Fibrosis

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Review

TGF-β as a Central Hub in Organ Fibrosis: Cross-Organ Mechanisms, Bidirectional Cell–Cell Communication, and Molecular Networks

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ABSTRACT: Fibrosis is a common pathological feature of advanced chronic diseases, including interstitial lung disease, cirrhosis, chronic kidney disease, and cardiovascular disease. It arises when tissue repair becomes dysregulated, leading to excessive extracellular matrix (ECM) deposition and structural remodeling. Transforming growth factor-β (TGF-β), a key regulator in the fibrotic network, coordinates oxidative and endoplasmic reticulum stress, immune microenvironment remodeling, myofibroblast activation from multiple cellular sources, and ECM metabolic imbalance through Smad-dependent and Smad-independent pathways. TGF-β also interacts with other pro-fibrotic molecules (such as platelet-derived growth factor, connective tissue growth factor, and angiotensin II), synergistically amplifying fibrotic signaling. This review provides a systematic analysis of the central role of TGF-β in fibrosis from the perspectives of cross-organ comparison, bidirectional cell-cell communication, and molecular network integration. We further discuss how these mechanisms may inform promising targets for anti-fibrotic drug discovery.

Keywords: TGF-β; Fibrosis; Extracellular matrix; Myofibroblasts; Cross-organ comparison

1. Introduction

Fibrosis is a progressive pathological process arising from dysregulated tissue repair following injury. Its hallmark is the abnormal deposition and remodeling of the extracellular matrix (ECM), which ultimately disrupts normal tissue structure and leads to functional decline. This process typically develops in response to chronic inflammation, persistent injury, or metabolic disorders. As a common final pathway of many chronic diseases, fibrosis can affect virtually all organs, particularly the heart, liver, lungs, and kidneys.

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Epidemiological data highlight its substantial global burden: approximately 32.7% of individuals with cardiometabolic conditions develop myocardial fibrosis [1]; advanced liver fibrosis and cirrhosis affect 3.3% and 1.3% of the general population, respectively [2]; idiopathic pulmonary fibrosis (IPF), the most common progressive fibrotic interstitial lung disease (ILD), has a global prevalence of roughly 17.7 per 100,000 [3]; and chronic kidney disease (CKD), which frequently progresses with fibrotic changes, affects about 8006 per 100,000 individuals worldwide [4].

The etiologies of fibrosis are diverse, encompassing genetic predispositions (e.g., mutations in the cystic fibrosis transmembrane conductance regulator gene cause cystic fibrosis) [5], environmental and occupational exposures (e.g., asbestos-induced pulmonary fibrosis) [6], pathogen infections (e.g., hepatitis B virus-driven liver fibrosis) [7], metabolic disorders (e.g., diabetes-associated cardiac and renal fibrosis) [8,9], and immune-inflammatory conditions (e.g., systemic sclerosis with multi-organ fibrosis due to fibroblast activation) [10].

Despite the heterogeneity of etiologies, fibrotic diseases share a common pathological core: persistent myofibroblast activation, excessive ECM deposition, and irreversible tissue remodeling. Transforming growth factor-β (TGF-β) is widely recognized as a central hub of this process. TGF-β also exerts context-dependent immunoregulatory and anti-inflammatory functions. This review focuses on its pro-fibrotic effects. TGF-β is a highly conserved, multifunctional cytokine that is essential for tissue homeostasis and repair. Because of this broad range of biological activities, the cellular sources of pathogenic TGF-β remain poorly defined in the fibrosis literature. Its activation acts on several cell types, including epithelial cells, fibroblasts, and immune cells, to establish a pro-fibrotic environment and ultimately lead to fibrotic diseases [11]. TGF-β signaling is further characterized by cross-organ, bidirectional cell-cell interactions and by integration into larger molecular network. Therefore, this review provides a systematic analysis of the central role of TGF-β in fibrosis from three integrated perspectives: cross-organ comparison, bidirectional cell-cell communication, and molecular network integration.

2. Methods: Literature Search Strategy

Databases, including but not limited to PubMed and Web of Science, were searched for articles published between January 2000 and September 2026, with classic or landmark studies included regardless of publication date. The search combined terms related to TGF-β, fibrosis, cell–cell communication, molecular mechanisms, and anti-fibrotic therapies. Boolean operators (AND, OR) were used to combine terms, and Medical Subject Headings (MeSH) and Web of Science topic terms were applied where appropriate. Inclusion criteria were original research, systematic reviews, or comments; studies directly addressing TGF-β and fibrosis; and mechanistic, translational, or therapeutic studies relevant to fibrosis. Studies were excluded if they focused exclusively on cancer or tumors without any fibrosis-related outcome.

3. Activation of TGF-β and Signal Transduction

3.1. Activation of Latent TGF-β

TGF-β activation is the first step in its signaling cascade. TGF-β is generally secreted in a biologically latent form called latent-TGF-β (L-TGF-β) [12]. To exert its biological functions, TGF-β must be released from this latent complex, a process mediated by integrins, proteases, reactive oxygen species (ROS), mechanical forces, or an acidic microenvironment. Specifically, the integrin αvβ6 applies mechanical forces to induce conformational changes in latency-associated peptide (LAP), thereby releasing active TGF-β [13]; certain proteases, including calpains, cathepsins, serine proteases, matrix metalloproteinases (MMPs), and members of the ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs) family, can activate TGF-β *in vitro* through hydrolysis [14]; and latent TGF-β directly disrupts the LAP backbone upon

exposure to extremes of pH or ROS, thereby releasing active TGF-β [15]. TGF-β signals through two major downstream pathways: Smad-dependent and Smad-independent (Figure 1).

