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TGF-β signaling, tumor microenvironment and tumor progression: the butterfly effect

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1. ABSTRACT

Transforming growth factor-beta (TGF-β) signals through receptor serine/threonine kinases and intracellular Smad effectors, regulating numerous epithelial cell processes. TGF-β plays a crucial role in the cancer initiation and progression through tumor cell autonomous signaling and interactions with tumor microenvironment, but is featured with a butterfly effect upon the stages of tumorigenesis. TGF-β signaling acts as a suppressor of epithelial cell tumorigenesis at early stages, but promotes tumor progression by enhancing migration, invasion, and survival of the tumor cells during the later stages. TGF-β signaling also cross-talks with other cell survival signaling pathways. Tumor microenvironment contains many distinct cell types, which substantially influences the tumor cell growth and survival, and the invasion and metastasis. TGF-β in the microenvironment, produced by cancer and/or stromal cells, is high and negatively correlates with disease progression and patient prognosis. Therefore, TGF-β may affect tumor progression by multiple mechanisms in addition to its direct action on tumor cells, and the diversities of TGF-β signaling in tumors imply a need for caution to TGF-β-targeted strategies of tumor prevention and/or therapeutics.

2. INTRODUCTION

Transforming growth factor beta (TGF-β) signaling, through receptor serine/threonine kinases and intracellular Smad effectors, regulates numerous epithelial cell processes, including transformation (1-3). TGF-β family comprises of three isoforms: TGF-β1, TGF-β2, and TGF-β3, belonging to a superfamily of proteins, which also includes inhibins, bone morphogenetic proteins (BMPs), and activins, decapentaplegic, and Vg-1 (1, 4). TGF-β is the former name for TGF-β1. TGF-β is a multifunctional secreted polypeptide, signaling by binding to type II TGF-β receptor (TβRII), which subsequently recruits the type I receptor (TβRI) to form a heterotetrameric signaling complex. TβRII phosphorylates and activates the TβRI that in turn phosphorylates Smad2 and Smad3. Phosphorylated (active) Smad2 and Smad3 associate with Smad4 and translocate together into the nucleus, regulating target gene expression (5) (Figure 1).

The role of TGF-β in cancer is complicated, acting as a crucial regulator of cancer initiation and progression through tumor cell autonomous signaling and interactions with tumor microenvironment (6). Early loss of TGF-β response in an initiated epithelial cell promotes the

