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REVIEW

The Function of the TGFβ Signaling Pathway in Connective Tissue Diseases: From Biology to Clinical Application

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Abstract: Connective tissue diseases (CTDs) are characterized by a diverse array of symptoms, including persistent inflammation, immune system dysfunction, and fibrosis. The transforming growth factor-β (TGFβ) signaling pathway is crucial in fibrosis, dysregulated immune responses, and vascular injury associated with CTDs. TGFβ signaling facilitates the pathological progression of CTDs by modulating fibroblast activation, extracellular matrix accumulation, and immune cell activity. Based on a systematic search of PubMed and Web of Science, this narrative review reveals the dual role of TGFβ signaling in CTD pathogenesis and its therapeutic challenges. This review examines the mechanistic role of the TGFβ signaling pathway in various CTDs, such as systemic sclerosis (SSc), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and Sjögren's syndrome (SS). The review further examines the interplay between classical and non-classical pathways of the TGFβ signaling system and its implications in fibrosis and immunomodulation. The clinical applications of TGFβ as a potential therapeutic target are also discussed, with a special focus on treatment of ameliorating CTDs-associated fibrosis and immune abnormalities. These findings underscore the pivotal role of TGFβ signaling in fibrosis and immune regulation, highlighting opportunities for more precise and individualized therapeutic strategies.

Keywords: TGF-β signaling pathway, connective tissue disorders, fibrosis, immunomodulation, therapeutic targets

Introduction

Connective tissue diseases (CTDs) are a group of systemic disorders defined by immune-mediated chronic inflammation.[1,2] Common CTDs include conditions such as systemic sclerosis (SSc), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and Sjögren's syndrome (SS).[3,4] Common characteristics of CTDs include aberrant immune system activation, systemic inflammation, and varied levels of fibrosis, which frequently result in structural and functional impairment of several organs.[5,6] While the precise pathophysiology of CTDs remains inadequately elucidated, accumulating data indicates that transforming growth factor-β (TGFβ) is pivotal in their pathogenic mechanisms, particularly in fibrosis and immunological dysregulation.[7,8]

TGFβ is a multifunctional cytokine essential for regulating cell proliferation, differentiation, migration, and immune responses, with a particularly notable role in tissue repair and immunosuppression.[9,10] TGFβ exhibits a dual, context-dependent role in pathophysiology: it is essential for maintaining tissue homeostasis and immune tolerance under physiological conditions, yet its dysregulation drives pathological fibrosis, chronic inflammation, and immune evasion.[11] This duality presents a significant therapeutic challenge, as selectively targeting its pathogenic signaling without impairing homeostatic functions remains difficult.[12] In CTDs, the overactivation or dysregulation of TGFβ is frequently linked to the onset of fibrosis.[12–14] In conditions such as SSc, SS, and RA, abnormal activation of the TGFβ signaling pathway can result in excessive fibroblast activation, resulting in collagen deposition and tissue sclerosis that

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leads to organ failure.[15,16] TGFβ is a crucial regulator of fibrosis formation and a significant contributor to immunological tolerance and immune evasion, hence worsening the clinical symptoms and progression of CTDs.[8,17]

Due to the significant role of TGFβ in CTDs, interventions targeting this signaling pathway have emerged as a focal point of therapeutic research in recent years. TGFβ inhibitors can effectively impede fibrosis progression, mitigate abnormal immune responses, and enhance organ function.[18,19] Strategies such as small molecule TGFβ inhibitors, anti-TGFβ antibodies, and gene therapies have shown potential therapeutic promise in preclinical and clinical studies and offer new targeted intervention options for clinical treatment.[20] Nonetheless, the clinical application of TGFβ inhibitors encounters numerous challenges, including concerns over therapeutic specificity, sustained efficacy, and management of adverse effects. Here, we review the mechanism of action, status of clinical application, and future research directions of TGFβ inhibitors in CTDs. Specifically, we evaluate the pathogenic role of TGFβ in various CTDs, analyze the research progress and clinical outcomes of current TGFβ-targeted therapies, and explore potential avenues for therapeutic development. This review aims to provide a theoretical foundation for the optimizing and advancing TGFβ-related treatments in clinical practice while guiding the development of novel pharmaceuticals and personalized therapies.

To provide a thorough overview, we conducted a comprehensive literature search of PubMed and Web of Science using keywords including "TGFβ", "fibrosis", and "connective tissue disorders", with an emphasis on studies that elucidate the underlying pathogenic mechanisms and inform therapeutic approaches.

The Molecular Mechanisms by Which TGFβ Regulates Fibrosis Progression in CTDs

The TGFβ-mediated fibrotic process is the core of the pathology of CTDs.[15] This process involves fibroblast activation, extracellular matrix (ECM) remodeling, and modulation of associated molecular pathways.[21] Recent studies using single-cell sequencing techniques have elucidated the subpopulation heterogeneity of fibroblasts and their pivotal roles in fibrosis, offering a novel viewpoint on the mechanisms underlying TGFβ-driven fibrosis.

TGFβ Promotes Fibroblast Activation

Fibroblasts are essential effector cells in the fibrotic process.[22] Stimulated by TGFβ, fibroblasts differentiate into myofibroblasts, which possess contractile properties and enhanced capability of ECM synthesis.[23] Single-cell sequencing revealed that fibroblasts are not a uniform population but comprise several functionally different subpopulations, with certain subpopulations (eg, myofibroblast precursors) exhibiting heightened sensitivity to TGFβ.[24] In SSc, TGFβ promotes the differentiation of fibroblast subpopulations into myofibroblasts by activating the Smad2/3 and MAPK pathways.[25] These activated fibroblasts exhibit high levels of α-smooth muscle actin (α-SMA) and secrete a large number of ECM components (eg, collagen type I COL1A1, collagen type III COL3A1, and fibronectin FN1), contributing to the fibrotic progression.[26] TGFβ also promotes the stability of the fibrotic phenotype in fibroblasts by modulating their epigenetic changes, including DNA methylation and histone acetylation.[27] In idiopathic pulmonary fibrosis (IPF), TGFβ prompted the overexpression of DNA methyltransferase (DNMT), which inhibited the expression of fibrosis-suppressor genes (eg, PPARγ), perpetuating the activation of fibroblasts.[28]

