transforming growth factor beta effects on expression of G1 cyclins and cyclin-dependent protein kinases. Proc Natl Acad Sci U S A. 1993; 90(21):10315–9. [PubMed: 7694291]
43. Pardali K, et al. Smad pathway-specific transcriptional regulation of the cell cycle inhibitor p21(WAF1/Cip1). J Cell Physiol. 2005; 204(1):260–72. [PubMed: 15690394]
44. Yagi K, et al. c-myc is a downstream target of the Smad pathway. J Biol Chem. 2002; 277(1):854–61. [PubMed: 11689553]
45. Seoane J, et al. TGFbeta influences Myc, Miz-1 and Smad to control the CDK inhibitor p15INK4b. Nat Cell Biol. 2001; 3(4):400–8. [PubMed: 11283614]
46. Kowanetz M, et al. Id2 and Id3 define the potency of cell proliferation and differentiation responses to transforming growth factor beta and bone morphogenetic protein. Mol Cell Biol. 2004; 24(10): 4241–54. [PubMed: 15121845]
47. Kang Y, Chen CR, Massague J. A self-enabling TGFbeta response coupled to stress signaling: Smad engages stress response factor ATF3 for Id1 repression in epithelial cells. Mol Cell. 2003; 11(4):915–26. [PubMed: 12718878]
48. Sun L, et al. Expression of transforming growth factor beta type II receptor leads to reduced malignancy in human breast cancer MCF-7 cells. J Biol Chem. 1994; 269(42):26449–55. [PubMed: 7929366]

49. Zhu Q, et al. Dual role of SnoN in mammalian tumorigenesis. Mol Cell Biol. 2007; 27(1):324–39. [PubMed: 17074815]
50. Heider TR, et al. Ski promotes tumor growth through abrogation of transforming growth factor-beta signaling in pancreatic cancer. Ann Surg. 2007; 246(1):61–8. [PubMed: 17592292]
51. Tachibana I, et al. Overexpression of the TGFbeta-regulated zinc finger encoding gene, TIEG, induces apoptosis in pancreatic epithelial cells. J Clin Invest. 1997; 99(10):2365–74. [PubMed: 9153278]
52. Jang CW, et al. TGF-beta induces apoptosis through Smad-mediated expression of DAP-kinase. Nat Cell Biol. 2002; 4(1):51–8. [PubMed: 11740493]
53. Valderrama-Carvajal H, et al. Activin/TGF-beta induce apoptosis through Smad-dependent expression of the lipid phosphatase SHIP. Nat Cell Biol. 2002; 4(12):963–9. [PubMed: 12447389]
54. Ribeiro A, et al. The transforming growth factor beta(1)-inducible transcription factor TIEG1, mediates apoptosis through oxidative stress. Hepatology. 1999; 30(6):1490–7. [PubMed: 10573529]
55. Atfi A, et al. Induction of apoptosis by DPC4, a transcriptional factor regulated by transforming growth factor-beta through stress-activated protein kinase/c-Jun N-terminal kinase (SAPK/JNK) signaling pathway. J Biol Chem. 1997; 272(40):24731–4. [PubMed: 9312063]
56. Ohgushi M, et al. Transforming growth factor beta-dependent sequential activation of Smad, Bim, and caspase-9 mediates physiological apoptosis in gastric epithelial cells. Mol Cell Biol. 2005; 25(22):10017–28. [PubMed: 16260615]
57. Wildey GM, Patil S, Howe PH. Smad3 potentiates transforming growth factor beta (TGFbeta)-induced apoptosis and expression of the BH3-only protein Bim in WEHI 231 B lymphocytes. J Biol Chem. 2003; 278(20):18069–77. [PubMed: 12637528]
58. Saltzman A, et al. Transforming growth factor-beta-mediated apoptosis in the Ramos B-lymphoma cell line is accompanied by caspase activation and Bcl-XL downregulation. Exp Cell Res. 1998; 242(1):244–54. [PubMed: 9665822]
59. Chipuk JE, et al. Bcl-xL blocks transforming growth factor-beta 1-induced apoptosis by inhibiting cytochrome c release and not by directly antagonizing Apaf-1-dependent caspase activation in prostate epithelial cells. J Biol Chem. 2001; 276(28):26614–21. [PubMed: 11320089]
60. Shima Y, et al. Activation of caspase-8 in transforming growth factor-beta-induced apoptosis of human hepatoma cells. Hepatology. 1999; 30(5):1215–22. [PubMed: 10534343]
61. Francis JM, et al. Transforming growth factor-beta 1 induces apoptosis independently of p53 and selectively reduces expression of Bcl-2 in multipotent hematopoietic cells. J Biol Chem. 2000; 275(50):39137–45. [PubMed: 10993901]
62. Perlman R, et al. TGF-beta-induced apoptosis is mediated by the adapter protein Daxx that facilitates JNK activation. Nat Cell Biol. 2001; 3(8):708–14. [PubMed: 11483955]
63. Gottfried Y, et al. The mitochondrial ARTS protein promotes apoptosis through targeting XIAP. EMBO J. 2004; 23(7):1627–35. [PubMed: 15029247]
64. Larisch-Bloch S, et al. Selective loss of the transforming growth factor-beta apoptotic signaling pathway in mutant NRP-154 rat prostatic epithelial cells. Cell Growth Differ. 2000; 11(1):1–10. [PubMed: 10672898]
65. Larisch S, et al. A novel mitochondrial septin-like protein, ARTS, mediates apoptosis dependent on its P-loop motif. Nat Cell Biol. 2000; 2(12):915–21. [PubMed: 11146656]
66. David CJ, et al. TGF-beta Tumor Suppression through a Lethal EMT. Cell. 2016; 164(5):1015–30. [PubMed: 26898331]
67. Dai JL, Bansal RK, Kern SE. G1 cell cycle arrest and apoptosis induction by nuclear Smad4/Dpc4: phenotypes reversed by a tumorigenic mutation. Proc Natl Acad Sci U S A. 1999; 96(4):1427–32. [PubMed: 9990040]
68. Yamamura Y, et al. Critical role of Smads and AP-1 complex in transforming growth factor-beta -dependent apoptosis. J Biol Chem. 2000; 275(46):36295–302. [PubMed: 10942775]
69. Guasch G, et al. Loss of TGFbeta signaling destabilizes homeostasis and promotes squamous cell carcinomas in stratified epithelia. Cancer Cell. 2007; 12(4):313–27. [PubMed: 17936557]

