Fibrosis

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Review

Organoid Models of Liver Fibrosis: Bridging Genetic and Epigenetic Mechanisms with Biomarker Discovery

Ralf Weiskirchen *

Institute of Molecular Pathobiochemistry, Experimental Gene Therapy and Clinical Chemistry (IFMPEGKC), RWTH University Hospital Aachen, D-52074 Aachen, Germany

* Corresponding author. E-mail: rweiskirchen@ukaachen.de (R.W.)

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ABSTRACT: Fibrosis is a pathological process characterized by excessive deposition of extracellular matrix, progressive tissue stiffening, and ultimately organ dysfunction. It represents a common endpoint of chronic injury in multiple organs, including the liver, lung, kidney, and heart, and contributes substantially to global morbidity and mortality. Increasing evidence indicates that genetic susceptibility and dynamic epigenetic regulation play important roles in determining individual responses to chronic injury and in shaping fibrogenic signaling pathways. Despite its clinical significance, effective therapies remain limited, partly due to an incomplete understanding of the complex cellular interactions and molecular mechanisms that drive fibrotic disease. Traditional experimental models, including two-dimensional cell cultures and animal systems, often fail to fully recapitulate human tissue architecture and disease complexity. Organoid technology has emerged as a promising platform for modeling human diseases *in vitro*. Organoids are three-dimensional multicellular structures derived from stem cells or primary tissues that self-organize to mimic key structural and functional aspects of native organs while preserving important genetic and epigenetic characteristics of the originating tissue. Recent advances have enabled the development of organoid-based models that capture critical features of fibrosis, including epithelial injury, fibroblast activation, and extracellular matrix remodeling. These systems provide powerful experimental platforms for investigating molecular mechanisms of fibrosis, studying the influence of genetic and epigenetic regulatory networks, and identifying candidate biomarkers associated with disease progression. This review summarizes current progress in the use of organoid systems to study fibrosis across different organs. The advantages and limitations of these models are discussed, and emerging technologies that may enhance their physiological relevance and utility for biomarker discovery and anti-fibrotic drug development are highlighted.

Keywords: Organoids; Liver fibrosis; Hepatic stellate cells; Extracellular matrix remodeling; Genetic susceptibility; Epigenetic regulation; Biomarker discovery; Anti-fibrotic therapy

1. Introduction

Fibrosis is a pathological process that occurs when normal tissue repair mechanisms become dysregulated following an injury [1]. Under physiological conditions, wound healing involves a tightly controlled sequence of events that restore tissue integrity after damage. However, if the injury is chronic or the repair process is improperly regulated, there is an excessive accumulation of extracellular matrix (ECM) components, leading to progressive scarring and disruption of tissue architecture. Over time, this fibrotic remodeling can impair organ function and eventually lead to organ failure. Fibrosis can affect almost any tissue in the body and is a key feature of many chronic diseases [2,3]. For example, liver fibrosis can progress to cirrhosis and liver failure [4], while pulmonary fibrosis can lead to a gradual loss of lung function and respiratory insufficiency [5]. In the kidney, fibrotic remodeling contributes to chronic kidney disease, and in the heart, fibrosis disrupts electrical conduction and impairs contractile function. Despite variations in the causes and specific characteristics of different fibrotic diseases, many of them share common molecular pathways and cellular mechanisms [5].

Fibrosis associated with metabolic liver disease demonstrates how fibrotic processes in various organs can arise from shared systemic mechanisms. In metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as non-alcoholic fatty liver disease (NAFLD), hepatic fibrosis often occurs alongside vascular remodeling and arterial wall fibrosis [6]. These processes are interconnected through common metabolic and inflammatory pathways. Insulin resistance, a key factor in MASLD, not only results in hepatic steatosis and stellate cell activation but also contributes to vascular dysfunction due to chronic hyperglycemia and hyperinsulinemia. These conditions activate the renin-angiotensin-aldosterone system and increase angiotensin receptor signaling, leading to hypertrophy and fibrosis of the arterial wall. Moreover, TGF-β signaling, a significant mediator of hepatic stellate cell activation and liver fibrosis, is also associated with vascular remodeling and intimal thickening. Oxidative stress from excessive lipid accumulation in hepatocytes can exacerbate these effects by promoting inflammatory activation of Kupffer cells and stellate cells, while also contributing to endothelial dysfunction. As a result, systemic inflammatory mediators may act as a mechanistic link between hepatic fibrosis and cardiovascular disease, with markers of advanced MASLD fibrosis correlating with more severe coronary artery disease and vascular damage [6]. These findings highlight the systemic nature of fibrotic diseases and underscore the importance of integrated experimental models for studying cross-organ mechanisms of fibrosis [6].

At the core of fibrosis is the activation of fibroblasts into myofibroblasts, specialized cells that produce large amounts of ECM proteins, such as collagen and fibronectin. These cells accumulate at the injury sites and contribute to tissue stiffening and structural remodeling. Various signaling pathways, such as transforming growth factor-β (TGF-β), Wnt signaling, platelet-derived growth factor (PDGF), and different inflammatory mediators, regulate the activation of fibroblasts [7]. The interactions between epithelial cells, stromal cells, immune populations, and the extracellular matrix also shape the fibrotic response.

Despite significant progress in identifying these pathways, many aspects of fibrosis remain poorly understood. One major challenge is the lack of experimental models that accurately mimic human disease. Furthermore, conventional cell culture plastic exhibits supraphysiological stiffness compared with most native tissues, which can profoundly influence cellular signaling and mechanotransduction pathways and therefore limit the physiological relevance of two-dimensional culture systems. Animal models, while providing physiological context, often differ significantly from human biology and may only partially recapitulate the biological processes underlying disease development; therefore, they may note reliably predict clinical outcomes [5].

Organoid technology has emerged as a powerful alternative for modeling human tissues *in vitro* [8]. Organoids are three-dimensional cell culture systems derived from stem cells or primary tissues that self-organize into structures resembling native organs [9]. These systems retain many features of native tissues, including cell type diversity, spatial organization, and functional characteristics. Because organoids can be generated from human cells and manipulated experimentally, they offer unique opportunities for studying disease mechanisms in a controlled environment.