TGFβ Is Involved in ECM Remodeling and Collagen Cross-Linking

ECM remodeling, the hallmark feature of fibrosis, involves the over-synthesis of ECM components and their structural and functional alterations.[29] TGFβ facilitates the excessive accumulation of ECM by upregulating the expression of ECM synthesis genes (eg, COL1A1, COL3A1, and FN1).[30] Meanwhile, TGFβ regulates the balance of ECM-degrading enzymes [eg, matrix metalloproteinases (MMPs)] and their inhibitors (eg, TIMPs) to inhibit ECM degradation and further exacerbate the process of fibrosis. Collagen cross-linking, a key process in ECM remodeling, is mediated by lysyl oxidase (LOX) and its cognate enzymes (LOXL1-4).[31] TGFβ promotes cross-linking of collagen fibrils by up-regulating the expression of the LOX/LOXL enzymes, which enhances the mechanical strength and degradation resistance of ECM.[32,33] In SSc and IPF, LOX/LOXL expression is significantly elevated, leading to excessive cross-linking of collagen fibers and hardening of tissues.[34] For example, in skin tissues of SSc patients, LOXL2 expression levels

were positively correlated with skin thickness and disease severity.[35] In IPF, LOXL2-mediated collagen cross-linking not only enhanced the mechanical strength of lung tissue but also further promoted fibroblast activation and ECM deposition, which in turn exacerbated the process of pulmonary fibrosis.[36]

TGFβ Initiates Fibrosis Signaling Pathway Cascade Responses

The TGFβ-driven fibrotic process relies on the synergistic action of the classical Smad and non-Smad pathways.[8] In the classical Smad pathway, after TGFβ binds to the receptor TGFβR1/2, Smad2/3 are phosphorylated and form a complex with Smad4, which enters the nucleus to regulate the expression of pro-fibrotic genes (eg, COL1A1, α-SMA).[11,37] This pathway is particularly critical in diseases such as SSc and IPF.[38] Among these regulators, overactivation of Smad3 promotes fibroblast-to-myofibroblast transformation and exacerbates ECM deposition.[39] Smad7 acts as a negative feedback regulator, limiting signaling overactivation through inhibition of Smad2/3 or degradation of the TGFβ receptor, but its expression is often suppressed in CTDs, leading to increased fibrosis.[40]

Non-Smad pathways, including MAPK, PI3K/Akt, also play important roles in TGFβ signaling.[41] For example, TGFβ in RA promotes synovial fibroblast proliferation and inflammatory factor release through the TAK1-JNK axis.[42–44] In SLE, the PI3K/Akt pathway regulates B cell differentiation and autoantibody production.[45,46] ERK1/2 activation in IPF promotes lung fibroblast proliferation and ECM deposition.[47–49] In addition, TGFβ signaling interacts with other pathways (eg, Wnt/β-catenin, Notch) to further exacerbate fibrosis. For example, the Wnt/β-catenin pathway in SSc enhances Smad3 transcriptional activity and induces COL1A1 and α-SMA expression.[50] The Notch pathway in IPF promotes fibronectin expression.[51] In summary, the pathological role of TGFβ signaling in CTDs is dependent on an interactive network of multiple pathways and exhibits disease-specific regulatory mechanisms, leading to heterogeneity of fibrosis and immune responses. The role of TGFβ signaling pathway in connective tissue diseases can be seen in Figure 1.

TGFβ Modulates Cell–Cell Interactions for Fibrotic Processes

TGFβ-driven fibrosis also involves multiple cell-to-cell interactions. For example, in SSc, TGFβ promotes fibroblast activation and ECM deposition by inducing endothelial to mesenchymal stromal cell (EndMT) transformation.[55] In IPF, TGFβ promotes the progression of pulmonary fibrosis by regulating the interaction between alveolar epithelial cells and fibroblasts.[56] In addition, TGFβ is involved in the immunoregulation of fibrosis by regulating the function of immune cells, such as macrophages and T cells. In SSc, TGFβ further promotes fibroblast activation and ECM deposition by inducing macrophage polarization towards M2 type.[57]

The Crosstalk of TGFβ with the Immune Microenvironment in CTDs

The interaction of the TGFβ signaling pathway with the immune microenvironment plays an important role in the pathological process of CTDs.[14,58,59] TGFβ is not only a core driver of fibrosis but also plays a key role in the differentiation, activation, and functional regulation of immune cells.[60] By regulating the function of immune cells, such as T cells, macrophages and B cells, TGFβ forms a complex immune microenvironment in CTDs, which in turn affects disease progression and prognosis (Figure 2).

TGFβ Regulates Th17/Treg Balance

The dual role of TGFβ in T cell differentiation makes it a central molecule in immune regulation.[61,64] In normal physiological condition, TGFβ promotes the differentiation of regulatory T cells (Treg), maintains immune tolerance and suppresses autoimmune responses.[65] However, in CTDs, dysfunctional TGFβ signaling leads to reduced Treg cell numbers and impaired function, which promotes hyperactivation of helper T cell 17 (Th17) and enhances autoimmune responses.[66] In SLE, dysfunction of TGFβ signaling is thought to be the main cause of dysregulation of the Treg/Th17 balance.[67] TGFβ induces Foxp3 expression through activation of the Smad2/3 pathway and promotes Treg cell differentiation.[68] However, in SLE patients, downregulation of TGFβ signaling or Smad7 overexpression leads to impaired Treg cell function, which further induces overactivation of Th17 cells.[69,70] TGFβ synergistically interacts with IL-6 to promote the differentiation of Th17 cells and induces the secretion of proinflammatory factors such as IL-17A and IL-21, thus exacerbating the autoimmune response in SLE. Clinical studies have shown that the proportion of Treg cells in the peripheral blood of SLE patients is lower and the