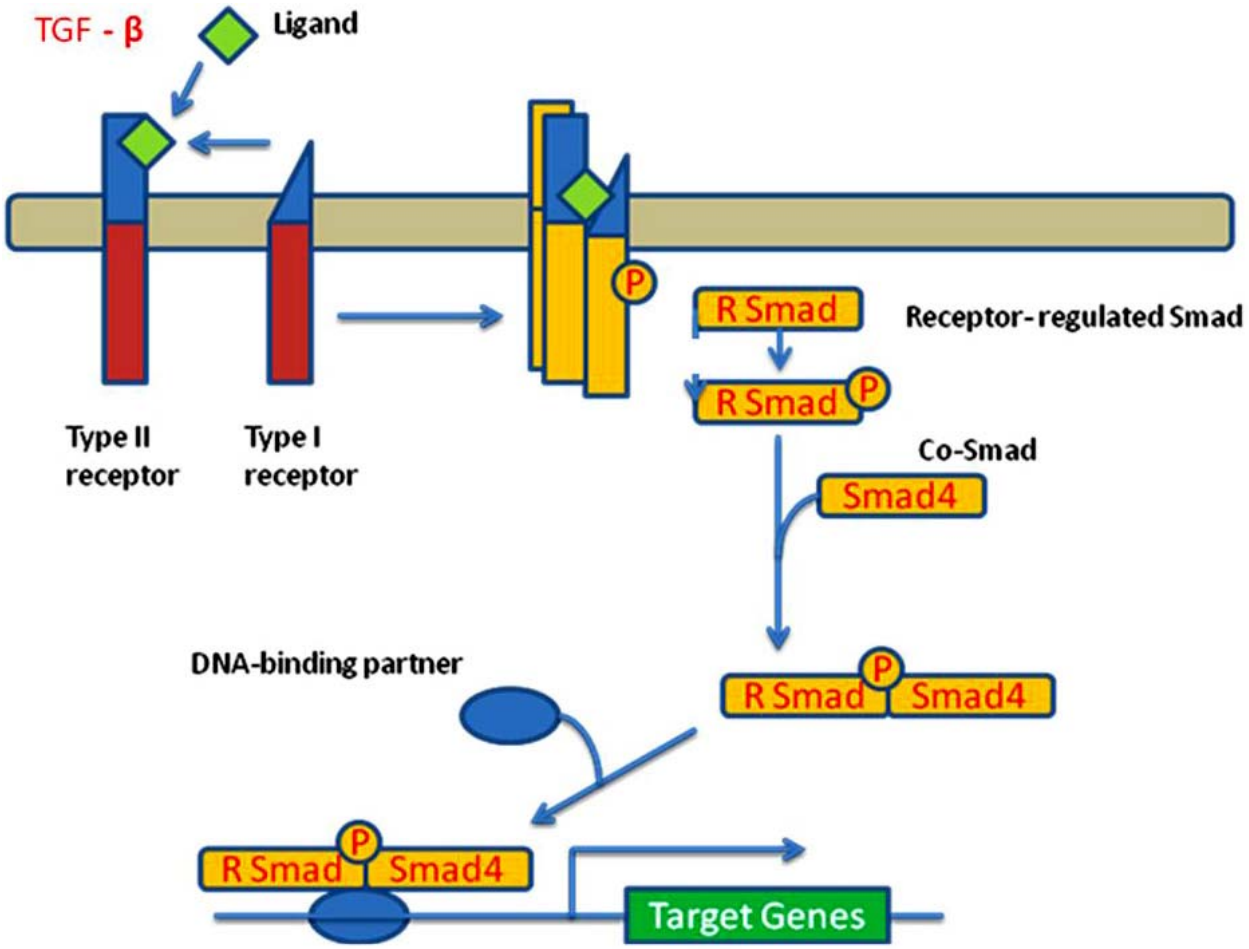

Figure 1. The transforming growth factor β (TGF- β)/SMAD pathway. All three TGF-β isoforms, TGF-β1 (i.e., TGF-β), TGF-β2 and TGF-β3, bind to type II receptor, TβRII, which then recruits type I receptor, TβRI, to form a heterotetrameric signaling complex. TGF-β1 is the isoform most commonly implicated in regulation of tumorigenesis. TGF-β localizes at the cell surface through binding with β-glycan or endoglin, two cell surface proteoglycans. TGF-β binding to TβRII results in phosphorylation and activation of TβRI by TβRII. Consequently, the receptor-associated Smads 2 and/or 3 (R-Smad) are phosphorylated by TβRI, and released from the hetero-oligomeric receptor complex. Phosphorylated Smad2 and/or 3 bind in a heterotrimeric complex with Smad4 and accumulate in the nucleus. In the nucleus, the heteromeric Smad complexes directly or indirectly interact with TGF-β-responsive promoters and regulate the transcription of target genes through cooperating with other transcription factors.

early stages of tumorigenesis through the impairment of cell autonomous suppressor mechanisms, such as growth inhibition, differentiation, apoptosis, and maintenance of genomic stability (6). The deficiency of TGF-β signaling in fibroblasts or inflammatory cells (stromal cells) promotes epithelial tumorigenesis via stimulating ectopic secretion of tumor-promoting growth factors and cytokines (6, 7). Therefore, at early stages, TGF-β signaling acts as a suppressor of epithelial cell tumorigenesis. In contrast, during the later stages, TGF-β signaling promotes tumor progression by enhancing migration, invasion, and survival of the tumor cells and by generating a tumor-promoting stroma, primarily through enhanced angiogenesis and suppression of immune surveillance. Alternatively, TGF-β may play different roles on a cell type-based mechanism. For instance, TGF-β controls fibroblast chemotaxis and activation, which results in a cancer-associated fibroblast-like state, activation of immune cells and stromal–epithelial signaling (7, 8). TGF-β signaling also cross-talks with other cell survival signaling pathways. For example, TGF-β induces an epithelial to mesenchymal transition in human immortal and malignant keratinocytes with the involvement of MAPK and AP-1 signaling pathways (6-8). The diversity of TGF-β signaling would have different implications for TGF-β-targeted strategies of tumor prevention and/or therapeutics.

It is now well known that tumor cell autonomous signaling plays a critical role in cancer initiation and progression, but the epithelial–microenvironmental and the stromal–epithelial interactions within the tumor may also be important players, which have become significant in the recent years. The advances in the studies of these interactions and perception of signals in the tumor microenvironments have enhanced our current understanding of tumor initiation, progression, and

metastasis. In this review, we update the current understanding of TGF-β signaling and its role in the tumor microenvironment and tumor progression and metastasis.

3. TGF-BETA SIGNALING PATHWAY

3.1. TGF-β and its receptors

TGF-β is secreted as an inactive latent disulfide-linked homodimeric polypeptide. Inactive TGF-β binds to extracellular proteins, such as latent TGF-β binding proteins (LTBPs) and resides in the extracellular matrix until it is activated (1). Upon appropriate signals, the latent complex is cleaved to form mature, bioactive TGF-β ligand that consists of the processed C-terminal homodimeric polypeptide. The TGF-β signals through a heteromeric cell-surface complex of two types of receptor transmembrane serine/threonine kinases, known as the TGF-β receptors. Depending on the structure and function, the TGF-β receptors are divided into two major groups: type I receptors (TβRI) and type II receptors (TβRII) (1, 3, 9, 10). Vertebrate TβRI are composed of three groups sharing similar kinase domains and signaling activities. Group 1 includes TβRI, ActR-IB, and ALK7; Group 2 contains BMPR-IA and IB; and Group 3 consists of ALK1 and ALK2 (11-14). Vertebrate TβRII consists of TβRII, BMPR-II, and AMHR, which selectively bind to TGF-β, BMPs, and MIS, respectively, whereas ActR-II and IIB type II receptors bind to activins when expressed alone or jointly with activin type I receptors (1, 3), or to BMPs 2, 4, and 7 and GDF5 in concert with BMP type I receptors (15).

Some TGF-β receptor members exist in alternative forms derived from the presence or absence of the followings: a 25–amino acid insert following the signal sequence in TβRII, a 61–amino acid insert in the same position in AMHR-II, two alternative N-terminal regions, two alternative extracellular juxtamembrane regions in ATR-I, small inserts in the extracellular and intracellular juxtamembrane regions of ActR-IIB, and a long C-terminal extension in BMPR-II (1, 3, 16, 17). These alternatives would change their binding tendency to ligands; for example, ActR-IIB with the extracellular insert has increased affinity to activins (13, 18).

In addition, a few accessory receptors, termed as Type III receptor (TβRIII), have been identified (1, 3, 19). The TβRIII do not have an intrinsic signaling function but regulate TGF-β access to TβRII, through concentrating TGF-β at the cell surface and stabilizing it in a conformation optimal for binding to the signaling receptors (18, 20).

