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REVIEW

Beyond Organ-Specific Therapies: A Unified Approach to Multi-Organ Fibrosis

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Abstract: Organ fibrosis, characterized by excessive scarring of tissues in the liver, kidney, lung, and heart, poses a significant and growing global health challenge, resulting in considerable morbidity and mortality, with a lack of effective treatment options. Most research and drug development efforts have traditionally focused on individual organs in isolation. This review aims to provide a comprehensive perspective on multi-organ fibrosis, highlighting recent advances that clarify the complex cellular and molecular mechanisms involved in the liver, kidney, lung, and heart. It examines both common and organ-specific factors that drive fibrogenesis. Additionally, the review discusses the current and future landscape of antifibrotic therapies, including innovative approaches to developing pan-organ antifibrotic drugs. Challenges and future directions in the design of clinical trials are also addressed.

Keywords: fibrosis, antifibrotic therapy, multi-organ disease, myofibroblast, extracellular matrix, precision medicine

Introduction

Organ fibrosis, which is characterized by the excessive accumulation of scar tissue in vital organs such as the liver, kidneys, lungs, and heart, poses a significant and growing global public health challenge. This pathological process is a major contributor to both morbidity and mortality.[1] Despite its clinical significance, there are few effective therapeutic options available, with organ transplantation remaining the primary treatment approach. This situation highlights the urgent need for novel therapeutic strategies.

Recent systematic analyses utilizing Global Burden of Disease (GBD) 2019 data underline the profound impact of fibrotic diseases, revealing that they were responsible for 17.8% of all global deaths in 2019, an increase from 16.5% in 1990.[2] Furthermore, when considering the role of fibrosis in tumor growth and metastasis (excluding acute lymphoid and myeloid leukemia), the contribution to global deaths rose significantly, from 28.7% in 1990 to 35.4% in 2019.[3] These statistics emphasize that fibrotic diseases remain substantial contributors to global mortality despite potentially being lower than earlier estimates, necessitating sustained research efforts to develop effective anti-fibrotic treatments.[4]

While clinical manifestations and initiating triggers of fibrosis can vary between different organs, the condition typically involves the replacement of functional tissue with non-functional scar tissue, which is predominantly composed of collagen,[5] with accumulating evidence demonstrating the existence of common underlying cellular and molecular mechanisms that drive fibrotic progression across diverse organs.[6] This shared pathophysiology provides a compelling rationale for developing broad-spectrum anti-fibrotic strategies applicable across multiple organs, potentially accelerating drug development and improving patient outcomes.

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This review aims to provide a comprehensive perspective on multi-organ fibrosis, highlighting recent advances that clarify the complex cellular and molecular mechanisms involved across the liver, kidney, lung, and heart. We will discuss common features and core pathways of fibrosis across organs; the current and future landscape of antifibrotic therapies, including innovative approaches to developing pan-organ antifibrotic drugs; and the challenges and future directions in the design of clinical trials for this novel approach.

Methods

To provide a comprehensive and up-to-date overview, we conducted a systematic literature search for articles published from 2000 to November 2025. This search was performed using the PubMed and Google Scholar databases, focusing exclusively on publications in English.

Our search strategy incorporated key terms related to core concepts such as fibrosis and antifibrotic therapy. We also included terms that emphasized the multi-organ and systemic nature of the disease, as well as essential cellular and molecular mechanisms, including myofibroblasts, extracellular matrix, inflammation, epigenetics, and metabolic reprogramming. Furthermore, we explored emerging therapeutic approaches such as precision medicine and cell-based therapies.

The selection process aimed to identify relevant original research articles, review articles, and clinical trial reports that offered valuable insights into the pathophysiology of multi-organ fibrosis, advancements in diagnosis, and the latest therapeutic strategies. This approach ensures a comprehensive scope for our review.

Global Burden of Fibrotic Diseases

Globally, over 844 million individuals suffer from chronic liver disease (CLD), resulting in over two million deaths annually.[7] Meta-analysis data indicate global prevalence rates of 3.3% for advanced liver fibrosis and 1.3% for cirrhosis.[8]

Major contributors include metabolic dysfunction-associated fatty liver disease (MAFLD), alcohol-related fatty liver disease, and infections (hepatitis B and C).[9,10] Fibrosis severity is a crucial determinant of cause-specific mortality and long-term outcomes, including liver transplantation, hepatic decompensation, and hepatocellular carcinoma.[11]

Approximately 10–14% of the global population has chronic kidney disease (CKD), often without early symptoms, complicating early detection.[12] As the disease progresses, kidney fibrosis becomes the final common pathway to end-stage renal failure.[13]

Primary causes leading to CKD include diabetes, hypertension, primary glomerulonephritis, chronic tubulointerstitial nephritis, and hereditary/cystic diseases.[14] Fibrosis in CKD is a progressive process that gradually reduces renal function by replacing parts of the functional kidney tissue with scars, decreasing blood supply, impairing kidney function, and ultimately leading to irreversible kidney failure.[15]

Lung fibrosis represents the main clinical outcome of chronic respiratory diseases, including pneumoconiosis and idiopathic pulmonary fibrosis (IPF). Global incidence of pneumoconiosis exceeds 0.6 million cases, while IPF affects approximately 3 million individuals worldwide.[16] The causes of chronic respiratory diseases include occupational inhalant exposure (pneumoconiosis) and various environmental/idiopathic triggers in IPF.[17] Pneumoconiosis is a significant occupational disease resulting from long-term inhalation of inorganic particles at work.[18] IPF is the most common type of interstitial lung fibrosis with an unknown cause, primarily affecting elderly adults and is associated with high mortality and morbidity.[19]