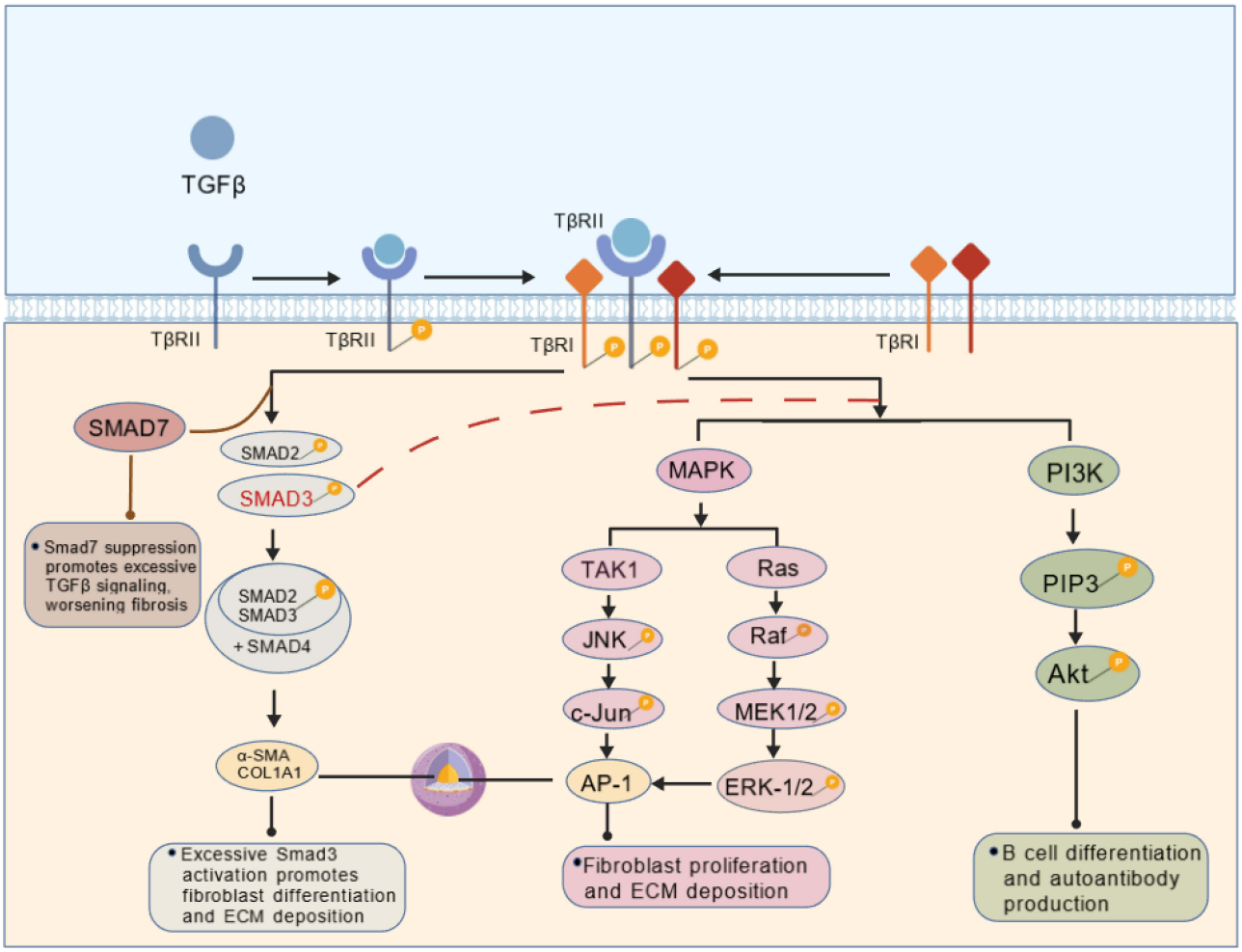

Figure 1 Schematic representation of the TGF-β-associated pro-fibrotic signaling pathway in connective tissue diseases.[52–54]

proportion of Th17 cells is higher, and that this trend is positively correlated with disease activity.[66] In RA, TGFβ is involved in synovial inflammation and joint destruction by regulating the Th17/Treg balance. TGFβ synergizes with IL-6 to promote Th17 cell differentiation and induces the secretion of IL-17A and IL-22, which further promote synovial fibroblast activation and the progression of joint inflammation.[71] In addition, dysfunctional TGFβ signaling leads to impaired immunosuppression of Treg cells, exacerbating the pathological process of RA.

TGFβ in Macrophage Regulation: The Pro-Fibrotic Role of M2-Type Polarization

Macrophages are important immunomodulatory cells during fibrosis, and their phenotypic polarization (M1-type versus M2-type) plays a key role in CTDs.[62,72] TGFβ participates in the progression of fibrosis by promoting macrophage polarization to M2-type.[73] M2-type macrophages secrete pro-fibrotic factors, such as TGFβ, IL-10, and PDGF, which further promote fibroblast activation and ECM deposition.[74] In SSc, TGFβ-induced M2-type macrophage polarization is an important driver of fibrosis.[57] TGFβ promotes macrophage polarization toward the M2 type through activation of the Smad2/3 and PI3K/Akt pathways and induces secretion of TGFβ, IL-10 and PDGF.[75] These pro-fibrotic factors stimulate fibroblast activation and ECM deposition, driving fibrosis in the skin and visceral organs. Clinical studies have shown that the proportion of M2-type macrophages is significantly higher in peripheral blood and diseased tissues of SSc patients, which is positively correlated with increased skin thickness and disease severity.[76] In IPF, TGFβ-induced polarization of M2-type macrophages also plays a key role in pulmonary fibrosis.[77] M2-type macrophages exacerbate pulmonary fibrosis by promoting activation of lung fibroblasts and ECM deposition through the secretion of TGFβ and PDGF. M2-type macrophages also inhibit the anti-fibrotic immune response through the secretion of IL-10 and TGFβ, which further contributes to fibrotic process.[62,78]