3.2. TGF-β signaling through Smads

TGF-β signals through a group of small, evolutionarily conserved intracellular effector proteins, termed as Smads (21). Three types of Smads are identified: receptor-activated Smads (R-Smads: Smad1, Smad2, Smad3, Smad5 and Smad8), common mediator Smads (Co-Smads: Smad4), and inhibitory Smads (I-Smads: Smad6 and Smad7) (21, 22). Smads are modular proteins containing a conserved N terminal Mad-homology 1 (MH1), intermediate linker and C-terminal MH2 domains. The MH1 domain participates in nuclear localization, DNA-binding and protein–protein interactions; and the linker domain accepts regulatory phosphorylation by other signaling kinases, such as mitogen activated protein kinases (MAPKs) or cyclin-dependent kinases (CDKs), and recruits ubiquitin ligases that regulate Smad and TGF-β receptor half-lives. The MH2 is a major protein–protein interaction domain, possessing phospho-serine-binding activity (22, 23). The activated, catalytically active TβRI phosphorylates the C-terminal serine residues of Smad2 and Smad3, two distinct proteins that play non-redundant functions in eliciting the biological effects of the TGF-β. Receptor-phosphorylated R-Smads exhibit high affinity to Co-Smad (Smad4). The Co-Smads are not phosphorylated by receptors but rapidly oligomerizes with phosphorylated Smad2 or Smad3 to form functional protein complexes (21, 22, 24-26). The monomeric Smad proteins constantly shuttle in and out of the nucleus, but the activated R-Smad/Co-Smad complexes favor the nuclear accumulation, where they associate with a plethora of transcription factors, co-activators or co-repressors and bind to DNA at Smad-binding elements, leading to transcriptional induction or repression of a diverse array of genes (21).

I-Smads are a distinct subclass of Smads, antagonizing TGF-β signaling. I-Smads compete with R-Smads for binding to activated type I receptors, thus inhibiting the phosphorylation of R-Smads; I-Smads also recruit E3-ubiquitin ligases, known as Smad ubiquitination regulatory factor 1 (Smurf1) and Smurf2, to the activated TβRI, resulting in receptor ubiquitination and degradation, and signaling termination (5, 21-23, 25, 27, 28). Smad6 is known to specifically inhibit BMP type I receptor mediated signaling, while Smad7 is a more general inhibitor and is able to block signaling mediated by a set of related TβRI, including th0se for BMP and TGF-β/Activin (29). Recently, it has been shown that Smad7 recruits a complex of GADD34 and protein phosphatase 1 catalytic subunit to and dephosphorylates the activated TβRI (30).

3.3. Crosstalk with other signaling pathways

Cross-talk between seemingly discrete signaling pathways is a universal mechanism of pathway regulation and signal integration. The TGF-β–dependent recruitment of Smad complexes to the transcription machinery allows the employment of additional co-activators or co-repressors, diversifying the transcriptional regulations of genes. The various interactions of TGF-β have been summarized in Figure 2. For instance, Smad4 engages a co-activator, MSG1 (CBP/p300-interacting transactivator 1 with a Glu/Asp-rich carboxyl-terminal domain), into the transcriptional complex to enhance the Smad response (31). In contrast, Smad3 and/or Smad2 interact with co-repressors Evi-1 and c-Ski, inhibiting TGF-β responses (32). Other non-Smad signaling proteins that participate in TGF-β signal transduction includes small GTPase Ras (6) and mitogen-activated protein kinases (MAPKs) ERKs, p38 and c-Jun N-terminal kinases (JNKs) (33). In cancer cells, the Smad-co-repressor interactions may contribute to the disturbance of TGF-β signaling, affecting tumor development and progression (23, 34, 35).