70. Yang J, Wahdan-Alaswad R, Danielpour D. Critical role of Smad2 in tumor suppression and transforming growth factor-beta-induced apoptosis of prostate epithelial cells. Cancer Res. 2009; 69(6):2185–90. [PubMed: 19276350]

71. Tang B, et al. Loss of responsiveness to transforming growth factor beta induces malignant transformation of nontumorigenic rat prostate epithelial cells. Cancer Res. 1999; 59(19):4834–42. [PubMed: 10519393]

72. Walker RA, Dearing SJ. Transforming growth factor beta 1 in ductal carcinoma in situ and invasive carcinomas of the breast. Eur J Cancer. 1992; 28(2–3):641–4. [PubMed: 1317202]

73. Dalal BI, Keown PA, Greenberg AH. Immunocytochemical localization of secreted transforming growth factor-beta 1 to the advancing edges of primary tumors and to lymph node metastases of human mammary carcinoma. Am J Pathol. 1993; 143(2):381–9. [PubMed: 8393616]

74. Fukai Y, et al. Reduced expression of transforming growth factor-beta receptors is an unfavorable prognostic factor in human esophageal squamous cell carcinoma. Int J Cancer. 2003; 104(2):161–6. [PubMed: 12569570]

75. Shim KS, et al. Elevated serum levels of transforming growth factor-beta1 in patients with colorectal carcinoma: its association with tumor progression and its significant decrease after curative surgical resection. Cancer. 1999; 85(3):554–61. [PubMed: 10091729]

76. Saito H, et al. The expression of transforming growth factor-beta1 is significantly correlated with the expression of vascular endothelial growth factor and poor prognosis of patients with advanced gastric carcinoma. Cancer. 1999; 86(8):1455–62. [PubMed: 10526273]

77. Hasegawa Y, et al. Transforming growth factor-beta1 level correlates with angiogenesis, tumor progression, and prognosis in patients with nonsmall cell lung carcinoma. Cancer. 2001; 91(5): 964–71. [PubMed: 11251948]

78. Friess H, et al. Enhanced expression of transforming growth factor beta isoforms in pancreatic cancer correlates with decreased survival. Gastroenterology. 1993; 105(6):1846–56. [PubMed: 8253361]