In recent years, organoid systems have been used to study fibrotic diseases [10]. By including stromal cells, applying fibrotic stimuli, or modifying ECM conditions, researchers have begun to recreate key aspects of fibrosis *in vitro*. As a result, these models provide new insights into the development of fibrotic processes and may facilitate the discovery of novel therapeutic strategies.

Recent advances in genomic and epigenomic profiling reveal that fibrotic diseases are not solely driven by environmental injury but are also influenced by inherited genetic variants and dynamic epigenetic regulation. Genome-wide association studies and large cohort analyses have identified several polymorphisms that impact susceptibility to liver fibrosis and the rate of disease progression. Variants in genes such as *PNPLA3*, *TM6SF2*, and *MBOAT7* are strongly associated with fibrotic progression in metabolic and viral liver diseases [11–13]. In parallel, epigenetic mechanisms including DNA methylation, histone modifications, and non-coding RNAs are increasingly recognized as key regulators of hepatic stellate cell activation and ECM production. These discoveries have sparked interest in identifying molecular biomarkers that reflect fibrogenic activity and may enable earlier diagnosis or prediction of disease progression. Organoid systems provide a promising experimental platform for integrating genetic background, epigenetic regulation, and functional readouts of fibrotic remodeling in a human tissue context. The conceptual integration of genetic susceptibility, epigenetic regulation, organoid modeling, and biomarker discovery in liver fibrosis research is summarized in Figure 1.

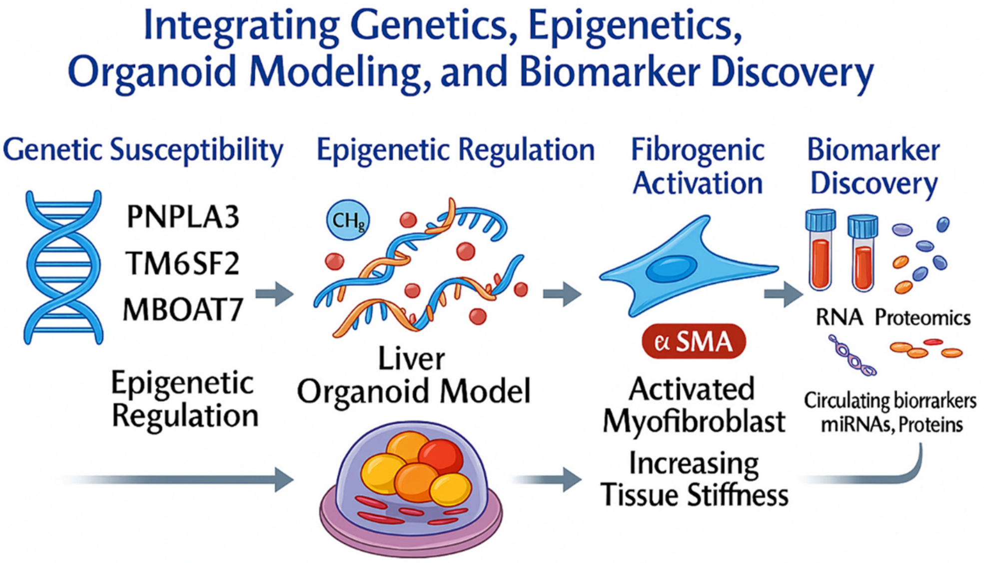

Figure 1. Integration of genetic, epigenetic, organoid modeling, and biomarker discovery approaches in liver fibrosis. The schematic illustrates a conceptual workflow linking inherited risk factors to disease modeling and translational readouts in liver fibrosis. Moving from left to right, genetic susceptibility is represented by key fibrosis- and steatosis-associated variants (e.g., *PNPLA3*, *TM6SF2*, *MBOAT7*). These genetic factors interact with epigenetic regulation, including DNA methylation (CH_3), chromatin modifications, and non-coding RNA-mediated control of gene expression. Genetic and epigenetic inputs are integrated in a liver organoid model, where hepatocyte-like cells and hepatic stellate cells are cultured in a three-dimensional extracellular matrix environment. This system allows for the recapitulation of fibrogenic activation, characterized by stellate cell activation into α-SMA-positive myofibroblasts, extracellular matrix production, and increasing tissue stiffness. Ultimately, signals derived from organoids and disease-associated information contribute to biomarker discovery, highlighting circulating RNA species, proteins, and other molecular signatures detectable in blood or plasma.

2. Cellular and Molecular Basis of Fibrosis

Fibrosis represents a complex and dynamic process involving multiple cell types and signaling pathways [1]. Although the precise mechanisms vary between organs and disease contexts, several core features are shared across fibrotic conditions. Fibrotic responses are typically initiated by tissue injury.

Damage to epithelial or parenchymal cells triggers the release of cytokines, growth factors, and damage-associated molecular signals that activate local immune responses. Immune cells, particularly macrophages and lymphocytes, accumulate at the site of injury and secrete additional mediators that promote tissue repair [1]. In acute injury, these signals eventually subside as the tissue heals. However, when injury persists, inflammatory signaling remains active, driving pathological remodeling. A central event in fibrosis is the activation of fibroblasts into myofibroblasts. These cells acquire contractile properties and express markers such as α-smooth muscle actin (α-SMA) [1]. Myofibroblasts produce large quantities of ECM components, including collagen type I and III, fibronectin, and hyaluronan. Excessive matrix deposition disrupts normal tissue architecture and increases tissue stiffness. The coordinated interaction of inflammatory signaling, fibroblast activation, and ECM accumulation ultimately drives progressive tissue remodeling and organ dysfunction. The key cellular events and signaling pathways involved in this fibrotic cascade are summarized in Figure 2.