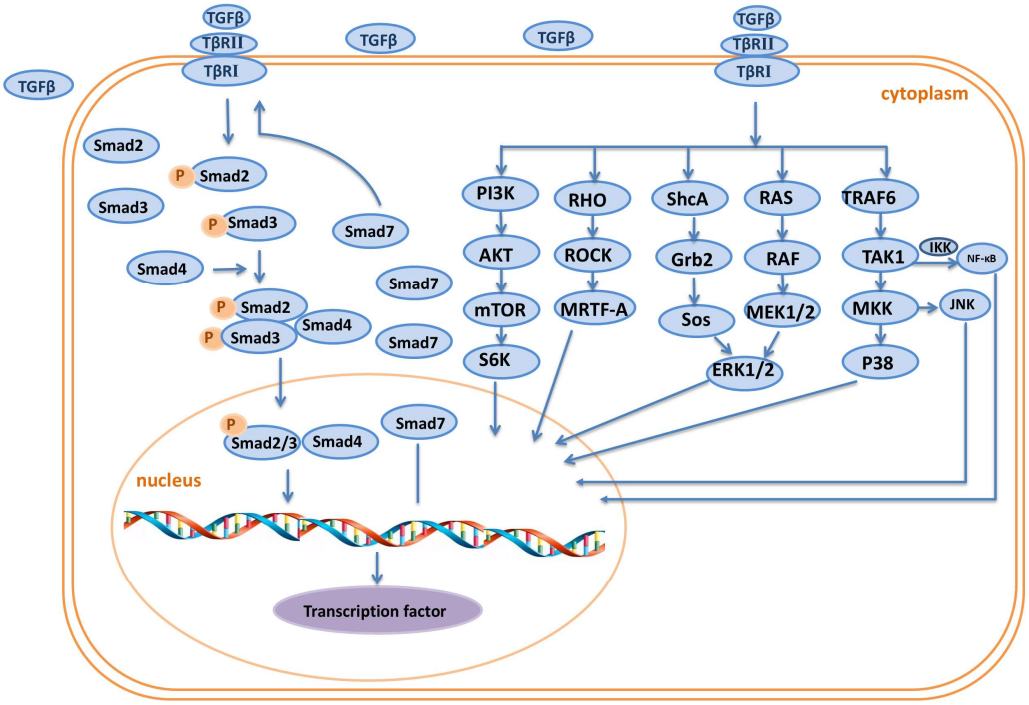

Figure 1. TGF-β-mediated Smad-dependent and Smad-independent signaling pathways. Following TGF-β binding, TβRII recruits and activates TβRI, which phosphorylates Smad2/3. Phosphorylated Smad2/3 complexes with Smad4 and translocates into the nucleus, where it regulates target gene transcription. In parallel, activated TβRI initiates Smad-independent pathways, including but not limited to PI3K/AKT, RHO/ROCK, RAS/ERK, TAK1/MKK/p38, and NF-κB signaling. These pathways converge on nuclear transcription factors to modulate gene expression. Smad7 acts as an inhibitory protein and negatively regulates this signaling cascade.

3.2. Smad-Dependent Signaling

The Smad family includes receptor-regulated Smads (R-Smads: Smad1/2/3/5/8), the common mediator Smad (Co-Smad: Smad4), and inhibitory Smads (I-Smads: Smad6/7) [16]. In the canonical Smad-dependent route, TGF-β first binds to the type II serine/threonine kinase receptor (TβRII) at the cell surface. TβRII then recruits and phosphorylates the type I receptor (TβRI/ALK5). The activated TβRI subsequently phosphorylates Smad2/3, enabling their association with Smad4 to form a complex [16]. This complex translocates to the nucleus and promotes ECM gene expression and fibrous tissue deposition [17]. Concurrently, Smad7 serves as a negative feedback regulator by competitively binding to TβRI, thereby inhibiting Smad2/3 phosphorylation and attenuating signal transduction [17].

3.3. Smad-Independent Signaling

Beyond the canonical pathway, TGF-β also exerts extensive regulatory effects via Smad-independent mechanisms. First, activated TβRI can recruit Shc adaptor protein A (ShcA), which in turn binds growth factor receptor-bound protein 2 (Grb2) and Son of sevenless (Sos) (Sos), initiating the downstream ERK/MAPK cascade (Ras/Raf/MEK/ERK) that modulates the synthesis of ECM proteins [18,19]. Second, TGF-β activates TGF-β-activated kinase 1 (TAK1) through a process that requires both TGF-β signaling and tumor necrosis factor receptor-associated factor 6 (TRAF6)-mediated Lys63-linked polyubiquitination at lysine residue 158 (K158) of TAK1. Once activated, TAK1 regulates downstream effectors IKK, JNK,

and p38, serving as a critical hub linking TGF-β signaling to inflammatory responses and multiple downstream pathways [20]. In addition, TGF-β can directly activate the RhoA/ROCK/MRTF-A axis, inducing cytoskeletal remodeling that promotes epithelial-mesenchymal transition (EMT) and α-smooth muscle actin (α-SMA) expression [21]; it also drives the differentiation of mesenchymal cells into myofibroblasts via the PI3K/AKT/mTOR/S6K pathway [22].

3.4. Oxidative Stress and ER Stress: Bidirectional Crosstalk with TGF-β

There is a bidirectional relationship between TGF-β signaling and cellular redox homeostasis, and this relationship constitutes the molecular basis for the self-perpetuation of fibrotic diseases. Oxidative stress is characterized by elevated intracellular levels of ROS, which are by-products of aerobic metabolism and include the superoxide anion ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), and hydroxyl radicals ($OH^{\bullet}$) [23]. TGF-β actively remodels the redox state of cells. Upon receptor binding, TGF-β induces Smad3-dependent expression of NADPH oxidase-4(NOX4) in organs such as the lung and the kidney [24,25]. Similarly, elevated NOX4 expression has been associated with TGF-β in the liver, although the underlying mechanism remains unknown [26]. NOX4 localizes predominantly to intracellular membranes in mitochondria, the endoplasmic reticulum, focal adhesions, and the nucleus, and generates ROS essential for TGF-β-induced myofibroblast differentiation, ECM production, and contractility in the lung, the kidney, and the liver [23–26]. Meanwhile, TGF-β inhibits nuclear factor (erythroid-derived 2)-like 2 (NRF2), a transcription factor that regulates the expression of antioxidant-response genes, thereby reducing the expression of NRF2 target genes encoding ROS-scavenging enzymes such as superoxide dismutase (SOD) and glutathione (GSH) peroxidase (GPx) [27]. Direct evidence for this TGF-β–NRF2 axis has been obtained in the kidney; its relevance to the liver has been inferred from the following observation: $NRF2^{-/-}$ mice are more susceptible to chemically induced oxidative stress and the resulting fibrotic lesions than wild-type mice [27,28]. Together, these effects drive cells into a state of redox imbalance characterized by increased ROS production and reduced ROS clearance.

Conversely, oxidative stress can amplify TGF-β signaling. ROS activate latent TGF-β in both cell cultures and cell-free systems [15]; this link is supported by *in vitro* evidence. Increased oxidative stress plays an important role in the development of fibrotic diseases in humans. Increased oxidative stress has been implicated in the onset and progression of fibrotic diseases in humans, particularly pulmonary fibrosis, as the lungs are directly exposed to the atmosphere and are a primary target of oxidative damage; increased oxidative stress in lung tissue is associated with increased TGF-β activation in animal models [29].

Endoplasmic reticulum (ER) stress is an emerging and increasingly recognized interface within this network. When TGF-β-driven ECM synthesis demands exceed the ER's folding capacity, misfolded proteins accumulate in the ER lumen, triggering the unfolded protein response (UPR). The UPR is mediated by three major ER-resident stress sensors—protein kinase R-like ER kinase (PERK), inositol-requiring enzyme 1 (IRE1), and activating transcription factor 6 (ATF6). Activated PERK phosphorylates eukaryotic initiation factor 2α (eIF2α) to inhibit the initiation of translation of most cellular proteins, while also localizing to mitochondria-associated membranes (MAMs) at the ER-mitochondrial junction, where it maintains mitochondrial homeostasis by inducing Parkin-mediated autophagy via activating transcriptional factor 4 (ATF4), thereby participating in mitochondrial signaling that promotes cell survival [30]. TGF-β downregulates mitofusin-2 (Mfn2) expression in cardiac fibroblasts, while Mfn2 deficiency promotes fibroblast activation by activating the ER stress-associated PERK/ATF4 pathway and increasing ROS production [31]; whether this pathway is similarly operative in other organs remains to be determined. As a target of the ATF4 and ATF6 UPR pathways, C/EBP homologous protein (CHOP) is a key mediator of ER stress-induced apoptosis and contributes to the onset and progression of fibrosis [32]. TGF-β induces collagen synthesis via the IRE1/XBP1 pathway in the kidney [33], while IRE1α drives epithelial progenitor dysfunction to establish a niche for fibrosis in the lung [34].