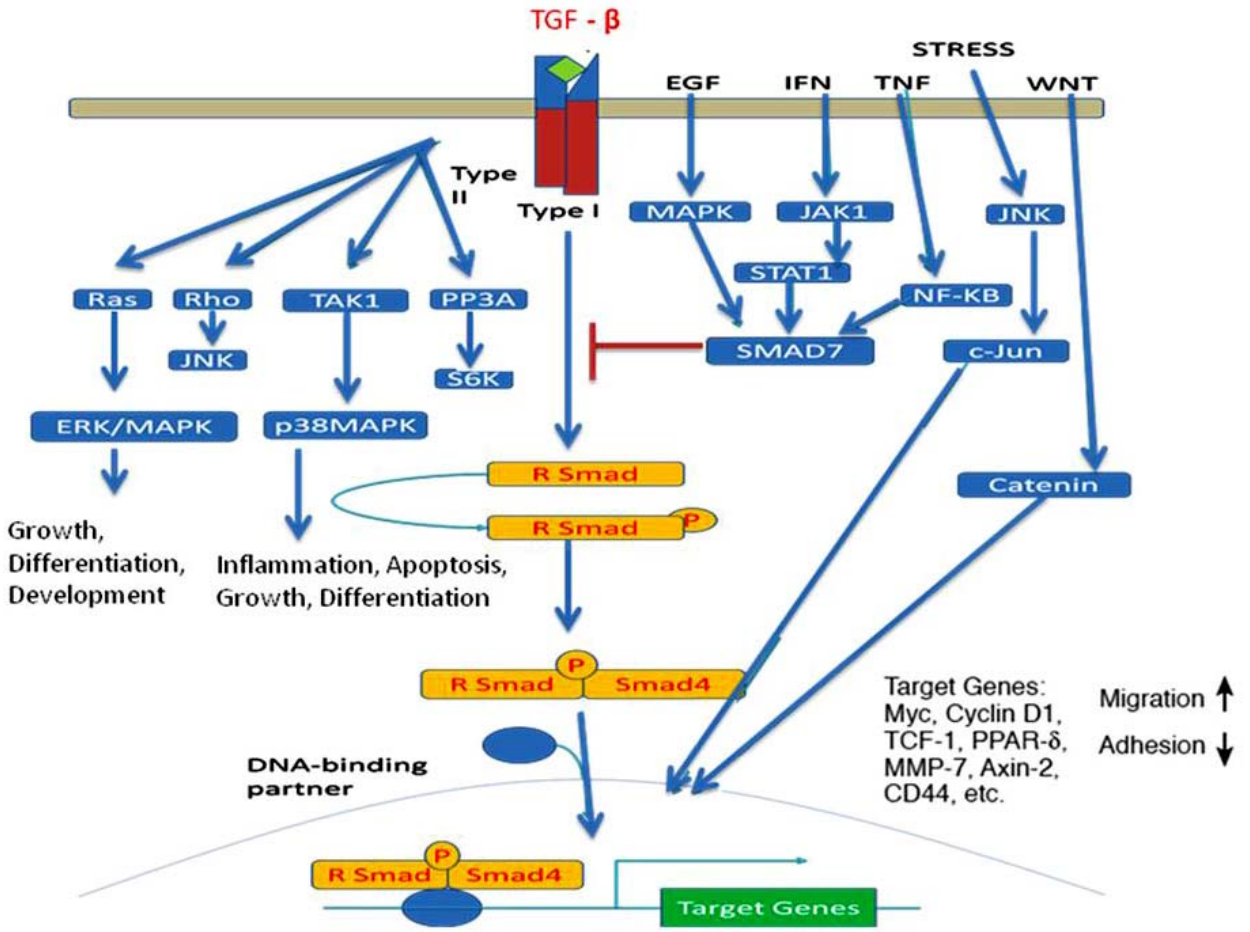

Figure 2. TGF-β signaling mediated through Smads and non-Smad mechanisms. Binding to TGF-β receptors phosphorylates and activates Smad2 and/or Smad3 that then associate with Smad4 and translocated into the nucleus to regulate gene expression. In response to EGF, WNT, interferon-γ (IFN-γ) or tumor necrosis factor-α (TNF-α), Smad7 is activated and competitively inhibits Smad2 and/or Smad3 activation by the receptors. TGF-β also activates Ras, RhoA, TAK1 and protein phosphatase 2A signaling pathways.

TGF-β type II receptor interacts with the proapoptotic adaptor protein Daxx, activating JNK and apoptosis of epithelial cells (36). The Daxx-JNK pathway also involves homeodomain-interacting protein kinase 2 (HIPK2), which interacts with and phosphorylates Daxx; this activates the MAPK kinases MKK4 and MKK7, which ultimately activate JNK and induce apoptosis (37). Direct link between receptor complexes and intracellular kinases involves the TGF-β-activated kinase 1 (TAK1), which can form a complex with the BMP receptors through its binding partner TAB1 and the inhibitor of apoptotic caspases XIAP, an E3 ubiquitin ligase (18, 38). TAK1 can also act downstream of TGF-β by initiating a kinase cascade that leads to Stat3 activation during mesoderm induction (39). XIAP was also found to interact with multiple type I receptors of the TGF-β superfamily, enhancing their signaling output (40). It has also been reported that TGF-β mediated BIM expression and apoptosis are regulated through Smad3-dependent expression of the MAPK phosphatase MKP2 (41).

MAP kinase p38 and its direct activator MKK6 are rapidly activated in response to TGF-β. Expression of dominant negative MKK6 or dominant negative TAK1 inhibits the TGF-β-induced transcriptional activation as well as the p38 activation (42). Activating transcription factor-2 (ATF-2), a nuclear target of p38, is also phosphorylated in the N-terminal activation domain in response to TGF-β, forming a complex with Smad4 (43). Thus, the p38 pathway is activated by TGF-β and is involved in the TGF-β-mediated transcriptional regulation. TGF-β affects the function of adherent junctions via Smads-mediated signaling, or alternatively Par6-provoked pathways. Through Smads signaling, TGF-β stimulates the expression of Snail, a transcriptional repressor of E-cadherin, leading to the dissolution of adherent junctions. Alternatively, TGF-β receptors constitutively associate with occludin and the polarity protein Par6. Upon ligand stimulation, the type II receptor phosphorylates Par6 and recruits ubiquitin ligase Smurf1 to ubiquitylate and degrade RhoA, thus leading to junction dissolution. The combined effects of the two pathways cooperatively promote EMT.

TGF-β also activates Rho GTPases, which activate ROCK, followed by phosphorylation and activation of Limk2 and subsequent phosphorylation and inhibition of cofilin (44). Cofilin is an actin-binding protein, causing actin depolymerization. BMP receptors bind directly to and activate Limk1, leading to the inhibition of cofilin (45, 46).

Migratory metastatic breast cancer cells are enriched with autocrine TGF- β that activate the PI3K/Akt and ERK pathways to drive the motility (47). MEKK1-knockout mice demonstrates that MEKK1 and the downstream MAPK and JNK are implicated in the migratory properties of the eyelid epithelium, underlying effects of the TGF-β or activin on the actin cytoskeleton (48). Similarly keratinocyte migration in response to activin needs the activation of the RhoA-ROCK-MEKK1-JNK/p38 pathway (49). The crosstalk between TGF-β signaling and Notch pathway is also critical to embryonic pattern formation and cell fate determination (50).

Such alternative signal transducers often regulate the Smad pathway itself and mediate signal transduction by other growth or morphogenetic factors. Therefore, TGF-β transmits biological signals to normal or cancer cells via the central Smad pathway and other alternative signaling proteins that regulate the quantitative output of the pathway and offer nodal points for crosstalk with other signal transduction pathways, governing the complex life of cells.