79. Friedman E, et al. High levels of transforming growth factor beta 1 correlate with disease progression in human colon cancer. Cancer Epidemiol Biomarkers Prev. 1995; 4(5):549–54. [PubMed: 7549813]

80. Wikstrom P, et al. Transforming growth factor beta1 is associated with angiogenesis, metastasis, and poor clinical outcome in prostate cancer. Prostate. 1998; 37(1):19–29. [PubMed: 9721065]

81. Assoian RK, et al. Expression and secretion of type beta transforming growth factor by activated human macrophages. Proc Natl Acad Sci U S A. 1987; 84(17):6020–4. [PubMed: 2888109]

82. Wakefield LM, et al. Latent transforming growth factor-beta from human platelets. A high molecular weight complex containing precursor sequences. J Biol Chem. 1988; 263(16):7646–54. [PubMed: 3163692]

83. De Wever O, et al. Stromal myofibroblasts are drivers of invasive cancer growth. Int J Cancer. 2008; 123(10):2229–38. [PubMed: 18777559]

84. Derynck R, et al. Synthesis of messenger RNAs for transforming growth factors alpha and beta and the epidermal growth factor receptor by human tumors. Cancer Res. 1987; 47(3):707–12. [PubMed: 3467839]

85. Yu Q, Stamenkovic I. Cell surface-localized matrix metalloproteinase-9 proteolytically activates TGF-beta and promotes tumor invasion and angiogenesis. Genes Dev. 2000; 14(2):163–76. [PubMed: 10652271]

86. Piek E, Heldin CH, Ten Dijke P. Specificity, diversity, and regulation in TGF-beta superfamily signaling. FASEB J. 1999; 13(15):2105–24. [PubMed: 10593858]

87. Kimelman D, Kirschner M. Synergistic induction of mesoderm by FGF and TGF-beta and the identification of an mRNA coding for FGF in the early Xenopus embryo. Cell. 1987; 51(5):869–77. [PubMed: 3479265]

88. Potts JD, Runyan RB. Epithelial-mesenchymal cell transformation in the embryonic heart can be mediated, in part, by transforming growth factor beta. Dev Biol. 1989; 134(2):392–401. [PubMed: 2744239]

89. Kaartinen V, et al. Abnormal lung development and cleft palate in mice lacking TGF-beta 3 indicates defects of epithelial-mesenchymal interaction. Nat Genet. 1995; 11(4):415–21. [PubMed: 7493022]

90. Piek E, et al. TGF-(beta) type I receptor/ALK-5 and Smad proteins mediate epithelial to mesenchymal transdifferentiation in NMuMG breast epithelial cells. J Cell Sci. 1999; 112(Pt 24): 4557–68. [PubMed: 10574705]

91. Moustakas A, Heldin CH. Signaling networks guiding epithelial-mesenchymal transitions during embryogenesis and cancer progression. Cancer Sci. 2007; 98(10):1512–20. [PubMed: 17645776]

92. Thuault S, et al. Transforming growth factor-beta employs HMGA2 to elicit epithelial-mesenchymal transition. J Cell Biol. 2006; 174(2):175–83. [PubMed: 16831886]

93. Ozdamar B, et al. Regulation of the polarity protein Par6 by TGFbeta receptors controls epithelial cell plasticity. Science. 2005; 307(5715):1603–9. [PubMed: 15761148]

94. Xu J, Lamouille S, Derynck R. TGF-beta-induced epithelial to mesenchymal transition. Cell Res. 2009; 19(2):156–72. [PubMed: 19153598]

95. Thannickal VJ, et al. Myofibroblast differentiation by transforming growth factor-beta1 is dependent on cell adhesion and integrin signaling via focal adhesion kinase. J Biol Chem. 2003; 278(14):12384–9. [PubMed: 12531888]

96. Portella G, et al. Transforming growth factor beta is essential for spindle cell conversion of mouse skin carcinoma in vivo: implications for tumor invasion. Cell Growth Differ. 1998; 9(5):393–404. [PubMed: 9607560]

97. Dumont N, Bakin AV, Arteaga CL. Autocrine transforming growth factor-beta signaling mediates Smad-independent motility in human cancer cells. J Biol Chem. 2003; 278(5):3275–85. [PubMed: 12421823]

98. Yin JJ, et al. TGF-beta signaling blockade inhibits PTHrP secretion by breast cancer cells and bone metastases development. J Clin Invest. 1999; 103(2):197–206. [PubMed: 9916131]