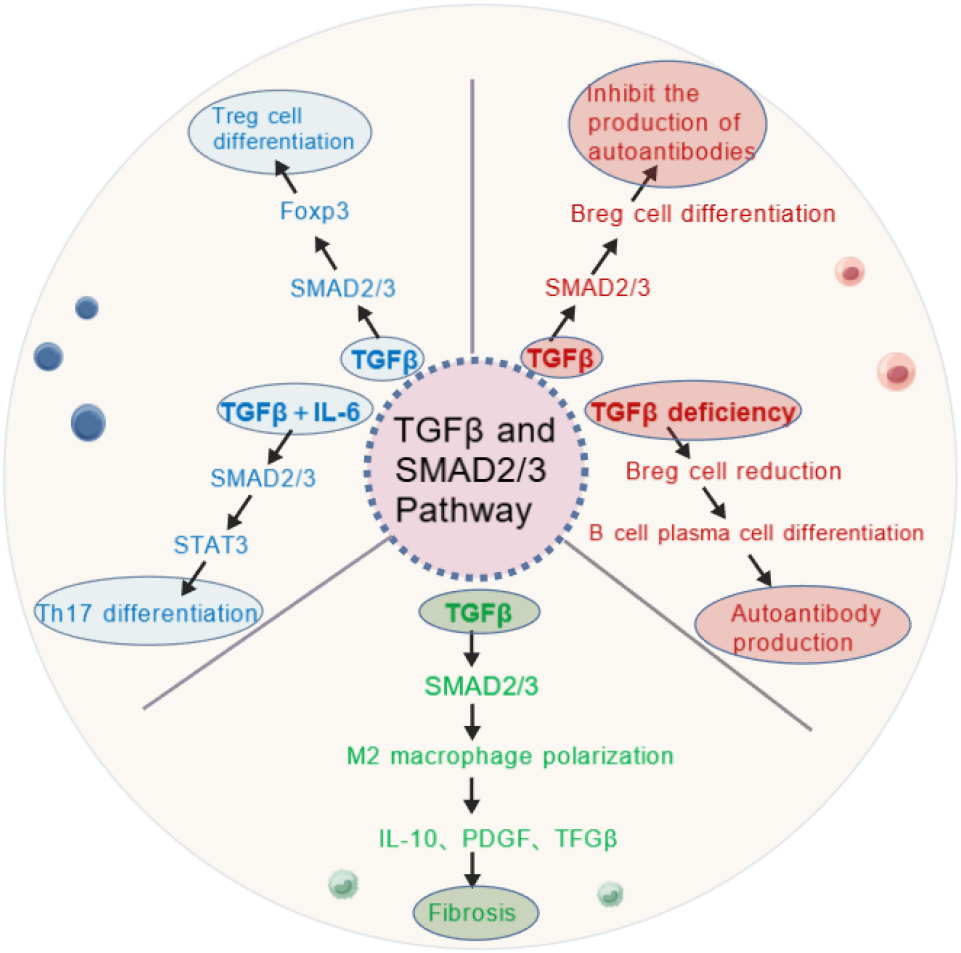

Figure 2 A concrete overview of the regulatory mechanisms by which TGFβ modulates immune cells.[61–63]

TGFβ Regulates B-Cells: Autoantibody Production and Pathology

B cells play a critical role in the autoimmune response in CTDs, and TGFβ participates in the pathological process of the disease by regulating B cell differentiation and function.[79,80] TGFβ promotes the differentiation of B cells to regulatory B cells (Breg), which suppresses the autoimmune response.[63] However, in CTDs, defective TGFβ signaling function leads to a reduction and impaired function of Breg cells, which in turn promotes the overproduction of autoantibodies.[81] In SSc, TGFβ is involved in disease progression by promoting the production of anti-Scl-70 antibodies by B cells. Anti-Scl-70 antibodies are specific autoantibodies in SSc, and their production is closely related to the activation of TGFβ signaling.[82] TGFβ promotes the differentiation of B cells to plasma cells through activation of the Smad2/3 pathway and induces the production of anti-Scl-70 antibodies.[63] After the formation of immune complexes, it activates the complement system and triggers tissue damage, which in turn exacerbates the fibrotic process of SSc. Clinical studies have shown that patients with anti-Scl-70 antibody-positive SSc usually exhibit more severe skin sclerosis and visceral organ involvement.[55] In SLE, downregulation of TGFβ signaling or Smad7 overexpression leads to dysregulation of Breg cell function and promotes autoantibody production, which in turn activates the complement system and exacerbates the pathological process of SLE.[83]

Advances in Drug Research Targeting TGFβ

The role of the TGFβ signaling pathway in fibrosis and its molecular mechanisms have been analyzed previously. With the deepening understanding of the role of TGFβ in CTDs, therapeutic strategies targeting this pathway have become the focus of research. Advances in pharmacology and molecular biology have propelled a variety of targeted drugs and biologics into

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preclinical studies and clinical trials, demonstrating the potential for treating CTDs. Next, the current major TGFβ inhibitors in the treatment of CTDs, including small molecule kinase inhibitors, biologics, nucleic acid drugs, gene editing technologies, and natural products, are discussed to assess their clinical translational progress and challenges (Table 1).

Small Molecule Kinase Inhibitors

Small molecule kinase inhibitors show significant potential in the treatment of CTDs by targeting the ATP-binding site of Transforming Growth Factor-β Type 1 Receptor (TβR1) and blocking the activation of Smad2/3 signaling pathway.[120,121] Galunisertib and Vactosertib, as representative agents, are administered orally and exert their effects through highly selective mechanisms, specifically inhibiting TGF-β1 and TGF-β3-mediated signaling pathways. This targeted inhibition effectively downregulates the expression of pro-fibrotic genes such as COL1A1 and α-SMA.[122,123] Preclinical studies

Table 1 Summary of Research Advances in Drugs and Therapies Targeting the TGFβ Signaling Pathway

Intervention		Mechanism	Type of Study	Effect	References
Small Molecule kinase inhibitors	Galunisertib (LY2157299)	Inhibition of TGFβ receptor I kinase activity blocks the TGFβ signaling pathway	Clinical research	Prolonging Overall Survival (OS) and Progression-Free Survival (PFS) in Patients with Advanced Hepatocellular and Pancreatic Cancer	[84–86]
	SB-431542	Selective inhibition of TGFβ receptor I kinase blocks Smad2/3 phosphorylation	Animal experiment	Reduces fibrosis and improves tissue regeneration	[87]
	LY2109761	Dual-targeted inhibition of TGFβ receptors I and II blocks TGFβ/Smad signaling	Animal experiment	Inhibition of tumor metastasis, reduction of fibrosis and inflammatory response	[88–90]
	Vactosertib	Highly selective inhibition of TGFβ receptor I and blockade of Smad2/3 phosphorylation	Clinical research	Improvement of skin sclerosis in SSc patients, inhibition of renal fibrosis, and attenuation of pulmonary function decline in IPF patients	[91, 92]
Biologics: Antibodies and Fusion Proteins	Fresolimumab (GC1008)	Neutralizes TGFβ1, TGFβ2 and TGFβ3 and blocks multiple TGFβ isoforms	Clinical research	Improvement of skin sclerosis and lung function in scleroderma patients and reduction of immunosuppression in the tumor microenvironment	[93, 94]
	Pamrevlumab (FG-3019)	Targeting TGFβ2 and inhibiting TGFβ2 activity	Clinical research	Improving lung function, slowing pancreatic cancer-related fibrosis, and improving quality of life in IPF patients	[95, 96]
	AVID200	Targeting receptors or key molecules on the surface of cancer cells	Clinical research	Reduces fibrosis and inhibits tumor growth	[97]
	1D11	Neutralization of TGFβ1, TGFβ2 and TGFβ3	Animal experiment	Reduces fibrosis, inhibits tumor growth and metastasis	[98]
	TGFβRII-Fc fusion protein	Blocking the binding of receptorTGFβ to its	Animal experiment	Reduces fibrosis and improves tissue regeneration	[99]
	Antisense oligonucleotide	Inhibits TGFβ its translation or transcription and reduces the expression of fibrogenic factors	Clinical research	Reduced fibrosis	[100, 101]