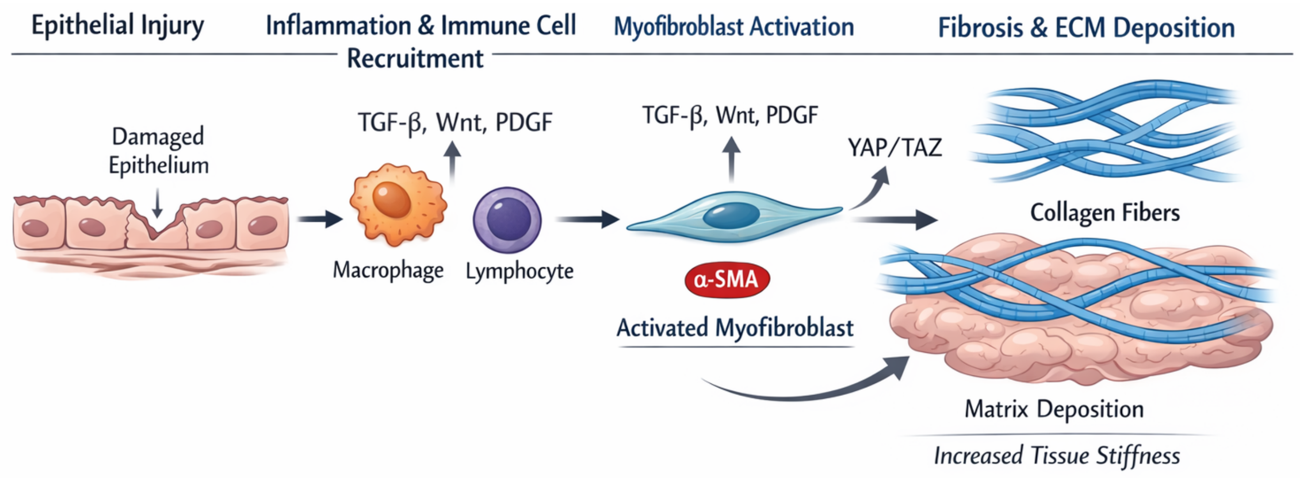

Figure 2. Cellular and molecular mechanisms driving fibrosis. Tissue injury triggers inflammatory signaling, which attracts immune cells like macrophages and lymphocytes. These cells release cytokines and growth factors that stimulate resident fibroblasts, causing them to transform into myofibroblasts. Activated myofibroblasts produce large quantities of extracellular matrix components (ECM), including collagen type I and III, fibronectin, and glucosaminoglycans such as hyaluronan, which contribute to matrix accumulation and tissue stiffness, eventually resulting in organ dysfunction. Key signaling pathways involved in this process include TGF-β, Wnt, PDGF, and mechanotransduction pathways like Yes-associated protein (YAP)/Transcription coactivator with PDZ-binding motif (TAZ).

TGF-β is widely considered the master regulator of fibrotic signaling [14]. This cytokine promotes fibroblast activation, stimulates ECM production, and suppresses matrix degradation. TGF-β signaling operates through both canonical SMAD-dependent pathways and non-canonical pathways involving MAP kinase and PI3K signaling [14]. Because of its central role, TGF-β signaling has become a major target for anti-fibrotic drug development. Mechanical signals also play a critical role in fibrosis progression. As ECM accumulates, tissues become progressively stiffer, altering cell behavior and promoting disease progression [15,16]. Cells sense these mechanical changes through integrins and cytoskeletal structures, activating mechanotransduction pathways such as YAP and TAZ [17,18]. These pathways reinforce fibroblast activation and promote further matrix deposition, creating a positive feedback loop that perpetuates fibrosis. However, in experimental models of liver injury, increases in liver stiffness have been observed to occur before detectable extracellular matrix accumulation, suggesting that early mechanical alterations may contribute to the activation of hepatic stellate cells and the initiation of fibrogenesis [19].

Beyond classical signaling pathways, genetic and epigenetic mechanisms are increasingly recognized as critical determinants of fibrotic susceptibility and progression. This is well-known for idiopathic pulmonary fibrosis [20,21]. Genome-wide association studies have identified several genetic variants that influence susceptibility to fibrotic liver disease and modify disease progression, including variants in *PNPLA3*, *TM6SF2*, and *MBOAT7* [11–13]. These genetic factors may affect pathways involved in lipid metabolism, inflammation, and ECM remodeling, thereby altering the cellular response to chronic injury. Epigenetic regulation further contributes to the dynamic control of fibrogenic gene expression [22]. DNA methylation, histone modifications, and chromatin remodeling influence the transcriptional programs that govern activation of hepatic stellate cells and other stromal populations [23,24]. In addition, non-coding RNAs, including microRNAs and long non-coding RNAs, have emerged as key regulators of fibrotic signaling networks [25,26]. Several microRNAs modulate TGF-β signaling, ECM synthesis, and inflammatory pathways, thereby shaping the balance between tissue repair and pathological fibrosis. These genetic and epigenetic layers of regulation add considerable complexity to the fibrotic response and represent promising targets for therapeutic intervention and biomarker development.

In addition to fibroblasts, several other cell types contribute to fibrotic processes. Injured epithelial cells can adopt aberrant phenotypes and secrete pro-fibrotic factors. Macrophages can assume distinct activation states that either promote or resolve fibrosis. Endothelial cells may undergo endothelial-to-mesenchymal transition (EndMT) in some contexts, further contributing to the pool of matrix-producing cells [1]. The interplay among these diverse cell populations ultimately determines whether tissue repair proceeds normally or progresses toward chronic fibrosis.

Understanding these complex interactions requires experimental systems that preserve multicellular architecture and signaling networks. Among emerging approaches, organoid models provide a promising platform for capturing these features *in vitro*.

3. Organoid Technology: An Overview

Organoids are three-dimensional cellular structures that arise from the intrinsic self-organizing ability of stem or progenitor cells [8]. However, in some cases, mature differentiated cells may regain proliferative capacity through dedifferentiation or reprogramming under defined culture conditions [27]. For example, mature epithelial cells from tissues like liver, intestine, or airway have been shown to generate organoid-like structures after injury-mimicking culture environments or genetic reprogramming. Nevertheless, the efficiency of organoid formation from terminally differentiated cells is generally lower than from stem or progenitor cells, and the mechanisms enabling this cellular plasticity remain incompletely understood. When cultured under suitable conditions, these cells proliferate and differentiate while organizing themselves into structures that mimic native tissues. Organoids typically consist of multiple cell types and often exhibit functional characteristics of the organ they originated from [28]. The advancement of organoid technology is propelled by progress in stem cell biology and tissue engineering. Initial studies showed that adult stem cells taken from intestinal crypts could create self-organizing epithelial structures when grown in a three-dimensional ECM environment [29]. These intestinal organoids replicated essential features of the intestinal epithelium, such as crypt-like regions and specialized cell types. Organoids can be produced from various sources. Organoids derived from adult stem cells are obtained directly from patient biopsies or surgical specimens [30]. These cultures frequently retain the genetic and epigenetic traits of the original tissue, making them valuable for investigating patient-specific disease mechanisms. Alternatively, organoids can be generated from pluripotent stem cells, including embryonic stem cells or induced pluripotent stem cells. By exposing these cells to specific combinations of developmental signaling factors, researchers can direct their differentiation towards particular organ lineages. A diagram outlining the creation of organoid systems from stem or patient-derived cells and their use in experimental disease modeling is depicted in Figure 3.