4. TGF-β Regulates the Immune Microenvironment

Following organ injury, TGF-β levels rise markedly. It drives the transition toward a pro-fibrotic state by remodeling immune cell phenotypes and functions, while simultaneously modulating key signaling molecules (Figure 2).

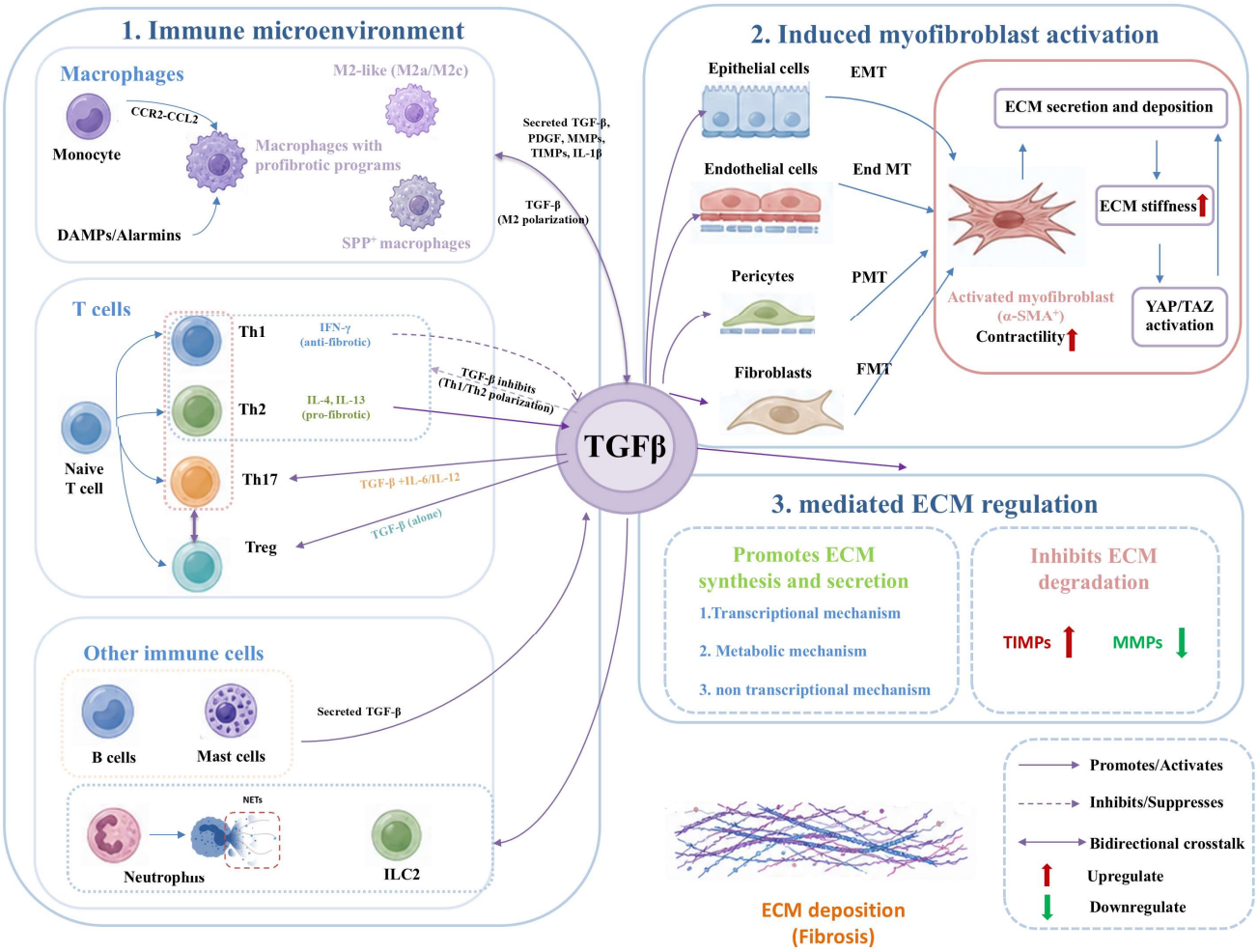

Figure 2. Multicellular interactions and ECM deposition in the fibrotic microenvironment. Schematic overview of how the immune microenvironment and TGF-β contribute to myofibroblast activation and fibrotic remodeling. (1) Immune microenvironment: Macrophages, T-cell subsets, B cells, mast cells, neutrophils, and ILC2s can influence TGF-β signaling and fibrotic responses. (2) Myofibroblast activation: TGF-β promotes the acquisition of myofibroblast-like features by fibroblasts and can drive EMT, EndMT, and PMT. Activated α-SMA$^+$ myofibroblasts secrete and deposit ECM, increasing matrix stiffness. The stiffer matrix activates YAP/TAZ signaling, which further promotes ECM deposition and sustains a self-reinforcing cycle. (3) ECM regulation: TGF-β promotes ECM synthesis and secretion through transcriptional, metabolic, and non-transcriptional mechanisms, while limiting ECM degradation by increasing TIMPs and reducing MMPs. The resulting ECM deposition contributes to fibrosis. Solid arrows indicate promotion or activation, dashed arrows indicate inhibition or suppression, and bidirectional arrows denote reciprocal crosstalk. Abbreviations: DAMPs, damage-associated molecular patterns; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; EndMT, endothelial-to-mesenchymal transition; PMT, pericyte-to-myofibroblast transition; FMT, fibroblast-to-myofibroblast transition; ILC2, group 2 innate lymphoid cell; MMPs, matrix metalloproteinases; NETs, neutrophil extracellular traps; TIMPs, tissue inhibitors of metalloproteinases; TGF-β, transforming growth factor-β.

4.1. Macrophages

Infiltrating monocytes have traditionally been classified as M1 (pro-inflammatory) or M2 (reparative/regulatory); however, macrophage activation in fibrosis is now recognized as highly plastic and

environment-dependent. Injury and persistent inflammation release damage-associated molecular patterns (DAMPs) and alarmins that activate resident macrophages. This activation triggers cytokine/chemokine production and recruits monocytes via C-C motif chemokine receptor 2 (CCR2)–C-C motif ligand 2 (CCL2) to sites of damage, where they differentiate into monocyte-derived macrophages with pro-fibrotic programs [35]. These macrophages directly activate fibroblasts by secreting TGF-β and platelet-derived growth factor (PDGF), and regulate the proliferation, survival, and activation of myofibroblasts to control ECM deposition. At the same time, they produce fibrotic cytokines and chemokines such as matrix metalloproteinases (MMPs), tissue inhibitors of metalloproteinases (TIMPs), and IL-1β, which modulate the recruitment of inflammatory cells and ECM turnover, thereby playing a key role in fibrosis [36]. Scar-associated macrophages (also known as $SPP1^+$ macrophages) are a type of human pre-fibrotic cell. During fibrotic pathology, $SPP1^+MAM^-$ macrophages show an increased propensity to polarise toward the MAM^+ state, a matrix-degrading, osteoclast-like phenotype [37].

