Review

Scaffold Proteins in Fibrotic Diseases of Visceral Organs

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Posted Date: 23 January 2025

doi: 10.20944/preprints202501.1657.v1

Keywords: Scaffold Proteins; Fibrosis; Signal Transduction

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Scaffold Proteins in Fibrotic Diseases of Visceral Organs

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Abstract: Fibrosis, characterized by excessive extracellular matrix (ECM) deposition, disrupts tissue architecture and impairs organ function, ultimately leading to severe health consequences and even failure of vital organs. Despite advances in understanding its underlying mechanisms, effective therapeutic options for fibrotic diseases remain limited. Emerging evidence highlights scaffold proteins as critical regulators in the progression of fibrosis. These multifunctional proteins act as molecular platforms that organize and coordinate key signaling pathways, facilitating precise spatial and temporal regulation of cellular processes, including ECM remodeling, cytoskeletal organization, and cell migration. Their pivotal role in orchestrating profibrotic and antifibrotic signals places scaffold proteins at the intersection of fundamental biological processes and fibrotic pathology. Furthermore, their dynamic, context-dependent regulation offers a unique therapeutic window for modulating fibrosis. This review examines the contributions of scaffold proteins to fibrotic diseases of the lung, heart, liver, and kidney, emphasizing their potential as novel therapeutic targets for managing and reversing fibrosis.

Keywords: scaffold proteins; fibrosis; signal transduction

1. Introduction

Fibrosis is a major contributor to global morbidity and mortality, marked by excessive extracellular matrix (ECM) accumulation that progressively disrupts tissue architecture and compromises organ function. This pathological process arises from persistent and repetitive injuries that overwhelm normal tissue repair mechanisms, triggering fibroblast activation and substantial collagen deposition. The initiation and amplification of fibrogenesis involve complex interactions among various cell populations, including epithelial and endothelial cells undergoing epithelial-mesenchymal and endothelial-mesenchymal transitions, as well as macrophages, which orchestrate immune and inflammatory responses. By secreting TGF-β and other profibrotic mediators, macrophages activate fibroblasts, amplify immune responses, and exacerbate fibrotic progression. Increased endothelial permeability further contributes to this cycle by facilitating immune cell infiltration into fibrotic niches. Fibrosis affects multiple organs, including the lungs, heart, liver, and kidneys, with devastating clinical consequences. Despite emerging evidence suggesting that fibrosis can be reversed under certain conditions, current therapeutic options remain limited, underscoring the urgent need to unravel the molecular mechanisms driving fibrosis and identify novel therapeutic targets.

Scaffold proteins, traditionally regarded as structural components facilitating protein-protein interactions, have recently gained attention for their active roles in modulating key signaling pathways implicated in fibrosis. These multifunctional proteins serve as platforms for organizing and integrating diverse signaling molecules, ensuring precise spatial and temporal regulation of cellular responses. Historically, technical challenges in studying scaffold proteins hindered progress, but

 doi:10.20944/preprints202501.1657.v1

recent advances in high-resolution imaging, protein interaction mapping, and molecular biology techniques have transformed the field. Cutting-edge approaches such as proteomics and single-cell transcriptomics have illuminated the dynamic roles of scaffold proteins in regulating ECM deposition, fibroblast activation, and immune-inflammatory signaling during fibrotic progression.

This review aims to address the central question: how do scaffold proteins function as pivotal regulators in the signaling networks underlying fibrosis **(Table 1)**? By examining their roles across different organs, including the lungs, heart, liver, and kidneys, we aim to uncover shared mechanisms and organ-specific nuances. Scaffold proteins integrate signals from mechanical, inflammatory, and immune pathways, positioning them as critical nodes in fibrosis pathogenesis. Their ability to orchestrate complex signaling networks presents both challenges and opportunities for therapeutic intervention. We propose a unified framework to explore these proteins' regulatory roles, highlighting their potential as novel targets for modulating fibrosis and improving patient outcomes **(Table 2)**.

2. Overview of Scaffold Proteins

Since the 1980s, the understanding of scaffold proteins has undergone a remarkable transformation, evolving from their initial perception as static "assembly platforms" to being recognized as dynamic regulators of cellular signaling. Early studies focused on how scaffold proteins cluster kinases, phosphatases, and receptors, as exemplified by Grb2 in the Ras/MAPK pathway[1–3]. By the early 2000s, it became evident that scaffold proteins extend beyond mere linkage roles. For instance, AKAPs emerged as precise organizers, anchoring PKA to specific intracellular locales to sharpen cAMP-mediated responses[4,5]. Advances in cryo-electron microscopy (cryo-EM) and proteomics further revealed their role in phase separation, showing how scaffold proteins form membraneless organelles and regulate RNA and protein metabolism[6,7].

Functionally, scaffold proteins exhibit immense versatility, operating within membranes, the cytoplasm, and the nucleus. This spatial distribution allows them to enhance signaling specificity and efficiency while minimizing pathway cross-talk. For example, caveolin-1, residing in membrane caveolae, orchestrates nitric oxide synthesis and TGF-β signaling, which are critical for endothelial function and fibrosis progression[8–10].Caveolin-1 also acts as a scaffold, organizing specific lipids and signaling molecules to modulate signal transduction[11]. Similarly, Annexin A2 associates with phospholipids in a calcium-dependent manner, serving as a plasma membrane scaffold that organizes lipid rafts and facilitates actin cytoskeleton assembly, essential for membrane trafficking and cell signaling[12]. IQGAP1 interacts with cytoskeletal and signaling components, regulating cell morphology, motility, and intracellular signaling [13–15]. In yeast, Ste5 assembles components of the MAP kinase signaling cascade in the cytoplasm, ensuring efficient signal transduction during mating responses [15,16]. Shank proteins in neuronal synapses bridge receptors to the cytoskeleton, modulating synaptic plasticity and signal conduction [17,18]. In the nucleus, nucleoporins like NUP133 serve as scaffolds within the nuclear pore complex, facilitating macromolecular transport and maintaining nuclear integrity [19]. Huntingtin, another nuclear scaffold protein, participates in DNA repair complexes, particularly under oxidative stress, contributing to genomic stability [20,21].

Scaffold proteins are now recognized as critical to cellular processes such as cell proliferation, differentiation, mechanotransduction, and phase separation. By temporally and spatially coordinating multiple pathways, they amplify specific signaling outputs or act as "dispatchers" integrating diverse signals. A striking example is the Raf-MEK-ERK module in the MAPK cascade, where scaffold proteins enable swift and precise phosphorylation events[22]. In mechanotransduction, integrin-associated scaffold proteins link the extracellular matrix (ECM) to the cytoskeleton, activating pathways like TGF-β that are vital in fibrosis[23]. Beyond these, scaffold proteins also regulate key signaling networks such as Hippo and Wnt, underscoring their broad regulatory potential.

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3. Scaffold Proteins in Pulmonary Fibrosis

Pulmonary fibrosis comprises a diverse group of interstitial lung diseases (ILDs), unified by the hallmark of excessive extracellular matrix (ECM) deposition leading to disrupted lung architecture and impaired gas exchange. IPF is the most common and severe subtype, characterized by progressive scarring of lung tissue with an unknown etiology. Other forms of fibrosis include connective tissue disease-associated ILD, hypersensitivity pneumonitis, and pneumoconiosis, such as silicosis, which result from environmental or occupational exposures[24]. Although these conditions share overlapping pathological features, the underlying molecular mechanisms often differ, with scaffold proteins emerging as critical regulators across these varied contexts.

3.1. Scaffold Proteins in Idiopathic Pulmonary Fibrosis

IPF is a severe disease with a median survival of 2–3 years[25]. Patients present with progressive dyspnea, chronic dry cough, and inspiratory crackles. Advanced stages lead to respiratory failure due to the loss of alveolar units, with HRCT revealing a typical usual interstitial pneumonia (UIP) pattern. The pathogenesis involves recurrent epithelial injury, aberrant fibroblast activation, and dysregulated immune responses, resulting in ECM accumulation. Despite identifying key pathways like TGF-β and Wnt/β-catenin, therapeutic options are limited, with current treatments like pirfenidone and nintedanib only slowing progression. This has led to exploration of novel targets, such as scaffold proteins, which actively organize pro-fibrotic signaling and could provide new therapeutic opportunities.

Table 1. List of scaffold proteins in fibrotic diseases of visceral organs.

Organ Fibrosis	Diseases	Regulator	Function	Mechanism	Sample	References
Pulmonary Fibrosis	IPF	ARRB1↑	Promoting fibrosis.	Influencing fibroblast activity and AEC2 regeneration.	Bleomycin model in ARRB1$^{-/-}$ mice	[26]
		IQGAP1↓	Amplifing fibroblast activation, exacerbating fibrogenesis.	Promoting differentiation and matrix production.	Fibroblast, IQGAP1 KO mice	[27,28]
		Cav1↓	Exacerbating fibrogenesis.	Promoting fibroblast activation and proliferation.	Fibroblast	[29,30]
		P62/SQSTM1↑	Promoting oxidative stress.	Promoting the interaction between P62 and SLC15A3.	Macrophage, bleomycin-mice model	[31]
		P62/SQSTM1↑	Disrupting autophagy flux and driving senescence.	Modulating the autophagy-lysosome pathway.	AT2 cells, bleomycin-induced mice model	[32]
		AGGF1↓	Exacerbating vascular remodeling, inflammation, and fibrosis.	Promoting Smad2/3 and ERK1/2 phosphorylation.	Mouse models of TAA	[33]
		A6-Integrin↑	Promoting proteolysis of basement membrane,	Enhancing the coupling with β1-integrin.	Myofibroblast	[34]

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		facilitating myofibroblast invasion.			
	Axin1↓	Promoting pulmonary fibrosis.	Promoting β-catenin degradation.	Fibroblast, bleomycin-induced mice	[35]
	Axin1↓	Promoting pulmonary fibrosis.	Activating Wnt signaling.	Fibroblasts, bleomycin-induced mice	[36]
	TRPV4-PI3Kγ↑	Promoting stiffened lung parenchyma.	Promoting myofibroblast differentiation and excessive ECM production	Myofibroblast, mice	[37,38]
	HER2↑	Promoting pulmonary fibrosis.	Enhancing , migration and ECM deposition.	Fibroblasts	[39]
	IQGAP1↑	Promoting pulmonary fibrosis.	Increasing TGF-β expression.	Myofibroblast, IQGAP1 KO mice	[40]
	BRD4↑	Promoting pulmonary fibrosis.	Recruiting acetyltransferase p300 to histones. Upregulating Nox4 expression.	Aged mice with established lung fibrosis	[41]
	TKS5↑	Mediating ECM degradation.	Localizing proteases such as MMP2, MMP9, and MMP14.	Lung fibroblasts, bleomycin-treated mice	[42,43]
	Numb↑	Promoting ECM deposition and fibrosis.	Activating β-catenin signaling in lung epithelial cells.	ATII cells	[44]
	TRAF6↑	Promoting pulmonary fibrosis.	Activating the IL-33.	BMDM, Usp38$^{-/-}$ mice	[45]
Silicosis	Cav-1↑	Promoting Autophagy, apoptosis, and fibrosis.	Interacting with LC3BII and p62.	AEC , PM2.5-induced mice	[46–49]
	SULF1↑	Promoting silicosis.	Enhancing WNT/β-catenin signaling.	Bronchial epithelial cells, SULF1 knockdown mice	[50]
	STING signaling pathway↑	Promoting senescence. Promoting fibrosis.	Damaging mtDNA and activating the cGAS-STING-NF-κB axis.	ATII cells	[51–53]
	LGALS3↑	Mediating endomt in Silicosis.	Activating PI3K/AKT Pathway.	Silica-induced mouse	[54,55]