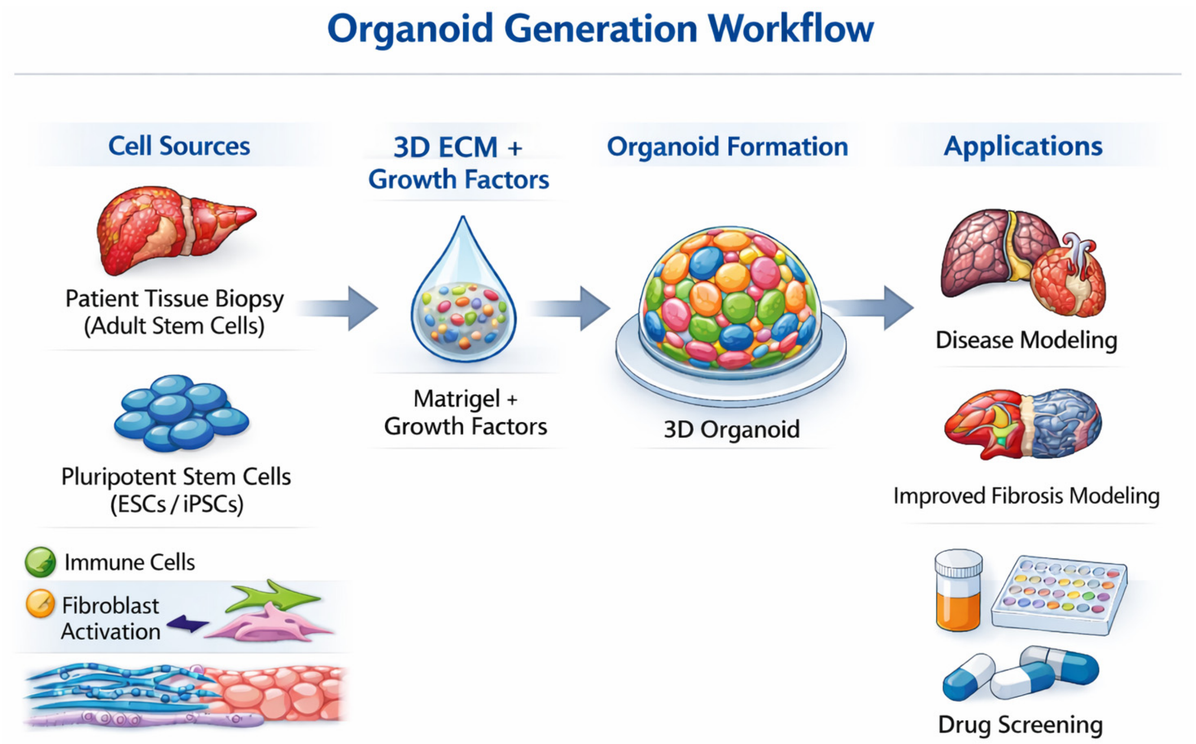

Figure 3. Generation and experimental use of organoid systems. Organoids can be generated from adult stem cells obtained from patient biopsies or from pluripotent stem cells, including embryonic stem cells or induced pluripotent stem cells. These cells are grown in a three-dimensional extracellular matrix scaffold, usually Matrigel, with specific growth factors that promote self-organization and differentiation. The resulting organoids consist of various cell types and mimic aspects of tissue architecture. These systems can then be utilized for genetic manipulation, disease modeling, drug screening, and mechanistic studies.

The culture environment is a crucial component of organoid formation. Most organoids are grown within a three-dimensional ECM matrix scaffold, commonly Matrigel, which provides mechanical support and biochemical cues that promote cell growth and organization [30]. Growth factors and signaling molecules are added to the culture medium to mimic developmental signaling pathways that drive tissue formation. Organoids recapitulate aspects of tissue architecture and cellular diversity, providing experimental advantages over conventional cell cultures. They allow researchers to study interactions between different cell types in a controlled environment and to perform genetic or pharmacological perturbations that would be difficult to perform *in vivo*. These properties make organoids particularly attractive for modeling complex diseases that involve multiple cell populations and structural changes, including fibrosis.

4. Organoid Models of Fibrosis Across Organs

The application of organoid technology to fibrosis research is relatively recent, but several organ systems have already been explored. These models aim to capture key aspects of fibrotic pathology by recreating interactions between epithelial cells, fibroblasts, and other stromal components. Organoid-based modeling approaches have been developed for various organ systems affected by fibrotic disease, allowing for comparative investigation of shared and tissue-specific mechanisms of fibrosis. Representative examples of fibrosis-related organoid models across different organs are shown in Figure 4.