In addition to pre-fibrotic macrophages, M2-like macrophages arising in response to distinct cues can promote the progression of fibrosis. TGF-β induces M2 polarization, and M2 macrophages produce high levels of TGF-β [38,39]. M2 macrophages can be further subdivided into M2a, M2b, M2c, and M2d. M2a-like ($CD206^+/CD68^+$) and M2c-like ($CD163^+/CD68^+$) macrophages are associated with fibrosis, suggesting that these subsets play a promoting role in the fibrotic process [40].

4.2. T Cells

T cells are also deeply involved in remodeling the immune microenvironment during fibrosis. The major polarized T-cell subsets—Th1, Th2, Th17, and regulatory T cells (Tregs)—exhibit distinct functional profiles, and their relative proportions and activation states collectively determine the inflammatory nature and intensity of the local immune milieu.

Th1 and Th2 cells play roles in clearing pathogen and parasite infections and participate in fibrotic regulation [41]. IFN-γ secreted by Th1 cells inhibits collagen synthesis and suppresses TGF-β mRNA expression in fibroblasts, thereby exerting anti-fibrotic activity [42]. The roles of Th2 cells are more context-dependent. During the early or resolving stages of injury, Th2-associated cytokines contribute to tissue repair and limit excessive inflammation; however, sustained or abnormally elevated levels of IL-4 and IL-13 promote fibrosis, indicating that the net effect of Th2 responses shifts with disease stage. In several organs, including the lung, liver, and skin, IL-13 and IL-4 share many functional similarities, as both cytokines utilize the IL-4Rα/STAT6 signaling pathway [43,44]. Of the two, IL-13 is the primary pro-fibrotic mediator; it promotes collagen synthesis by fibroblasts and further activates TGF-β by upregulating MMPs, thereby promoting fibrosis. TGF-β inhibits the polarization of both Th1 and Th2 cells by suppressing the phosphorylation of the Tec family kinase Itk, which in turn blocks calcium influx and reduces nuclear factor of activated T cells (NFATc) nuclear translocation and ERK/MAPK activation [45].

Th17 cells are pro-inflammatory, whereas Tregs exert immunosuppressive functions. The differentiation balance between Th17 and Tregs is precisely regulated by the cytokine environment, with TGF-β serving as a common foundational factor essential for both differentiation pathways. In the presence of TGF-β alone, T cells tend to differentiate into Tregs, as TGF-β suppresses IL-23 receptor (IL-23R) and activates forkhead box protein p3 (Foxp3), which directly binds to retinoic acid-related orphan receptor gamma t (RORγt) to inhibit its function; however, when IL-6 or IL-21 coexists with TGF-β, they can activate RORγt, upregulate IL-23R, and promote Th17 polarization, thereby suppressing Treg generation [46,47]. The JAK/STAT, PI3K/AKT/mTOR, and TGF-β/Smad signaling pathways involved in fibrosis can also cause Th17/Tregs imbalance [46].

Tregs play a dual role in the fibrotic process, and their function remains controversial and depends on the stage of the disease. On the one hand, Tregs influence the progression of fibrosis by regulating the balance between Th1, Th2, and Th17 responses: Tregs can suppress Th1 production of IFN-γ, thereby

promoting fibrosis; conversely, the downregulation and depletion of Tregs can shift the response from Th2-dominant to Th1-dominant, thereby alleviating fibrosis; Furthermore, Tregs can also promote the generation of Th17 cells via TGF-β and IL-1β; On the other hand, the effects of Tregs are dual-sided: while they can inhibit TGF-β-induced fibrosis by releasing IL-10, under non-inflammatory conditions, the TGF-β they secrete promotes collagen deposition and induces the secretion of the pro-fibrotic molecule PDGF [48].

4.3. Other Immune Cells

Beyond macrophages and T cells, TGF-β also regulates the involvement of neutrophils, type 2 innate lymphoid cells (ILC2), B cells, and mast cells in fibrogenesis. While B cells and mast cells recruited by inflammatory cytokines promote fibrosis primarily through TGF-β secretion, neutrophils and ILC2s are regulated more directly by TGF-β signaling.

Macrophages in the immune microenvironment secrete TGF-β, which stimulates neutrophils to form neutrophil extracellular traps (NETs). Components carried by NETs, such as DNA, activate Toll-like receptors 9 (TLR-9) through the NF-κB pathway, promoting IL-6 expression. IL-6, in turn, drives fibroblast to myofibroblast differentiation and enhances ECM secretion via autocrine or paracrine mechanisms [49].

TGF-β regulation of ILC2 exhibits tissue-specific patterns. In skin fibrosis, ILC2 numbers increase significantly and correlate positively with disease severity; TGF-β promotes proliferation of native ILC2 ($KLRG1^-$ ILC2) while suppressing secretion of the anti-fibrotic cytokine IL-10, thereby directly driving collagen deposition [50]. In pulmonary fibrosis, TGF-β binds to neuropilin-1 (Nrp1) on the ILC2 surface and upregulates suppression of tumorigenicity 2 (ST2) expression, enhancing ILC2 activation. This prompts ILC2s to secrete IL-13, which exacerbates fibrotic injury [51].

B cells secrete cytokines such as TGF-β, TNF-α, IL-β1, and IL-6, which promote fibrosis progression [52]. Mast cells abundance also correlates with the severity of fibrosis. As ECM deposition increases mechanical stress in fibrotic tissues, mast cells undergo degranulation and release tryptase, chymase, and TGF-β [53]. Among these, TGF-β further activates myofibroblasts, driving fibrosis progression.

5. TGF-β-Induced Myofibroblast Activation

Myofibroblasts serve as key effector cells in tissue fibrosis and wound healing, and their activation and transformation are highly dependent on TGF-β signaling. Activated myofibroblasts exhibit increased α-smooth muscle actin (α-SMA) expression, enhanced contractile capacity, and robust ECM production and secretion. TGF-β facilitates the acquisition of a myofibroblast-like phenotype from various cellular origins, including epithelial cells, endothelial cells, pericytes, and fibroblasts. However, the contributions of processes such as epithelial-mesenchymal transition (EMT), endothelial-to-mesenchymal transition (EndMT), pericyte-to-myofibroblast transition (PMT), and fibroblast-to-myofibroblast transition (FMT) vary depending on the organ, injury model, and experimental approach. Definitive evidence of cell fate conversion *in vivo* requires lineage tracing. These transitions should therefore be considered context-dependent mechanisms rather than established universal sources of myofibroblasts.