99. Oft M, Heider KH, Beug H. TGFbeta signaling is necessary for carcinoma cell invasiveness and metastasis. Curr Biol. 1998; 8(23):1243–52. [PubMed: 9822576]

100. Cui W, et al. TGFbeta1 inhibits the formation of benign skin tumors, but enhances progression to invasive spindle carcinomas in transgenic mice. Cell. 1996; 86(4):531–42. [PubMed: 8752208]

101. Araki S, et al. TGF-beta1-induced expression of human Mdm2 correlates with late-stage metastatic breast cancer. J Clin Invest. 2010; 120(1):290–302. [PubMed: 19955655]

102. Adorno M, et al. A Mutant-p53/Smad complex opposes p63 to empower TGFbeta-induced metastasis. Cell. 2009; 137(1):87–98. [PubMed: 19345189]

103. Giampieri S, et al. Localized and reversible TGFbeta signalling switches breast cancer cells from cohesive to single cell motility. Nat Cell Biol. 2009; 11(11):1287–96. [PubMed: 19838175]

104. Edlund S, et al. Transforming growth factor-beta-induced mobilization of actin cytoskeleton requires signaling by small GTPases Cdc42 and RhoA. Mol Biol Cell. 2002; 13(3):902–14. [PubMed: 11907271]

105. Yu JR, et al. TGF-beta/Smad signaling through DOCK4 facilitates lung adenocarcinoma metastasis. Genes Dev. 2015; 29(3):250–61. [PubMed: 25644601]

106. Lee JD, et al. The type III TGF-beta receptor suppresses breast cancer progression through GIPC-mediated inhibition of TGF-beta signaling. Carcinogenesis. 2010; 31(2):175–83. [PubMed: 19955393]

107. Zu L, et al. The feedback loop between miR-124 and TGF-beta pathway plays a significant role in non-small cell lung cancer metastasis. Carcinogenesis. 2016; 37(3):333–43. [PubMed: 26818357]

108. Zhang F, et al. MicroRNA-187, a downstream effector of TGFbeta pathway, suppresses Smad-mediated epithelial-mesenchymal transition in colorectal cancer. Cancer Lett. 2016; 373(2):203–13. [PubMed: 26820227]

109. Stankic M, et al. TGF-beta-Id1 signaling opposes Twist1 and promotes metastatic colonization via a mesenchymal-to-epithelial transition. Cell Rep. 2013; 5(5):1228–42. [PubMed: 24332369]

110. Korpal M, et al. Imaging transforming growth factor-beta signaling dynamics and therapeutic response in breast cancer bone metastasis. Nat Med. 2009; 15(8):960–6. [PubMed: 19597504]