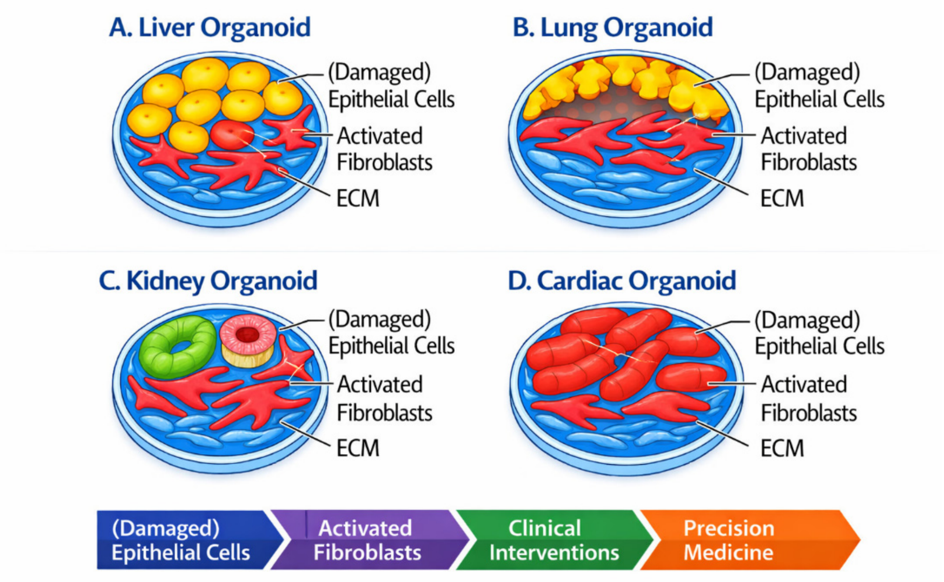

Figure 4. Organoid models are used to study fibrosis in various organs. Organoid technologies have been utilized across multiple organ systems to simulate fibrotic diseases. (**A**) Liver organoids can replicate hepatocyte injury and hepatic stellate cell activation, ultimately leading to extracellular matrix (ECM) deposition. (**B**) Lung organoids provide the opportunity to investigate epithelial injury and fibroblast activation, which are associated with pulmonary fibrosis. (**C**) Kidney organoids, which contain nephron-like structures, can mimic epithelial injury and interstitial matrix accumulation. (**D**) Cardiac organoids, consisting of cardiomyocytes, fibroblasts, and endothelial cells, allow for the analysis of fibroblast activation and fibrotic remodeling that impacts cardiac function.

4.1. Liver Fibrosis

Liver fibrosis is one of the most intensively studied fibrotic diseases and has served as an early testbed for organoid-based modeling approaches. Chronic liver injury caused by viral hepatitis, alcohol abuse, or metabolic disorders triggers activation of hepatic stellate cells, which are the primary drivers of fibrotic matrix deposition in the liver [31]. Organoid systems derived from liver progenitor cells or pluripotent stem cells have been used to recreate aspects of hepatic tissue architecture, including hepatocyte-like cells and cholangiocyte populations [32]. To model fibrosis, researchers often incorporate hepatic stellate cells or fibroblasts into liver organoid cultures [33]. Exposure to pro-fibrotic stimuli such as TGF-β or inflammatory cytokines induces activation of these stromal cells and promotes ECM deposition. In some models, lipotoxic stress or metabolic perturbations are used to mimic non-alcoholic fatty liver disease, a major cause of liver fibrosis. These systems have revealed important insights into how hepatocyte injury signals can activate stellate cells and initiate fibrotic remodeling.

Recent work has further advanced liver fibrosis modeling by integrating multiple liver cell types into microphysiological systems. For example, a liver-on-a-chip model combining human adult liver stem cell-derived hepatobiliary organoids with induced pluripotent stem cell-derived Kupffer cells and hepatic stellate cells successfully recapitulated key features of metabolic dysfunction–associated steatohepatitis (MASH/NASH), including steatosis, inflammation, hepatocellular injury, and stellate cell activation leading to fibrosis [34]. By exposing the system to metabolic and gut-derived factors such as free fatty acids, fructose, lipopolysaccharides, and phenylacetic acid, the model reproduced disease hallmarks and enabled drug testing with responses that paralleled clinical trial outcomes. This approach highlights the potential of complex organoid-based platforms for studying fibrotic liver disease and evaluating therapeutic strategies.

Other studies have highlighted the importance of genetic and epigenetic factors in shaping the progression of liver fibrosis. Variability in disease susceptibility among individuals with similar environmental exposures suggests that host genetic background plays a critical role in determining fibrotic outcomes. Several polymorphisms associated with lipid metabolism, immune regulation, and inflammatory signaling are linked to accelerated fibrosis progression in chronic liver diseases [11–13]. Understanding how these genetic variants influence hepatic stellate cell activation and hepatocyte stress responses remains an active area of investigation.

Large-scale genetic studies provide important insights into interindividual variability in fibrosis progression. Among the most robustly replicated findings is the association between the *PNPLA3* I148M variant and increased risk of steatohepatitis, accelerated fibrosis progression, and hepatocellular carcinoma. Additional variants in *TM6SF2*, *MBOAT7*, and *HSD17B13* further modulate susceptibility to metabolic liver disease and fibrotic outcomes [11–13]. These genetic determinants influence pathways such as lipid metabolism, hepatocellular stress responses, and inflammatory signaling, thereby shaping the microenvironment that promotes hepatic stellate cell activation. Incorporating these variants into experimental organoid systems, either through the use of patient-derived tissues or CRISPR-based genome editing, offers a powerful strategy to dissect how specific genetic backgrounds influence fibrogenic signaling and therapeutic responsiveness.

Epigenetic mechanisms also profoundly influence fibrogenic pathways in the liver. Activation of hepatic stellate cells is accompanied by extensive chromatin remodeling and alterations in DNA methylation patterns that promote expression of genes involved in ECM production [35]. Histone modifications can regulate the accessibility of profibrotic transcriptional programs, while non-coding RNAs modulate post-transcriptional gene regulation. Increasing evidence suggests that specific microRNAs act either as drivers or suppressors of fibrosis by targeting key signaling molecules within the TGF-β and Wnt pathways [36,37]. Organoid models provide a powerful platform for investigating these regulatory mechanisms in a human cellular context. Because organoids can be derived from patient tissues, they allow researchers to study how individual genetic backgrounds influence fibrotic responses. Integration of CRISPR-based gene editing with organoid systems further enables functional testing of candidate genes and regulatory elements implicated in fibrosis susceptibility.