5.1. EMT

In cultured epithelial cells derived from the lung and kidney, TGF-β induces EMT, which is characterized by downregulation of epithelial markers such as E-cadherin and ZO-1, and upregulation of mesenchymal markers including N-cadherin, vimentin, and α-SMA [54,55]. However, these *in vitro* findings alone do not establish that epithelial cells differentiate into ECM-producing myofibroblasts *in vivo*. While studies have identified fibroblasts of epithelial origin in renal fibrosis, conflicting evidence from lineage-tracing studies challenges this conclusion [56,57]. This transition of epithelial cells toward a mesenchymal phenotype involves the synergistic participation of both Smad-dependent and Smad-

independent pathways. Within this process, Smad3 exhibits a context-dependent dual regulatory role. Under physiological conditions, Smad3 inhibits the transcriptional activity of myocardin-related transcription factor (MRTF), thereby limiting α-SMA expression and suppressing excessive fibroblast proliferation. However, during TGF-β-driven EMT, phosphorylated Smad3 levels increase while unphosphorylated Smad3 levels decrease correspondingly, relieving MRTF inhibition and promoting α-SMA expression and myofibroblast formation [58]. In parallel, TGF-β also promotes EMT through Smad-independent mechanisms, such as RhoA/ROCK/MRTF-A and NF-κB signaling pathways [21,59].

5.2. EndMT

Endothelial cells can contribute to TGF-β-driven myofibroblast generation through EndMT, although the extent of this contribution varies across organs and experimental models. TGF-β promotes EndMT by downregulating junctional proteins and CD31 while upregulating the expression of mesenchymal markers such as α-SMA and fibronectin, thereby expanding the myofibroblast pool during fibrosis [60]. In a mouse model of chronic kidney disease, Zeisberg et al. found that approximately 30–50% of myofibroblasts co-expressed the endothelial marker CD31 [61]. This finding, however, reflects marker co-expression and should not be interpreted as proof of lineage conversion. Lineage-tracing studies conducted by LeBleu et al. addressed this question directly, demonstrating that only 10% of the myofibroblasts originated from endothelial cells [62].

Unlike EMT, TGF-β-driven EndMT primarily relies on Smad-dependent pathways. For instance, elevated levels of TGF-β1, phosphorylated Smad2/3, and Smad7 were observed in fibrotic pulmonary arteries, highlighting their role in driving EndMT [63]. At the molecular level, Smad2/3 induces Midkine expression in the kidney, which subsequently upregulates C/EBPβ protein and enhances its binding affinity to the promoters of EndMT-related genes such as ACTA2 [64]. Simultaneously, Smad2/3 can induce miR-181b expression, which activates the LIMK/p-cofilin signaling axis by inhibiting Sema3A expression, contributing to EndMT in the heart [65].

5.3. PMT and FMT

Pericytes are a population of multifunctional stromal cells primarily distributed along the walls of microvessels. Although historically understudied, these cells have recently garnered significant attention due to their critical role in fibrosis across multiple organs. Upon TGF-β stimulation, pericytes can differentiate into myofibroblasts, thereby promoting organ fibrosis. However, the fibrosis process differs among organs. In retinal fibrosis, TGF-β synergistically induces the transformation of choroidal pericyte-to-myofibroblast through the dual Smad2/3 and AKT/mTOR signaling pathways [66]. In renal fibrosis, TGF-β induces perirenal cells to express type I collagen and reorganize α-SMA into contractile fibers via Smad2/3 and TLR-4 signaling, establishing perirenal cells as a primary source of fibroblasts [67].

Fibroblasts are mesenchymal cells widely distributed in the stroma of various tissues and organs; under normal physiological conditions, they remain in a quiescent state. During fibrosis, TGF-β activates fibroblasts, promoting their proliferation and inducing their transformation into activated myofibroblasts. Concurrently, TGF-β drives FMT and ECM deposition by facilitating metabolic reprogramming (e.g., enhanced glycolysis and mitochondrial damage) and oxidative stress (e.g., elevated ROS levels) [68].

6. TGF-β Promotes Excessive ECM Deposition

Excessive ECM deposition is a central pathological feature of organ fibrosis, primarily manifested as the abnormal accumulation of collagen, fibronectin (FN), and proteoglycans. As a master pro-fibrotic cytokine, TGF-β drives this process through a dual mechanism of promoting ECM synthesis and secretion while simultaneously inhibiting ECM degradation (Figure 2).

6.1. TGF-β Promotes ECM Synthesis and Secretion

TGF-β promotes ECM component synthesis through multiple convergent pathways. At the transcriptional level, TGF-β activates the collagen I promoter via Smad3 to upregulate collagen expression [69]. Beyond transcriptional regulation, TGF-β also modulates metabolic supply. Glycine is the most abundant amino acid in collagen. O'Leary et al. demonstrated that TGF-β activates the PI3K/AKT/mTORC1 signaling axis to promote the accumulation of activating transcription factor 4 (ATF4), which in turn upregulates rate-limiting enzymes of the serine-glycine synthesis pathway [70]. This enhances glycine biosynthesis, providing the necessary precursor for collagen production and ultimately driving excessive collagen deposition. In addition to these canonical mechanisms, TGF-β employs several non-transcriptional routes to augment ECM production. TGF-β upregulates fibronectin via RhoA/Rho kinase in a manner requiring caveolae and caveolin-1 interaction with RhoA [71]. It can also induce tyrosine phosphorylation via receptor serine/threonine kinases, activating the PI3K/AKT signaling pathway to stimulate fibronectin expression [72]. Moreover, TGF-β can directly bind to the intracellular domains of the fibronectin receptor α5β1 via TβRII, triggering membrane trafficking and recycling of fibronectin independent of transcriptional pathways [73]. Collectively, these transcriptional, metabolic, and non-transcriptional mechanisms act synergistically to drive pathological ECM accumulation, underscoring the multifaceted nature of TGF-β's pro-fibrotic actions.

6.2. TGF-β Inhibits ECM Degradation

Under normal physiological conditions, a dynamic equilibrium exists between tissue inhibitor of metalloproteinases (TIMPs) and matrix metalloproteinases (MMPs), which precisely regulates the physiological degradation and remodeling of the ECM. During fibrosis, TGF-β disrupts this balance through a dual strategy—upregulating TIMPs while downregulating MMPs—thereby promoting excessive ECM deposition and driving organ pathology.

The vertebrate TIMP family consists of TIMP-1, TIMP-2, TIMP-3, and TIMP-4. Unlike the other family members, TIMP-3 is retained in the ECM and can inhibit all MMPs [74]. In fibroblasts, TGF-β induces TIMP-3 expression through Smad3 and Smad4; P38 MAPK and ERK1/2 also contribute by cooperating with Smad3 [74]. This increase in TIMP-3 restrains the activity of the MMPs that it can inhibit, although it does not mean that TGF-β reduces the expression or activity of every MMP. TGF-β's effects on MMPs depend on the cell type and pathological context. TGF-β can mediate the transcriptional repression of specific MMPs, including MMP-1 and MMP-3, with TGF-β inhibitory elements (TIEs) identified in their promoters [75]. Additionally, an NF-κB binding site is required for the suppressive activity of TGF-β in the regulation of MMP-9 transcription [75]. Thus, these findings apply to the MMPs and experimental settings examined, rather than to the MMP family generally.