Often resulting from myocardial infarction, hypertension, or cardiomyopathy, cardiac fibrosis significantly impairs cardiac function and contributes to heart failure and arrhythmias.[20] Systematic review data indicate approximately one-third of individuals with cardiometabolic conditions, such as hypertension, type 2 diabetes, and obesity, develop myocardial fibrosis, with hypertension associated with the highest prevalence (35.2%).[21] Hypertension, diabetes, and obesity interact synergistically to drive cardiac remodelling and myocardial fibrosis.[22] Furthermore, key factors associated with myocardial fibrosis include increased LV (left ventricular) mass/LV hypertrophy, reduced LV function, and myocardial stiffness.[23] Other contributing factors may also involve poorer glycaemic control,[24] elevated LV end-diastolic pressure, and male gender.[25]

The widespread prevalence and severe outcomes of these fibrotic diseases underscore the urgent need for innovative therapeutic strategies that can effectively prevent, halt, or even reverse fibrosis across various organs.

Common Features and Core Pathways of Fibrosis Across Organs

Despite organ-specific triggers and clinical presentations, pathological fibrosis exhibits remarkably shared underlying features (Figure 1). Understanding these commonalities is crucial for developing broadly applicable anti-fibrotic therapies.

Initial Tissue Injury and Epithelial/Endothelial Dysfunction

Recurrent or persistent injury to parenchymal cells is a common initiating event across fibrotic diseases.[26] Chronic damage to epithelial cells (hepatocytes, renal tubular epithelial cells, alveolar epithelial cells) stimulates the over-production of cytokines and growth factors.[5] This initial injury triggers cellular stress responses, including endoplasmic reticulum (ER) stress and oxidative stress, potentially leading to cell death via apoptosis or necrosis.[27] While the direct impact of epithelial cell death on downstream fibrotic pathways remains debated, severe injury frequently triggers surviving cells to initiate fibrosis.[28]

Dysregulated metabolic pathways in injured cells, such as disrupted ATP production and elevated reactive oxygen species (ROS), further compromise the microenvironment, sustaining injury and promoting fibrogenesis.[29] Moreover, some injured epithelial cells may undergo epithelial–mesenchymal transition (EMT), potentially contributing to the myofibroblast pool, although the quantitative contribution of EMT to overall fibrosis remains subject to ongoing research.[30]

