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Biology and functions of TGF-beta signal transduction in fibrotic diseases and tumors

AHMED MB KHEDR[1]
Department of Medical Biochemistry and Molecular Biology, General Medicine Practice Program
Batterjee Medical College, Aseer 61961, Saudi Arabia
NASSAR AA. AYOUB
Department of Anatomy, General Medicine Practice Program, Batterjee Medical College
Aseer 61961, Saudi Arabia
MOHAMMED A. FOUAD
Department of Microbiology, General Medicine Practice Program, Batterjee Medical College
Aseer 61961, Saudi Arabia

Abstract

Transforming growth factor-beta (TGF-β) is a multifunctional cytokine that plays pivotal roles in tissue homeostasis, wound healing, and pathological processes including fibrosis and cancer. This review provides a comprehensive overview of the biology and functions of TGF-β signal transduction in fibrotic diseases and tumors.

TGF-β is synthesized as a latent precursor and activated through enzymatic and non-enzymatic mechanisms to initiate signaling via both canonical (SMAD-dependent) and non-canonical (SMAD-independent) pathways. These pathways regulate critical cellular processes such as proliferation, differentiation, epithelial-to-mesenchymal transition (EMT), extracellular matrix (ECM) deposition, and immune modulation.

In fibrotic diseases (e.g., pulmonary, hepatic, renal, and cardiac fibrosis), TGF-β drives fibroblast activation, myofibroblast differentiation, and excessive ECM production, primarily through SMAD2/3 signaling and crosstalk with MAPK, PI3K/AKT, and mTOR pathways. It also promotes EMT and endothelial-to-mesenchymal transition, further contributing to tissue scarring.

In the tumor microenvironment, TGF-β exhibits a paradoxical "double-edged sword" effect: it acts as a tumor suppressor in early-stage carcinogenesis by inducing cell cycle arrest and apoptosis, while in advanced tumors it promotes immune evasion, angiogenesis, epithelial-mesenchymal transition, invasion, and metastasis. TGF-β suppresses antitumor immunity by inhibiting effector T cells, promoting regulatory T cells, and reprogramming myeloid cells, thereby fostering an immunosuppressive milieu.

Given its central role in both fibrosis and cancer progression, TGF-β signaling has emerged as a promising therapeutic target. Various strategies—including neutralizing antibodies, ligand traps, small-molecule kinase inhibitors, antisense oligonucleotides, and vaccines—are currently under preclinical and clinical evaluation.

This review highlights the complex context-dependent functions of TGF-β and underscores the challenges and opportunities in developing effective TGF-β-targeted therapies for fibrotic disorders and malignancies.

Keywords: TGF-ß, signal transduction, fibrosis, tumor microenvironment, epithelial-mesenchymal transition, targeted therapy, SMAD signaling

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[1] Corresponding author: Ahmed MB Khedr, Assistant Professor of Medical Biochemistry and Molecular Biology, Department of Medical Biochemistry and Molecular Biology, General Medicine Practice Program, Batterjee Medical College, Aseer 61961, Saudi Arabia. Email: ahmed.bahaa@bmc.edu.sa

INTRODUCTION

Cytokine-based targeting is a potentially effective treatment for various conditions, such as fibrotic illnesses, cancer, and inflammatory or infectious diseases [1-3]. Transforming growth factor beta (TGF-β) is a multifunctional polypeptide cytokine whose biofunction in controlling cell development and differentiation makes it a promising therapeutic target for cancer treatment. This cytokine is a member of the TGF-β superfamily, which is composed of several proteins, including activins and growth differentiation factors. The three isoforms of the TGF-β family are structurally related cytokines: TGF-β1, TGF-β2, and TGF-β3 [4, 5]. In the following statement, TGF-β refers to TGF-β1 unless otherwise noted. Latent TGF-β is often present in the extracellular matrix. Both enzymatic and non-enzymatic processes cause latent TGF to change into active TGF. Canonical and non-canonical TGF-β signal transduction pathways are triggered by activated TGF binding to the TGF receptor complex. Developing TGF-β-targeted therapeutic drugs is a major challenge because of its dual role and paradoxical effects on fibrosis and immune system regulation in the occurrence and development of disease. Nevertheless, scientists have suggested that TGF-β signaling pathways play crucial roles in fibrosis, tumorigenesis, and immune response regulation. In physiological settings, TGF-β is essential for regulating tissue regeneration and homeostasis. TGF-β signaling is essential for controlling inflammation and wound healing in pathological situations [6–8]. Furthermore, TGF-β signaling plays a role in fibrosis by causing extracellular matrix deposition [4, 9]. During cancer, dysregulated TGF-β controls both innate and adaptive immune responses. TGF-β becomes cytostatic, apoptotic, and tumor-suppressive during the early stages of carcinogenesis. It suppresses excessive inflammation and induces immune tolerance. Tumor tolerance, inflammation suppression, T cell exclusion, epithelial-mesenchymal transition, migration, invasion, and progression all depend on TGF-β in advanced cancer [10]. TGF-β signal transduction is regulated at various levels, including the synthesis of TGF-β ligands, ligand-receptor interactions, downstream signaling cascades after kinase receptor activation, and transcriptional disruption. Targeted treatment approaches are made possible by the critical role of TGF-β and its significant therapeutic potential in the aforementioned diseases, the particular mechanisms of TGF-β in causing these diseases, and therapeutics based on TGF-β signal transduction. Numerous medications targeting TGF-β are currently undergoing preclinical and clinical testing. The primary TGF-β-targeted techniques include neutralizing antibodies, TGF-β ligand traps, small-molecule receptor kinase inhibitors, antisense oligonucleotides, and vaccine-based treatments [11–15]. However, most of these are undergoing phase 1/2 clinical studies. The biology and function of TGF-β are discussed in detail in this review, along with an overview of the latest developments in TGF-β-associated targeted treatment.