7. TGF-β Forms a Regulatory Network with Other Fibrogenic Molecules

As a master regulator of fibrosis, TGF-β does not operate in isolation but coordinates with other pro-fibrotic mediators, including platelet-derived growth factor (PDGF), connective tissue growth factor (CTGF), and angiotensin II (Ang II), within a complex, interconnected regulatory network.

7.1. Platelet-Derived Growth Factor

Platelet-Derived Growth Factor (PDGF) is secreted by multiple cell types, including platelets, endothelial cells, epithelial cells, and immune cells. It serves as a potent chemoattractant for fibroblasts and exerts synergistic pro-fibrotic effects with TGF-β. The PDGF family comprises five dimeric subtypes (PDGF-AA, PDGF-BB, PDGF-AB, PDGF-CC, PDGF-DD) and two receptors (PDGFR-α, PDGFR-β) [76]. Among these, the PDGF-BB/PDGFR-β ligand–receptor pair is most closely associated with fibrotic lesions,

whereas the other pairs primarily play supportive roles. Upon binding to PDGFR-β, PDGF-BB significantly downregulates the circular RNA HIPK3; this downregulation promotes fibroblast-to-myofibroblast differentiation and relieves the inhibition of downstream TGF-β signaling pathways, including ERK, PI3K/AKT, and p38 MAPK, thereby enhancing collagen synthesis and establishing a positive feedback loop [77,78].

7.2. Connective Tissue Growth Factor

Connective Tissue Growth Factor (CTGF, CCN2) is one of the most important pro-fibrotic mediators downstream of TGF-β. On the one hand, CTGF acts as a major effector molecule of TGF-β-mediated fibrosis, sustaining fibrotic progression through positive feedback mechanisms. For example, TGF-β directly activates CTGF gene transcription via the ALK5-Smad2/3 pathway, thereby inducing its expression [79]. On the other hand, even in the absence of TGF-β or under conditions of low TGF-β levels, CTGF can still exert pro-fibrotic effects independently. Using a mouse model with TGF-β receptor knockout, Keiko Sakai et al. demonstrated that CTGF can mediate a portion of the fibrotic process in a non-TGF-β-dependent manner [80]. In addition to direct TGF-β stimulation, other factors, including vascular endothelial growth factor, acetaldehyde, PDGF-BB, and lipid peroxidation products (HNE, MDA), can increase CTGF mRNA transcription, further promoting its expression [81]. These non-TGF-β sources of CTGF underscore its capacity to exert pro-fibrotic effects independently of TGF-β signaling.

7.3. Angiotensin II

Angiotensin II (Ang II) is the primary effector peptide of the renin-angiotensin system and acts synergistically with TGF-β to promote fibrosis. Ang II can increase TGF-β expression in cells, leading to CTGF and collagen expression [82]. In addition to directly activating the Smad pathway, Ang II amplifies fibrotic signaling through collateral mechanisms. Upon binding to angiotensin II receptor type 1 (AT1R), Ang II activates the RhoGEF/RhoA/ROCK cascade, which promotes the expression or activation of NF-κB, PAI-1, MAPK/ERK 1/2, and NADPH oxidase, thereby increasing oxidative stress. This activation of the MAPK/ERK pathway ultimately contributes to organ remodeling and tissue fibrosis [83].

8. Cross-Organ Framework: Shared and Organ-Specific Mechanisms

Fibrosis across different organs converges on a conserved TGF-β-driven core program, while also exhibiting organ-specific features (Table 1).

8.1. Shared Mechanisms

Despite differences in initiating insults, cellular sources of TGF-β, and myofibroblast precursors among organs, the downstream program is highly conserved. Latent TGF-β is released as active TGF-β through integrins [13], proteases [14], and ROS [15]. It then initiates transcriptional programs via Smad-dependent and Smad-independent pathways, driving the differentiation of multiple cell types into α-SMA^{+} myofibroblasts and promoting ECM deposition [16,17,21,22]. This shared core program constitutes the common therapeutic axis across organs, whereas the initiating injury, the dominant cellular source of TGF-β, and the principal myofibroblast precursor are organ-specific.

8.2. Organ-Specific Mechanisms

8.2.1. Lungs

Pulmonary fibrosis is a group of chronic, progressive interstitial lung diseases triggered by intrinsic factors (e.g., genetic predisposition and aging) and extrinsic factors (e.g., air pollution, smoking,

occupational/environmental exposures, and microbial infections) [84]. Repeated damage to epithelial cells, particularly AT2 cells, is the central event that triggers fibrosis [85]. These damaged epithelial cells recruit immune cells and secrete pro-fibrotic factors such as TGF-β, CTGF, CCL2, and C-X-C motif chemokine ligand 10 (CXCL10), which then promote fibroblast activation and ECM deposition, ultimately leading to fibrosis [86–88]. The integrin αvβ6, expressed on the surface of epithelial cells, disrupts the LAP structure of latent TGF-β and releases active TGF-β [89]. CCL2 and CXCL10 can attract immune cells to the injured area, further amplifying the inflammatory response [88]. Beyond these inflammatory and pro-fibrotic mediators, the role of EMT in pulmonary fibrosis has been extensively discussed. EMT has been proposed to drive the transformation of epithelial cells into ECM-secreting myofibroblasts; however, lineage-tracing studies present contradictory results, with some reporting evidence supporting this transition and others finding negligible contributions [90]. Consequently, the origin of myofibroblasts from alveolar epithelial cells remains controversial, and changes in epithelial markers should not be equated with a confirmed cellular fate transition *in vivo*.

Macrophages activate fibroblasts upon first contact by initiating TGF-β1 signaling or mechanical stimulation (or both), the two pivotal mechanisms of myofibroblast activation [91]. Fibroblasts and myofibroblasts, as the primary effector cells in pulmonary fibrosis, demonstrate a pathologic phenotype characterized by uncontrolled proliferation and survival. These cells accumulate in the lung interstitium, where they deposit excessive amounts of collagen-I-rich ECM and ultimately organize into fibroblastic foci [92]. In human fibrotic lung tissue, YAP and TAZ expression is increased compared with healthy lung tissue, while *in vitro* pathological matrix stiffness promotes their nuclear accumulation and combined knockdown attenuates fibroblast matrix synthesis, contraction, and proliferation specifically on stiff matrices; *in vivo*, adoptive transfer of fibroblasts expressing active YAP or TAZ promotes lung fibrosis [93].