111. Thomas RJ, et al. Breast cancer cells interact with osteoblasts to support osteoclast formation. Endocrinology. 1999; 140(10):4451–8. [PubMed: 10499498]
112. Kang Y, et al. A multigenic program mediating breast cancer metastasis to bone. Cancer Cell. 2003; 3(6):537–49. [PubMed: 12842083]
113. Waning DL, et al. Excess TGF-beta mediates muscle weakness associated with bone metastases in mice. Nat Med. 2015; 21(11):1262–71. [PubMed: 26457758]
114. Frantz C, Stewart KM, Weaver VM. The extracellular matrix at a glance. J Cell Sci. 2010; 123(Pt 24):4195–200. [PubMed: 21123617]
115. Hinz B. Formation and function of the myofibroblast during tissue repair. J Invest Dermatol. 2007; 127(3):526–37. [PubMed: 17299435]
116. De Wever O, Mareel M. Role of tissue stroma in cancer cell invasion. J Pathol. 2003; 200(4):429–47. [PubMed: 12845611]
117. Massague J. TGFbeta in Cancer. Cell. 2008; 134(2):215–30. [PubMed: 18662538]
118. Desmouliere A, et al. Transforming growth factor-beta 1 induces alpha-smooth muscle actin expression in granulation tissue myofibroblasts and in quiescent and growing cultured fibroblasts. J Cell Biol. 1993; 122(1):103–11. [PubMed: 8314838]
119. Martin M, Pujuguet P, Martin F. Role of stromal myofibroblasts infiltrating colon cancer in tumor invasion. Pathol Res Pract. 1996; 192(7):712–7. [PubMed: 8880872]
120. Kojima Y, et al. Autocrine TGF-beta and stromal cell-derived factor-1 (SDF-1) signaling drives the evolution of tumor-promoting mammary stromal myofibroblasts. Proc Natl Acad Sci U S A. 2010; 107(46):20009–14. [PubMed: 21041659]
121. Cheng N, et al. Loss of TGF-beta type II receptor in fibroblasts promotes mammary carcinoma growth and invasion through upregulation of TGF-alpha-, MSP- and HGF-mediated signaling networks. Oncogene. 2005; 24(32):5053–68. [PubMed: 15856015]
122. Bhowmick NA, et al. TGF-beta signaling in fibroblasts modulates the oncogenic potential of adjacent epithelia. Science. 2004; 303(5659):848–51. [PubMed: 14764882]
123. Hawinkels LJ, et al. Interaction with colon cancer cells hyperactivates TGF-beta signaling in cancer-associated fibroblasts. Oncogene. 2014; 33(1):97–107. [PubMed: 23208491]
124. Allinen M, et al. Molecular characterization of the tumor microenvironment in breast cancer. Cancer Cell. 2004; 6(1):17–32. [PubMed: 15261139]
125. Calon A, et al. Dependency of colorectal cancer on a TGF-beta-driven program in stromal cells for metastasis initiation. Cancer Cell. 2012; 22(5):571–84. [PubMed: 23153532]
126. Krstic J, Santibanez JF. Transforming growth factor-beta and matrix metalloproteinases: functional interactions in tumor stroma-infiltrating myeloid cells. Scientific World Journal. 2014; 2014:521754. [PubMed: 24578639]
127. Hagedorn HG, Bachmeier BE, Nerlich AG. Synthesis and degradation of basement membranes and extracellular matrix and their regulation by TGF-beta in invasive carcinomas (Review). Int J Oncol. 2001; 18(4):669–81. [PubMed: 11251160]
128. Kominsky SL, et al. MMP-13 is over-expressed in renal cell carcinoma bone metastasis and is induced by TGF-beta1. Clin Exp Metastasis. 2008; 25(8):865–70. [PubMed: 18709334]
129. Mendonsa AM, et al. Host and tumor derived MMP13 regulate extravasation and establishment of colorectal metastases in the liver. Mol Cancer. 2015; 14:49. [PubMed: 25880591]
130. Leight JL, et al. Matrix rigidity regulates a switch between TGF-beta1-induced apoptosis and epithelial-mesenchymal transition. Mol Biol Cell. 2012; 23(5):781–91. [PubMed: 22238361]
131. Tian M, Schiemann WP. The TGF-beta paradox in human cancer: an update. Future Oncol. 2009; 5(2):259–71. [PubMed: 19284383]
132. Oh SP, et al. Activin receptor-like kinase 1 modulates transforming growth factor-beta 1 signaling in the regulation of angiogenesis. Proc Natl Acad Sci U S A. 2000; 97(6):2626–31. [PubMed: 10716993]
133. Choi ME, Ballermann BJ. Inhibition of capillary morphogenesis and associated apoptosis by dominant negative mutant transforming growth factor-beta receptors. J Biol Chem. 1995; 270(36):21144–50. [PubMed: 7673146]

134. Oshima M, Oshima H, Taketo MM. TGF-beta receptor type II deficiency results in defects of yolk sac hematopoiesis and vasculogenesis. Dev Biol. 1996; 179(1):297–302. [PubMed: 8873772]

135. Li DY, et al. Defective angiogenesis in mice lacking endoglin. Science. 1999; 284(5419):1534–7. [PubMed: 10348742]

136. Arthur HM, et al. Endoglin, an ancillary TGFbeta receptor, is required for extraembryonic angiogenesis and plays a key role in heart development. Dev Biol. 2000; 217(1):42–53. [PubMed: 10625534]

137. Dickson MC, et al. Defective haematopoiesis and vasculogenesis in transforming growth factor-beta 1 knock out mice. Development. 1995; 121(6):1845–54. [PubMed: 7600998]

138. Pertovaara L, et al. Vascular endothelial growth factor is induced in response to transforming growth factor-beta in fibroblastic and epithelial cells. J Biol Chem. 1994; 269(9):6271–4. [PubMed: 8119973]

139. Shimo T, et al. Involvement of CTGF, a hypertrophic chondrocyte-specific gene product, in tumor angiogenesis. Oncology. 2001; 61(4):315–22. [PubMed: 11721179]