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			Regulating Cellular Processes.	Promoting endomt and Fibrosis.		
		YWHAZ↑	Promoting fibrosis and inflammation.	Enhancing Wnt/β-catenin and TGF-β Signaling.	Human bronchial epithelial cells	[56]
Cardiac fibrosis	Myocardial infarction	C-Cbl↑	Promoting cardiac fibrosis.	degradating SERCA2a, and impairing calcium cycling	Ischemic HF models	[57]
		JAK2↑	Promoting cardiac fibrosis.	Elevating circulating PCSK9 levels via JAK2/STAT3 signaling.	Myofibroblast, rat MI models	[58]
		PW1↑	Promoting ECM production.	Activating PFAS.	Cardiac fibroblasts, PW1 knockout mice	[59,60]
		AKAP2↓	Exacerbating cardiac dysfunction.	Inhibiting ERα via camp signaling.	Cardiomyocytes	[61,62]
		NDP52↓	Facilitating autophagosome-lysosome fusion and promoting mitophagy.	Interacting with TBK1 and RAB7.	Cardiomyocyte	[63]
	Heart failure	ERBB2↑ (HER2)	Promoting Heart Regeneration.	Activating YAP and triggering EMT-like processes.	Cardiomyocytes	[64]
		Shank3↑	Promoting cardiac fibrosis.	Altering Ca^{2+} homeostasis	Cardiomyocytes, overexpressing-Shank3 mice	[65]
		BRD4↑	Promoting fibroblast activation and cardiac dysfunction.	Facilitating the formation of IL-1β, activating RELA-dependent enhancers.	Heart failure models	[66,67]
	Other cardiac fibrosis	Cav1↓	Promoting fibrosis and hypertrophy.	Reducing transverse tubule organization and Ca^{2+} homeostasis.	Cav1 knockout mice	[68]
		Cav1↓	Promoting diabetic cardiomyopathy.	Activating NF-κB pathway.	Models treated with PD	[69]
		Peli1↑	Facilitating fibroblast and inflammasome activation.	Activating NF-κB and AP-1, upregulating mir-494-3p	CM-fibroblast	[70,71]
		STRN↑	Promoting left ventricular hypertrophy and cardiac fibrosis.	Modulating hypertrophic signaling	Cardiomyocyte	[72]

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		GIPC1↓	Activating fibroblast and promoting ECM accumulation.	Stabilizing β1 receptors expression and modulating MAPK signaling.	Isoproterenol-induced cardiac fibrosis models	[73,74]
		Grb2↑	Promoting fibrotic remodeling of the heart.	Facilitating the activation of ERK1, and phosphorylating WAVE2.	Cardiac myofibroblast	[62]
		BRD4↑	Promoting pathological cardiac hypertrophy.	Increasing, ROS generation.	Fibroblast	[75,76]
		Myd88↓	Exacerbating cardiac fibrosis.	Modulates TCR-dependent signaling pathways.	T-cell	[77]
		PML↑	Activating fibroblast.	Stabilizing and activating p53, amplifying TGF-β1-driven profibrotic signaling.	Fibroblast	[78]
		RACK1↓	Exacerbating ECM production and cardiac fibrosis.	Promoting Smad3-mediated CF activation.	TGF-β1-treated cardiac fibroblasts, MI mouse model	[79]
		SHARPIN↑	Promoting CF activity and ECM deposition.	Promoting fibroblast proliferation, and myofibroblast transformation.	An angio-induced MF mouse model	[80]
		SKI↓	Mitigating heart fibrosis.	Repressing TGF-β1/Smad signaling and activating the Hippo pathway.	A post-MI rat model	[81]
		RIP2↑	Promoting pro-inflammatory responses and hypertrophic remodeling.	Facilitating activation of NF-κB and MAPK/GATA4/p300 pathways.	A mouse model of TAC	[82]
		BCL10↑	Fueling, cardiomyocyte hypertrophy and fibroblast-driven fibrosis.	Activating NF-κB.	Macrophages	[83]
Heptic fibrosis	Liver injury	AKAP12↓	Exacerbating liver damage.	Increasing PCSK6 and enhancing STAT3 and NF-κB signaling.	Models of ALI and chronic liver fibrosis	[84–86]
		ARRB1↑	Promoting liver fibrosis.	Activating Rab27A and amplifying the release of small EVs.	Murine models of CCl_4 or MCD	[87,88]

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	Cav1↑	Promoting liver fibrosis.	Driving vesicular trafficking and exocytosis of TIMP-1.	HSCs	[89]
	Gab1↓	Promoting rapid regeneration and inflammation.	Enhancing Bcl-xl expression, and suppressing STAT3 signaling.	Mcl-1 knockout mice	[90–92]
MASH	Cbl↓	Promoting liver fibrosis.	Inhibiting degrading PYK2, and promoting PYK2-JNK signaling.	CBL mutant cells	[93,94]
	FLNA↑	Promoting inflammation and fibrogenesis.	Increasing TGF-β1 and CCL2 while inhibiting the activity of MMP-1 and MMP-2.	Macrophages, HSCs	[95]
	SLC9A1 （NHE1）↑	Promoting apoptosis and liver fibrosis.	Increasing inflammatory signaling through the p38 MAPK pathway.	PA-induced steatosis models in AML12 and hepg2 hepatocytes.	[96]
	BRD4↑	Promoting autophagy activation.	Suppressing the SIRT1/Beclin1 axis.	An ethanol-fed mouse model and Aml-12 hepatocytes	[97]
	Myd88 ↑	Promoting liver fibrosis.	Exacerbating B-cell activation.	Intrahepatic B cells	[98]
	Hic-5↑	Promoting MASH and liver fibrosis.	Modulating Smad2 phosphorylation and promoting LOX expression.	HSCs	[99]
	TRAF6↑	Promoting inflammation and fibrosis.	Promoting ASK1 activation.	Overexpression of OTUB1 in murine models	[100,101]
	β-TrCP	Promoting liver fibrosis.	Targeting YAP/TAZ	HSCs	[102]
Other hepatic fibrosis	AKAP150↓	Destroying cardiac function under stress.	Regulating calcium (Ca^{2+}) cycling and myocardial contractility.	AKAP150 knockout mice	[103,104]
	AKAP150↑	Contributing to hyperglycemia-induced fibrosis and dysfunction.	Modulating the Akt/GSK3β pathway, suppressing BK channel activity.	AKAP150 knockout mice	[103,104]
	Arrb2↑	Promoting liver fibrosis.	Promoting higher NOX4 and increasing ROS levels.	Arrb2-KO mice	[83,105–107]

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GRAP↑	Promoting liver fibrosis.	Activating ERK signaling.	HSCs	[108]
IQGAP1↑	Promoting liver fibrosis.	Activating Cdc42/Rac1 signaling pathways.	high-fat diet-induced fibrotic mouse livers	[109]
PTPN12↓	Exacerbating HSC activation and fibrosis.	Modulating NLRP3 signaling	HSCs	[110]
P62 (SQSTM1) ↑	Promoting metabolic reprogramming and tumorigenesis.	Activating Nrf2 by sequestering Keap1.	Models of Atg5/Atg7 KO and Tsc1 KO	[111]
P62 (SQSTM1) ↓	Promoting HSC activation and fibrosis.	Mediating interactions with the vitamin D receptor.	Models of Atg5/Atg7 KO and Tsc1 KO	[111]
BRD4↑	Driving HSC activation and excessive ECM deposition.	Enhancing PLK1 expression Through the P300/h3k27ac/PLK1 axis.	HSCs	[112]
PML↑	Alleviating ECM production, and protecting the liver from fibrosis.	Interacting with TILAM, stabilizing the level of PML protein, regulating ECM gene expression.	HSCs	[113]
NCK2↑	Contributing to oxidative stress and liver fibrosis.	Regulating of T cell receptor signaling.	gut microbiome	[114]
TIRAP↑	Driving HSC activation, ECM deposition, and persistent fibrotic phenotypes.	Enhancing TIRAP mRNA stability, activating, NF-κB and JNK/Smad2 pathways.	HSCs	[115]
VCAM1↑	Activating HSCs and promoting liver fibrosis.	Promoting LSEC capillarization.	Murine models induced by choline-deficient high-fat diet	[116]
Shb↑	Promoting liver fibrosis.	Reducing TGF-β/TGF-βRI/Smad2 and PDGFR-β pathways.	A ccl4-induced liver fibrosis model	[117]
FADD↑	Activating caspase.	Enhancing NF-κB signaling and anti-apoptotic protein expression.	Hepatocytes	[118]

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Renal Fibrosis	Renal injury	AKAP12↑	Promoting kidney fibrosis.	Modulating TGF-β1-driven signaling pathways.	Murine models of unilateral ureteral obstruction	[119]
		BRD4↑	Promoting kidney fibrosis.	Binding to acetylated histones, recruiting STAT3, STAT5, GR, and HNF4A.	AKI mice	[120]
		Num↑	Promoting autophagy initiation and kidney fibrosis.	Disrupting the interaction between β-trcp2 and SKP1.	UUO model	[121]
		Num↑	Promoting renal interstitial fibrosis.	Modulating HIF-1α protein stability.	Renal proximal tubular cells	[122]
	DKD	C-Cbl↑	Promoting diabetic renal fibrosis.	Enhancing interaction with Sirt1 and promoting K48-linked polyubiquitination.	high glucose (HG)-induced GMCs and kidneys of diabetic mice	[123]
		NLRP3↑	Exacerbating renal inflammation and fibrosis.	Increasing production of pro-inflammatory cytokines like IL-1β.	HK-2 cells, mouse mesangial cells, Male db/db mice	[124]
		CUL4B↑	Promoting macrophage infiltration and fibrosis.	Repressing mir-194-5p transcription, elevating expression of integrin α9.	DKD models	[125]
		CKIP-1↓	Promoting renal fibrosis in diabetic models.	Inhibiting Nrf2 pathway activation.	CKIP-1 knockout mice.	[126]
		CKIP-1↓	Exacerbating diabetic renal fibrosis.	Promoting Src-mediated ubiquitination of CKIP-1.	Primary GMCs, CKIP-1$^{-/-}$ mice	[127]
	Other renal fibrosis	Bcl10↓	Promoting kidney fibrosis.	Transducing Ang II and immune-receptor signals to NF-κB.	Mice lacking Bcl10	[128]
		Dvl1↑	Promoting renal fibrosis.	driving Wnt/β-catenin aberrant activation	Sprague Dawley rats	[129]
		Lncrna6524, mir-92a-2-5p, and Dvl1↑	Driving excessive ECM deposition and fibrosis.	Enhancing the Wnt/β-catenin pathway, inhibiting the GSK-3β-AXIN-APC complex.	TGF-β1-induced fibrosis in renal tubular cells	[130]