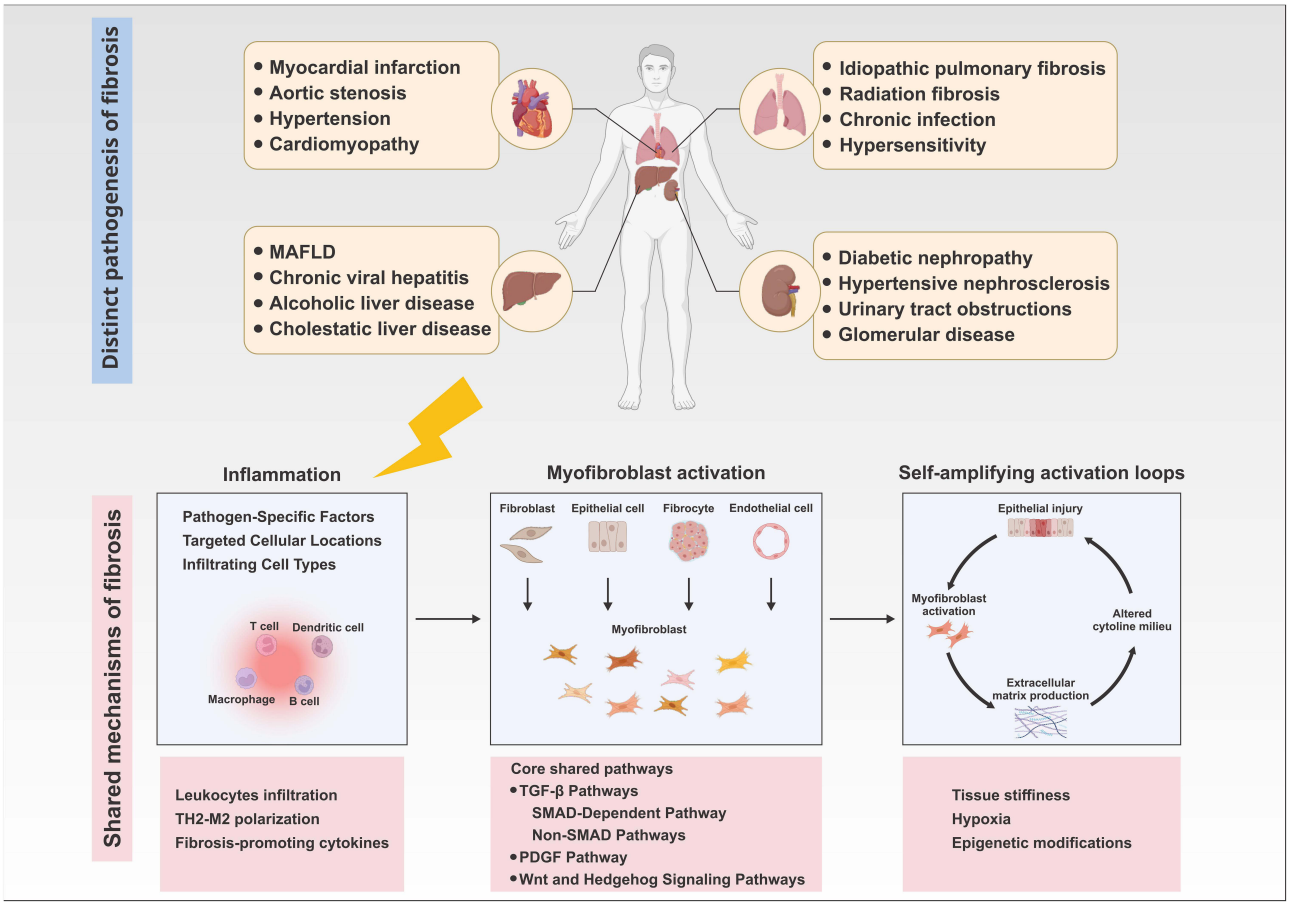

Figure 1 Pathogenesis of Fibrotic Diseases: From Organ-Specific Manifestations to Shared Molecular Mechanisms. This figure provides an overview of fibrotic diseases, illustrating both their distinct clinical presentations across various organs and the common cellular and molecular mechanisms driving their progression. Fibrosis manifests uniquely in the heart (eg, myocardial infarction, hypertension), lung (eg, idiopathic pulmonary fibrosis, chronic infection), liver (eg, MAFLD, viral hepatitis), and kidney (eg, diabetic nephropathy, urinary tract obstructions). Despite these varied etiologies, a shared sequence of events underlies fibrosis: an initial inflammation phase, driven by pathogen-specific factors and immune cell infiltration (T cells, macrophages), leads to a pro-fibrotic cytokine milieu. This environment triggers myofibroblast activation and differentiation from various cellular sources, including resident fibroblasts, epithelial cells, fibrocytes, and endothelial cells. This activation is mediated by core signalling pathways like TGF-β (SMAD-dependent and non-SMAD), PDGF, Wnt, and Hedgehog. These activated myofibroblasts excessively produce extracellular matrix (ECM), initiating self-amplifying activation loops where increased tissue stiffness, hypoxia, and epigenetic modifications perpetuate myofibroblast activity and ECM deposition, ultimately leading to persistent fibrosis and organ dysfunction.

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Inflammation and Immune Response

Initial inflammatory responses are frequent phenomena in fibrotic diseases, characterized by infiltration, activation, and accumulation of leukocytes in the affected tissue.[31] Although organ-specific inflammatory responses vary, they commonly evolve toward T helper 2 (Th2) cell and M2 macrophage polarization.[31] These M2-like macrophages release significant quantities of pro-fibrotic cytokines and activate downstream myofibroblasts, perpetuating fibrosis progression.[31] Key pro-fibrotic cytokines include interleukin-13 (IL-13) and IL-17.[5]

Macrophages engage in crosstalk with cellular effectors such as hepatic stellate cells (HSCs) in the liver, further driving fibrosis.[32] Recent evidence highlights the critical role of scar-associated $SPP1^{+}$ macrophages as key drivers of fibrosis across liver, kidney, lung, and heart.[33] These macrophages, often derived from circulating monocytes, promote myofibroblast activation through various pro-fibrotic cytokines (FGFs, PDGFs, VEGFs, IL-6, IL-13, TGF-β1) and direct cell-cell interactions.[34] Similarly, other cells like hepatic dendritic cells can also contribute to this pro-fibrotic environment by triggering hepatic inflammation in metabolic steatohepatitis through lipid.[35]

Dysregulated toll-like receptor (TLR) signaling and subsequent inflammatory consequences are implicated in severe disease outcomes. TLRs expressed on hepatic immune and stellate cells respond to gut-derived pathogen-associated molecular patterns (PAMPs), activating HSCs and driving fibrotic progression.[36] In the kidney, TLRs widely expressed in various cell types are involved in renal fibrosis activation, particularly through endogenous ligands in models of chronic kidney disease.[37] In the heart, TLR4 expressed in cardiac fibroblasts modulates TGF-β-induced fibrotic changes.[38] Similarly, in pulmonary fibrosis, TLRs are recognized to link innate and adaptive immune responses, regulating wound healing and fibrosis, with their specific effects varying based on the cellular microenvironment.[39]

Thus, dysregulated TLR signalling broadly contributes to inflammation and fibrosis across organs. Notably, membrane bound O-acyltransferase domain containing 7 (MBOAT7) has been identified as a negative regulator of TLR signalling in macrophages.[40] Phenome-wide association studies (PheWAS) of MBOAT7 genetic variants reveal pleiotropic associations with liver injury and inflammation-related traits, underscoring its broad impact on disease pathophysiology.[40]

Myofibroblast Activation and Persistence

Myofibroblasts are key effector cells in fibrosis, which have diverse cellular origins, functionally defined by their capacity for excessive extracellular matrix (ECM) production and contraction, this process, termed fibroblast-to-myofibroblast activation, is crucial for scar formation.[41]

The primary contributors include the activation of resident mesenchymal cells; for instance, in the liver, HSCs are the main myofibroblast precursors. In a healthy liver, HSCs are quiescent and store Vitamin A, but upon injury they activate, lose vitamin A, proliferate, migrate, and secrete pro-fibrotic factors.[42] In the kidney, local fibroblasts and pericytes are similarly stimulated by damage,[13] while in the lung, fibroblasts differentiate into active myofibroblasts, often stimulated by alveolar epithelial cells (AECs).[43] Pericytes can also differentiate into myofibroblasts upon activation and microvascular detachment.[44] Additionally, bone marrow-derived fibrocytes and circulating precursors contribute to myofibroblast pools, though their quantitative significance varies by organ and disease context.[6]

A critical aspect of pathological fibrosis is myofibroblast persistence, unlike their clearance in physiological healing.[45] This persistence results from chronic injury signals, enhanced longevity (resistance to apoptosis/senescence), epigenetic manifestations of myofibroblast traits, and autocrine activation within a self-generated fibrotic microenvironment.[46]

A central element driving this positive feedback loop is the mechanical state of the ECM.[47] Myofibroblast-driven ECM production and tissue contraction cause tissue stiffening, which further promotes myofibroblast accumulation and sustains their activity.[46] Transmembrane integrins function as primary cell surface receptors sensing altered ECM stress and transmitting contractile forces.[48]