140. Darland DC, D'Amore PA. TGF beta is required for the formation of capillary-like structures in three-dimensional cocultures of 10T1/2 and endothelial cells. Angiogenesis. 2001; 4(1):11–20. [PubMed: 11824373]

141. Nishida N, et al. Angiogenesis in cancer. Vasc Health Risk Manag. 2006; 2(3):213–9. [PubMed: 17326328]

142. Ito N, et al. Positive correlation of plasma transforming growth factor-beta 1 levels with tumor vascularity in hepatocellular carcinoma. Cancer Lett. 1995; 89(1):45–8. [PubMed: 7882301]

143. Ivanovic V, et al. Elevated plasma levels of TGF-beta 1 in patients with invasive prostate cancer. Nat Med. 1995; 1(4):282–4. [PubMed: 7585049]

144. Junker U, et al. Transforming growth factor beta 1 is significantly elevated in plasma of patients suffering from renal cell carcinoma. Cytokine. 1996; 8(10):794–8. [PubMed: 8980881]

145. Wang J, et al. Transforming growth factor beta-regulated microRNA-29a promotes angiogenesis through targeting the phosphatase and tensin homolog in endothelium. J Biol Chem. 2013; 288(15):10418–26. [PubMed: 23426367]

146. Ueki N, et al. Excessive production of transforming growth-factor beta 1 can play an important role in the development of tumorigenesis by its action for angiogenesis: validity of neutralizing antibodies to block tumor growth. Biochim Biophys Acta. 1992; 1137(2):189–96. [PubMed: 1384712]

147. Ananth S, et al. Transforming growth factor beta1 is a target for the von Hippel-Lindau tumor suppressor and a critical growth factor for clear cell renal carcinoma. Cancer Res. 1999; 59(9): 2210–6. [PubMed: 10232610]

148. Liu Y, et al. Effects of the combination of TRC105 and bevacizumab on endothelial cell biology. Invest New Drugs. 2014; 32(5):851–9. [PubMed: 24994097]

149. Paauwe M, et al. Endoglin targeting inhibits tumor angiogenesis and metastatic spread in breast cancer. Oncogene. 2016

150. Safina A, Vandette E, Bakin AV. ALK5 promotes tumor angiogenesis by upregulating matrix metalloproteinase-9 in tumor cells. Oncogene. 2007; 26(17):2407–22. [PubMed: 17072348]

151. Wang X, et al. Endothelial cells enhance prostate cancer metastasis via IL-6-->androgen receptor-->TGF-beta-->MMP-9 signals. Mol Cancer Ther. 2013; 12(6):1026–37. [PubMed: 23536722]

152. Yoshimura A, Muto G. TGF-beta function in immune suppression. Curr Top Microbiol Immunol. 2011; 350:127–47. [PubMed: 20680806]

153. Yang L. TGFbeta and cancer metastasis: an inflammation link. Cancer Metastasis Rev. 2010; 29(2):263–71. [PubMed: 20437081]

154. Thomas DA, Massague J. TGF-beta directly targets cytotoxic T cell functions during tumor evasion of immune surveillance. Cancer Cell. 2005; 8(5):369–80. [PubMed: 16286245]

155. Fu S, et al. TGF-beta induces Foxp3 + T-regulatory cells from CD4 + CD25 - precursors. Am J Transplant. 2004; 4(10):1614–27. [PubMed: 15367216]

156. Liu Y, et al. A critical function for TGF-beta signaling in the development of natural CD4+CD25+Foxp3+ regulatory T cells. Nat Immunol. 2008; 9(6):632–40. [PubMed: 18438410]

157. Somasundaram R, et al. Inhibition of cytolytic T lymphocyte proliferation by autologous CD4+/CD25+ regulatory T cells in a colorectal carcinoma patient is mediated by transforming growth factor-beta. Cancer Res. 2002; 62(18):5267–72. [PubMed: 12234995]

158. Vivier E, et al. Functions of natural killer cells. Nat Immunol. 2008; 9(5):503–10. [PubMed: 18425107]

159. Wilson EB, et al. Human tumour immune evasion via TGF-beta blocks NK cell activation but not survival allowing therapeutic restoration of anti-tumour activity. PLoS One. 2011; 6(9):e22842. [PubMed: 21909397]

160. Crane CA, et al. TGF-beta downregulates the activating receptor NKG2D on NK cells and CD8+ T cells in glioma patients. Neuro Oncol. 2010; 12(1):7–13. [PubMed: 20150362]