4. TGF-BETA AND TUMOR PROGRESSION

Tumor formation and progression in humans is a complex process that involves multiple events occurring over a period of time. Cancer cells need acquiring several abilities that most normal cells do not possess, such as the capability of replication without limit or resistance to growth inhibition, of invasion, of metastasis, of proliferation without dependence on growth factors, and of evading apoptosis and immune surveillance. TGF-β signaling has a complicated biphasic role in cell transformation and tumor progression. The autocrine and paracrine effects of TGF-β on tumor cells and the tumor microenvironment exert both positive and negative influences on cancer. Accordingly, the TGF-β signaling has been considered as a tumor suppressor or promoter, upon the stages of tumor development (34, 51, 52).

4.1. TGF-β as a suppressor of tumorigenesis

In TGF-β transgenic mice, primary tumor number induced by chemical carcinogens is significantly less than that in the control, suggesting that TGF-β suppresses the tumorigenesis (53, 54). It is known that TGF-β acts as a suppressor of proliferation in normal epithelial cells and early well-differentiated epithelial tumor cells through the inhibition of cyclin-dependent kinases (CDKs) (3, 8, 11, 13, 14, 18, 19, 55, 56). TGF-β activates Smad signaling and induces the transcription of target genes: p21, Runx3, p27, p57 and p15, or represses transcription of c-Myc, leading to cell cycle arrest [27]. Runx3 propagates p21 response, while c-Myc represses transcriptionally p21 and p15 expression. TGF-β signaling in regulating the gene expression is affected by other proteins, which may be attributed to its disturbance in cancer cells. Oncogenic proteins, such as Ski, SnoN, Evi-1, Smurf and Ras directly interact with or post-translationally modify the Smad complex, thus repressing its functionality (57); on the contrary, tumor suppressors, Elf, menin and cPML interact with activated Smads and enhance the signaling pathway (57).

Clinical evidence that TGF-β signals as a tumor suppressor is derived from the fact of frequent dysfunctional mutations of TGF-β receptor and/or downstream effectors in colon and gastric cancers with microsatellite instability (3, 8, 13, 14, 19, 55, 56). TβRII down-regulation is common in cancer and may account for a major mechanism of tumor cell resistance to the TGF-β suppressive effects (58). In TGF-β-insensitive breast cancer cells, restoring TGF-β signal transduction through the addition of TβRII lowers down the malignancy (58). In addition, Menin, a nuclear tumor suppressor protein, interacts with nuclear Smad complexes and cooperates in their transcriptional function (59). In some endocrine tumors, Menin mutants with an inactivating truncation antagonize TGF-β signaling rather than promote. The growth inhibitory response of epithelial cells to TGF-β thus appears to be governed by gene expression programs regulated by a combination of Smad and non-Smad signaling molecules.

4.2. TGF-β as a stimulator of malignant progression

Several laboratory-based experiments have shown that enhanced TGF-β signaling is involved in tumor progression. Xenografted prostate tumors over-expressing TGF-β in mice is 50% larger and more metastatic compared to the control. Lung metastases of breast adenocarcinoma xenografts in syngeneic rats are substantially accelerated by pretreatment of the cells with TGF-β, but fully inhibited by neutralizing antibodies against TGF-β (60-63). It is believed that TGF-β1 enhances metastasis of lung carcinoma cells through the impairment of the lung basement membrane (64). In the mice with conditional TGF-β over-expression in keratinocytes, a dual action on chemical carcinogenesis was observed: TGF-β suppresses the tumorigenesis as indicated by reduced primary tumor number, but enhanced the invasiveness and metastatic potential of the tumors (53, 54). TGF-β may enhance the malignancy through promoting epithelial to mesenchymal transformation (EMT)—the loss of epithelial cell characteristics in favor of an aggressive, migratory phenotype (57). A study of skin papillomas has indicated that TGF-β reduces tumor cell-adhesion, and via cooperation with ErbB2 receptors, induces migration in invasion chambers and basement membrane culture (18, 52, 65-70).

Clinical studies demonstrate that elevated TGF-β levels are predictive of metastases to bone and regional lymph nodes in breast, prostate, and liver cancer, as well as in muscle-invasive transitional cell carcinomas and bladder carcinomas (8, 13, 35, 58, 71). In the patients with metastatic melanoma, the plasma TGF-β2 levels are elevated; whereas plasma TGF-β1 are high in breast cancer with advanced and lymph node metastasis (13). In addition,

plasma BMPs are increased in aggressive bone tumors and esophagous squamous cell carcinoma (18, 52, 68-70). Taken together, no matter produced by the tumor or stromal cells, TGF-β is an important mediator of cancer development and progression.

4.3. TGF-β and epithelial-to-mesenchymal transformation

Epithelial-to-mesenchymal transformation (EMT), a feature of embryogenesis, is essential for many morphogenetic events, such as gastrulation and organogenesis, tissue remodeling, and fibrosis and wound healing (53). A hallmark of EMT is the loss of E-cadherin expression, an important caretaker of the epithelial phenotype, by which an epithelial cell becomes a more motile mesenchymal cell (53). Therefore, EMT is an important feature of invasive and metastatic cancer cells.