8.2.2. Liver

Liver fibrosis is a common pathological precursor to cirrhosis and can develop from chronic liver diseases such as viral hepatitis, alcoholic hepatitis, nonalcoholic steatohepatitis, and autoimmune hepatitis [94]. TGF-β levels are low in the healthy liver. When the liver is damaged, Kupffer cells (resident macrophages in the liver) release significant amounts of TGF-β to promote collagen synthesis [95]. During the early stages of fibrosis, liver sinusoidal endothelial cells upregulate inflammatory factors (IL-1 and IL-6) [96]. These pathological changes activate hepatic stellate cells (HSCs), further deteriorating the liver microenvironment and driving the progression of liver fibrosis. HSCs are liver-specific pericellular cells located around the hepatic sinusoids; they exhibit four known phenotypes—quiescent, activated, inactivated, and senescent—each of which has distinct functional implications in liver fibrosis; upon injury, they undergo myofibroblastic transformation and become the primary source of myofibroblasts, thereby promoting fibrosis [97]. The activation of HSCs not only leads to increased ECM deposition, triggering portal hypertension and hypoxia, but also enhances the transcriptional activity of hypoxia-inducible factors (HIFs) through autocrine/paracrine signaling. This establishes a positive feedback loop linking hypoxia to HIFs and HSC activation, thereby continuously driving the progression of liver fibrosis [98].

8.2.3. Kidney

Renal fibrosis is a hallmark pathological change of chronic kidney disease (CKD), primarily characterized by tubular atrophy/interstitial fibrosis, glomerulosclerosis, chronic inflammatory infiltration, and vascular rarefaction; its underlying causes include diabetes and hypertension [99,100]. In renal fibrosis, epithelial cells rarely transform into myofibroblasts [57]. Under the influence of pathogenic factors, proximal tubular epithelial cells undergo damage and secrete pro-fibrotic factors such as TGF-β and PDGF; TGF-β can drive the transformation of specific subsets of pericytes into myofibroblasts [101]. Damaged

tubular cells also secrete Sonic Hedgehog (SHH), which upregulates leukemia inhibitory factor (LIF) expression in fibroblasts; as LIF receptors are expressed on renal tubular cells, this "SHH–LIF axis" forms a positive feedback loop [102].

8.2.4. Heart

Cardiac fibrosis includes reparative fibrosis and pathological fibrosis (interstitial and perivascular fibrosis). Pathological fibrosis is characterized by excessive activation of fibroblasts and ECM deposition following myocardial injury, which can lead to ventricular stiffness, diastolic dysfunction, and heart failure. Pathological fibrosis results from the combined effects of various factors, including cardiac pressure and volume overload, metabolic dysfunction, and aging [103]. Early platelet infiltration releases large amounts of TGF-β; TGF-β derived from platelets and macrophages can induce fibroblasts to differentiate into myofibroblasts; myofibroblasts establish an autocrine TGF-β feedback loop that continuously sustains pro-fibrotic signaling [104].

Table 1. Cross-organ comparison of TGF-β-driven fibrotic mechanisms.

Comparison Dimension	Lungs	Liver	Kidneys	Heart
Initiating injury	Genetic predisposition, aging, air pollution, smoking, occupational exposures, environmental exposures, microbial infections [6,84]	Viral hepatitis (HBV/HCV), alcoholic hepatitis, nonalcoholic steatohepatitis, autoimmune hepatitis [7,94]	Diabetes, hypertension [9,100]	Diabetes, cardiac pressure overload, cardiac volume overload, metabolic dysfunction, aging [8,103]
Signal-producing cells	Macrophages, epithelial cells (particularly AT2 cells) [85,91]	Kupffer cell, liver sinusoidal endothelial cells [95,96]	Proximal tubular epithelial cell [101]	Platelet, macrophages, fibroblasts, myofibroblasts [8,104]
Responding cells	Fibroblasts, myofibroblasts [92]	Hepatic stellate cell [97]	Pericytes [101]	Fibroblasts, myofibroblasts [8,104]
Intermediate mediators	TGF-β, CTGF, CCL2, CXCL10 [86–88]	TGF-β, IL-1, and IL-6 [95,96]	TGF-β, PDGF [101]	TGF-β [8,104]
Feedback loops	pathological matrix–YAP/TAZ–ECM deposition [93]	Activation of HSCs–ECM deposition–portal hypertension and hypoxia–HIFs–Activation of HSCs [98]	renal tubular cells–SHH–fibroblasts–LIF–renal tubular cells [102]	Fibroblasts–myofibroblasts–TGF-β–myofibroblasts–ECM deposition [104]
Evidence source	*in vitro*/cell experiments [86,91,93], animal models [93], human tissue [87,93]	*in vitro*/cell experiments [7,95,96] human tissue [7]	*in vitro*/cell experiments [101], animal models [9,57,101,102]	*in vitro*/cell experiments [8], animal models [8]

Note: "*In vitro*/cell experiments" refer to results obtained from studies conducted under controlled laboratory conditions using isolated cells. "Animal models" refer to findings derived from experiments performed on animals to simulate human biological conditions. "Human tissue" denotes evidence obtained from studies conducted on human samples. Evidence from human tissue can only demonstrate a correlation between specific cell populations or signaling pathways; it does not necessarily prove a causal relationship.

9. Approved Drugs

The shared and organ-specific mechanisms described above have begun to be translated into clinically approved anti-fibrotic therapies. Two anti-fibrotic medications, pirfenidone and nintedanib, have been demonstrated to slow the progression of IPF, and both are FDA-approved treatments for this disease [84,85]. Pirfenidone is a multi-target, broad-spectrum anti-fibrotic drug that achieves therapeutic effects by inhibiting inflammation, reducing oxidative damage, and blocking fibrotic pathways, thereby slowing the

progression of pulmonary fibrosis [105]. Nintedanib is a highly selective anti-fibrotic drug approved for the treatment of IPF, and targets vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and fibroblast growth factor receptor (FGFR) to curtail disease progression [106]. Recently, nerandomilast, a selective phosphodiesterase-4B (PDE4B) inhibitor, was approved as an add-on therapy for IPF, supported by findings from a Phase III clinical trial demonstrating its ability to significantly mitigate disease progression in patients with IPF [107].

While these approved drugs have demonstrated therapeutic efficacy, the molecular pathways underlying this efficacy remain unclear. Evidence from *in vitro* and animal model studies has suggested potential links between their effects and TGF-β-related signaling pathways: pirfenidone alleviates pulmonary fibrosis by regulating the downstream MKK3/p38 MAPK and Smad2/3 signaling pathways associated with TGF-β, as well as the Wnt/GSK-3β/β-catenin signaling pathway [108,109]; nintedanib inhibits TGF-β-induced collagen and MMPs in fibroblasts [106]; nerandomilast raises intracellular cAMP and thereby attenuates TGF-β–driven pro-fibrotic signaling, including Smad-dependent and PI3K/Akt-dependent pathways [110,111].

10. Outlook

As a key regulator of fibrosis, TGF-β drives remodeling of the immune microenvironment, induces myofibroblast activation, promotes ECM synthesis while suppressing its degradation, and synergizes with pro-fibrotic mediators such as PDGF, CTGF, and Ang II to perpetuate irreversible tissue remodeling, culminating in organ fibrosis. Under normal physiological conditions, TGF-β performs essential functions, including the regulation of immune homeostasis and tissue repair. Therefore, future TGF-β-targeted therapies for fibrosis must achieve breakthroughs in precision, specificity, and safety. The primary directions include the following four aspects (Figure 3).