161. Donatelli SS, et al. TGF-beta-inducible microRNA-183 silences tumor-associated natural killer cells. Proc Natl Acad Sci U S A. 2014; 111(11):4203–8. [PubMed: 24586048]

162. Diamond MS, et al. Type I interferon is selectively required by dendritic cells for immune rejection of tumors. J Exp Med. 2011; 208(10):1989–2003. [PubMed: 21930769]

163. Fuertes MB, et al. Host type I IFN signals are required for antitumor CD8+ T cell responses through CD8{alpha}+ dendritic cells. J Exp Med. 2011; 208(10):2005–16. [PubMed: 21930765]

164. Papaspyridonos M, et al. Id1 suppresses anti-tumour immune responses and promotes tumour progression by impairing myeloid cell maturation. Nat Commun. 2015; 6:6840. [PubMed: 25924227]

165. Novitskiy SV, et al. Deletion of TGF-beta signaling in myeloid cells enhances their anti-tumorigenic properties. J Leukoc Biol. 2012; 92(3):641–51. [PubMed: 22685318]

166. Hanks BA, et al. Combinatorial TGF-{beta} signaling blockade and anti-CTLA-4 antibody immunotherapy in a murine BRAFV600E-PTEN−/− transgenic model of melanoma. ASCO Meeting Abstracts. 2014; 32(15 suppl):3011.

167. Fridlender ZG, et al. Polarization of tumor-associated neutrophil phenotype by TGF-beta: "N1" versus "N2" TAN. Cancer Cell. 2009; 16(3):183–94. [PubMed: 19732719]

168. Gong D, et al. TGFbeta signaling plays a critical role in promoting alternative macrophage activation. BMC Immunol. 2012; 13:31. [PubMed: 22703233]

169. Sica A, et al. Tumour-associated macrophages are a distinct M2 polarised population promoting tumour progression: potential targets of anti-cancer therapy. Eur J Cancer. 2006; 42(6):717–27. [PubMed: 16520032]

170. Xu J, et al. 14-3-3zeta turns TGF-beta's function from tumor suppressor to metastasis promoter in breast cancer by contextual changes of Smad partners from p53 to Gli2. Cancer Cell. 2015; 27(2):177–92. [PubMed: 25670079]

171. Sporn MB, Liby KT. NRF2 and cancer: the good, the bad and the importance of context. Nat Rev Cancer. 2012; 12(8):564–71. [PubMed: 22810811]

172. Genrich G, et al. The anti-oxidative transcription factor Nuclear factor E2 related factor-2 (Nrf2) counteracts TGF-beta1 mediated growth inhibition of pancreatic ductal epithelial cells -Nrf2 as determinant of pro-tumorigenic functions of TGF-beta1. BMC Cancer. 2016; 16(1):155. [PubMed: 26915435]

173. Sakurai T, et al. RNA-binding motif protein 47 inhibits Nrf2 activity to suppress tumor growth in lung adenocarcinoma. Oncogene. 2016

174. Zhong Z, et al. Anti-transforming growth factor beta receptor II antibody has therapeutic efficacy against primary tumor growth and metastasis through multieffects on cancer, stroma, and immune cells. Clin Cancer Res. 2010; 16(4):1191–205. [PubMed: 20145179]

175. Rosen LS, et al. A phase I first-in-human study of TRC105 (Anti-Endoglin Antibody) in patients with advanced cancer. Clin Cancer Res. 2012; 18(17):4820–9. [PubMed: 22767667]

176. Bendell JC, et al. Phase I study of ACE-041, a novel inhibitor of ALK1-mediated angiogenesis, in patients with advanced solid tumors. ASCO Meeting Abstracts. 2011; 29(15 suppl):3070.

177. Goff LW, et al. Phase I study of PF-03446962, a fully human mAb against ALK 1, a TGF{beta} receptor involved in tumor angiogenesis. ASCO Meeting Abstracts. 2011; 29(15 suppl):3009.