EMT is a dynamic process triggered by stimuli from microenvironments, including extracellular matrix (for example collagen and hyaluronic acid) and many secreted soluble factors, such as TGF-β, Wnt, Hedgehog, epidermal growth factor (EGF), hepatocyte growth factor (HGF), and cytokines (72-74). TGF-β is considered as a "master switch" of this process during both embryonic development and tumor progression *in vivo* (72, 75). In cultured normal and transformed mammary epithelial cells, TGF-β induces an EMT morphological change accompanied with the re-organization of actin cytoskeleton and down-regulation of epithelial proteins, such as E-cadherin, tight junction protein ZO- 1, and keratins, as well as up-regulation of certain mesenchymal proteins, such as fibronectin, fibroblast specific protein 1, α-smooth muscle actin, and vimentin (76, 77). In EpRas mammary epithelial cells, TGF-β, cooperating with Ras, induces a spindly phenotype, loss of cell-cell junction integrity, and cytoplasmic localization of E-cadherin and β-catenin, leading to increase of invasion (78). In animals, knockout of Smad3 blocks TGF-β-induced EMT in primary tubular epithelial cells; and the reduction of Smad2 and Smad3 associates with the decreased metastatic potential of xenografted breast cancer cells (64, 79, 80). The concentrations of factors such as TGF-β at the primary tumor site might initially be responsible for the EMT, resulting in invasion and intravasation, but the ultimate histological appearance of metastatic tumors depends on the local concentrations of these factors. Thus switch to an invasive fibroblastic phenotype by this scenario is transient and will be re-converted to an epithelial morphology, dependent on the local microenvironment.

5. TGF-BETA AND TUMOR MICROENVIRONMENT

Tumor microenvironment contains many distinct cell types, including endothelial cells and precursors, pericytes, smooth muscle cells, fibroblasts, carcinoma-associated fibroblasts (CAFs), myofibroblasts, neutrophils, eosinophils, basophils, mast cells, T and B lymphocytes, natural killer cells and antigen presenting cells (APC), such as macrophages and dendritic cells (81, 82). The tumor microenvironment is also enriched with various cytokines, chemokines, and growth factors, such as tumor necrosis factor-α (TNF-α), TGF-β, VEGF, and interleukins 1 (IL-1) and 6 (IL-6) (81, 83). Therefore, tumor microenvironment influences the tumor growth and survival, and the invasion and metastasis. On the other hand, tumor cells orchestrate directly (e.g. through the release of factors) or indirectly (through the induction of tissue hypoxia or appearance of necrosis) the modifications of the micro-environment by attracting or activating many non-tumoral cells, such as endothelial cells and immune and inflammatory cells (8, 81). Tumor cells can also deposit or modify the extracellular matrix (53). Most of the stromal modifications start early during tumor progression, often at the transition stage from premalignant to malignant lesions. High levels of TGF-β are produced by many types of cancer cells, such as the breast, colon, esophagus, stomach, liver, lung, pancreas, and prostate cancer and melanoma, as well as hematologic malignancy (17, 18, 20, 84-86), and/or the surrounding stromal cells in the microenvironment (86-89). Therefore, tumors are full of the TGF-β. Retrospective analyses of archival tumors have suggested a negative relationship between tumor TGF-β levels and disease progression, metastasis, and patient prognosis in breast, colon and lung cancer (14, 55, 90). Therefore, TGF-β may affect tumor progression by multiple mechanisms in addition to its direct action on tumor cells, such as angiogenesis and immune surveillance.

5.1. TGF-β and tumor immune responses

Immune surveillance plays a critical role in tumorigenesis; several observations have shown that TGF-β promotes tumorigenicity by locally repressing immune functions. TGF-β inhibits the proliferation and functional differentiation of T and B lymphocytes, lymphokine activated killer cells, NK cells, neutrophils, and macrophages (Figure 3). $CD8^+$ cytotoxic T cells (CTL) and natural killer (NK) cells play a critical role in the prevention, killing, and clearance of tumor cells. TGF-β could influence the T lymphocytes at all stages of development, from proliferation, differentiation to activation, serving as a paradigm for the pleiotropic nature of this cytokine.(10, 84, 91-93). Genetically modified mouse models illustrate the critical role for TGF-β in suppressing conventional $CD4^+$ and $CD8^+$ T cells; and TGF-β null mice develop a multifocal inflammatory disease associated with a significant increase of inflammatory cytokine (94-97). In addition, TGF-β also contributes to immuno-suppression by promoting the generation of Tregs (Figure 3). In cancer patients, Tregs levels are frequently high in the peripheral blood and lymph nodes and in the tumors (98-101).

TGF-β also affects proliferation, normal maturation and differentiated functions of the B cells. This includes the regulation of expression of cell surface molecules, such as the inhibition of IgM, IgD, IgA, CD23 and the transferring receptor expression and the induction of MHC class II expression on both pre-and mature B cells (102).