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JAK2↑	Contributing to pathological fibrosis.	Promoting the phosphorylation of STAT5.	A novel mouse model of chronic kidney disease	[131,132]
LGALS3↑	Exacerbating kidney inflammation and fibrosis.	Enhancing NLRP3 inflammasome activation.	Gal-3 knockout models.	[133]
PDZK1↓	Promoting kidney fibrosis.	Exacerbating TGF-β1-induced EMT under oxidative stress conditions.	Renal tubular epithelial cells	[134]
SPAG9 (JLP) ↓	Promoting TGF-β1-induced EMT, ECM production, apoptosis, and autophagy.	Regulating Beclin-1 and disrupting profibrotic signaling.	Mouse models.	[100]
P62 (SQSTM1) ↑	Promoting kidney fibrosis.	Suppressing MAP1LC3-II expression, and restoring MMP.	TGF-β-induced renal fibrosis	[135]
Myd88↑	Driving inflammation, apoptosis, and fibrotic remodeling.	Activating myd88/p38 MAPK pathway.	A transgenic mouse model	[136]
SH2B3↑	Driving renal inflammation, macrophage recruitment, and subsequent fibrosis.	Promoting IL-12 signaling, enhancing Stat4 phosphorylation and IFNγ production.	Immune cell	[137]
RACK1↑	Promoting unilateral ureteral obstruction-induced renal fibrosis.	Enhancing interaction with FAK and activating downstream signaling pathways.	Fibroblast	[138,139]
ATP6V0C↓	Promoting tubular cell G2/M arrest and ECM deposition.	Inhibiting interactions with SNARE proteins STX17 and VAMP8.	UUO-induced renal fibrosis models	[140]
STAP2 ↑	Promoting fibroblast activation and ECM deposition.	Promoting HSP27 phosphorylation and driving PI3K/AKT signaling.	UUO, IRI, HK-2 cells.	[141]
TG2↑	Amplifying M2 macrophage polarization.	Upregulating ALOX15.	UUO model	[142]

Beta-arrestins, particularly beta-arrestin 1 (ARRB1), are crucial regulators in pulmonary fibrosis by influencing fibroblast activity and alveolar epithelial type 2 cell (AEC2) regeneration[26]. Using fibroblast-specific ARRB1 knockout mice and bleomycin-induced lung fibrosis models, researchers demonstrated that ARRB1 deletion reduces fibrosis severity, as indicated by decreased extracellular

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matrix deposition, enhanced lung function, and improved histological scores, underscoring its potential as therapeutic targets.

IQGAP1, a key scaffolding protein, plays a critical role in pulmonary fibrosis by integrating cytoskeletal remodeling and growth factor signaling pathways, including MAPK, β-catenin, ERK, and TGF-β[27,28]. In pulmonary fibrosis, decreased IQGAP1 expression is associated with enhanced fibroblast differentiation and matrix production, as its suppression by TGF-β and lysophosphatidic acid (LPA) amplifies fibroblast activation and exacerbates fibrogenesis[143].Elevated IQGAP1 expression in lung fibroblasts, particularly in scleroderma-associated interstitial lung disease and bleomycin-induced fibrosis models, facilitates the organization of α-smooth muscle actin (SMA) into stress fibers, promoting contractile activity and fibrotic tissue remodeling[40].IQGAP1 knockout (KO) mice demonstrate reduced actin polymerization, SMA expression, and contractility, leading to decreased TGF-β expression, less fibrosis, and reduced lung stiffness, without significant changes in inflammation.

Cav1 (Caveolin-1) modulates fibroblast activation and ECM deposition in IPF through regulatory interactions with circRNA TADA2A. CircTADA2A sponges miR-526b and miR-203, upregulating Cav1 and Cav2 to suppress fibroblast activation and proliferation[29]. A detailed review of Cav1's role in IPF can be found in a comprehensive article [30].

p62/SQSTM1, a multifunctional scaffold protein, regulates oxidative stress and autophagy pathways in IPF progression. In macrophage-mediated fibrogenesis, p62 interacts with SLC15A3, driving oxidative stress via the p62-NRF2 antioxidant pathway[31]. Disrupting this interaction reduces ROS production, mitigates macrophage recruitment, and preserves pulmonary homeostasis in bleomycin- or radiation-induced fibrosis. Additionally, p62 modulates the autophagy-lysosome pathway, impaired in IPF due to ROS-induced lysosomal membrane permeabilization (LMP), which disrupts autophagy flux and promotes cellular senescence. ROS scavengers like N-acetylcysteine (NAC) restore autophagy balance, alleviating senescence-associated secretory phenotype (SASP) markers[32].

AGGF1, a multifunctional protein with scaffold-like properties, regulates TGF-β signaling and fibrotic processes, including IPF[33]. AGGF1 enhances the interaction between integrin α7 and LAP-TGF-β1, preventing LAP cleavage to mature TGF-β1 and attenuating Smad2/3 and ERK1/2 phosphorylation, key drivers of fibrosis. In thoracic aortic aneurysm (TAA) models, AGGF1 deficiency worsened vascular fibrosis and inflammation, while AGGF1 supplementation reversed these effects. Pirfenidone, an IPF treatment, mitigates fibrosis through TGF-β inhibition, but its efficacy depends on AGGF1 expression. These findings highlight AGGF1 as a critical scaffold protein in integrin-TGF-β signaling, suggesting a combined therapeutic strategy targeting AGGF1 and TGF-β pathways could improve outcomes in IPF and related fibrotic diseases.

α6-Integrin, a scaffold protein[144] , is a key mechanosensitive regulator in IPF, mediating myofibroblast invasion and basement membrane remodeling in response to matrix stiffening[34]. The α6B isoform, upregulated in IPF patients and bleomycin-induced mouse models via a ROCK-dependent c-Fos/c-Jun pathway, couples with β1-integrin to enhance MMP-2-driven collagen IV proteolysis, facilitating myofibroblast invasion. Genetic deletion or pharmacological inhibition of α6-integrin reduced lung fibrosis, ECM deposition, and myofibroblast invasiveness. By organizing mechanotransduction complexes at the cell-matrix interface, α6-integrin links mechanical cues to intracellular signaling, sustaining the fibrotic phenotype.

Axin1, a scaffold protein in the β-catenin destruction complex of the Wnt/β-catenin signaling pathway, plays a dual role in IPF. In fibroblasts, inhibition of fatty acid synthase (FASN) via shRNA or the C75 inhibitor increases Axin1 and GSK3B levels, promoting β-catenin degradation and suppressing fibroblast activation, migration, and myofibroblast differentiation while inducing dedifferentiation into adipofibroblasts. In vivo, C75 alleviated bleomycin-induced fibrosis by modulating Axin1-regulated pathways[35]. Conversely, in alveolar type II (AT2) stem cells, Axin1 knockdown using AAV6-based CasRx RNA stabilized β-catenin, activating Wnt signaling to promote AT2 proliferation and alveolar regeneration without profibrotic Wnt activation in fibroblasts. These

 doi:10.20944/preprints202501.1657.v1

findings highlight Axin1's context-dependent roles and therapeutic potential in balancing antifibrotic and regenerative pathways to combat IPF[36].

Mechanical stress plays a central role in IPF pathogenesis due to stiffened lung parenchyma. The TRPV4-PI3Kγ complex operates as a mechanotransduction scaffold that translates heightened mechanical cues into intracellular signals promoting myofibroblast differentiation and excessive ECM production[37,38]. TRPV4, a mechanosensitive calcium channel, is crucial for this conversion of mechanical input into biochemical output. Disrupting TRPV4 channel activity or its interaction with PI3Kγ has yielded promising results in curtailing the fibrotic machinery. By targeting this mechanotransduction axis, therapies could effectively reduce the impact of pathologic tissue stiffness on ongoing fibrotic progression.

The HER2 (ERBB2) signaling pathway plays a critical role in fibroblast invasion and fibrosis in IPF. Single-cell RNA sequencing revealed that invasive fibroblasts in IPF patients exhibit a metastatic cancer-like gene signature, with HER2 activation as the most upregulated upstream regulator. HER2 signaling induces invasive genetic programs in normal fibroblasts, enhancing migration and ECM deposition. Blocking HER2 in IPF fibroblasts reversed these traits and reduced fibrosis in vivo. Paralleling its role in cancer metastasis, HER2 emerges as a master regulator of fibroblast invasiveness. Therapeutic targeting of HER2, such as with pertuzumab, has shown promise in animal models, highlighting its potential as a novel antifibrotic strategy in IPF[39].

Bromodomain-containing protein 4 (BRD4), a scaffold protein in the BET family, plays a central role in the epigenetic regulation of IPF[41]. BRD4 facilitates chromatin remodeling by recruiting acetyltransferase p300 to histones, thereby promoting the expression of profibrotic genes such as NADPH oxidase 4 (Nox4), a ROS-generating enzyme implicated in myofibroblast activation. BRD4 inhibition with BET inhibitors (e.g., OTX015, JQ1) disrupts the BRD4-p300-histone complex at the Nox4 promoter, downregulating Nox4 expression and activity. In aged mice with established lung fibrosis, BRD4 inhibition restored fibrosis resolution, decreased Nox4 levels, and improved lung architecture, demonstrating its antifibrotic efficacy.

TKS5, a scaffold protein essential for podosome formation, plays a critical role in ECM invasion and IPF pathogenesis[42,43]. Elevated TKS5 expression in lung fibroblasts (LFs) from IPF patients and bleomycin-treated mice correlates with increased ECM invasion and fibrosis. TKS5 drives podosome rosette formation, which localizes proteases (e.g., MMP2, MMP9, MMP14) for ECM degradation. Haploinsufficient $Tks5^{+/-}$ mice resist bleomycin-induced fibrosis due to reduced podosome formation and LF invasiveness. TGFβ induces TKS5 expression and podosome formation, while stiffened ECM perpetuates TKS5-mediated remodeling. Src kinase inhibition disrupts podosome dynamics, reducing ECM invasion and fibrosis in preclinical models. These findings identify TKS5 as a central regulator of LF invasion and a promising therapeutic target, with Src inhibitors offering potential antifibrotic strategies.

Numb regulates β-catenin signaling in alveolar type II (ATII) cells, playing a critical role in IPF[44]. Depleting Numb and its homolog Numblike in murine lung epithelial cells attenuates bleomycin-induced fibrosis, preserving lung function and survival. Mechanistically, Numb interacts with casein kinase 2 (CK2) to stabilize β-catenin, enhancing transcriptional activity that drives pro-fibrotic cytokine secretion, EMT, and mesenchymal stem cell differentiation into myofibroblasts, leading to ECM deposition and fibrosis. Without Numb, CK2-mediated β-catenin activation is diminished, reducing fibrotic responses. Targeting the Numb/CK2/β-catenin pathway offers a promising therapeutic approach for IPF.