Extracellular Matrix Generation and Tissue Stiffness

Fibrosis involves dramatic shifts in ECM composition and architecture. Normal organs contain delicate basement membranes rich in laminins and type IV collagen, whereas fibrosis replaces this with stiff, collagen-rich scar tissue composed predominantly of type I and III collagen, fibronectin, and proteoglycans.[49] This architectural distortion directly contributes to organ dysfunction. Crucially, abnormal ECM stiffening acts as a mechanotransducive stimulus for

myofibroblast activation, perpetuating the fibrotic process.[50] This creates a self-reinforcing feedback loop where increasing stiffness promotes further ECM deposition. Additionally, altered ECM composition affects growth factor and cytokine bioavailability, influencing cellular behaviour and the overall fibrotic response.[51]

Core Signalling Pathways

Multiple core signalling pathways are commonly activated in fibrotic diseases, mediating myofibroblast differentiation and ECM production (Figure 2).

Transforming growth factor-β (TGF-β) is arguably the most prominent and universally recognized pro-fibrotic cytokine.[52] It activates both Suppressor of Mother Against Decapentaplegic (SMAD)-dependent and non-SMAD pathways.[53] In the canonical SMAD pathway, TGF-β binds to its receptors (TβRII and TβRI), leading to the phosphorylation of SMAD2/3. Phosphorylated SMADs form heterocomplexes with SMAD4, translocate to the nucleus, and regulate the transcription of pro-fibrotic genes such as alpha-smooth muscle actin (α-SMA) and connective tissue growth factor (CTGF),[54] with SMAD7 acting as a negative regulator.[53]

Non-SMAD pathways activated by TGF-β include MAPK (ERK, P38, c-JNK), PI3K/Akt/mTOR, Rho-associated kinases, and JAK2/STAT3.[53] These non-SMAD pathways are involved in cell proliferation, adhesion, and migration, and have been implicated in the activation of HSCs during liver fibrosis.[55] While systemic suppression of TGF-β inhibits fibrosis, it carries risks of negative consequences due to its essential roles in tumour suppression and immune regulation,[56] necessitating highly specific targeting approaches.[57]

Platelet-Derived Growth Factor (PDGF) is a significant mitogen for mesenchymal cells, capable of inducing collagen gel contraction.[58] PDGFRα and PDGFRβ, are expressed in various mesenchymal cells.[59] PDGFRα is a reliable marker