178. Hanks BA, et al. Type III TGF-beta receptor downregulation generates an immunotolerant tumor microenvironment. J Clin Invest. 2013; 123(9):3925–40. [PubMed: 23925295]

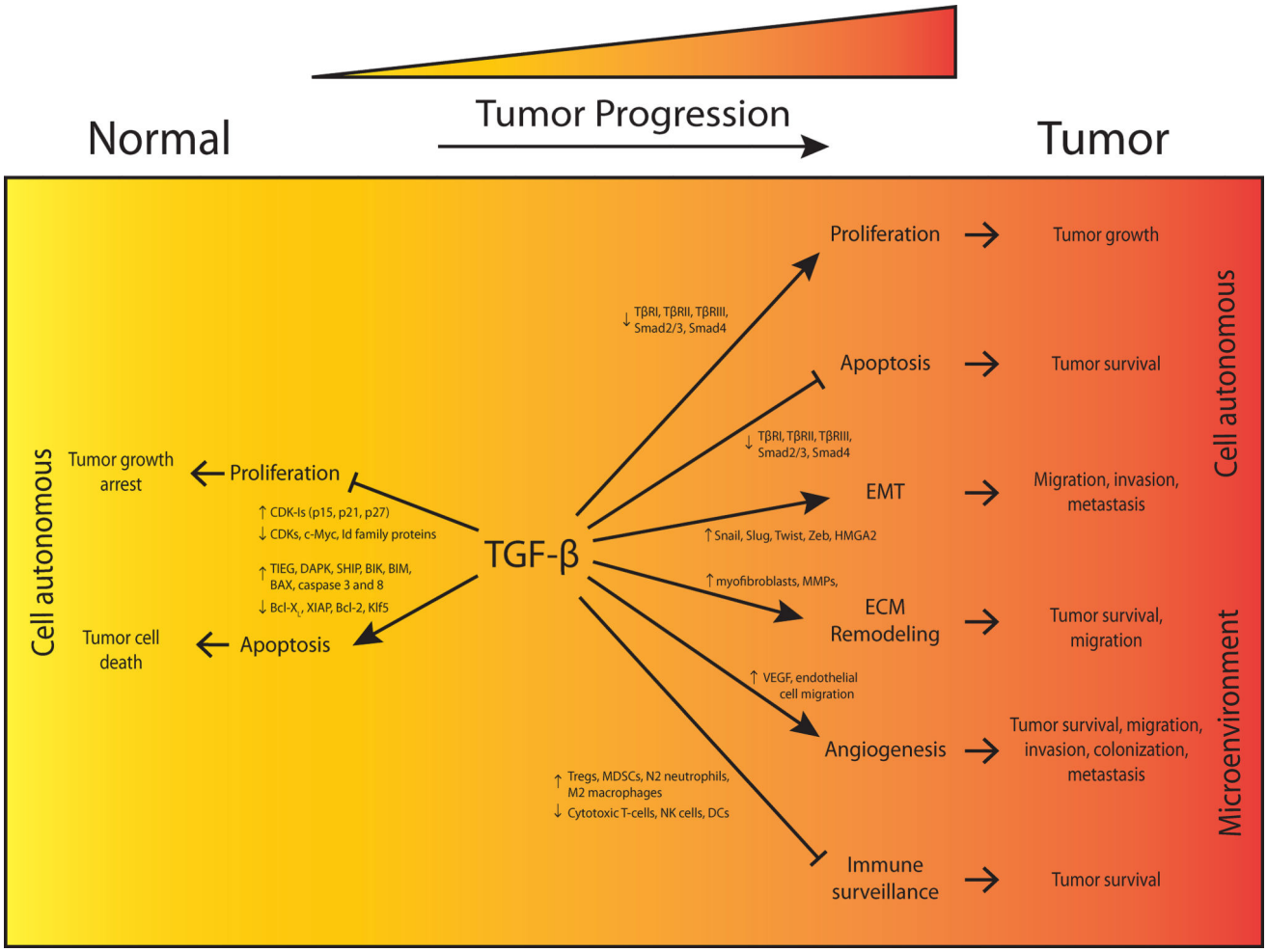

Figure 1.

TGF-β has cell autonomous roles as a tumor suppressor and promoter by controlling proliferation, apoptosis and EMT, as well as non-cell autonomous tumor promoting roles in the microenvironment by remodeling the extracellular matrix, inducing angiogenesis and suppressing immune surveillance.

Abbreviations: CDK-I (cell-dependent kinase inhibitors), CDKs (cell-dependent kinases), TβRI (type 1 TGF-β), TβRII (type II TGF-β receptor), TβRIII (type III TGF-β receptor), MMPs (matrix metalloproteinases), Tregs (regulatory T cells), MDSCs (myeloid-derived suppressor cells), NK cells (natural killer cells), DCs (dendritic cells)