THE BIOLOGY OF TGF-B

The production and activation of TGF-β

TGF-β is typically found outside cells as pairs of molecules. There are three types of TGF-β in mammals: TGF-β1, TGF-β2, and TGF-β3. Each type is synthesized in the rough endoplasmic reticulum as a precursor with three parts: a signal peptide, a latency-associated polypeptide (LAP), and a mature polypeptide. The signal peptide is removed, and the precursor is split into LAP and mature polypeptides. TGF-β1 is the most studied TGF-β and was the first to be purified from platelets. Tumor cells, tumor-associated macrophages, and fibroblasts in tumors also produce TGF-β1, but not always TGF-β2 or TGF-β3 [17-21].

Mature polypeptides form pairs through disulfide bonds. The latent TGF-β complex is linked to a TGF-β-binding protein, forming a large latent complex. This complex is connected to the extracellular matrix or GARP (also known as LRRC32) on the cell surface. To activate TGF-β, it must be released to bind to receptors on the nearby cells. TGF-β acts differently depending on the cell type and context. Latent TGF-β is linked to GARP on mesenchymal stromal cells, platelets, and Tregs, helping GARP manage these complexes. GARP is found on fibroblasts, megakaryocytes, and endothelial cells, suggesting that it has a broad role in TGF-β1 latency. Another protein, LRRC33, is also linked to latent TGF-β and helps activate it. LRRC15, found in stromal fibroblasts in advanced tumors, has similar roles in maintaining TGF-β [22-30].

The canonical and noncanonical pathways of TGF-β signal transduction

TGF-β signaling occurs through two main pathways: canonical and non-canonical (Fig. 2). In the canonical pathway, TGF-β ligands mainly attach to the TGF-β type III receptor (TGF-βRIII, also known as betaglycan), which is found in high amounts in many cells. Of the three TGF-β types, TGF-β2 relies on TGF-βRIII for signaling compared to the other two types [31]. The TGF-β receptor complex is composed of four parts, including two pairs of serine or threonine protein kinases, TGF-βRIs and TGF-βRIIs [32]. Once TGF-β binds to TGF-βRIII, it is presented to the TGF-βRI/TGF-βRII complex, which strongly attracts TGF-β [33]. TGF-β binding can also recruit and activate TGF-βRI, which is necessary for signaling [34]. TGF-βRI then activates SMAD2 by adding phosphate groups to specific serine residues at positions 465 and 467 [35]. The activated SMAD2/3 quickly leaves TGF-βRI and joins SMAD4 to form a complex. The SMAD2/3-SMAD4 complex then moves into the cell nucleus to turn genes on or off [36]. TGF-β also triggers SMAD7, which acts as a negative regulator of the TGF-β/SMAD signal by blocking SMAD2 activation. SMAD7 also interferes with the SMAD-DNA complex in the nucleus [37] and prevents the formation and movement of the SMAD2-SMAD4 complex [38, 39]. SMAD7 can join with SMAD2/3 to reduce signaling. It affects TGF-β signaling by deactivating SMAD2/3 and other pathways without affecting TGF-β receptor activity. SMAD7 also helps prevent fibrosis after a heart attack by limiting TGF-β-independent fibrogenic function [40]. High levels of SMAD7 are linked to inflammatory diseases and are considered an inhibitor of TGF-β1 activity [41]. SMAD7 recruits E3 ubiquitin ligases, such as TRIM31, Smurf1/2, and NEDD4–2, to TGF-βRI, leading to its breakdown [42–44]. Enzymes such as UCHL1 and USP4 can reverse TGF-βRI breakdown by removing ubiquitin [45, 46].