TRAF6 regulates lung fibrosis by stabilizing the IL-33 receptor (IL-33R) through K27-linked polyubiquitination at K511, preventing autophagic degradation and promoting activation[45]. This enhances downstream MyD88-TRAF6-TAK1-NF-κB signaling, driving inflammation and fibrosis. Conversely, USP38 deubiquitinates IL-33R, facilitating its autophagic degradation and reducing IL-33-induced inflammation and fibrosis. The TRAF6-USP38 interplay ensures precise control of IL-33R activity, balancing pro-inflammatory and anti-fibrotic responses. As a scaffold protein, TRAF6

 doi:10.20944/preprints202501.1657.v1

integrates these signaling components, positioning the TRAF6-USP38 axis as a promising therapeutic target for IL-33-mediated lung fibrosis.

3.2. Scaffold Proteins in Silicosis

Silicosis is an incurable occupational lung disease caused by crystalline silica dust inhalation, leading to chronic cough, dyspnea, and fatigue. Advanced stages result in respiratory failure. HRCT typically shows nodular opacities in the upper lobes and progressive massive fibrosis (PMF). The disease is driven by alveolar macrophage activation, chronic inflammation, and fibroblast proliferation, leading to ECM deposition and pulmonary fibrosis. Key pathways like inflammasome activation, TGF-β signaling, and oxidative stress are involved. Treatment is mainly supportive, with limited therapeutic options. Research into scaffold proteins regulating fibrotic pathways may offer new therapeutic targets.

Caveolin-1 (Cav-1), a scaffold protein in caveolae, regulates autophagy, apoptosis, and fibrosis in pulmonary diseases like silicosis and PM2.5-induced lung injury. Silica exposure enhances Cav-1 interaction with LC3BII and p62, disrupting autophagy and inducing alveolar epithelial cell (AEC) apoptosis[46]. he Cav-1-derived peptide CSP7 disrupts these interactions, suppresses p53, restores autophagy, and reduces ECM deposition (e.g., Col1, α-SMA), mitigating fibrosis in mouse models. Cav-1 also modulates fibrinolytic signaling by regulating p53-mediated PAI-1 and uPA expression; CSP blocks p53-PP2A-C interaction, restoring fibrinolytic balance and reducing AEC apoptosis[47,48]. In PM2.5-induced fibrosis, Cav-1 degradation via ER stress and autophagy activates TGF-β1/Smad3 signaling, promoting ECM accumulation and apoptosis[49]. Blocking autophagy restores Cav-1, inhibits TGF-β1/Smad3, and alleviates fibrosis. These findings position Cav-1-derived peptides like CSP7 as promising therapeutic interventions for silicosis and related fibrosis.

Sulfatase-1 (SULF1) regulates the sulfation of heparin-sulfate proteoglycans (HSPGs), key scaffolds in lung epithelial cell signaling, playing a dual role in silicosis pathogenesis[50]. Early crystalline silica (CS) exposure downregulates SULF1 in bronchial epithelial cells and rat lungs, increasing sulfated-HSPGs, which may protect against initial damage. Prolonged CS exposure, however, upregulates SULF1, promoting fibrogenic gene expression, collagen deposition, epithelial-mesenchymal transition (EMT), and WNT/β-catenin signaling. SULF1 overexpression exacerbates fibrosis and cell death, while its knockdown mitigates these effects.

The STING signaling pathway serves as a central scaffold-like adaptor, linking mitochondrial DNA (mtDNA) damage to inflammatory and fibrotic responses in silicosis. Silica exposure induces senescence in alveolar type II (ATII) cells, activating the cGAS-STING-NF-κB axis via mtDNA damage[51,52]. Honokiol (HKL), a natural compound, mitigates ATII senescence and fibrosis by restoring SIRT3 activity, enhancing SOD2 deacetylation, reducing mtDNA damage, and suppressing cGAS-STING signaling to inhibit NF-κB-driven inflammation. Silica exposure also triggers the release of double-stranded DNA (dsDNA), activating STING in alveolar macrophages (AMs) and promoting TNF-α, IL-6, and TGF-β secretion, creating a pro-fibrotic microenvironment that activates lung fibroblasts[53]. In fibroblasts, STING activation drives migration, proliferation, and myofibroblast differentiation via TGF-β1 signaling. Inhibiting STING in macrophages and fibroblasts reduces silica-induced inflammation and fibrosis in vitro and in vivo. These findings establish STING as a key therapeutic target for managing silicosis by coordinating mitochondrial stress, macrophage polarization, and fibroblast activation.

LGALS3 (Galectin-3) is pivotal in silicosis pathogenesis, mediating silica-induced endothelial-to-mesenchymal transition (EndoMT) via the PI3K/AKT signaling pathway[54]. In a silica-induced mouse model, LGALS3 expression was elevated in endothelial cells, promoting mesenchymal marker expression and reducing endothelial markers. LGALS3 activates the PI3K/AKT pathway, driving EndoMT. Knockdown of LGALS3 using siRNA or inhibition of PI3K with LY294002 reduced EndoMT and alleviated pulmonary fibrosis in vitro and in vivo. As a scaffold-like protein, LGALS3 interacts with integrins and signaling molecules, regulating processes like proliferation and cytoskeletal remodeling. These findings position the LGALS3/PI3K/AKT axis as a promising

 doi:10.20944/preprints202501.1657.v1

therapeutic target for silicosis. A detailed review of LGALS3's broader role in lung diseases is available in related studies[55].

YWHAZ, a 14-3-3 protein family member, plays a key role in lung fibrosis, especially after exposure to environmental pollutants like diesel exhaust particles (DEPs). This scaffold protein interacts with β-catenin and other phosphoserine-containing proteins to regulate fibrosis- and inflammation-related pathways[56]. DEP exposure upregulates YWHAZ, β-catenin, vimentin, and TGF-β in bronchial epithelial cells and murine lungs, enhancing Wnt/β-catenin and TGF-β signaling, collagen deposition, and epithelial-mesenchymal transition (EMT). YWHAZ and vimentin synergistically modulate cytoskeletal reorganization, exacerbating fibrosis. PCR and proteomics studies in DEP-exposed models confirm YWHAZ as a mediator of fibrosis and a potential biomarker and therapeutic target in pollution-induced lung diseases.

4. Cardiac Fibrosis

Cardiac fibrosis, a common hallmark of various heart conditions, arises from excessive extracellular matrix (ECM) deposition that increases myocardial stiffness, compromises contractility, and can ultimately lead to heart failure. In the setting of myocardial infarction, fibrosis takes on a reparative nature: the abrupt death of large numbers of cardiomyocytes provokes an inflammatory response, followed by myofibroblast activation and subsequent scar formation. By contrast, in cardiac disorders such as hypertension, aging, obesity, and diabetes, fibrosis tends to develop gradually within the interstitium and perivascular regions, often without the substantial loss of cardiomyocytes. Here, the progressive accumulation of ECM proteins stiffens the myocardium, precipitating cardiac dysfunction and eventual failure. Despite diverse etiologies, these conditions converge on the activation of myofibroblasts and dysregulated ECM remodeling, processes tightly orchestrated by scaffold proteins. These proteins not only serve as platforms for assembling signaling complexes but also integrate mechanical and biochemical cues, making them crutial players in regulating fibrotic signaling networks in the heart.

C-Cbl, an E3 ubiquitin ligase, regulates cardiac function and remodeling by promoting SERCA2a degradation, a key calcium-handling protein in cardiomyocytes. Recent studies show that Mettl13, a protein lysine methyltransferase, counteracts cardiac fibrosis and dysfunction by inhibiting C-Cbl activity[57]. In ischemic heart failure models, reduced Mettl13 levels lead to increased C-Cbl activity and SERCA2a degradation, worsening calcium cycling and cardiac function. Conversely, overexpressing Mettl13 restores SERCA2a levels, improves calcium transients, and reduces fibrosis. Mettl13 achieves this by methylating C-Cbl, destabilizing it and decreasing its activity on SERCA2a. Knocking down C-Cbl mitigates the adverse effects of reduced Mettl13 under oxidative stress, highlighting the Mettl13/C-Cbl/SERCA2a pathway as a therapeutic target for ischemic heart failure.

JAK2 is pivotal in cardiac fibrosis, mediating PCSK9-induced myofibroblast transformation and extracellular matrix (ECM) deposition via the JAK2/STAT3 pathway[58]. Elevated PCSK9 levels in myocardial infarction (MI) patients and rat models drive cardiac fibroblast-to-myofibroblast transformation, increasing collagen I, collagen III, and α-SMA expression. STAT3 inhibition with S3I-201 effectively counteracts these fibrotic effects. As a scaffold protein, JAK2 stabilizes and activates STAT3, amplifying the pro-fibrotic signaling initiated by PCSK9. Targeting the JAK2/STAT3 axis presents a potential therapeutic approach to mitigate PCSK9-driven cardiac fibrosis post-MI.

PW1 (Paternally Expressed Gene 3) is upregulated in cardiac fibroblasts after myocardial infarction, promoting ECM production by activating phosphoribosylformylglycinamidine synthase (PFAS), a key enzyme in purine biosynthesis[59,60]. This process supports fibroblast proliferation and ECM synthesis. PW1 knockout mice subjected to myocardial injury demonstrated reduced ECM deposition and improved cardiac function. Bisulfite sequencing revealed reduced methylation of the PW1 imprinting control region, leading to its enhanced expression post-injury. This evidence underscores PW1's role as a regulator of fibrosis via metabolic reprogrammingcardiac fibrosis.

AKAP2 regulates cardioprotective and pro-fibrotic pathways as a scaffold protein. In cardiomyocytes, it forms a complex with PKA and Src3 to activate ERα via cAMP signaling,

 doi:10.20944/preprints202501.1657.v1

promoting anti-apoptotic (Bcl2) and pro-angiogenic (VEGFa) gene expression[61,62]. AKAP2 loss exacerbates MI-induced dysfunction, apoptosis, and impaired angiogenesis. In myofibroblasts, AKAP2 associates with F-actin and facilitates ERK1-WAVE2 signaling for actin polymerization and migration. Silencing AKAP2 disrupts this axis, reducing fibrosis and motility. These findings position AKAP2 as a critical molecular scaffold integrating survival, angiogenesis, and motility pathways, making it a promising therapeutic target for cardiac fibrosis and remodeling.

NDP52 protects against myocardial infarction (MI) by facilitating autophagosome-lysosome fusion and promoting mitophagy through interactions with TBK1 and RAB7[63]. After MI, impaired mitophagy leads to mitochondrial dysfunction, ROS accumulation, cardiomyocyte apoptosis, and fibrosis. NDP52 recruits TBK1, which phosphorylates RAB7, enhancing lysosomal clearance of damaged mitochondria, reducing ROS, and limiting cell death. As a selective autophagy adaptor, NDP52 serves as a scaffold protein, orchestrating key signaling complexes in mitophagy and preserving myocardial function.

ERBB2 (HER2), a receptor tyrosine kinase, is critical for cardiac fibrosis and heart failure recovery[64]. Beyond its oncogenic role, ERBB2 promotes heart regeneration via mechanotransduction, activating EMT-like processes such as cytoskeletal remodeling, extracellular matrix changes, and cardiomyocyte migration to replace scar tissue. This mechanism involves YAP, activated independently of the Hippo pathway through ERK-dependent phosphorylation, linking cytoskeletal dynamics to nuclear responses. Scaffold proteins facilitate ERBB2-YAP interactions, modulating transient ERBB2 signaling to balance regeneration and oncogenic risks. Hence, ERBB2-driven mechanotransduction through YAP represents a vital pathway for cardiac repair post-injury, offering significant insights for heart failure therapy.