4.2. Lung Fibrosis

Pulmonary fibrosis, especially idiopathic pulmonary fibrosis, is characterized by progressive scarring of the lung interstitium and destruction of alveolar architecture. Modeling this disease has historically been challenging due to the structural complexity of lung tissue. Recent advances in lung organoid technology enable the generation of airway and alveolar structures containing multiple epithelial cell types. In lung fibrosis models, epithelial organoids are often co-cultured with fibroblasts or mesenchymal cells. Injury to epithelial cells can be simulated through exposure to chemical toxins, inflammatory mediators, or genetic perturbations associated with idiopathic pulmonary fibrosis. Hyaluronan (HA) is a major component of the ECM that becomes strongly upregulated in injured or remodeling tissues and has been increasingly recognized as an important regulator of pulmonary fibrosis. In fibrotic lung diseases such as idiopathic pulmonary fibrosis (IPF), HA accumulates in the lung interstitium and contributes to inflammation, fibroblast activation, and excessive extracellular matrix deposition [38]. A key mechanism underlying these effects involves interactions between HA and its principal cell-surface receptor CD44. The binding of HA to CD44 can regulate fibroblast migration, activation, and survival, thereby promoting the accumulation of myofibroblasts that produce collagen and other matrix components. In addition, HA-CD44 signaling has been linked to the acquisition of an invasive fibroblast phenotype, enabling fibroblasts to infiltrate damaged tissue and contribute to progressive matrix remodeling and fibrotic expansion [38]. These findings support the concept that HA is not merely a structural matrix component but also an active signaling molecule that modulates fibroblast behavior and tissue remodeling. These interactions are well suited for experimental interrogation in organoid-based co-culture systems. Lung organoids have also been used to investigate how aging, environmental exposures, and genetic risk factors influence susceptibility to fibrosis [39,40].

4.3. Kidney Fibrosis

Kidney fibrosis is a hallmark of chronic kidney disease and is closely associated with progressive loss of renal function. Organoid models of the kidney are typically generated from pluripotent stem cells and contain structures that resemble developing nephrons, including glomerular and tubular components [41]. While these organoids mainly represent early stages of kidney development, they have proven to be valuable for investigating the initial mechanisms of renal injury and fibrosis. By inducing injury in kidney organoids experimentally, researchers can stimulate the activation of stromal cells and the increased deposition of ECM components. These responses mimic some aspects of interstitial fibrosis seen in chronic kidney disease. These models allow exploration of how damage to the epithelial cells in the nephron triggers activation of surrounding stromal cells and the process of fibrotic remodeling. Fibrotic remodeling is also a feature of several inherited cystic kidney diseases, such as autosomal dominant and autosomal recessive polycystic kidney disease, where progressive cyst expansion is accompanied by interstitial fibrosis.

4.4. Cardiac Fibrosis

Cardiac fibrosis occurs in response to myocardial infarction, pressure overload, or other forms of cardiac stress. It is characterized by the accumulation of collagen and other extracellular matrix components within the myocardium, which disrupts electrical conduction and impairs mechanical function. Cardiac organoids and engineered heart tissues composed of cardiomyocytes, fibroblasts, and endothelial cells have been used to model aspects of cardiac fibrosis [42]. In these systems, fibroblast activation can be induced through exposure to TGF-β or mechanical stress. Activated fibroblasts deposit ECM within the organoid, leading to increased tissue stiffness and altered electrical signaling. Such models provide a platform for studying how fibrotic remodeling affects cardiac function and for evaluating potential anti-fibrotic therapies.

5. Advantages of Organoid Models for Fibrosis Research

Organoid systems offer several advantages that make them particularly valuable for studying fibrotic diseases. One of the most important strengths of organoids is their ability to capture aspects of human tissue biology that are difficult to reproduce in conventional experimental models. Because organoids are derived from human cells, they retain species-specific gene expression patterns, signaling pathways, and cellular responses that may differ significantly from those observed in animal models. Another major advantage is the preservation of three-dimensional architecture. Tissue structure plays a critical role in regulating cell behavior, and the spatial arrangement of cells influences how signals are transmitted and interpreted. In organoids, cells interact with each other and with the surrounding extracellular matrix in ways that more closely resemble their natural environment. This spatial organization allows researchers to study processes such as epithelial injury, fibroblast activation, and ECM remodeling within a context that approximates real tissue. Organoid cultures also allow controlled manipulation of the cellular microenvironment. Researchers can introduce specific growth factors, cytokines, or mechanical stimuli to probe the mechanisms that drive fibrosis. Genetic manipulation using CRISPR-based approaches further enables the investigation of disease-associated genes and signaling pathways [43]. These capabilities make organoids powerful tools for dissecting complex molecular networks involved in fibrotic disease.

A particularly exciting aspect of organoid technology is the possibility of generating patient-specific models from different tissues such as liver, prostate, and kidney [44–47]. Organoids derived from individual patients retain many of the genetic and epigenetic features of the original tissue. This opens the possibility of studying how different individuals respond to injury or therapeutic interventions. In the future, patient-derived organoids may be used to test candidate treatments and guide personalized therapeutic strategies for fibrotic diseases.

An additional advantage of organoid platforms is their potential for biomarker discovery and for validating drug sensitivity and resistance [48]. Organoids can be generated from patient-derived tissues and cultured under controlled experimental conditions, providing a unique opportunity to identify molecular signatures associated with fibrotic progression. Transcriptomic, epigenomic, and proteomic analyses performed on organoid cultures can reveal candidate biomarkers that reflect early stages of disease or predict therapeutic responses. Moreover, integrating organoid systems with emerging analytical technologies such as single-cell sequencing and spatial transcriptomics enables detailed characterization of cell-type-specific signaling pathways and cellular diversity involved in fibrosis [49]. These approaches may facilitate the identification and validation of novel circulating biomarkers derived from extracellular vesicles, secreted proteins, or nucleic acids that could improve non-invasive diagnosis and monitoring of liver fibrosis.

An important aspect of validating organoid models is determining how closely their molecular profiles resemble those of human tissues affected by disease. Recent transcriptomic and single-cell sequencing studies have begun to compare gene expression signatures of organoids with those observed in patient-derived fibrotic tissues. These analyses indicate that organoid cultures can reproduce key transcriptional programs associated with epithelial injury, inflammatory signaling, and fibrogenic activation. At the same time, such comparisons also reveal differences in cellular composition and maturation states between organoids and native tissues, highlighting areas where further model refinement is required. Systematic integration of organoid transcriptomics with datasets derived from human fibrotic tissue will therefore be important for benchmarking model fidelity and identifying cell-type-specific disease signatures.

In addition to providing mechanistic insights, organoid systems may also help in identifying clinically relevant biomarkers. Profiling the secretome of organoid cultures can reveal proteins, extracellular vesicles, and nucleic acids released during fibrotic remodeling [34,50]. These molecules could potentially serve as candidate circulating biomarkers that reflect disease activity in patients. For example, microRNAs associated with fibrosis, collagen fragments, and enzymes involved in matrix remodeling are found in patient serum and are currently being studied as non-invasive markers of liver fibrosis. By combining organoid models with high-throughput multi-omics approaches, such as transcriptomics, epigenomics, proteomics, and metabolomics, researchers will be able to systematically identify molecular signatures linked to early fibrogenesis and treatment response. These integrative analyses have the potential to expedite the translation of experimental findings into clinically valuable diagnostic tools.