(*Continued*)

Table 1 (Continued).

Intervention		Mechanism	Type of Study	Effect	References
Nucleic acid drugs and gene editing	TGFβ siRNA	Reduces TGFβ levels	Animal experiment	Reduces fibrosis and improves tissue regeneration	[102]
	LNP-siTGFβR1	Blocking the TGFβ signaling pathway	Preclinical studies	Improvement of fibrosis symptoms and reduction of fibroblast activation in SSc and IPF patients	[103]
	CRISPR-Cas9 gene editing	Blocking the TGFβ signaling pathway	Animal experiment	Reduced fibrosis and improved immune microenvironment	[104–106]
	Smad3 knockout	Blocking TGFβ-driven fibrosis	Preclinical studies	Significant improvement of dermatosclerosis and pulmonary fibrosis in animal models of SSc and IPF	[107, 108]
Natural product	Curcumin	Inhibition of the TGFβ signaling pathway reduces Smad2/3 phosphorylation and nuclear translocation	Animal experiment	Reduced fibrosis, improved immune microenvironment, antioxidant and anti-inflammatory effects	[109, 110]
	Tripterygium Wilfordii Glycosides	Inhibits Smad2/3 phosphorylation and blocks activation of the TGFβ/Smad signaling pathway	Preclinical studies	Reduced skin and lung fibrosis, attenuated collagen deposition and fibroblast activation in SSc and IPF models	[111, 112]
	Tanshinone IIA	Blockade of TGFβR1 and PI3K/Akt signaling pathways	Animal experiment	Improvement of fibroblast function and inhibition of collagen and fibronectin over-synthesis in SSc patients	[113–115]
	Curcumin Nanoparticles	Inhibition of TGFβ signaling pathway	Preclinical studies	Enhanced skin penetration of curcumin significantly improves skin fibrosis and anti-inflammatory effects in SSc model	[116, 117]
	Resveratrol & Baicalein	Inhibition of TGFβ signaling pathway	Preclinical studies	Enhancement of anti-fibrotic effect, modulation of inflammatory factor release, and improvement of immune microenvironment	[118, 119]

have shown that both exhibit significant antifibrotic activity in a variety of fibrosis models.[124,125] In clinical trials in the field of CTDs, Galunisertib showed preliminary improvement in skin sclerosis and lung function in SSc and IPF.[84,123] Vactosertib, on the other hand, has shown a favorable safety profile and potential to improve fibrosis and disease activity in SSc and IPF.[91,126] Both are currently undergoing in-depth validation in clinical trials in SSc and IPF as important directions for the precision treatment of CTDs. Future studies are needed to further evaluate their long-term efficacy and safety to promote their clinical translational applications.

Biological Agents: Antibodies and Fusion Proteins

With the in-depth study of the TGFβ signaling pathway, biologics targeting TGFβ have gradually become a research hotspot, including monoclonal antibodies and receptor fusion proteins, which inhibit the over-activation of the signaling pathway by specifically neutralizing TGFβ or its receptor. For monoclonal antibodies, Fresolimumab (GC1008) is a pan-TGFβ-neutralizing antibody that inhibits the activity of TGFβ1, TGFβ2 and TGFβ3 simultaneously.[93] Early clinical trials showed its potential, but its broad inhibition of multiple TGFβ isoforms may trigger side effects such as immunosuppression and tumorigenesis, limiting its application. Pamrevlumab (FG-3019), a monoclonal antibody specifically targeting TGFβ2, has been shown to have a favorable safety profile and anti-fibrosis effects in clinical trials of IPF

and pancreatic cancer-related fibrosis, especially in IPF, where it significantly improved lung function and quality of life.[93] For receptor fusion proteins, SRK-181 is a TGFβ1-specific trap protein that blocks TGFβ1's interaction with the receptor.[127] Preclinical studies have shown that SRK-181 has a significant antifibrotic effect in a variety of fibrosis models and has little effect on TGFβ2 and TGFβ3 activity, reducing the risk of potential side effects. SRK-181 is now in clinical trials and preliminary results showed its potential to improve fibrosis.[127,128]

Nucleic Acid Drugs and Gene Editing

The rapid development of nucleic acid drugs and gene editing technologies has provided new therapeutic strategies for targeting the TGFβ signaling pathway. These technologies achieve the regulation of the TGFβ signaling pathway by directly interfering with gene expression or precisely editing the genome, opening up new directions for research in this field.

siRNA

Small interfering RNA (siRNA) technology inhibits the overactivation of the TGFβ signaling pathway by specifically silencing the expression of target genes through the RNA interference (RNAi) mechanism. In therapies targeting the TGFβ signaling pathway, siRNAs usually target TGFβ receptor 1 (TGFβR1) or other key molecules (eg, Smad2/3) to inhibit aberrant signaling.[102,129] In recent years, the development of nanoparticle delivery systems (eg, lipid nanoparticles, LNP) has significantly improved the stability and targeting of siRNAs.[130] For example, LNP-siTGFβR1 is a lipid nanoparticle-based siRNA delivery system that efficiently delivers siRNA to target cells and specifically silences TGFβR1 expression. In preclinical studies, LNP-siTGFβR1 showed significant anti-fibrotic effects with little side effect on normal tissues. In addition, this technique inhibited fibroblast activation and excessive deposition of ECM, providing new ideas for the treatment of fibrosis-related diseases.[131]