Shank3, known for its synaptic roles, also drives cardiac fibrosis by disrupting calcium signaling. Overexpression of Shank3 in cardiomyocytes enhances L-type Ca^{2+} channel activity, prolongs action potential duration, and elevates cytosolic calcium, triggering fibroblast activation and ECM deposition[65]. Transgenic mice overexpressing Shank3 exhibited severe fibrosis, arrhythmias, reduced contractility, and decreased troponin I levels, exacerbating cardiac dysfunction. These findings identify Shank3 as a key regulator of fibrosis progression via calcium signaling, highlighting its potential as a therapeutic target in cardiac fibrosis.

Caveolin-1 (Cav1) anchors proteins like Junctophilin-2 (JP2), SERCA2a, and ryanodine receptors, coordinating Ca^{2+} signaling and preventing maladaptive remodeling under stress. In heart failure (HF), Cav1 dysfunction contributes to fibrosis and structural remodeling. Calpain-resistant JP2 knock-in (JP2CR) mice, which maintain Cav1 scaffolding interactions, show reduced fibrosis and hypertrophy by preserving transverse tubule organization and Ca^{2+} homeostasis[68]. In diabetic cardiomyopathy (DCM), Cav1 exerts cardioprotective effects, as shown in polydatin (PD)-treated models where PD enhances Cav1 expression and inhibits NF-κB-driven inflammation and fibrosis. Cav1 knockout nullifies these protective effects, highlighting its essential role as a scaffold protein in maintaining myocardial integrity [69].

Peli1, an E3 ubiquitin ligase, drives pressure overload (PO)-induced cardiac fibrosis by mediating cardiomyocyte (CM)-fibroblast communication via miR-494-3p-enriched exosomes[70]. Peli1 deletion in CMs reduces PO-induced fibrosis, highlighting its pathological role. Mechanistically, Peli1 activates NF-κB and AP-1 in CMs, inducing miR-494-3p expression. This miRNA, packaged into exosomes from stretched CMs, activates cardiac fibroblasts (CFs) by suppressing PTEN and enhancing AKT, SMAD2/3, and ERK phosphorylation, promoting fibrosis. Additionally, Peli1 interacts with scaffold proteins like ASC to activate inflammasomes via K63 ubiquitination. Peli1's roles in miRNA-mediated signaling and inflammation make it a promising therapeutic target for cardiac fibrosis and related conditions. Supporting this, Peli1 gene therapy reduces myocardial ischemic damage[71].

Striatin (STRN), a scaffold protein in STRiatin-Interacting Phosphatase and Kinase (STRIPAK) complexes, is crucial in early cardiac remodeling in hypertensive heart disease[72]. STRIPAK complexes tether protein phosphatase 2A (PP2A) to kinases, regulating hypertrophic signaling

 doi:10.20944/preprints202501.1657.v1

pathways. In mouse models, STRN deletion inhibited Angiotensin II (AngII)-induced ventricular hypertrophy and fibrosis without affecting baseline cardiac function. STRN modulates cardiomyocyte hypertrophy via GCK family kinases and reduces pro-fibrotic factor release (e.g., FGF2), mitigating fibrosis. Unlike STRN, STRN3, another STRIPAK component, showed no effect on AngII-induced remodeling when heterozygously deleted, suggesting distinct roles. These findings highlight STRN-based STRIPAKs as potential therapeutic targets in hypertensive heart disease.

GIPC1 is a multifunctional scaffold protein that interacts with β1-adrenergic receptors, stabilizing their expression and modulating downstream MAPK signaling[73,74]. This stabilization limits fibroblast activation and reduces ECM accumulation. In isoproterenol-induced cardiac fibrosis models, GIPC1 overexpression attenuated ECM deposition and preserved cardiac function. Conversely, GIPC1 knockout exacerbated fibrosis and systolic dysfunction, emphasizing its protective role in cardiac remodeling.

Grb2 is crucial in cardiac fibrosis by participating in the AKAP2-anchored signaling complex that regulates cardiac myofibroblast migration, key in fibrotic heart remodeling[62]. Myofibroblasts exhibit enhanced migration and extracellular matrix (ECM) secretion, contributing to myocardial stiffening and dysfunction. AKAP2, a scaffold protein at the leading edge, binds actin filaments and assembles a signaling complex with Grb2 and ERK1. Grb2 facilitates ERK1 activation, which phosphorylates WAVE2, promoting actin polymerization and Arp2 translocation, enabling migration. Disrupting the AKAP2-F-actin interaction or silencing AKAP2 impairs the ERK-WAVE2 signaling axis, reducing myofibroblast motility. These findings highlight Grb2's integral role within the AKAP2-actin scaffold in mediating pro-migratory signaling, offering potential therapeutic targets to mitigate cardiac fibrosis by inhibiting myofibroblast migration pathways.

Bromodomain-containing protein 4 (BRD4), a scaffold protein, integrates inflammatory and epigenetic pathways to regulate cardiac fibrosis. BRD4 mediates chromatin remodeling and transcriptional activation, facilitating immune-fibroblast cross-talk during stress and inflammation[66,67]. In heart failure models, BRD4 deletion in Cx3cr1+ macrophages reduces fibroblast activation and cardiac dysfunction. Mechanistically, BRD4 forms super-enhancers near proinflammatory cytokine genes like IL-1β by recruiting IRF3 and NF-κB/p65, driving fibroblast activation via RELA-dependent enhancers near MEOX1. Additionally, the non-canonical STING-PERK pathway links BRD4 regulation to oxidized mtDNA-triggered endothelial responses, enhancing cytokine production and fibrosis. Endothelial-specific deletion of STING or BRD4 mitigates inflammation and fibrosis. BRD4 inhibition also alleviates cardiac hypertrophy by reducing ROS, fibrosis, and inflammation[75,76]. These findings position BRD4 as a central mediator of inflammatory and fibrotic pathways.

Myeloid differentiation primary response protein 88 (MyD88), a key adaptor in Toll-like receptor (TLR) and interleukin-1 receptor (IL-1R) signaling, plays a distinct role in T-cell regulation during cardiac inflammation and fibrosis[77]. Unlike its pro-inflammatory function in myeloid cells, MyD88 in T-cells limits overactivation and inflammation in response to cardiac stress. In a transverse aortic constriction (TAC) model, MyD88 deletion in T-cells exacerbated cardiac fibrosis, enhanced T-cell survival, and promoted adhesion to fibroblasts and endothelial cells, driving maladaptive remodeling. Mechanistically, MyD88 modulates TCR-dependent, but not TLR-dependent, signaling, dampening p-AKT and ZAP70 phosphorylation to reduce T-cell activation and cytokine-induced fibroblast activation. Without MyD88, excessive T-cell activity fosters a profibrotic environment. These findings underscore MyD88's dual role across immune cells and suggest its targeted modulation in T-cells as a potential strategy to prevent fibrosis while preserving innate immune responses.

Promyelocytic leukemia protein (PML) drives cardiac fibrosis through a transcriptional feedback loop with p53, amplifying TGF-β1 signaling and fibroblast activation[78]. Upregulated in fibrotic tissue and activated fibroblasts, PML stabilizes p53 by preventing its ubiquitin-mediated degradation and promotes PML nuclear body (PML-NB) formation. These structures enhance transcription of profibrotic genes, including extracellular matrix proteins. PML is transcriptionally

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regulated by p53, creating a reciprocal relationship that amplifies TGF-β1-driven profibrotic signaling. SUMOylation of PML further stabilizes its interactions with Smad proteins, linking PML to the TGF-β pathway. Pharmacological disruption of the PML/p53 axis or silencing UBC9 and RNF4 to manipulate PML SUMOylation reduces fibroblast activation and collagen deposition, highlighting this axis as a therapeutic target for cardiac fibrosis and myocardial remodeling[145].

RACK1, a scaffold protein, regulates cardiac fibrosis by modulating the Smad3 signaling pathway via interaction with SPOP, an adaptor for the CUL3/RING E3 ligase complex[79]. In myocardial infarction (MI) models and TGF-β1-treated cardiac fibroblasts (CFs), elevated SPOP expression promotes RACK1 ubiquitination and degradation by binding its Ser/Thr-rich motifs. RACK1 loss disrupts its scaffolding role, enhancing Smad3-mediated CF activation, myofibroblast transformation, and ECM production, thereby exacerbating fibrosis. Forced RACK1 expression counteracts SPOP-induced fibrosis, highlighting its protective role.

SHARPIN, a multifunctional adaptor protein, drives myocardial fibrosis (MF) by regulating cardiac fibroblast (CF) activity and extracellular matrix (ECM) deposition[80]. Upregulated in fibrotic myocardium, SHARPIN enhances TGF-β1-induced collagen synthesis, CF proliferation, and myofibroblast transformation. In an Angiotensin II (AngII)-induced MF model, SHARPIN knockdown reduced cardiac dysfunction and ECM remodeling, confirming its fibrogenic role. Transcriptomic and single-cell analyses identify SHARPIN as a scaffold protein coordinating signaling and ECM dynamics. The rs117299156_C allele of SHARPIN correlates with lower stroke risk in myocardial infarction (MI) patients, suggesting SHARPIN as both a therapeutic target for MF and a genetic biomarker for cardiovascular outcomes.

SKI, a transcriptional regulator with scaffold-like functions, mitigates heart fibrosis by modulating TGF-β1/Smad signaling and activating the Hippo pathway[81]. SKI represses TGF-β1 and interacts with LIMD1 to promote TAZ degradation via the Hippo pathway, preventing cardiac fibroblast activation. In a post-myocardial infarction (MI) rat model and primary fibroblast cultures, SKI overexpression suppressed TAZ, altered actin cytoskeleton dynamics, and inhibited myofibroblast transformation. BioID2 interactomics revealed SKI's association with LIMD1 and actin-modifying proteins, coordinating focal adhesion signaling to enhance Hippo activation. LATS2, not LATS1, mediated TAZ downregulation in SKI-overexpressing cells, highlighting the pathway's specificity.

RIP2, an adaptor protein in the Nod1/RIP2 innate immune signaling pathway, drives cardiac fibrosis and hypertrophy under stress conditions like pressure overload[82]. In a transverse aortic constriction (TAC) model, RIP2 expression increased in cardiomyocytes, forming a complex with Nod1 and MAVS, which integrates inflammatory signaling and mitochondrial regulation. RIP2 activates NF-κB and MAPK/GATA4/p300 pathways, promoting inflammation and hypertrophic remodeling. RIP2 deficiency improved cardiac function, reduced fibrosis, and increased survival, highlighting its role in maladaptive remodeling. MAVS, as a scaffold protein, anchors Nod1/RIP2 interactions via CARD domains, coordinating mitochondrial fission/fusion, mitophagy, and energy metabolism.