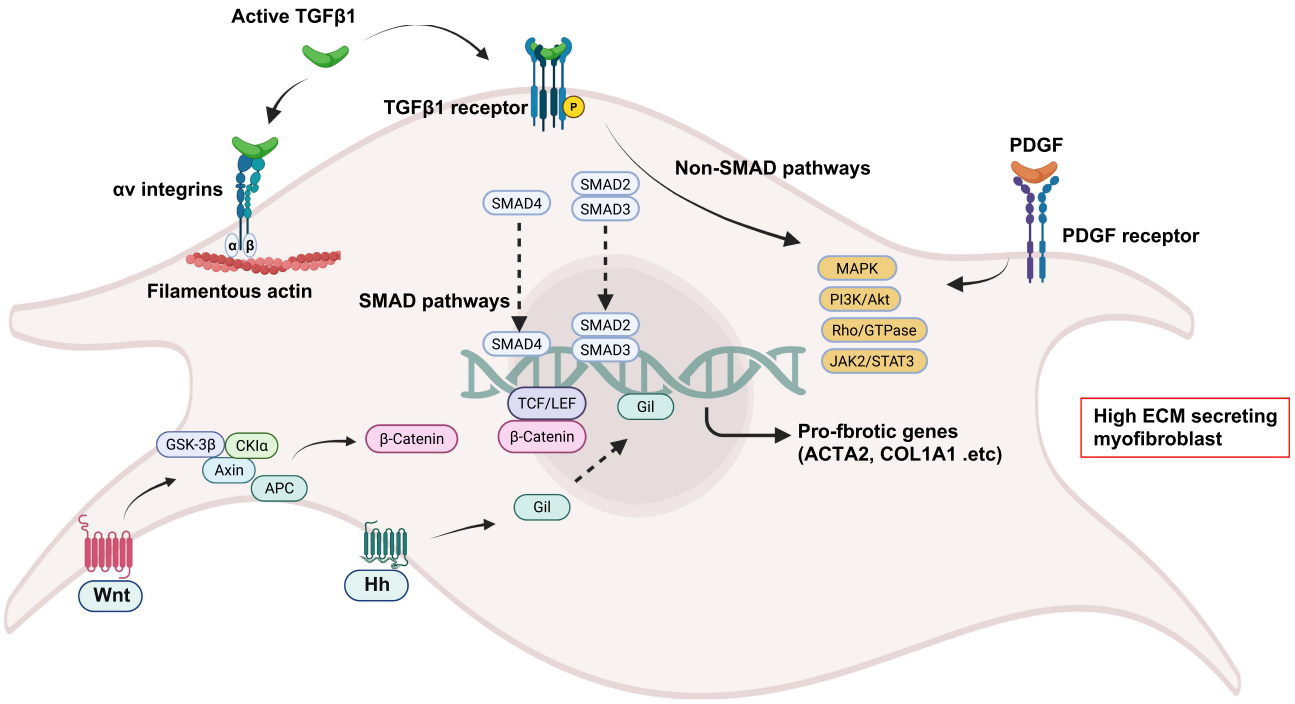

Figure 2 Core Signalling Pathways in Myofibroblast Activation. Key signalling pathways are illustrated, demonstrating how they mediate myofibroblast differentiation and extracellular matrix (ECM) production. Fibroblasts differentiate into highly ECM-secreting myofibroblasts through the activation of several core pathways. Active Transforming Growth Factor-β1 (TGF-β1) binds to its receptor, initiating both canonical SMAD-dependent and non-SMAD pathways. αv integrins are shown associated with intracellular filamentous actin, which is depicted influencing SMAD pathways. In the SMAD pathway, TGF-β1 receptor activation leads to the phosphorylation and nuclear translocation of SMAD2 and SMAD3, which then form a heterocomplex with SMAD4 to regulate the transcription of pro-fibrotic genes. Non-SMAD pathways activated by TGF-β1 include MAPK, PI3K/Akt, Rho/GTPase, and JAK2/STAT3. Similarly, Platelet-Derived Growth Factor (PDGF) binding to its receptor activates various non-SMAD pathways such as MAPK, PI3K/Akt, Rho/GTPase, and JAK2/STAT3, contributing to the fibrotic phenotype. The Wnt pathway, upon ligand binding, inhibits the degradation complex (GSK-3β, CK1α, Axin, APC), allowing β-Catenin to translocate to the nucleus and interact with TCF/LEF to drive gene expression. The Hedgehog (Hh) pathway, through ligand binding, leads to the activation and nuclear translocation of the transcription factor Gli. Collectively, the activation of these pathways leads to the expression of pro-fibrotic genes (eg, ACTA2, COL1A1) and the development of a highly ECM-secreting myofibroblast.

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for fibroblasts,[60] while PDGFRβ has broader expression in mesenchymal cells and pericytes.[59] PDGF signalling, through interaction with its receptors, activates MAPKs and phosphoinositide 3-kinases, influencing cell motility and enhancing fibrosis.[59] Notably, PDGF acts synergistically with TGF-β to potentiate fibrosis.[61]

The Renin-Angiotensin-Aldosterone System (RAAS) represents another crucial mechanism in multi-organ fibrosis pathogenesis.[62] Angiotensin II (Ang II), a key hormone of the classical RAAS pathway, promotes fibrosis by stimulating the synthesis and secretion of TGF-β.[63] Ang II exerts pro-fibrotic effects through the activation of MAPK and SMAD pathways, similar to TGF-β, resulting in pro-fibrotic gene transcription.[64]

Wnt and Hedgehog pathway activation occurs in various fibrotic diseases and plays pivotal roles in crosstalk with TGF-β signalling, regulating cell differentiation, proliferation, and tissue remodelling.[65]

Therapeutic Strategies and Drug Development

The elucidation of shared fibrotic mechanisms across multiple organs has the potential to reshape drug development for fibrotic diseases, fostering optimism for a unified approach to multi-organ fibrosis. Therapeutic strategies include direct inhibition of master regulators (TGF-β, PDGF), modulation of myofibroblast activity, promotion of healthy ECM remodelling, and targeting of diverse inflammatory and immune modulators.[66]

Targeting Core Pro-Fibrotic Pathways

TGF-β Inhibition

Recognizing its central and multifaceted role, targeting TGF-β signalling remains a cornerstone of therapeutic strategy. Approaches encompass direct inhibition of TGF-β ligands or receptors (eg, fresolimumab) and blocking the activation of latent TGF-β through integrin αvβ6 blockade (eg, STX-100).[67] However, a Phase 2 trial tested fresolimumab, an anti-TGFβ antibody, to directly inhibit TGFβ signalling in patients with focal segmental glomerulosclerosis and diabetic nephropathy, but it showed no significant effect.[68] A phase IIb study (NCT01371305) of the monoclonal antibody STX-100, which targets the epithelium-specific TGFβ1-activating integrin αvβ6, was also terminated early due to safety issues.[69] Systemic TGF-β inhibition carries risks of negative consequences due to essential roles in tumour suppression and immune regulation,[56] underscoring the imperative for highly specific targeting strategies to maximize therapeutic benefit while minimizing off-target complications.[57]

Beyond direct TGF-β inhibition, alternative specific regulators are being explored. MERTK (TAM receptor tyrosine kinase) inhibition has shown preclinical efficacy across multiple organ fibrosis models.[70] Small molecule MERTK inhibitors, such as UNC569, demonstrate preclinical efficacy.[71] Other specific strategies include targeting TGF-β-activating integrins (αvβ1 and αvβ6 inhibitors like bexotegrast and STX-100).[72] Downstream of TGF-β, Yes-associated protein 1 (YAP)/transcriptional coactivator with PDZ-binding motif (TAZ) and myocardin-related transcription factor A (MRTFA) pathways are critical targets.[73] YAP/TAZ inhibitors such as verteporfin show promise in preclinical models,[74] while MRTFA inhibitors (eg, CCG-203971, CCG-100602, and CCG-222740) alleviate fibrosis in murine models.[75] The Rho-ROCK pathway, acting in parallel with TGF-β signalling, is also targeted with inhibitors like fasudil and relaxin demonstrating antifibrotic efficacy.[76] These focused approaches offer potential to modulate fibrotic responses while minimizing systemic risks associated with broad TGF-β blockade.