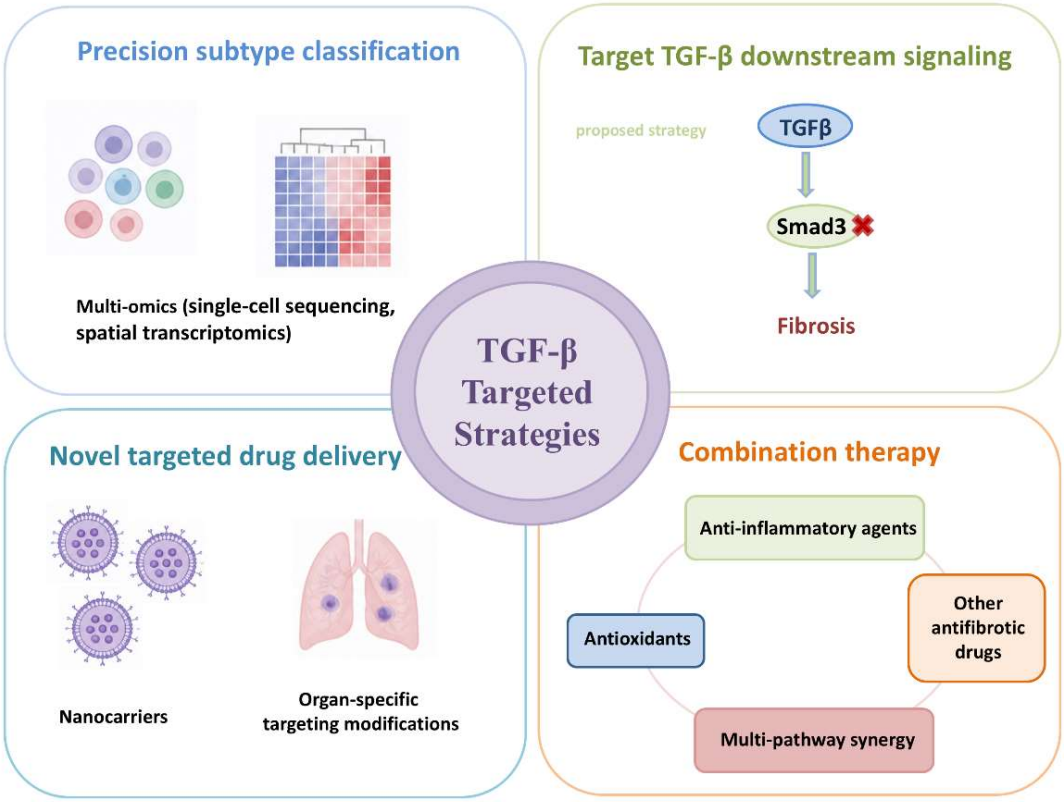

Figure 3. Schematic illustration of TGF-β-targeted strategies.

This figure outlines four potential therapeutic approaches targeting the TGF-β signaling pathway: (1) Precision subtype classification using multi-omics (single-cell sequencing, spatial transcriptomics). (2) Targeted modulation of downstream signaling: a proposed strategy to selectively inhibit Smad3-mediated fibrosis. (3) Novel targeted drug delivery via nanocarriers for organ-specific targeting. (4) Combination therapy integrating antioxidants, anti-inflammatory agents, and other anti-fibrotic drugs for multi-pathway synergy.

(1) Precise subclassification of fibrosis subtypes based on multi-omics technologies. TGF-β-mediated regulation of the immune microenvironment exhibits stage- and cell-type specificity; the dominant immune cell subsets and signaling pathways vary across different fibrotic stages and organs. Leveraging advanced technologies such as single-cell sequencing and spatial transcriptomics, we can precisely characterize patient-specific fibrosis subtypes and elucidate the dynamic transcriptional states and functional evolution of distinct cell subsets (e.g., T-cell and macrophage subsets) during fibrogenesis. This approach will facilitate the differentiation of pathological features across organs and stages, thereby providing a foundation for personalized, precision treatment regimens.

(2) Target specific downstream signaling molecules of TGF-β. The pro-fibrotic effects of TGF-β are primarily mediated through the canonical Smad2/3-Smad4 pathway, while Smad7 exerts negative feedback inhibition; moreover, Smad3 and Smad2 exhibit functional divergence. Compared with broad-spectrum TGF-β blockade, some studies have suggested that selectively inhibiting core pro-fibrotic mediators, such as Smad3, can more precisely block ECM deposition and myofibroblast activation, while potentially preserving the physiological functions of TGF-β mediated through Smad2 or non-Smad pathways, such as immune homeostasis and tissue repair. Furthermore, TAK1, as a key hub linking TGF-β, inflammation, and multiple downstream pathways, represents a potential target for selective intervention. If this strategy is validated clinically, it may mitigate (rather than completely eliminate) the side effects associated with systemic TGF-β inhibition. However, this remains merely a proposed strategy rather than an established clinical outcome.

(3) Develop novel targeted drug delivery systems. The systemic distribution of TGF-β and its physiological roles in diverse tissues render molecular targeting alone insufficient to ensure site-specific delivery. To circumvent the issues of low drug utilization and off-target systemic exposure associated with conventional administration, advanced strategies—such as nanocarriers and organ-specific targeting modifications—can be employed. These approaches enable precise delivery of therapeutic agents to affected organs, achieving high local concentrations while minimizing systemic exposure and associated adverse effects.

(4) Develop combination therapy strategies. Fibrosis is sustained not by a single factor but by a complex regulatory network involving synergistic interactions among TGF-β, inflammatory cytokines, growth factors (PDGF, CTGF), and vasoactive peptides (Ang II). Monotherapy targeting TGF-β alone is therefore unlikely to adequately block the compensatory activation of this network. Although combination therapy is increasingly viewed as a promising future direction, its clinical advantages over monotherapy have yet to be demonstrated. Preclinical studies suggest that the appropriate combination of TGF-β inhibitors with anti-inflammatory agents, antioxidants, and other anti-fibrotic drugs targeting different pathways may achieve synergistic, multi-pathway inhibition of the fibrotic cascade. Such combination therapy holds promise for improving overall treatment outcomes and reducing the risk of compensatory responses associated with single-target interventions. However, these hypotheses require validation through prospective clinical studies.

In summary, by systematically advancing and integrating precise subtype classification, targeted modulation of downstream signaling molecules, novel drug delivery systems, and combination therapy strategies, TGF-β-targeted therapy holds promise for overcoming current clinical bottlenecks and may drive a shift in treatment paradigms from “broad-spectrum suppression” to “precision intervention”. Whether

these strategies can yield clinical benefits for patients with fibrotic diseases remains to be determined through rigorous clinical validation.

Statement of the Use of Generative AI and AI-Assisted Technologies in the Writing Process

During the preparation of this manuscript, the authors used DeepSeek in order to polish the language and improve the readability of the text. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Author Contributions

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