BCL10, a key scaffold protein in the CARD9-BCL10-MALT1 (CBM) complex, drives pro-inflammatory responses in isoproterenol (ISO)-induced cardiac remodeling[146]. ISO upregulates the deubiquitinase OTUD1 in macrophages, which deubiquitinates CARD9, promoting CBM assembly and activating NF-κB. This leads to the overproduction of inflammatory mediators, driving cardiomyocyte hypertrophy and fibroblast-mediated fibrosis. Genetic ablation of CARD9 or OTUD1 in myeloid cells significantly reduces cardiac inflammation, remodeling, and dysfunction under chronic ISO infusion. These findings highlight BCL10's central role in the CBM complex, linking innate immunity to cardiac fibrosis, and position the OTUD1-CARD9-BCL10 axis as a promising therapeutic target for ISO-induced heart failure.

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5. Heptic Fibrosis

Hepatic fibrosis is a pathological hallmark of chronic liver diseases, characterized by excessive extracellular matrix (ECM) deposition that disrupts liver architecture and impairs function. It arises as a response to persistent liver injury caused by chronic viral hepatitis, non-alcoholic steatohepatitis (NASH), alcohol-induced liver damage, autoimmune disorders, and parasitic infections. The progression of fibrosis involves the activation of hepatic stellate cells (HSCs) into myofibroblast-like cells, which produce the ECM proteins driving fibrotic scarring. If untreated, hepatic fibrosis can advance to cirrhosis, liver failure, or hepatocellular carcinoma. The underlying molecular mechanisms include dynamic interactions between mechanical and biochemical signals that regulate HSC activation, ECM remodeling, and inflammatory responses, offering potential targets for therapeutic intervention to halt disease progression.

AKAP12 (A-kinase anchor protein 12), a scaffold protein, protects against liver injury and fibrosis by regulating signaling pathways and maintaining cellular stability. Hepatocyte-specific deletion of AKAP12 (AKAP12Δhep) in liver injury models activates the PI3K/AKT/PCSK6 axis, increasing PCSK6 expression, which exacerbates damage through macrophage infiltration, oxidative stress, inflammatory cytokines, and apoptosis[84]. PCSK6 knockdown in AKAP12Δhep mice reverses these effects, highlighting the pathway's role. AKAP12 also inhibits STAT3 and NF-κB signaling, reducing inflammation and fibrosis. AKAP12 levels decline during disease progression, but their restoration correlates with fibrosis resolution. In hepatic stellate cells (HSCs), phosphorylated AKAP12 loses its scaffolding function, impairing interactions with HSP47 and promoting ECM accumulation and ER stress[85,86]. Gene editing to restore AKAP12 activity reduces fibrosis, ER stress, and inflammation. Additionally, AKAP12 modulates the cAMP pathway in portal fibroblasts and liver sinusoidal endothelial cells, suppressing fibroblast activation, normalizing angiogenesis, and remodeling ECM.

β-Arrestin 1 (ARRB1), traditionally a scaffold protein in GPCR regulation, plays a broader role in liver fibrosis through G-protein-dependent and -independent pathways[87]. In human fibrotic liver tissues and murine models (CCl_4 and MCD-induced fibrosis), ARRB1 is upregulated in hepatocytes, disrupting autophagic-lysosomal degradation of multivesicular bodies, activating Rab27A, and increasing small extracellular vesicle (EV) release[88]. These EVs, enriched with MASP1, activate p38 MAPK/ATF2 signaling in hepatic stellate cells (HSCs), driving profibrotic transformation and ECM deposition. Silencing MASP1 or inhibiting ARRB1-dependent EV release significantly reduces fibrosis, with ARRB1 deficiency halving collagen accumulation in mice. However, ARRB1's metabolic roles, such as stabilizing IRS-1 and activating PPARγ, present challenges in conditions like NASH, highlighting its complex role in liver disease.

Grb2-associated binder 1 (Gab1), an adaptor protein, plays a dual role in liver biology by promoting regeneration after acute injury and mitigating chronic damage from persistent hepatocyte apoptosis[90]. In liver fibrosis, Gab1 protects against chronic injury by suppressing apoptosis, reducing fibrosis, and lowering cancer risk. Under apoptotic stimuli, Gab1 is cleaved into a p35-Gab1 fragment that enhances Bcl-xL expression, a key anti-apoptotic factor. Gab1 deficiency exacerbates apoptosis, suppresses Bcl-xL posttranscriptionally, and activates STAT3 signaling, increasing hepatocyte proliferation, fibrosis, and tumorigenesis. As a scaffold protein, Gab1 integrates receptor tyrosine kinase signals with anti-apoptotic pathways, highlighting its therapeutic potential in chronic liver diseases. Additionally, Gab1 promotes hepatocyte proliferation and suppresses inflammation in skin fibrosis, underscoring its versatile role in regulating tissue responses across pathologies[91,92].

Caveolin-1 (Cav1), a key scaffold protein regulating membrane dynamics and mechanotransduction, plays a crucial role in liver fibrosis by linking substrate stiffness to extracellular matrix (ECM) remodeling. In hepatic stellate cells (HSCs), elevated ECM stiffness characteristic of fibrosis increases membrane tension via the β1 integrin/RhoA axis, driving vesicular trafficking and exocytosis of TIMP-1—a critical inhibitor of ECM degradation—in a Cav1-dependent manner[89]. This mechanism highlights how Cav1-mediated caveolae formation and vesicle

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trafficking buffer membrane tension while promoting fibrosis progression. Elevated Cav1 expression in cirrhosis and hepatocellular carcinoma underscores its pathological relevance, as demonstrated in fibrosis-mimicking 3D models. Targeting Cav1 to modulate plasma membrane tension and exocytosis presents a promising therapeutic avenue for managing ECM remodeling in chronic liver disease.

Casitas B-lineage lymphoma (Cbl), an E3 ubiquitin ligase and signaling adaptor, regulates non-receptor tyrosine kinases and downstream pathways critical for liver fibrosis[93]. In metabolic dysfunction-associated steatohepatitis (MASH), Cbl collaborates with TRAF6-binding protein (T6BP) to degrade proline-rich tyrosine kinase 2 beta (PYK2) via ubiquitin-mediated proteolysis[94]. This disrupts PYK2-JNK signaling, reducing hepatic lipid accumulation, inflammation, and fibrogenesis. A peptide-proteolysis targeting chimera (P-PTC) mimicking T6BP function effectively blocks PYK2 dimerization and signaling, further demonstrating Cbl's role as a scaffold and regulator. These findings highlight Cbl's therapeutic potential in targeting pro-fibrotic kinases.

Filamin A (FLNA), an actin-binding scaffolding protein, drives liver fibrosis progression in NASH[95]. FLNA is highly expressed in macrophages and hepatic stellate cells (HSCs) in NASH patients and animal models. In macrophages, FLNA knockdown reduces pro-inflammatory cytokines (IL-6, TNF-α) and chemokines (CXCL10), suppresses STAT3 signaling, and attenuates LPS-TLR4-mediated immune responses. In HSCs, FLNA silencing decreases profibrotic markers (TGF-β1, CCL2) and enhances matrix-degrading enzymes (MMP-1, MMP-2), improving ECM remodeling. Mechanistically, FLNA scaffolds cytoskeletal components and TLR4-STAT3 signaling to promote inflammation and fibrosis. These findings position FLNA as a promising therapeutic target for mitigating inflammation and fibrosis in NASH.

SLC9A1 (NHE1), a sodium-hydrogen exchanger, drives liver fibrosis progression in NAFLD by mediating hepatocyte injury and hepatocyte-HSC crosstalk[96]. In palmitate (PA)-induced steatosis models, PA upregulates NHE1 mRNA but decreases its protein expression and intracellular pH. NHE1 knockout in hepatocytes reduces p38 MAPK-mediated inflammatory signaling, lipotoxicity (evidenced by decreased 4-HNE), and apoptosis (reduced PARP cleavage). Additionally, conditioned medium from PA-treated hepatocytes induces NHE1 and TIMP-2 expression in LX-2 HSCs, a process blocked by hepatocyte-specific NHE1 knockout. These findings highlight NHE1's role in amplifying hepatocyte damage and pro-fibrotic mediator release, suggesting its inhibition as a potential therapeutic strategy to disrupt the hepatocyte-HSC signaling axis and mitigate liver fibrosis in NAFLD.

Bromodomain-containing protein 4 (BRD4), a key scaffold protein in epigenetic regulation, plays a significant role in liver fibrosis by modulating diverse signaling pathways. In a CCl4-induced hepatic fibrosis (HF) model, BRD4 expression was aberrantly elevated, driving hepatic stellate cell (HSC) activation and excessive extracellular matrix (ECM) deposition[112]. Mechanistically, BRD4 mediates its profibrotic effects through the P300/H3K27ac/PLK1 axis, where P300-mediated acetylation of H3K27 at the PLK1 promoter enhances PLK1 expression, promoting HSC proliferation and inhibiting apoptosis. BRD4 knockdown, achieved via adeno-associated virus serotype 8 (AAV8)-shRNA, attenuated fibrosis and HSC activation in mice, suggesting its therapeutic potential.

In alcoholic liver disease (ALD), BRD4 contributes to liver injury by impairing autophagy. In an ethanol-fed mouse model and Aml-12 hepatocytes, BRD4 overexpression suppressed the SIRT1/Beclin1 axis, a critical pathway for autophagy activation[97]. Chromatin immunoprecipitation and luciferase assays demonstrated that BRD4 directly binds to the SIRT1 promoter, repressing its transcription and downstream autophagic processes. Blocking BRD4 restored autophagic flux, alleviated lipid accumulation, and reduced inflammatory infiltration in alcohol-damaged hepatocytes. Collectively, these studies highlight BRD4 as a pivotal regulator of liver fibrosis and injury, offering insights into targeting BRD4 for therapeutic interventions in HF and ALD. Additionally, BRD4 plays a crucial role in TGF-β1-induced hepatic stellate cell activation, influencing the progression of liver fibrosis[147–149].The development of dual- or multi-target therapies, similar to strategies used in cancer treatment, is an emerging area of research for liver fibrosis treatment[150].

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MyD88 plays a central role in liver fibrosis during NASH by mediating the activation of intrahepatic B cells through innate immune signaling. In NASH, intrahepatic B cells adopt a pro-inflammatory phenotype, secreting cytokines like IL-6 and TNF-α, presenting antigens, and activating T cells. MyD88 functions as an adaptor protein downstream of Toll-like receptors (e.g., TLR4) and B-cell receptor signaling, integrating innate and adaptive immunity[98]. B-cell-specific MyD88 deletion in murine models reduced T cell-mediated hepatic inflammation and fibrosis but did not affect steatosis. Gut microbiota dysbiosis exacerbates B-cell activation via MyD88, as fecal microbiota transplantation from human NAFLD donors into mice replicated the disease phenotype. These findings position MyD88 as a key node in the gut-liver axis and a potential therapeutic target for mitigating B-cell-driven liver fibrosis in NASH.