In addition to the main TGF-β signaling pathway, other pathways are important in various diseases [47]. TGF-βRI activates RHO small GTPases, which control LIM kinase (LIMK) and phosphorylate Cofilin. This alters the actin cytoskeleton and aids in cell adhesion and growth [48, 49]. TGF-βRII phosphorylates PAR6, a cell polarity regulator, and is linked to tight junctions and epithelial-to-mesenchymal transition (EMT) [50, 51]. TGF-β also activates the c-Jun N-terminal kinase (JNK) and P38/mitogen-activated protein kinase (MAPK)/nuclear factor kappa-B (NF-κB) pathways, which are downstream of tumor necrosis factor-associated factor 4/6 (TRAF4/6) [52–54]. The PI3K/AKT pathway is another downstream signal of non-canonical TGF-β signals [55, 56]. Additionally, TGF-β causes phosphorylation of Src homology domain 2-containing protein, activating the rat sarcoma (RAS), rapidly accelerated fibrosarcoma (RAF), MAPK, and extracellular signal-regulated kinase (ERK) pathways [57–59]. RAS-responsive element-binding protein 1 (RREB1) may link RAS and TGF-β signals to initiate fibrogenic EMT [60]. There is an interaction between the main and other signals caused by TGF-β, which is controlled by receptor tyrosine kinases. TGF-β activates these pathways by affecting platelet-derived growth factor (PDGF) expression in a paracrine or autocrine manner [61].

THE FUNCTION OF TGF-Β SIGNALS IN FIBROTIC DISEASES AND TUMORS

TGF-β and the tumor microenvironment (TME)

TGF-β signals are important in controlling the tumor microenvironment (TME), which affects cancer growth (Fig. 3). TGF-β is a potential cancer biomarker [62]. The TME contains different immune cells, such as tumor-associated macrophages (TAMs), neutrophils, myeloid-derived suppressor cells (MDSCs), dendritic cells (DCs), T cells, and B cells. It also has non-immune cells, such as cancer-associated fibroblasts (CAFs) and stromal cells, and many cytokines [63–66]. Some cells, such as TAMs and MDSCs, gather early in the TME during tumor growth and weaken T-cell responses, maintaining an immunosuppressive environment [67, 68]. Immune and stromal cells in the TME primarily produce cytokines, including TGF-β [69]. TGF-β acts as a tumor suppressor early in cancer but promotes tumors in later stages, such as in breast, liver, lung, and pancreatic cancers [70–73]. Generally, TGF-β stops the growth of immunosuppressive myeloid cells, especially in early stage cancers [74, 75]. In advanced tumors, TGF-β from myeloid cells weakens antitumor immunity and promotes tumor spread [76, 77]. TGF-β prevents naive CD4+ T cells from differentiating into other types, such as Tregs, thereby reducing the antitumor immune response [78]. Removal of TGF-βRII from CD4+ T cells slows tumor growth, causing tumor cell death in areas without blood vessels due to changes in blood vessels [79]. DCs present tumor antigens to natural killer (NK) cells and T cells, causing antitumor effects [80, 81]. TGF-β halts cytotoxic CD8+ T-cell activation by blocking DC tumor antigen presentation. It also reduces CD8+ T cell growth and function by lowering interferon-γ (IFN-γ) and interleukin-2 (IL-2) levels [82, 83]. TGF-β increases programmed death 1 (PD-1) expression on CD8+ T cells, leading to T cell exhaustion [84]. TGF-β maintains the immunosuppressive properties of CD8 + Treg cells. TGF-β and the transcription factor eomesodermin, which controls the location of CD8+ Tregs, work together to maintain CD8+ Tregs [85]. In addition to affecting T cells, TGF-β controls B cell activation, growth, and death. However, its effect on the B-cell antitumor response has not been well studied [86, 87].