Myofibroblast Modulation

Given that myofibroblasts are central effector cells in fibrosis, therapeutic strategies extensively target their activity through inhibition of activation and proliferation (by targeting PDGF or CTGF pathways), promotion of apoptosis, or induction of reversion to quiescent phenotypes through epigenetic modulation, which influences myofibroblast traits and persistence.[77]

Novel targets are being explored to directly control myofibroblast state. For instance, repositioned drugs like statins have been identified as regulators of YAP (Yes-associated protein 1) and TAZ (transcriptional coactivator with PDZ-binding motif) in human lung fibroblasts, offering a way to modulate myofibroblast activity.[78] YAP and TAZ are co-transcription factors whose nuclear translocation is promoted by high mechanical cell stress, driving the expression of pro-fibrotic genes.[79]

The endocannabinoid system, particularly Cannabinoid receptors type 1 (CB1) and Cannabinoid receptors type 2 (CB2) receptors, has emerged as a target given their upregulation in fibrotic fibroblasts and their role in modulating ECM production and myofibroblast activation.[80] Additionally, the CB2 agonist lenabasum, by targeting the endocannabinoid system, has shown potential in Phase II trials for diffuse cutaneous systemic sclerosis (SSc) by improving skin fibrosis and reducing pro-inflammatory and profibrotic gene expression in skin biopsies and is also expanding the application in other organ fibrosis treatment.[81] These approaches aim to tackle myofibroblast activity through diverse, and sometimes indirect, mechanisms.

ECM Remodelling

Strategies to restore normal tissue architecture involve actively reducing ECM accumulation and stiffness, Lysyl oxidase-like 2 (LOXL2) inhibitors target collagen cross-linking enzymes; for example, GS-6624 (simtuzumab) showed modest effects in a phase II trial for metabolic dysfunction-associated steatohepatitis (MASH) with liver fibrosis.[82]

Another approach involves enhancing the activity of matrix metalloproteinases (MMPs) to degrade excessive ECM components;[83] ARO-MMP7 (an MMP7 inhibitor) is being tested in patients with IPF.[66] Integrins, crucial for sensing altered ECM stress, are also key targets; therapies exploring α11β1 and αVβ8 integrin antagonists modulate cellular responses to mechanical cues.[84] Inhibitors targeting αvβ6 integrins, such as bexotegrast (PLN 74809) and GSK 3008348, have been investigated for various fibrotic conditions.[85,86]

Anti-Inflammatory and Immunomodulatory Approaches

Given the integral role of inflammation in fibrogenesis, modulating immune responses is a critical therapeutic axis. This involves strategically targeting pro-fibrotic cytokines, such as IL-13 and IL-17,[19] with neutralizing antibodies and inhibitors of their receptors showing efficacy in experimental models and clinical trials for pulmonary fibrosis, SSc, and other conditions.[87] Alternatively, approaches promote phenotypic shifts toward pro-resolving macrophage subsets (eg, M2 activation) associated with reduced inflammation and enhanced resolution through IL-10 induction.

Pentraxin-2 analogs (eg, PRM-151) demonstrate potential in regulating macrophage function to resolve both inflammation and fibrosis.[88] Pentraxin-2 (PRM-151) has been found to have good therapeutic effects in preclinical models and clinical trials for IPF, while recent Phase III trials for IPF did not show efficacy.[89,90] Emerging targets include IL-11, IL-4, and IL-13, with inhibitors or neutralizing antibodies showing efficacy in preclinical models and early clinical trials for cardiac, lung, and kidney fibrosis.[91]

Emerging Therapeutic Approaches

The landscape of antifibrotic therapy continues to evolve, with novel approaches targeting fibrosis pathogenesis from genetic predispositions to cellular and molecular reprogramming.[66] This includes leveraging insights from genetic and epigenetic research, developing advanced cell-based therapies, each offering distinct yet complementary avenues for intervention.[92]

A foundational area of advancement stems from genetic research, particularly genome-wide association studies (GWAS), which serve as powerful tools for dissecting disease susceptibility and identifying novel therapeutic targets.[93] These extensive studies have revealed numerous independent genetic loci associated with fibrosis across organs, offering critical insights into both shared and unique disease drivers.[94] Notably, targets with human genetic links demonstrate doubled success rates in phase 2 clinical trials and FDA approval.[95]

For example, genetic variants associated with type 2 diabetes mellitus (T2DM) identified by GWAS include genes encoding glucagon-like peptide-1 (GLP-1) receptor agonists, already used clinically.[96] Recently, Wegovy (semaglutide), a GLP-1 receptor agonist (GLP-1 RA), received FDA approval for adults with MASH and moderate to advanced liver fibrosis.[97]

Epigenetic alterations are increasingly recognized as crucial drivers of fibrotic processes orchestrating multiple disease aspects, including myofibroblast persistence. Given their reversible nature, they represent an attractive avenue for anti-fibrotic drugs. Changes in DNA methylation and histone modifications, influenced by genetic background and environmental factors, are particularly evident in fibrotic conditions.[98] This understanding opens novel therapeutic

avenues through targeting epigenetic enzymes, such as histone deacetylases (HDACs) or DNA methyltransferases (DNMTs) to reverse aberrant gene expression patterns contributing to fibrosis.[99]

Further understanding of cellular function in fibrosis has highlighted metabolic reprogramming as a promising therapeutic frontier. Fibrotic cells exhibit distinct metabolic profiles deviating from healthy cellular metabolism.[100] Activated HSCs show increased glucose uptake fuelling fibrogenic activities.[101] This metabolic shift can be influenced by genetic and epigenetic factors and targeting these altered metabolic pathways and restoring metabolic homeostasis in fibrotic cells could reduce fibrogenic activity and potentially reverse fibrosis.[100]

Finally, complementing these molecular approaches, advanced cell-based therapeutic strategies are under active investigation, particularly utilizing various types of stem cells like mesenchymal stromal/stem cells (MSCs).[102] These therapies hold immense promise through their multi-faceted potential: replacing damaged parenchymal cells, secreting anti-fibrotic factors inhibiting scar formation, and modulating immune responses to create pro-resolving microenvironments.[103] This offers dual regenerative and anti-fibrotic benefits for damaged organs, with applications explored in areas such as dermal and ocular fibroses.[104] Collectively, these diverse and interconnected emerging strategies highlight a multifaceted and integrated approach to combating fibrosis by targeting its genetic, epigenetic, metabolic, and cellular underpinnings.