Hic-5, a focal adhesion adaptor protein induced by hydrogen peroxide and TGF-β1, drives liver fibrosis in HSCs by promoting ECM remodeling[99]. In advanced metabolic dysfunction-associated steatohepatitis (MASH), Hic-5 expression rises in tandem with fibrosis progression, as shown by scRNA-seq data from human and murine studies. Antisense oligonucleotides (ASOs) targeting Hic-5 demonstrated significant therapeutic potential, lowering Hic-5 levels, reducing α-SMA and collagen production, and alleviating fibrosis and steatosis in vivo. Mechanistically, Hic-5 modulates Smad2 phosphorylation via Smad7 and elevates LOX expression, contributing to ECM crosslinking and rigidity. Unlike LOXL2 inhibitors, which have shown limited efficacy, Hic-5 inhibition reduces multiple LOX isoforms, suggesting broader antifibrotic effects. With efficient liver delivery and systemic stability, ASOs represent a promising therapeutic approach for advanced fibrosis and steatosis by targeting Hic-5's scaffold-like regulatory functions.

TRAF6, a key adaptor protein in signaling pathways, plays a central role in liver fibrosis[151] by promoting inflammation and fibrosis through lysine 63-linked polyubiquitination and activation of apoptosis signal-regulating kinase 1 (ASK1)[101]. This pathway amplifies hepatocyte injury, inflammation, and extracellular matrix deposition, hallmark features of NASH. Recent studies reveal that OTUB1, a deubiquitinase, directly binds to TRAF6, suppressing its polyubiquitination and inhibiting ASK1 activation. Hepatocyte-specific overexpression of OTUB1 in murine models significantly reduces diet-induced hepatic steatosis, inflammation, and fibrosis, highlighting its regulatory role in the TRAF6-ASK1 axis. By modulating TRAF6, which functions as a scaffold integrating upstream metabolic and inflammatory signals with downstream fibrotic responses, targeting the OTUB1-TRAF6-ASK1 pathway emerges as a promising therapeutic strategy for NASH and liver fibrosis.

A-Kinase Anchoring Protein 150 (AKAP150) is a critical scaffold protein that regulates calcium (Ca^{2+}) cycling and myocardial contractility, essential for maintaining cardiac function under stress[103]. By organizing key signaling complexes, including ryanodine receptor (RYR2), SERCA, phospholamban (PLN), protein kinase A (PKA), and protein kinase C (PKC), AKAP150 ensures efficient excitation-contraction coupling through precise PKA-mediated phosphorylation of Ca^{2+} handling proteins. Cardiac-specific AKAP150 knockout models demonstrate that its loss exacerbates pathological remodeling, including interstitial fibrosis, ventricular dilation, and impaired contractility, following myocardial infarction or pressure overload. Additionally, in vascular systems, AKAP150 contributes to hyperglycemia-induced fibrosis and dysfunction by modulating the Akt/GSK3β pathway, suppressing BK channel activity, and reducing BK-β1 subunit expression, critical for vascular tone[104]. AKAP150 deficiency in vascular models alleviates fibrosis, restores BK channel function, and reduces maladaptive cell proliferation through enhanced Akt phosphorylation and suppressed NFATc3 signaling.

β-Arrestin 2 (Arrb2), a key scaffold protein in hepatic fibrosis, orchestrates receptor trafficking and intracellular signaling critical for disease progression[105,106]. Structural studies reveal that Arrb2 binds MAPK cascade members—cRaf, MEK1, and ERK2—scaffolding MEK1 and ERK2 in its active conformation to facilitate sequential phosphorylation. This function depends on the ATP-bound status of MEK1 or ERK2, fine-tuning kinase activation[107]. In CCl_4-induced fibrosis, Arrb2-knockout mice exhibit reduced oxidative stress, collagen deposition, and NADPH oxidase 4 (NOX4)

 doi:10.20944/preprints202501.1657.v1

expression, correlating with lower ROS levels[83]. In hepatic stellate cells, Arrb2 depletion attenuates NOX4-mediated ROS production, α-SMA expression, and fibrogenic activity by suppressing ERK and JNK signaling. These findings position β-arrestin 2 as a molecular hub linking kinase cascades to oxidative stress pathways, suggesting its inhibition as a potential therapeutic strategy to prevent or reverse liver fibrosis.

Grb2-related adaptor protein (GRAP) regulates liver fibrosis by driving hepatic stellate cell (HSC) activation and transition into myofibroblasts, key contributors to fibrotic remodeling[108]. In CCl_4-induced fibrosis models, GRAP expression is upregulated during HSC-myofibroblast transition. Serum response factor (SRF) and MRTF-A bind to the GRAP promoter, promoting its transcription. GRAP amplifies pro-fibrotic signaling via ERK activation, as ERK inhibition attenuates GRAP-induced HSC activation. Silencing GRAP with siRNA inhibits HSC transition in vitro, while AAV6-mediated knockdown in vivo reduces liver fibrosis. These findings highlight GRAP's role as a scaffold adaptor in pro-fibrotic pathways, making it a promising therapeutic target for liver fibrosis.

IQGAP1, a cytosolic scaffold protein, mediates bone marrow mesenchymal stromal cell (BMSC) recruitment to fibrotic livers, playing a critical role in liver fibrosis[109]. Elevated IQGAP1 expression in methionine-choline-deficient and high-fat (MCDHF) diet-induced fibrotic mouse livers correlates with fibrosis markers in both mice and humans. IQGAP1 facilitates sphingosine 1-phosphate (S1P)-induced BMSC migration by aggregating at the plasma membrane via S1P receptor 3 (S1PR3) and activating Cdc42/Rac1 signaling, coordinating cytoskeletal remodeling and motility. Silencing IQGAP1 with siRNA blocks BMSC migration, disrupts cytoskeletal dynamics, and reduces liver recruitment. In vivo, IQGAP1 silencing alleviates liver fibrosis in MCDHF-diet models. These findings identify IQGAP1 as a key scaffold linking cytoskeletal regulation and S1P signaling, offering a therapeutic target to mitigate liver fibrosis by disrupting BMSC recruitment.

PTPN12, a protein tyrosine phosphatase, plays a critical regulatory role in liver fibrosis by modulating oxidative stress and inflammasome activation in hepatic stellate cells (HSCs). PTPN12 contains a C-terminal PEST motif, facilitating interactions with cytoskeletal and adhesion-related proteins, and is implicated in maintaining cell structure and mobility. Recent findings reveal that sulfiredoxin 1 (SRXN1), an enzyme that reverses cysteine sulfinylation (Cys-SO2H) modifications, de-sulfinylates PTPN12 in activated HSCs, enhancing its phosphatase activity and stability[110]. This suppresses tyrosine phosphorylation and inhibits the activation of the pro-fibrotic NLRP3 inflammasome. Loss of SRXN1 or inhibition of PTPN12 exacerbates HSC activation and fibrosis, highlighting the protective role of the SRXN1-PTPN12 axis. Overexpression of PTPN12, particularly its S-sulfinylation-resistant mutant, further amplifies the anti-fibrotic effects by dampening NLRP3 signaling. These findings establish PTPN12 as a key player in the regulation of liver fibrosis, with its scaffold protein interactions and modulation of NLRP3 offering promising therapeutic avenues.

p62 (SQSTM1) plays a multifaceted role in liver fibrosis and tumorigenesis, acting as both a pro- and anti-tumorigenic factor depending on the cellular context and signaling pathways. As a scaffolding protein and selective autophagy receptor, p62 accumulates in autophagy-deficient conditions, leading to the activation of Nrf2 by sequestering Keap1. In hepatocytes, p62-mediated Nrf2 activation supports metabolic reprogramming and tumorigenesis, as seen in models of impaired autophagy (Atg5/Atg7 KO) and mTORC1 activation (Tsc1 KO)[111]. Conversely, p62 also exhibits anti-fibrotic and anti-tumorigenic functions in hepatic stellate cells (HSCs) by mediating interactions with the vitamin D receptor (VDR) to suppress HSC activation and fibrosis. Deletion of p62 in hepatocytes reduces ductular reaction and improves survival in certain models but paradoxically promotes liver tumor formation, highlighting its tumor-suppressive role in hepatocytes under defective autophagy and hyperactive mTORC1. Furthermore, p62 influences signaling pathways like NF-κB, mTORC1, and TRAF6, amplifying its regulatory complexity. These findings underscore the duality of p62's functions in liver fibrosis and tumorigenesis, emphasizing its potential as a therapeutic target in liver diseases where autophagy and metabolic pathways are dysregulated.

PML plays a key role in liver fibrosis by interacting with the long noncoding RNA TILAM, which is selectively expressed in HSCs during chronic liver injury[113]. TILAM stabilizes PML protein

 doi:10.20944/preprints202501.1657.v1

levels, driving the expression of extracellular matrix (ECM) genes such as COL1A1 and TGF-β2. PML, a scaffold protein within nuclear bodies, collaborates with TILAM to reinforce a TGF-β2-driven feedback loop, enhancing PML nuclear localization, interaction with PIN1, and fibrotic gene transcription. Depleting TILAM in HSCs or liver organoids reduces PML levels, suppresses ECM production, and alleviates fibrosis in mouse models. These findings establish the TILAM-PML axis as a critical regulator of fibrosis progression and a promising therapeutic target for liver fibrosis with minimal off-target effects.

NCK2 has been implicated in liver fibrosis through its genetic association with gut microbiome alterations, particularly in high-risk Hispanic populations with NAFLD[114]. SNPs in the NCK2 gene (rs3769502 and rs7573751) are linked to decreased NCK2 expression and increased Prevotella abundance, an immunogenic commensal associated with inflammation and liver fibrosis. As an adaptor protein, NCK2 modulates T-cell receptor signaling, potentially influencing immune responses and contributing to the dysregulated microbiome environment observed in fibrosis. Functional microbiome changes, such as altered urea cycle pathways, L-fucose biosynthesis, and reduced antioxidant biosynthesis, exacerbate oxidative stress, a key driver of fibrosis progression. These findings highlight the interplay between host genetics, microbiome composition, and metabolic dysregulation, positioning NCK2 as a potential therapeutic target for inflammation and immune regulation in fibrotic liver diseases.

TIRAP, a toll-interleukin 1 receptor (TIR) domain adaptor, drives radiation-induced liver fibrosis (RILF) through ALKBH5-mediated m6A RNA demethylation[115]. In HSCs, radiation-induced ALKBH5 upregulates TIRAP, activating NF-κB and JNK/Smad2 pathways, which enhance HSC activation and ECM deposition. ALKBH5 also promotes CCL5 secretion, recruiting monocytes and inducing M2 macrophage polarization. In turn, polarized monocytes secrete CCL20, further increasing ALKBH5 and TIRAP levels in HSCs and hepatocellular carcinoma (HCC) cells, worsening RILF and reducing radiosensitivity. As a scaffold protein, TIRAP assembles the signaling complexes that sustain fibrosis and diminish radiotherapy efficacy. Combined ALKBH5 knockdown and CCR6 inhibition alleviate RILF and improve HCC radiosensitivity in preclinical models, highlighting the therapeutic value of targeting the ALKBH5/TIRAP axis.