6. Limitations of Current Organoid Models

Despite their considerable promise, organoid models still face several important limitations that must be addressed before they can fully recapitulate fibrotic disease. One major challenge is the incomplete representation of the cellular diversity found in native tissues. Many organoid systems are primarily composed of epithelial cells and lack the full complement of stromal, immune, and vascular components that participate in fibrosis *in vivo*. Because these cell populations interact extensively during fibrotic remodeling, their absence can limit the physiological relevance of the model. Another limitation involves the ECM environment used for organoid culture. Most organoids are grown in Matrigel, a gelatinous basement membrane-like ECM derived from Engelbreth-Holm-Swarm mouse sarcoma cells that contains laminin, collagen IV, entactin, heparan sulfate proteoglycans, and various growth factors [51]. Although Matrigel provides a supportive scaffold for organoid growth, its composition is complex, poorly defined, and can exhibit significant batch-to-batch variability [51]. Moreover, its mechanical properties do not necessarily match those of fibrotic tissues, which are typically much stiffer [52]. As a result, conventional organoid cultures may fail to capture the mechanical cues that strongly influence fibroblast activation and matrix deposition. Reproducibility and standardization also present challenges. Organoid cultures can vary significantly depending on factors such as the source of cells, culture conditions, and handling procedures.

This variability can complicate comparisons between studies and hinder the development of standardized experimental protocols. Consequently, efforts are underway to establish systematic workflows to improve functionality and reproducibility in work with organoids. These will allow the transfer of organoid technology from an artisanal laboratory method into a more standardized, high-throughput platform for realizing practical clinical and industrial applications with full Good Manufacturing Practice (GMP) compliance [53].

Additionally, many organoid systems remain difficult to scale for high-throughput applications. Finally, fibrosis is typically a chronic process that develops over long periods of time *in vivo*. Replicating such long-term disease progression in organoid cultures is challenging, as these systems are often maintained for relatively short durations. Developing culture conditions that support long-term stability and maturation will be important for more accurately modeling chronic fibrotic diseases. Moreover, generating organoids directly from fibrotic tissues would be a valuable complementary apporoach for investigating the fibrotic environment in detail.

7. Emerging Technologies Enhancing Fibrosis Organoid Models

Recent technological advances are helping to overcome some of the limitations of current organoid systems [53]. One promising approach involves incorporating additional cell types through co-culture strategies. By introducing fibroblasts, endothelial cells, or immune cells into organoid cultures, researchers can recreate more complex tissue microenvironments [54]. These multicellular systems enable the investigation of how interactions among different cell populations contribute to fibrosis [55]. Recent technological developments are further expanding the capabilities of organoid systems by enabling more physiologically relevant microenvironments and more detailed molecular analyses. An overview of several emerging technologies that enhance organoid-based fibrosis models is presented in Figure 5.

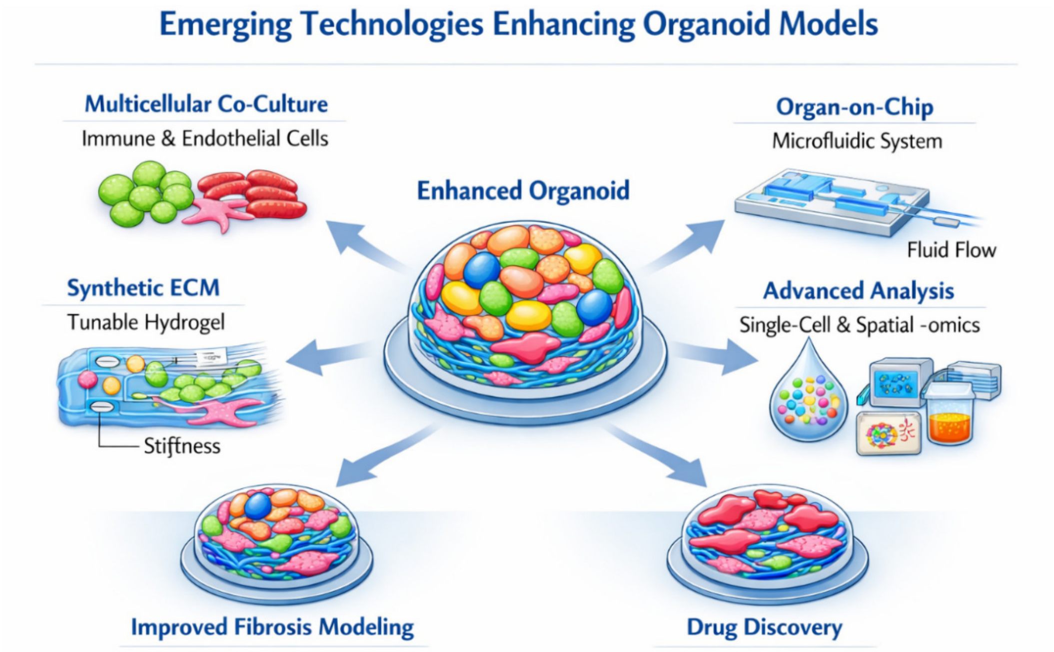

Figure 5. Emerging technologies enhancing organoid models for fibrosis research. Several technological innovations are improving the physiological relevance of organoid systems. Co-culture strategies incorporate stromal, endothelial, and immune cells to recreate complex tissue microenvironments. Microfluidic organ-on-chip devices enable controlled mechanical forces, fluid flow, and chemical gradients. Synthetic extracellular matrices allow precise tuning of biochemical composition and stiffness to mimic fibrotic tissue. Advanced analytical approaches such as single-cell RNA sequencing, spatial transcriptomics, and high-resolution imaging provide detailed insights into cellular interactions and molecular pathways within organoids. Together, these technologies expand the utility of organoid platforms for studying fibrotic diseases and developing anti-fibrotic therapies.