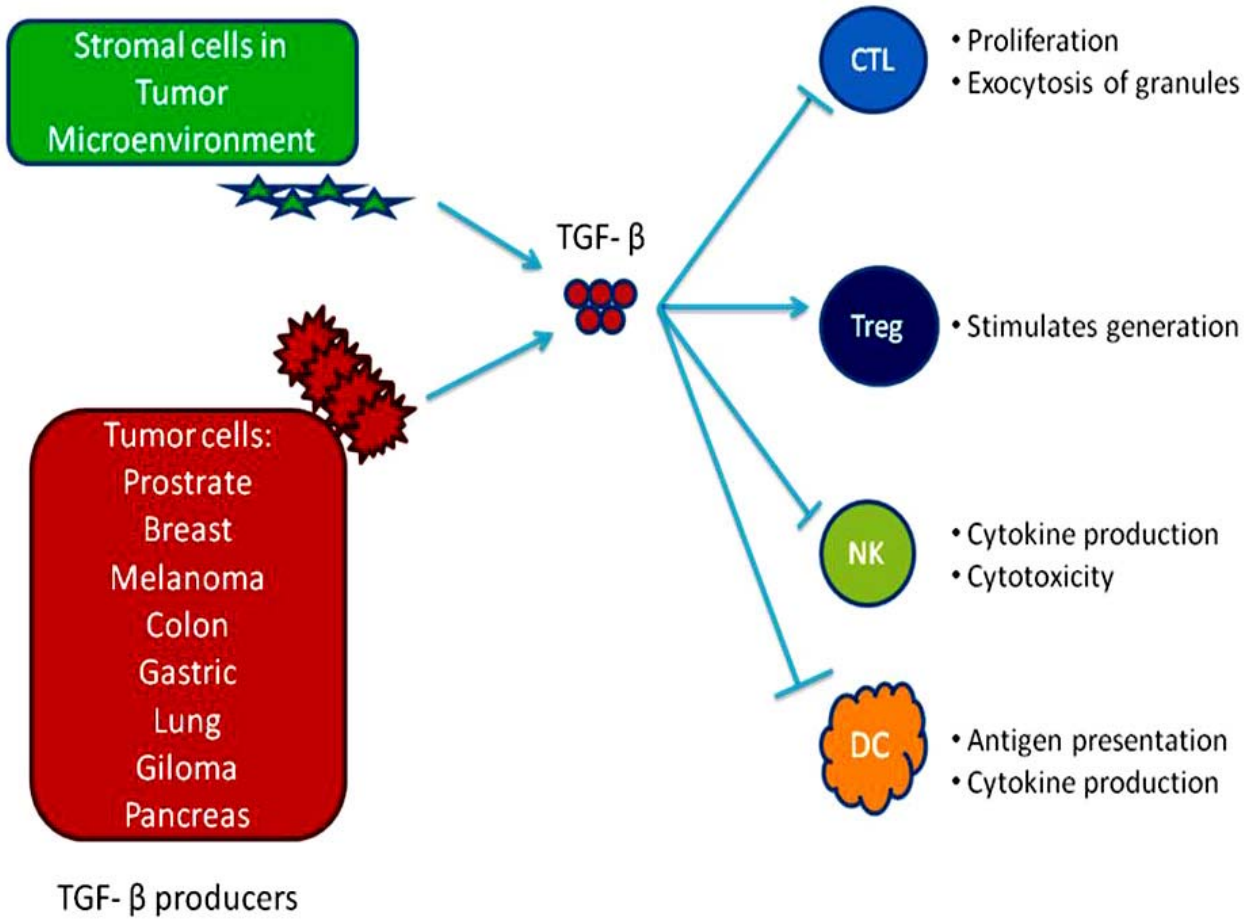

Figure 3. TGF-β in the tumor microenvironment and its effects on immune cells. TGF-β is produced by tumor and stromal cells and exerts immunosuppressive roles for the immune cells involved in the antitumor responses. CTL, cytotoxic T lymphocytes; Treg, regulatory T cells; NK, natural killer cells; and DC, dendritic cells.

The importance of TGF-β in Dendritic cells (DC) development is also emphasized by recent studies in the TGF-β knockout mouse, where the complete absence of the epidermal Langerhans cells (LC) is a striking feature of the phenotype. In the TGF-β knockout mice, a generalized activation of most immune cell populations and widespread tissue inflammation are recognized (103-105) . TGF-β may also have an important role in another highly specialized class of antigen-presenting cell, the follicular dendritic cell (FDC). Localization of TGF-β within the FDC of lymphoid follicles, combined with its ability to inhibit antigen-induced rescue of germinal center (GC) B cells, suggests a specific functional role for TGF-β in FDC (91, 106).

5.2. TGF-β and angiogenesis

Tumor angiogenesis is crucial for tumor growth and invasion. TGF-β acts as a potent inducer of angiogenesis. In animals, TGF-β or TβRII gene knockout results in embryonic lethality owing to defective vasculogenesis and angiogenesis. Similar phenotypes are also seen in TβRI and activin receptor-Like Kinase (ALK-1) null mice (33, 107). On the contrary, increased expression of TGF-β in prostate carcinoma or Chinese hamster ovary cells enhances tumor angiogenesis xenografted in immunodeficient mice. Similar results were obtained by local administration of neutralizing TGF-β antibody (55). In cancer clinics, TGF-β messenger RNA levels in human breast tumors associates with increased microvessel density and poor patient prognosis. It has been suggested that high tumor burden and circulating plasma levels of TGF-β are associated with enhanced tumor angiogenesis and poor patient prognosis (6).

The mechanisms of angiogenic stimulation by TGF-β are complicated. TGF-β induces expression of VEGF, which stimulates the proliferation and migration of endothelial cells (108). Ras may synergistically act with TGF-β in regulating VEGF expression. In RIE: iRas cells and colon cancer cells, VEGF is induced in a dose-dependent manner by both TGF-β and Ras (78); and in the endothelial cells cultured on collagen matrix, TGF-β induces capillary formation (8, 19). TGF-β may also stimulate angiogenesis as a potent chemoattractant for monocytes that release angiogenic cytokines (109-114). TGF-β signaling may be implicated in several steps of the angiogenesis, including vessel wall integrity, smooth muscle cell recruitment, extracellular matrix deposition,

and endothelial cell differentiation into more specialized endothelium (115-118).

5.3. TGF-β and tumor microenvironment

TGF-β mediates the immune cell proliferation and functional maturation and the angiogenesis in tumors, affecting cancer formation and development. TGF-β also profoundly affects the tumor microenvironment, influencing tumor progression and invasion/metastasis. TGF-β stimulates synthesis of extracellular matrix proteins, such as metallo-proteases MMP-2 and MMP-9, but down-regulates protease inhibitor TIMP in tumor cells, which enhances the migratory and invasive properties (38, 119). TGF-β mediates fibroblast- and immune-derived stromal–epithelial interactions during carcinoma initiation and progression. Experimental studies have shown that dysfunction of TβRII (fibroblasts) or Smad4 (T-cells) in the stromal compartment can initiate tumorigenesis (6). The loss of TβRII in fibroblasts abolishes TGF-β-mediated growth inhibition and results in secretion of HGF, MSP, and TGF-α. These factors induce cell cycle dysregulation, transformation, and increased motility and invasion of nearby epithelial cells in the prostate, forestomach, and breast.