CRISPR/Cas9 Gene

CRISPR/Cas9 gene editing technology has become a powerful tool for targeting the TGFβ signaling pathway with its efficient and precise genome editing capabilities. The technology achieves gene knockout, insertion or modification by specifically cutting the target gene sequence. In the TGFβ signaling pathway, CRISPR/Cas9 can be used to knock down key molecules such as Smad3 to inhibit the over-activated signaling pathway.[104] For example, preclinical studies have shown that fibroblast-specific knockdown of Smad3 significantly inhibited TGFβ-driven fibrotic progression without significant side effects. In addition, CRISPR/Cas9 can be used to edit other key molecules in the TGFβ signaling pathway, such as TGFβR1 or Smad2.[105] Fibroblast-specific knockdown of TGFβR1 or Smad2 significantly ameliorated dermatosclerosis and pulmonary fibrosis in preclinical models of SSc and IPF, further validating its potential in the treatment of fibrosis in CTDs.[132,133]

Natural Products

Natural products and traditional Chinese medicine (TCM) show unique potential in regulating the TGFβ signaling pathway, and their multi-target and multi-pathway mechanisms of action provide new ideas for the treatment of CTDs. In recent years, based on the integrated research of modern pharmacology and nanotechnology, the role of active ingredients of TCM and their complexes in antifibrosis and immunomodulation has been gradually verified scientifically.

Chinese Medicine Monomers

Tripterygium Wilfordii Glycosides is a diterpenoid extracted from Tripterygium wilfordii.[111,134] Studies have shown that tretinoin blocks the activation of the TGFβ/Smad signaling pathway by inhibiting the phosphorylation and nuclear translocation of Smad2/3.[135] In addition, tretinoin significantly reduced the expression of collagen (COL1A1) and α-SMA, also inhibited the NF-κB signaling pathway to reduce the release of inflammatory factors, demonstrating a dual effect of antifibrotic and anti-inflammatory.[136,137]

Tanshinone IIA is the main active ingredient extracted from Salvia miltiorrhiza.[113] Studies have shown that Tanshinone IIA blocks the over-activation of TGFβ signaling by simultaneously inhibiting the TGFβR1 and PI3K/Akt signaling pathways.[138] Its ability to inhibit TGFβR1 phosphorylation and Smad2/3 activation reduces fibroblast to myofibroblast transformation and decreases ECM synthesis.[139] In primary fibroblasts from SSc patients, tanshinone

IIA significantly reduced COL1A1 and fibronectin expression. These research advances provide an important scientific basis for the role of natural products in regulating the TGFβ signaling pathway and anti-fibrosis.

Compound Chinese Medicines

Classical compound Chinese medicines, such as Xu Fu Zhu Yu Tang, have shown potential in regulating the TGFβ signaling pathway. Studies have shown that Xu Fu Zhu Yu Tang can reduce serum TGFβ1 levels and alleviate fibrosis by inhibiting the TGFβ/Smad signaling pathway and down-regulating LOX/LOXL activity. The advantage of compound Chinese medicine lies in the synergistic effect of its multiple components, which can regulate multiple targets simultaneously, but its complexity and diversity still need to be elucidated by further systematic pharmacological studies.[140]

Integration of Natural Products and Nanotechnology

Nanotechnology provides new ways to address the low bioavailability and non-specific distribution of natural products. Encapsulation of natural products using nanocarriers (eg, liposomes, polymer nanoparticles) can significantly improve their stability and targeting.[141] For example, the skin penetration ability and antifibrotic effect of curcumin were significantly enhanced by nanocarrier loading, and the mechanism involved the inhibition of TGFβR1 and the modulation of ROS signaling pathway.[142,143] In addition, natural products such as resveratrol and baicalein have also been enhanced in bioavailability by nanotechnology, showing potential in antifibrosis and anti-inflammation.[118] These advances provide new technical support for the clinical application of natural products.

TGF-β Inhibitors in Connective Tissue Diseases

Systemic Sclerosis (SSc)

SSc is a severe connective tissue disease characterized by fibrosis of the skin and internal organs, vasculopathy, and immune dysregulation.[82,144] Hyperactivation of the TGFβ signaling pathway is the central driving mechanism of its fibrosis, which is manifested by abnormal fibroblast activation, endothelial cell damage, and immune system dysregulation.[145,146] In recent years, therapeutic strategies targeting TGFβ have made significant progress in the management fibrosis and vascular complications. Pamrevlumab (FG-3019), a monoclonal antibody targeting TGFβ2, attenuates dermal fibrosis in SSc mouse models. It was shown that FG-3019 significantly reduced fibrosis induced by angiotensin II (Ang II), with effects similar to CTGF knockdown in fibroblasts. This suggests that FG-3019, as a potential treatment for SSc, may act by inhibiting collagen deposition and myofibroblast accumulation, which are key features of fibrosis.[147] Compared with pan-TGFβ inhibitors (eg, Fresolimumab), Pamrevlumab offers safety for long-term use by reducing systemic side effects such as severe infections or thrombocytopenia due to subtype selectivity.

Combination therapies have received much attention as a potential strategy for the treatment of SSc-associated interstitial lung disease (SSc-ILD), especially when used in combination with conventional treatments such as morphenicol (MMF). For example, a Phase II clinical trial (NCT03221257) is investigating the combination of MMF with the antifibrotic drug pirfenidone, showing potential for SSc-ILD.[148] The challenge with this type of combination therapy is patient intolerance, especially gastrointestinal side effects. In the management of vascular complications, the TGF-β signaling pathway plays a key role in SSc vascular development and homeostasis maintenance. Studies have shown that BMPR-II mutations may lead to aberrant BMP/Smad signaling and enhance TGF-β/ALK5/Smad2/3 signaling, which in turn triggers vascular smooth muscle cell proliferation and vascular remodeling, leading to complications such as pulmonary hypertension. The vascular wall of patients with SSc has abnormal compositions, and by regulating these compositions, TGF-β contributes to vasculopathy. Preclinical studies have shown that TGF-β antibodies and gene editing techniques attenuate pulmonary vasculopathy, demonstrating the important role of TGF-β signaling in vasculopathy. However, the results of clinical studies have been inconsistent, with some studies failing to show significant clinical benefit, which may be related to inadequate drug dosage or other factors.[149] Nonetheless, therapies targeting the TGF-β signaling pathway have potential and need to be further explored in the future in SSc-associated vascular complications.