Overcoming Challenges: Future Directions in Antifibrotic Drug Development

Despite significant progress in elucidating fibrosis mechanisms and identifying potential targets, translating knowledge into effective therapies remains challenging, underscored by numerous clinical trial failures due to inadequate efficacy or unacceptable toxicity.[66] The recent Phase 3 clinical trial outcomes for pamrevlumab, a CTGF inhibitor, strikingly exemplify this; mechanistic plausibility does not guarantee clinical success, likely due to disease heterogeneity or pathway redundancy.[105] This underscores the need to move beyond broad clinical labels towards mechanism-based stratification, leveraging single-cell and spatial multi-omics.[106] By precisely defining disease subtypes, interventions can be matched to patients most likely to respond, advancing true precision medicine in fibrosis. This might be attributed to the complex nature of the disease, diagnostic limitations, and the intricacies of clinical trial design.[57]

It is crucial to recognise that many existing fibrotic datasets remain single-organ and are not easily comparable, thereby limiting our understanding of truly shared versus organ-specific mechanisms. Future research must proactively address this by promoting cross-organ reference mapping, ideally utilizing publicly available cross-tissue fibroblast atlases to define commonalities and distinctions. Furthermore, the prevailing tendency to treat fibroblasts as a single entity is a significant limitation; instead, fibrosis should be framed as a disease driven by dynamic and targetable cell states.[107] This perspective shifts the focus towards proposing "state switching" as a key experimental endpoint, testing the reversibility of fibrotic states and driving cells back towards repair or resolution.[45]

Another key challenge is the absence of robust, non-invasive biomarkers for accurately diagnosing early-stage fibrosis, precisely tracking progression, and reliably predicting treatment response.[108] This diagnostic gap profoundly impedes drug development, as current histological methods are invasive, risky, and prone to sampling variability.[109] While advanced imaging techniques and novel circulating biomarkers offer promise,[110] their widespread clinical validation and integration remain crucial. This limitation is particularly acute in kidney fibrosis, where conventional markers like estimated glomerular filtration rate (eGFR) often fail to detect early disease, complicating endpoint identification.[111]

Box 1 Key Areas for Future Research and Strategy Development

- How can health inequity in genetic research be addressed through improved representation of diverse populations?
- What are the essential shared molecular pathways required for developing systemic antifibrotic strategies?
- How can multi-omic and single-cell data be utilized to customize treatments for specific disease subtypes?
- What combination of therapies effectively targets multiple pro-fibrotic pathways and immune modulators?
- How can tissue mechanics be integrated into treatment strategies for fibrosis?
- Which mechanisms can be enhanced to support the resolution of established fibrosis?