Microengineering technologies are transforming organoid research. Organ-on-chip platforms use microfluidic devices to control fluid flow, hydrodynamic parameters, mechanical forces, and chemical gradients within cultured tissues. Integrating organoids with these systems allows researchers to mimic aspects of physiological circulation and mechanical stress that are difficult to reproduce in static cultures [56]. Such platforms may be particularly valuable for studying how mechanical forces influence fibrotic remodeling. Another area of innovation involves the development of synthetic ECMs. Unlike Matrigel, synthetic hydrogels can be engineered with precisely defined biochemical and mechanical properties [53]. By tuning matrix stiffness or incorporating specific signaling molecules, researchers can create environments that more closely resemble fibrotic tissues. This capability enables systematic investigation of how mechanical and biochemical cues regulate fibroblast activation and ECM production. Advances in imaging and molecular profiling are also enhancing the study of fibrosis in organoids. Techniques such as single-cell RNA sequencing, spatial transcriptomics, and high-resolution microscopy allow detailed characterization of cellular states and interactions within organoid cultures. These tools provide unprecedented insight into the cellular dynamics that drive fibrotic remodeling.

Epigenomic profiling technologies are beginning to play an important role in organoid-based fibrosis research. Methods such as ATAC-seq, ChIP-seq, and single-cell DNA methylation profiling allow detailed mapping of chromatin accessibility and regulatory elements that control fibrogenic gene expression [57–59]. Applying these techniques to organoid systems can reveal how epigenetic landscapes change during hepatic stellate cell activation and fibrotic remodeling. Organoids can be derived from genetically diverse patients, making comparative epigenomic analyses valuable in identifying regulatory networks that distinguish progressive from non-progressive disease states. This information could ultimately support the discovery of epigenetic biomarkers and therapeutic targets.

Another emerging direction involves the characterization of biomechanical properties in organoid systems. Tissue stiffness is a defining feature of fibrotic remodeling and plays a central role in activating mechanotransduction pathways such as YAP/TAZ signaling. While stiffness has been extensively studied in fibrotic tissues *in vivo*, quantitative measurements of mechanical properties in fibrosis-related organoid models remain relatively limited. Incorporating techniques such as atomic force microscopy, traction force microscopy, or tunable synthetic hydrogels could enable systematic investigation of how mechanical cues regulate fibroblast activation and extracellular matrix accumulation within organoid systems. Developing such approaches will be important for determining whether organoids faithfully recapitulate the biomechanical environment characteristic of fibrotic tissues.

8. Future Directions

As organoid technology continues to evolve, several developments are likely to further expand its utility for fibrosis research. One important goal is to incorporate immune components into organoid systems. Immune cells play essential roles in both promoting and resolving fibrosis, yet they are largely absent from most current models. Developing strategies to integrate macrophages, lymphocytes, and other immune populations into organoid cultures will be critical for capturing the full complexity of fibrotic responses. Another key objective is the generation of vascularized organoids [60–62]. Blood vessels play central roles in tissue homeostasis and repair, and endothelial dysfunction is increasingly recognized as an important contributor to fibrosis. Incorporating vascular networks into organoid systems could improve nutrient delivery, enable modeling of vascular-stromal interactions, and enhance the physiological relevance of these models. Developing culture systems that allow organoids to mature and persist over extended periods will also be important. Such systems would enable modeling of chronic disease progression and allow researchers to study how fibrotic processes evolve over time. Improvements in biomaterials, culture media, and bioreactor technologies may help achieve this goal. In parallel, organoid models are likely to play an expanding role in drug discovery [63]. High-throughput screening platforms based on organoids could enable systematic testing of candidate anti-fibrotic compounds in human tissue contexts. Because organoids can be derived from individual patients, they also offer opportunities for personalized medicine approaches in which therapeutic responses are evaluated in patient-specific models. Finally, integrating organoid experiments with computational modeling and systems biology approaches may help unravel the complex regulatory networks that govern fibrosis. By combining experimental and computational methods, researchers may be able to identify key molecular drivers of fibrotic disease and develop more effective therapeutic strategies.

9. Conclusions

Fibrosis represents a significant clinical challenge affecting multiple organs and contributing significantly to the global disease burden. Although substantial progress has been made in understanding the molecular pathways involved in fibrotic remodeling, the development of effective therapies has been hindered by limitations in existing experimental models. Organoid technology offers a powerful new approach for modeling fibrotic diseases *in vitro*. By recreating aspects of tissue architecture and cellular diversity, organoids provide a more physiologically relevant platform than traditional cell culture systems while maintaining the experimental accessibility of *in vitro* models. Early studies across the liver, lung, kidney, and cardiac systems show that organoids reproduce key features of fibrotic pathology, including fibroblast activation, ECM deposition, and altered tissue function. Despite these advances, current organoid models remain imperfect representations of native tissues. Challenges such as incomplete cellular complexity, lack of vascularization, and difficulties in modeling long-term disease progression must be addressed. Ongoing developments in bioengineering, microfluidics, biomaterials, and single-cell analysis are likely to overcome many of these limitations. In particular, integrating organoid technologies with genomic and epigenomic profiling approaches may open new avenues for identifying molecular drivers and biomarkers of fibrosis. Patient-derived organoids, combined with high-throughput sequencing technologies, could enable a systematic investigation of genetic susceptibility, epigenetic regulation, and treatment response in fibrotic disease. Such strategies may help bridge the gap between mechanistic studies and clinical translation, ultimately supporting the development of precision medicine approaches for patients with chronic liver disease. Beyond their application to individual organs, future organoid platforms may also help elucidate systemic interactions between metabolic, inflammatory, and biomechanical processes that drive fibrotic remodeling across multiple tissues. Importantly, organoid systems provide a promising bridge between mechanistic studies and clinical biomarker discovery. Integrating patient-derived organoids with genomic and epigenomic profiling may enable the identification of molecular signatures that predict disease progression or therapeutic response.

As these technologies mature, organoid models are poised to become indispensable tools for studying fibrosis. They hold promise not only for elucidating fundamental mechanisms of disease but also for accelerating drug discovery and enabling personalized therapeutic strategies. The ability to recapitulate fibrosis in controlled laboratory systems may ultimately transform our understanding of fibrotic diseases and accelerate the development of new therapeutic strategies.

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

During the preparation of this manuscript, the author used EditMyEnglish to polish the language. After using this tool/service, the author reviewed and edited the content as needed and takes full responsibility for the content of the published article.

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