6. TGF-BETA SIGNALING AS A THERAPEUTIC TARGET FOR HUMAN CANCER

Enhanced TGF-β signaling occurs in many types of tumors and is frequently associated with poor prognosis, making it a potential therapeutic target. Currently, several approaches targeting TGF-β signaling pathway have been investigated, which target tumor cell, tumor microenvironment, or systemic levels. These anti–TGF-β therapies could reverse the immunosuppressive effects on the host, decrease extracellular matrix formation, angiogenesis, and osteolytic activity, or increase the sensitivity of the malignant cells to cytotoxic therapy and immunotherapy. Various inhibitors of TGF-β signaling that are being evaluated in preclinical models and early clinical trials include soluble protein receptors, TGF-β antibodies, small-molecule kinase inhibitors, oligonucleotides, peptide aptamers, and tumor vaccines (108, 120-131).

Anti-TGF-β antibodies and anti-sense RNA represent a class of agents that inhibit tumor progression. Intraperitoneal injection of anti-TGF-β antibodies that neutralize the three TGF-β isoforms inhibits tumorigenicity of the human breast carcinoma MD-MB-231 cells in mouse xenograft models (60). Treatment with TGF-β neutralizing antibodies or TGF-β2 anti-sense oligonucleotides stimulates the activity of natural killer cells and restores inhibition of growth of human breast cancer cells by tamoxifen in mice with active natural killer cells (132). Anti-sense RNA inhibition of TGF-β1 or TGF-β2 synthesis in breast cancer, mesothelioma, or glioma cells has been documented to restore tumor immunogenicity and the cytotoxic T-lymphocyte response, and inhibits tumor development (80, 133, 134). Several reports have shown that ectopic expression of TGF-β binding proteins, including proteoglycans like decorin, glypican-1, and biglycan, and extracellular domains of TβRI and TβRII, can inhibit tumor formation, tumor growth, and metastasis of several xenograft models, such as glioma, hepatoma, and carcinomas of the breast, colon, and pancreas (132, 135-142). In another study, it was observed that the ectopic expression of a recombinant soluble TβRIII antagonizes TGF-β activity and inhibits both anchorage-dependent and independent growth of MDA-MB-231 breast cancer cells *in vitro* (143). Systemic administration of the same recombinant soluble TβRIII inhibits growth, angiogenesis, and lung metastasis of orthotopic tumors from human breast cancer cells in syngeneic mice (135). In another study, anti-TGF-β antibodies prevent the cyclosporine induced metastasis of adenocarcinoma cells in immunodeficient SCID-beige mice (144); and combination of anti-TGF-β antibodies with IL-2 reduces tumor formation in highly metastatic melanoma cells that are not affected by either anti-TGF-β antibodies or IL-2 alone (145). In addition, Latency associated peptides (LAP) have been shown to inhibit all three forms of TGF-β *in vitro* and also after intraperitoneal administration in a murine model (146). LAP is readily absorbed from the peritoneal cavity and accumulated sufficiently in tissues to inhibit TGF-β. These studies show the potential role of TGF-β inhibitors/ antagonists in the adjuvant settings.

Anti-TGF-β also reverses tumor drug resistance. Tamoxifen resistance correlates with increased expression of TGF-β, which may suppress NK cell activity and results in the failure of tamoxifen therapy. Accordingly, anti-TGF-β antibodies are able to successfully reverse tamoxifen resistance of breast tumor cells (51, 147-152).

Small chemical antagonists represent another approach targeting TGF-β signaling. Tranilast, (N-[3,4 dimethyloxycinnamoyl]-anthranilic acid), an anti-allergy compound used clinically to control atopic and fibrotic diseases, inhibits DNA synthesis and proliferation of human malignant glioma cells and promotes $p21^{Cip1}$ accumulation without cytotoxicity. It has also been shown that Tranilast reduces release of TGF-β and thus inhibits migration, chemotactic responses, and invasiveness. In human malignant glioma, Tranilast abrogates the malignant phenotype and antagonizes TGF-β-associated immunosuppression. Therefore, Tranilast is a potent therapeutic agent for cancer. Another small chemical, halofuginone can inhibit the phosphorylation of Smad2 and Smad3, elevate Smad7 expression, decrease cytosolic and membrane TGF-β RII, and lessen radiation-induced fibrosis in humans, exhibiting the potential in cancer clinics (153-156). Currently, great attention has been paid to develop the selective small molecules as inhibitors of the TGF-β signaling pathway, targeting the small-molecule-amenable TGF-β receptors and downstream effector kinases, such as TβRI inhibitors SD-208 and SD-093 (157, 158) and activin receptor-like kinase 5 inhibitor A-83-01 (159).

7. CONCLUSION

TGF-β profoundly participates in various aspects of tumor development and progression. TGF-β signaling is a complicated pathway and is characterized with a biphasic action upon on tumor stages and cell types. However, data

compiled from *in vitro* and *in vivo* studies have enriched our understanding of its function in growth inhibition and cell cycle regulation, as well as its cross-talking with other signaling pathways, aiding in the design of therapeutic strategies targeting this pathway, i.e., selecting patients who most likely benefit from anti-TGF-β therapy.

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