Systemic Lupus Erythematosus (SLE)

The TGFβ signaling pathway has a dual role in SLE: in physiological state, it maintains immune tolerance by inducing Treg differentiation; in pathological state, its dysregulation leads to defective Treg function and auto-reactive B cell activation, which exacerbates immune imbalance and organ damage. Inhibitors targeting TGFβ show potential in SLE therapy.[150,151]

In terms of immunomodulation, the pathological effects of TGFβ are mainly characterized by defective Treg function and abnormal B cell activation.[152] A phase II clinical trial (NCT04161855) of the pan-TGFβ neutralizing antibody Fresolimumab showed that treatment of patients with moderate-to-severe SLE resulted in a significant reduction in serum anti-dsDNA antibody titers (42% vs 18%, p=0.03) and was associated with an improvement in the disease activity index (SLEDAI). The study demonstrated that Fresolimumab rebuilds immune tolerance by increasing the proportion of functional Treg and reducing Th17 cell infiltration, but its clinical use requires attention to thrombocytopenia and infection risk, suggesting the need for optimization of dosage and patient selection strategies.[153]

In terms of renoprotection, TGFβ drives the fibrotic process in lupus nephritis (LN) by promoting renal fibroblast activation and podocyte injury.[150,154,155] Preclinical studies have shown that the Smad3 inhibitor SIS3 significantly reduces glomerular thylakoid matrix expansion and collagen deposition and decreases urinary protein levels by 60% in an MRL/lpr mouse model.[156] In addition, an antisense oligonucleotide sequence targeting TGFβ1 (ISIS 369645) significantly inhibited TGFβ1 expression and reduced tubulointerstitial fibrosis scores in renal biopsy tissues from patients with LN ($p<0.01$).[157] A phase II trial (NCT05292547) evaluated the efficacy of small molecule inhibitor of TGFβR1, LY3200882, in LN treatment, with preliminary data showing that combination therapy reduced the urinary protein/creatinine ratio (UPCR) by up to 35% and improved the renal pathologic activity index.

Rheumatoid Arthritis (RA)

RA is a chronic autoimmune disease characterized by synovitis, bone erosion, and systemic complications, and its pathogenesis involves dysregulation of the immune system, synovial hyperplasia, and bone destruction.[158–160] The TGFβ signaling pathway plays a dual role in RA: it is involved in tissue repair in physiological states, and it exacerbates the disease progression by promoting synovial hyperplasia, bone destruction, and systemic fibrosis in pathological states.[161,162] In recent years, TGFβ inhibitors have demonstrated potential in controlling local joint damage with systemic complications, and have become an important research direction for RA treatment.

In synovial-targeted therapy, TGFβ drives synovial invasion and bone destruction by activating fibroblast-like synoviocytes (FLS) and osteoclasts.[163] Preclinical studies (mouse model of collagen-induced arthritis) demonstrated that Galunisertib (TGFβR1 inhibitor, 5 mg/kg, twice weekly, intra-articular injections) significantly inhibited synovial hyperplasia and bone erosion, with a 62% reduction in the volume of bone erosion compared to the control group ($p<0.001$), as well as down-regulating the expression of COL1A1 and MMP-3 in synovial tissue. Mechanistic studies showed that Galunisertib inhibited FLS migration and invasion by blocking the TGFβ/Smad2/3 pathway and decreased the RANKL/OPG ratio to inhibit osteoclast differentiation.[123] Preliminary data from the Phase I clinical trial (NCT04879810) showed that after 4 weeks of Galunisertib treatment, the joint swelling index (SJC) was reduced by 40%, suggesting a significant potential for its topical application.

In terms of systemic effects, TGFβ plays a central role in RA-associated extra-articular fibrotic complications such as ILD and cardiovascular fibrosis. Serum TGFβ1 levels were positively correlated with HRCT fibrosis scores in patients with RA-ILD ($r=0.71$, $p<0.01$).[164] Preclinical studies have shown that oral administration of Vactosertib (TGFβR1 inhibitor) inhibits lung fibroblast activation and reduces lung collagen deposition (55% decrease).[165] In addition, TGFβ promotes myocardial fibrosis through activation of cardiac fibroblasts, and left ventricular end-diastolic volume (LVEDV) improves more dramatically in RA patients treated with TGFβ inhibitors, suggesting its potential efficacy in cardiovascular fibrosis.[166]

Sjögren's Syndrome (SS): TGFβ-Mediated Salivary Gland Fibrosis

SS is an autoimmune disease characterized by salivary gland lymphocyte infiltration and fibrosis. Abnormal activation of the TGFβ signaling pathway is its core pathological mechanism.[167] Studies have shown that TGFβ1 expression is significantly upregulated in the salivary glands of SS patients, inducing fibroblast-to-myofibroblast transformation through activation of the Smad2/3 pathway and promoting collagen and α-SMA

overexpression.[168] Single-cell sequencing revealed the presence of a subpopulation of pro-fibrotic fibroblasts (marker genes: POSTN, CTHRC1) significantly enriched in genes related to the TGFβ pathway (eg, SMAD3, TGFBR1). In addition, TGFβ synergistically promotes the vicious cycle of inflammation and fibrosis by inducing epithelial–mesenchymal transition (downregulation of E-cadherin, upregulation of Vimentin) and modulating Th17/Treg imbalance (2.5-fold increase in Th17 cell infiltration), and M2-type macrophage polarization (40% elevated percentage of CD206+ cells).[169] Preclinical studies have shown that blockade of TGFβR1 reverses the fibrotic process and restores salivary secretory function (50% increase in salivary flow rate in a mouse model).[170]

In terms of targeted therapies, the Smad3 inhibitor SIS3 significantly reduced salivary gland fibrosis and lymphocyte infiltration in a mouse model, while a TGFβ1-neutralizing antibody (1D11) significantly inhibited collagen expression and restored salivary flow rates to 80% of normal levels.[171] In clinical trials, topical injections of Galunisertib (phase I trial, NCT04968938) resulted in a 35% increase in salivary production and a 25% reduction in fibrosis scores. A phase II trial (NCT05331053) of AVID200 (TGFβ1/3 trap protein) is exploring the efficacy of its systemic administration on salivary gland function and extra-glandular complications. These studies provide an important basis for targeted therapy for pSS.