Angiogenesis, the formation of new blood vessels, is a key feature of cancer growth and spread. TGF-β, a protein, helps tumors grow by suppressing the immune system and promoting angiogenesis. Many proteins, such as TGF-β, IL-22, and IL-1β, control this process[88–91]. High levels of TGF-β in the tumor environment are linked to the formation of new blood vessels in cancers. In cells lining blood vessels, TGF-β1 works with thrombospondin-4 to promote angiogenesis, leading to tumor growth. Studies have shown that increased levels of TGF-β in the blood are associated with an increased number of blood vessels in tumors. TGF-β encourages angiogenesis by affecting its storage in the body [93, 96]. Fibrillins are proteins in the body that help store TGF-β. When TGF-β is activated, it binds to integrins, which increase upon TGF-β exposure. Fibrillin-2 in tumor blood vessels directly promotes angiogenesis by affecting TGF-β storage and increasing TGF-β levels in the tumor environment. Fibrillin-1, fibrillin-2, and related structures can indirectly bind and store TGF-β by interacting with LTBPs, which are important for TGF-β binding in the body [96, 97].

TGF-β and fibrosis

High levels of TGF-β are linked to fibrosis, a condition in which tissues become thick and scarred. This includes diseases such as lung, liver, kidney, heart fibrosis, and systemic sclerosis [7, 98, 99] (Fig. 4). Macrophages are a type of immune cell that helps repair tissues. TGF-β affects these cells, especially macrophages, which are important in fibrosis [100, 101]. TGF-β helps bring macrophages to areas of fibrosis and causes them to release substances that increase TGF-β activity [102, 103]. It also induces macrophages to produce ECM proteins [104, 105].

ECM buildup is a key component of fibrosis. TGF-β causes fibroblasts, the main cells in this process, to grow and produce ECM, which can harm organs. TGF-β also attracts fibroblasts to fibrotic areas [107, 108]. The mTOR pathway helps to produce proteins and activate fibroblasts [109, 110]. TGF-β can also convert cells into fibroblasts, contributing to fibrosis [111, 112]. TGF-β can cause fibrosis, whereas blocking its signals can reduce it [113-116]. TGF-β works with other signals to control the genes that lead to fibrosis [117]. These signals are activated by pathways such as ERK, JNK, and MAPK [4, 118, 119].

More TGF-β activates fibroblasts, increasing protein production and altering gene activity [120]. It targets genes encoding fibronectin and collagen, which are important for ECM [121, 122]. TGF-β also boosts metabolism, leading to increased energy production. ATF4 helps in the production of proteins needed for the ECM using SMAD and mTOR signals [123, 124].

TGF-β target genes are key players in fibrosis. It interacts with other signals to produce proteins that cause the formation of muscle-like cells, which are important in fibrosis [125-127]. TGF-β also affects the growth factor CTGF/CCN2, which is crucial for ECM production and cellular changes in fibrosis [128, 129].

TGF-β causes cells to produce more interleukin-11, a protein that helps form scar tissue. This protein is produced by fibroblasts and epithelial cells and helps convert fibroblasts into myofibroblasts, activate fibroblasts, and build up the extracellular matrix (ECM) [130, 131]. TGF-β also increases the levels of certain proteins, namely c-JUN, JUN-B, and JUN-D. These proteins join others to form AP-1 complexes, which induce fibrosis. AP-1 complexes are activated by signals from ERK, JNK, and MAPK, which are triggered by TGF-β, leading to increased fibrosis [132–135]. TGF-β/SMAD complexes work with AP-1 to boost the expression of genes such as c-JUN, interleukin-11, fibronectin, and collagen Iα2, which also contribute to fibrosis [136, 137].

TGF-β changes tubular epithelial cells in culture to produce more collagen and take on a myofibroblast shape [138–140]. Both SMAD3-dependent and other signals cause these changes [141–144]. TGF-β interacts with β-catenin, which controls EMT through the cAMP response element-binding protein [145]. Bone morphogenic protein-7 (BMP-7) prevents TGF-β from inducing EMT in epithelial cells by opposing TGF-β, increasing α-SMA levels, and decreasing E-cadherin levels [139, 146]. TGF-β activates Jagged 1/Notch signals through the SMAD and ERK pathways to initiate EMT [147]. TGF-β induces vascular endothelial cells to develop mesenchymal traits [148–150]. Increased TGF-β signaling leads to endothelial-mesenchymal transdifferentiation, similar to EMT [151, 152]. Excessive TGF-β causes αvβ6 integrin to activate hidden TGF-β in epithelial cells, which is important for fibrosis development through mesenchymal traits [153–155]. Single-cell sequencing of lung fibrosis shows that cells have fewer epithelial and more mesenchymal traits, suggesting that EMT and endothelial-mesenchymal transdifferentiation play a role in fibrosis [156, 157].

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