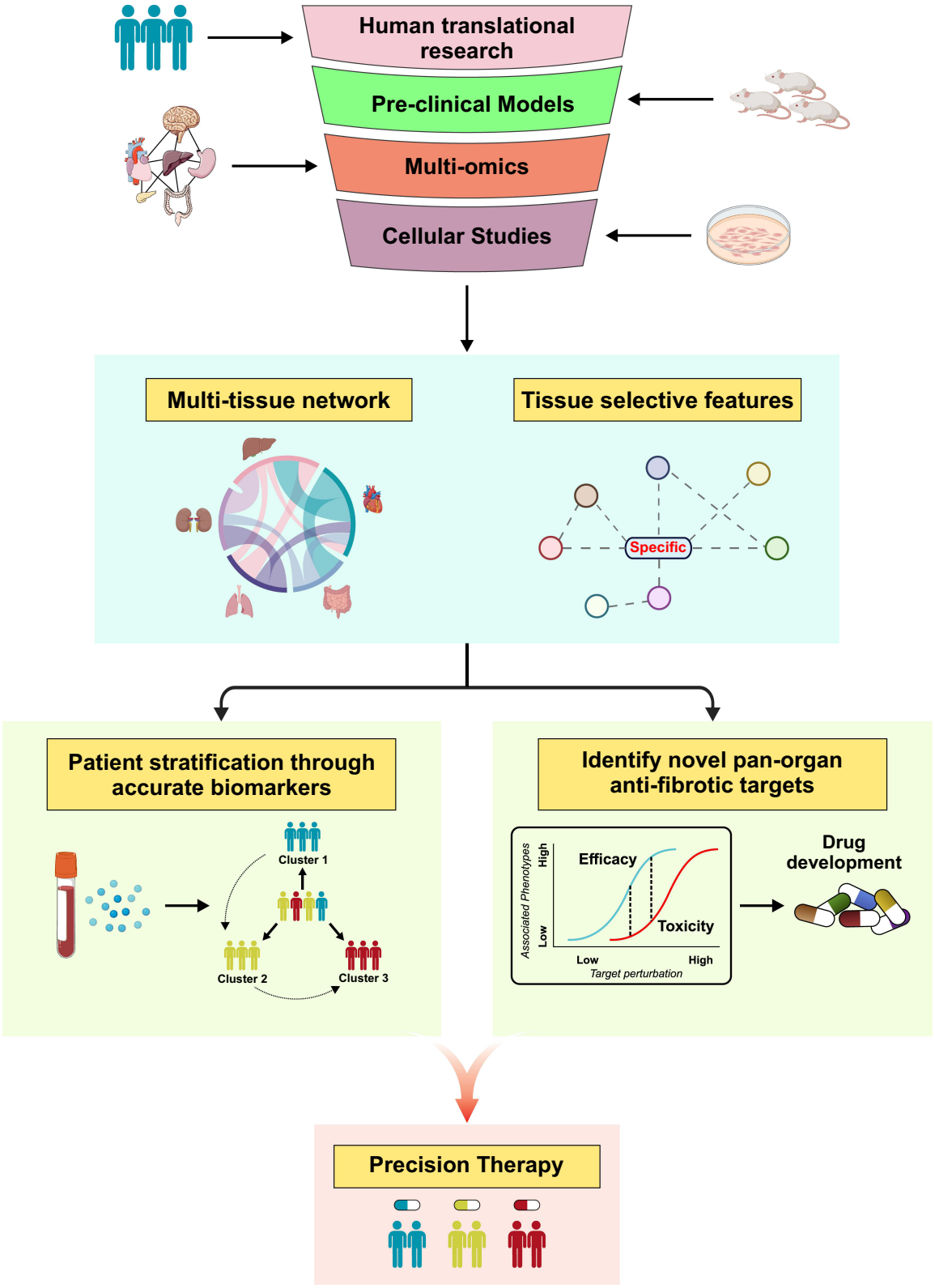

Figure 3 Integrative Multi-Omics Framework for Fibrosis Research and Therapeutic Advancement. An integrative multi-omics framework for understanding fibrotic diseases and accelerating therapeutic development. It integrates foundational genetic, transcriptomic, and proteomic data to construct a multi-tissue network. This approach elucidates both tissue-selective features and shared fibrosis pathways, revealing unique organ-specific and conserved molecular mechanisms. This mechanistic understanding drives translational research, including the development of improved systemic animal models, identification of precise therapeutic targets, discovery of effective biomarkers for diagnosis and monitoring, and the design of novel clinical trials. This multi-pronged approach aims to revolutionize fibrosis management through tailored interventions and the advancement of precision medicine.

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Although essential for drug target discovery and validation, preclinical animal models often fail to replicate the complex, multifaceted nature of human fibrosis.[112] Commonly used toxic injury models (eg, for liver or lung fibrosis) do not fully replicate diverse disease causes and progression patterns.[5] Future efforts require developing more physiologically relevant in vivo and in vitro systems, such as precision-cut liver slices (PCLS), organoids, and liver-on-a-chip models, along with improved primary cell lines.[113]

Additionally, designing effective clinical trials for fibrotic diseases is inherently challenging due to slow progression rates, considerable patient heterogeneity,[5] and difficulty validating appropriate endpoints.[114] Off-target effects from broad-spectrum antifibrotic drugs further complicate trial design and regulatory approval.[115]

Future efforts must focus on several key areas that are summarized in Box 1. Precision medicine approaches are crucial, utilising comprehensive multi-omic and single-cell data to personalise treatments for specific disease subtypes and improve efficacy.[116,117] Another significant challenge to the transnational application of genetic and functional genomic studies, however, remains the underrepresentation of certain populations.[118] Addressing health inequity through improved representation of diverse populations in genetic databases is also crucial for equitable therapeutic development. Moreover, gaining deeper understanding of inter-organ crosstalk and shared molecular pathways is essential for developing comprehensive, systemic antifibrotic strategies.[119] Due to the complex and redundant nature of fibrotic signalling, thorough investigation of combination therapies targeting multiple pro-fibrotic pathways, immune modulators, and tissue mechanics is essential (Figure 3). Finally, enhancing understanding of intrinsic fibrosis resolution mechanisms, such as myofibroblast inactivation and ECM degradation, provides significant therapeutic benefits for actively reversing established fibrosis.[120]

Conclusion

Fibrotic diseases represent a significant and growing global health challenge driven by complex cellular and molecular mechanisms requiring unified therapeutic strategies. The past decade has witnessed remarkable progress in elucidating common drivers across diverse organs, including sustained epithelial-endothelial injury, myofibroblast activation and persistence, dynamic ECM remodelling, and immune cell dysregulation. While significant challenges persist, this shared understanding provides a strong foundation for developing multi-organ therapeutic strategies.

Promoting collaborative research incorporating underrepresented populations, leveraging multi-omics approaches including genetic, epigenetic, and metabolic insights, and developing integrated combination therapies hold immense promise for creating innovative treatments. This approach is paving the way for a new era in which effective therapies can substantially reduce the burden of multi-organ fibrosis, ultimately improving the quality and longevity of life for millions worldwide.

Abbreviations

GBD, Global Burden of Disease; CLD, chronic liver disease; MAFLD, metabolic dysfunction-associated fatty liver disease; CKD, chronic kidney disease; IPF, idiopathic pulmonary fibrosis; LV, left ventricular; ER, endoplasmic reticulum; ROS, reactive oxygen species; EMT, epithelial–mesenchymal transition; Th2, T helper 2; IL-13, interleukin-13; HSC, hepatic stellate cell; TLR, toll-like receptor; PAMP, pathogen-associated molecular pattern; TGF-β, transforming growth factor-β; MBOAT7, membrane bound O-acyltransferase domain containing 7; PheWAS, Phenome-wide association studies; ECM, excessive extracellular matrix; AEC, alveolar epithelial cell; SMAD, suppressor of mother against decapentaplegic; α-SMA, alpha-smooth muscle actin; CTGF, connective tissue growth factor; PDGF, Platelet-Derived Growth Factor; RAAS, Renin-Angiotensin-Aldosterone System; Ang II, Angiotensin II; YAP1, yes-associated protein 1; MRTFA, myocardin-related transcription factor A; CB1, Cannabinoid receptors type 1; CB2, Cannabinoid receptors type 2; SSc, systemic sclerosis; LOXL2, Lysyl oxidase-like 2; MASH, metabolic dysfunction-associated steatohepatitis; MMP, matrix metalloproteinase; GWAS, genome-wide association studies; T2DM, type 2 diabetes mellitus; GLP-1, glucagon-like peptide-1; GLP-1 RA, GLP-1 receptor agonist; MSC, mesenchymal stromal/stem cell; PCLS, precision-cut liver slices.

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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Disclosure

The authors report no conflicts of interest in this work.

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