Interstitial Lung Disease (ILD)

ILD is a common complication of several CTDs including SSc and RA.[172,173] Despite their different primary etiologies, fibroblast activation and ECM remodeling driven by the TGFβ signaling pathway are common core mechanisms of ILD progression.[174] In recent years, inhaled therapies targeting TGFβ have emerged as an emerging direction in the treatment of ILD due to their local delivery advantages and potential to reduce systemic toxicity.[175]

In terms of molecular mechanisms, SSc-ILD and RA-associated interstitial lung disease (RA-ILD) showed significant commonality in fibroblast activation and ECM deposition.[176] TGFβ released from alveolar epithelial cell injury induces the transformation of lung fibroblasts into myofibroblasts and secretion of large amounts of collagen (eg, COL1A1, COL3A1) and fibronectin.[177] Single-cell sequencing studies demonstrated the presence of specific pro-fibrotic fibroblast subpopulations (eg, THY1+, PDGFRα+) with highly overlapping transcriptional profiles (eg, high expression of LOXL2, POSTN) in the two types of ILD, confirming that TGFβ-driven activation of fibroblasts is a key component of ILD progression. In addition, TGFβ promotes lung fibrosis by regulating macrophage polarization (M2-type) and T-cell differentiation (Th17/Treg imbalance).[178]

In terms of therapeutic strategies, the TGFβR1 inhibitor dry powder inhaler (PRM-151) offers a new direction for ILD treatment.[179] Localized inhalation delivery increases intrapulmonary concentrations of the drug while reducing systemic exposure and systemic side effects.[180] Preliminary data from a phase I clinical trial of PRM-151 (NCT05541879) showed that a single inhalation dose (10–100 μg) was well tolerated, with an incidence of mild cough and throat irritation of <15%. Bronchoalveolar lavage fluid (BALF) analysis showed a 50% reduction in TGFβ activity in the treatment group compared to baseline (p=0.01) and a 35% downregulation of COL1A1 mRNA expression. Lung carbon monoxide diffusion (DLCO) increased by an average of 8% in patients in the treatment group after 4 weeks (control group decreased by 2%), suggesting its potential to improve lung function. However, inhaled therapy still faces challenges such as uneven drug distribution and long-term safety, and further optimization is needed.[181]

Future Challenges and Directions

TGFβ inhibitors have demonstrated potential in the treatment of CTDs, but many challenges remain. Notably, clinical development of pan-TGFβ inhibitors like fresolimumab has yielded mixed results, likely due to the dual homeostatic and pathogenic roles of TGFβ signaling across different tissues and disease contexts. TGFβ has multiple physiological functions, and its prolonged inhibition may interfere with tissue repair and immune homeostasis, increasing the risk of side effects. Therefore, the development of more selective inhibitors such as isoform-specific antibodies or receptor-specific approaches and organ-targeted therapeutic strategies is crucial. For example, in SLE, renal-specific delivery systems (eg, hyaluronic acid-modified liposomes) and combination therapies (eg, with belimumab or JAK inhibitors) reduce systemic side effects and enhance efficacy. In SSc and RA, the combination of TGFβ inhibitors with antifibrotic agents (eg, nidanib) or anti-inflammatory agents (eg, JAK inhibitors) is expected to synergistically inhibit fibrosis and inflammation and optimize therapeutic efficacy. In SS, topical administration (eg, ultrasound-guided nanoparticle

delivery) and hydrogel carriers (eg, hyaluronic acid-TGFβ inhibitor couplings) can enhance drug distribution and retention time, subject to monitoring of glandular atrophy and risk of infection, and the combination of B-cell-targeting drugs (eg, rituximab) or JAK inhibitors can further suppress immune infiltration and fibrosis.

This review systematically explores the central mechanisms of the TGFβ signaling pathway in fibrosis and immune dysregulation across various connective tissue diseases while evaluating the potential and limitations of different therapeutic strategies targeting this pathway. Future research should focus on the development of precision stratified therapies, combination strategies and novel delivery systems. Individualized interventions can be achieved by screening high response patient groups (eg, serum TGFβ1, KL-6, or COL3A1 levels in BALF). Meanwhile, nanoparticle- or liposome-encapsulated TGFβ inhibitors can improve targeting and retention time to optimize efficacy. Despite the potential of small molecule kinase inhibitors, biologics, nucleic acid drugs, gene editing technologies, and natural products in targeting the TGFβ signaling pathway, their clinical application still faces obstacles, especially as long-term inhibition may trigger side effects such as immunosuppression and tumorigenesis. Therefore, there is a need to develop more selective inhibitors. Future studies will aim to optimize treatment strategies, enhance efficacy, reduce side effects, and promote the integration of traditional Chinese medicine with modern biotechnology to provide more comprehensive solutions for the treatment of connective tissue diseases.

Summary

The TGFβ signaling pathway, as an important therapeutic target for CTDs, has demonstrated significant clinical potential. However, existing therapeutic approaches still face many challenges in terms of specificity, efficacy sustainability and side effect control. Future research should focus on optimizing existing therapeutic strategies and exploring more precise and personalized therapeutic regimens to improve efficacy, reduce side effects, and promote the application of TGFβ-targeted therapies in more connective tissue diseases. Through precise stratification of treatment, development of selective inhibitors, innovative delivery systems, and optimization of combination therapy strategies, it is expected that more comprehensive and efficient treatment solutions will be provided for patients with CTDs.

Abbreviations

CTDs, Connective tissue diseases; TGFβ, The transforming growth factor-β; TβR1, Transforming Growth Factor-β Type 1 Receptor; SSc, systemic sclerosis; SLE, systemic lupus erythematosus; LN, lupus nephritis; RA, rheumatoid arthritis; SS, Sjögren's syndrome; IPF, idiopathic pulmonary fibrosis; ILD, Interstitial Lung Disease; SSc-ILD, SSc-associated interstitial lung disease; RA-ILD, RA-associated interstitial lung disease; siRNA, Small interfering RNA; RNAi, RNA interference; ECM, extracellular matrix; α-SMA, α-smooth muscle actin; MMPs, matrix metalloproteinases; FLS, fibroblast-like synoviocytes; EndMT, mesenchymal stromal cell.

Data Sharing Statement

No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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The authors declare no conflicts of interest.

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