VCAM1, upregulated on liver sinusoidal endothelial cells (LSECs) during injury, goes beyond its role in leukocyte adhesion to drive liver fibrosis by promoting LSEC capillarization—loss of fenestrae and basement membrane formation—which in turn activates hepatic stellate cells (HSCs) via YAP1 signaling[116]. In murine models of diet- or toxin-induced fibrosis, endothelial-specific VCAM1 deletion or pharmacological inhibition reduced capillarization and fibrosis, evidenced by lower α-SMA expression, collagen deposition, and HSC activation markers. In vitro, recombinant VCAM1 directly induced a fibrogenic phenotype in HSCs. These findings establish VCAM1 as a key regulator of LSEC-HSC crosstalk and a promising therapeutic target against chronic liver disease.

Shb, an adaptor protein in VEGFR-2 signaling, drives angiogenesis and intrahepatic vascular remodeling, contributing to portal hypertension (PHT) in liver fibrosis[117]. In a CCl_4-induced fibrosis model, Empagliflozin (EMPA), an SGLT2 inhibitor, showed dose-dependent antifibrotic effects by suppressing the VEGF-A/VEGFR-2/Shb pathway. EMPA reduced Shb expression and downregulated key profibrogenic signals (TGF-β/TGF-βRI/Smad2, PDGFR-β), collagen type I (Col1A1), and Gal-1/NRP-1 in hepatic stellate cells (HSCs) and sinusoidal endothelial cells (HSECs). By inhibiting VEGFR-2/Shb signaling, EMPA impaired endothelial cell migration and angiogenesis, alleviating PHT (reduced ET-1 and increased eNOS). Histological analyses showed improved fibrosis scores, emphasizing the therapeutic potential of targeting Shb and its scaffold interactions in VEGFR-2 signaling to mitigate liver fibrosis and vascular complications.

FADD, a key adaptor in apoptotic signaling, contributes to liver fibrosis by mediating hepatocyte apoptosis and inflammation[118]. In OTULIN-deficient hepatocytes, elevated apoptosis triggers chronic inflammation, fibrosis, and hepatocellular carcinoma (HCC). Deleting FADD or inhibiting RIPK1 kinase reduces these pathological outcomes, underscoring FADD's centrality in disease progression. Additionally, linear ubiquitination by the LUBAC complex protects against

 doi:10.20944/preprints202501.1657.v1

FADD-driven apoptosis through enhanced NF-κB signaling and anti-apoptotic protein expression. These findings highlight the therapeutic potential of targeting FADD and its associated pathways to prevent apoptosis-driven liver inflammation and fibrosis.

β-TrCP, an adaptor protein within the ubiquitin-proteasome system, plays a pivotal role in regulating liver fibrosis by targeting YAP/TAZ, key mechanotransducers in hepatic stellate cell (HSC) activation[102]. In liver fibrosis, YAP/TAZ activity is heightened due to mechanosignaling triggered by matrix stiffness, perpetuating a feed-forward cycle of fibrosis. Inhibition of acid ceramidase (aCDase), an enzyme elevated in activated HSCs, promotes the accumulation of ceramide, a bioactive sphingolipid, which enhances β-TrCP-mediated proteasomal degradation of phosphorylated YAP/TAZ. Experimental models demonstrated that pharmacologic aCDase inhibition or genetic knockout in HSCs reduced fibrosis, stromal stiffness, and YAP/TAZ activity in vivo. Mechanistically, ceramide-induced β-TrCP activation disrupts YAP/TAZ nuclear localization, mitigating downstream transcriptional activation of profibrotic genes. Importantly, ceramide responsiveness correlates with fibrosis severity, suggesting its potential as a biomarker for targeted therapy. These findings position β-TrCP as a central scaffold protein in the aCDase-ceramide-YAP/TAZ axis, highlighting its therapeutic relevance in disrupting the fibrosis signaling cascade while maintaining specificity for HSCs, sparing hepatocytes and reducing adverse effects. Consistent with these findings, targeting the NRF2/β-TrCP axis has shown beneficial effects in NASH [152].

6. Renal Fibrosis

Renal fibrosis is a central pathological feature of kidney diseases, characterized by excessive accumulation of myofibroblasts and extracellular matrix (ECM) proteins in the renal interstitium and glomeruli, leading to progressive structural and functional impairment. It plays a pivotal role in the progression of both acute kidney injury (AKI) and chronic kidney disease (CKD), which encompasses conditions such as diabetic nephropathy, hypertensive nephropathy, ischemia-reperfusion injury, and glomerulonephritis. These processes culminate in high morbidity and mortality rates associated with renal disease complications. The fibrotic process is driven by key cellular players, including fibroblasts, myofibroblasts, and epithelial cells undergoing epithelial-to-mesenchymal transition (EMT). While renal fibrosis shares similarities with fibrosis in other organs, its molecular mechanisms are distinct.

AKAP12, also known as A-kinase anchoring protein 12, has emerged as a significant player in the progression of kidney fibrosi. In murine models of unilateral ureteral obstruction (UUO), a well-established model of renal fibrosis, AKAP12 has been implicated in modulating TGF-β1-driven signaling pathways—a central driver of fibrotic processes[119]. Functioning as a scaffold protein, AKAP12 integrates various signaling molecules and coordinates cellular responses during EMT, including cytoskeletal reorganization and transcriptional regulation. These findings underscore the importance of AKAP12 in organizing key molecular events in renal fibrosis, suggesting its potential as a therapeutic target to mitigate the fibrotic progression in CKD.

BRD4 regulates kidney fibrosis by controlling enhancer dynamics that drive repair and fibrosis-related gene expression. In acute kidney injury (AKI), BRD4 recruits transcription factors like STAT3, STAT5, GR, and HNF4A to promote epithelial cell repair[120]. BET inhibitors like JQ1 have dual effects: early inhibition impairs recovery and increases mortality, while delayed inhibition suppresses pro-fibrotic TGF-β/Smad3 signaling, reducing ECM deposition and fibrosis. These findings highlight BRD4 as a therapeutic target, with timing critical for balancing repair and anti-fibrotic effects.

Numb, a multifunctional adaptor protein, regulates kidney fibrosis by modulating autophagy and interacting with the SCFβ-TrCP2 complex[121]. In CKD patients and UUO mice, Numb expression is elevated. It initiates autophagy by disrupting the β-TrCP2-SKP1 interaction, stabilizing DEPTOR, and enhancing autophagic flux (increased LC3B-II and p62 degradation). Deletion of Numb in renal tubular cells impaired autophagy and reduced fibrosis. Numb also regulates other SCF targets and HIF-1α stability, linking it to broader fibrosis pathways[122].

 doi:10.20944/preprints202501.1657.v1

C-Cbl, an E3 ubiquitin ligase, contributes to diabetic renal fibrosis by mediating Sirt1 ubiquitination and degradation, disrupting antioxidant defense[123]. Fyn, a Src kinase, phosphorylates C-Cbl at Tyr731, promoting its interaction with Sirt1 and K48-linked polyubiquitination at Lys377 and Lys513, reducing Sirt1 levels. This impairs the Sirt1/Foxo3a pathway, elevates oxidative stress, and increases ECM accumulation and glomerulosclerosis. Inhibiting Fyn reduces C-Cbl phosphorylation and Sirt1 ubiquitination, restoring Sirt1 levels, activating Foxo3a, and enhancing antioxidant defenses to alleviate renal fibrosis. These findings suggest the Fyn-C-Cbl-Sirt1/Foxo3a axis as a novel therapeutic target for diabetic nephropathy, with potential strategies involving Fyn inhibitors or C-Cbl modulation.

NLRP3, a key inflammasome scaffold protein, plays a central role in kidney fibrosis by driving inflammation and promoting fibrotic progression. In diabetic kidney disease (DKD), NLRP3 activation is enhanced through a CRP-Smad3-dependent pathway, where CRP upregulates Smad3, which binds to the NLRP3 promoter, amplifying its expression and inflammasome activity[124]. This leads to increased production of pro-inflammatory cytokines like IL-1β, exacerbating renal inflammation and fibrosis. Inhibiting CRP signaling with anti-CD32 antibodies or blocking Smad3 pharmacologically or genetically has been shown to reduce NLRP3 activation, alleviating inflammation and fibrotic damage in DKD. These findings position the CRP-Smad3-NLRP3 axis as a promising therapeutic target for kidney fibrosis, emphasizing the pivotal role of NLRP3 in regulating immune responses and tissue remodeling in renal pathology. Interestingly, NLRP3 also plays a significant role in radiation-induced lung fibrosis [153].

CUL4B, a scaffold protein in the CUL4B-RING E3 ligase complex, promotes DKD by enhancing macrophage infiltration and fibrosis via the miR-194-5p/ITGA9 axis[125]. Hyperglycemia-induced CUL4B upregulation in macrophages represses miR-194-5p, increasing ITGA9, which facilitates macrophage migration and ECM deposition. Myeloid-specific CUL4B deletion alleviates fibrosis. CUL4B regulates this axis by organizing the CRL4B complex with PRC2 and HDAC. Targeting the CUL4B/miR-194-5p/ITGA9 pathway may offer a therapeutic approach for DKD.

CKIP-1, a scaffold adaptor protein, plays a key role in mitigating diabetic kidney fibrosis by mediating Nrf2 activation downstream of Cx43[126]. Overexpression of Cx43 alleviated renal fibrosis in diabetic models by activating the Nrf2 pathway, but this effect was lost in CKIP-1 knockout mice. Cx43 interacts with CKIP-1 through its CT domain, stabilizing CKIP-1 and facilitating Nrf2 nuclear translocation, enhancing the antioxidant response. Immunoprecipitation and immunofluorescence confirmed this interaction, which was reduced under high glucose conditions. These findings highlight CKIP-1 as a mediator in the Cx43-Nrf2 pathway, suggesting it as a therapeutic target for diabetic nephropathy. Additionally, Src-mediated ubiquitination of CKIP-1 exacerbates fibrosis[127].

Bcl10, a central scaffold in the CARMA-Bcl10-MALT1 (CBM) signalosome, has a complex role in Ang II-driven kidney fibrosis. In Bcl10 knockout (KO) mice, Ang II infusion results in less renal fibrosis and fewer immune cell infiltrates compared to wild-type (WT) controls, indicating reduced proinflammatory signaling[128]. However, these KO mice develop more severe albuminuria and greater podocyte injury, characterized by lower nephrin levels and fewer podocytes, suggesting Bcl10's importance for podocyte integrity under hypertensive conditions. Transplant studies show that WT recipients of Bcl10 KO kidneys experience reduced infiltration but increased albuminuria, emphasizing Bcl10's protective role within the kidney. Beyond NF-κB regulation, Bcl10 may stabilize podocyte cytoskeletal architecture, akin to its role in actin remodeling in immune cells. Thus, Bcl10's function varies across cell types: its deficiency reduces inflammation and fibrosis but impairs glomerular integrity. Targeting Bcl10 in kidney fibrosis requires a balanced approach that considers its dual roles in inflammation and podocyte health.

Dvl1, an intracellular adaptor in the Wnt/β-catenin pathway, plays a crucial role in renal fibrosis, particularly under selenium (Se) deficiency[129]. Se deficiency induces oxidative stress, reduces antioxidant capacity, and disrupts extracellular matrix (ECM) homeostasis, contributing to fibrosis. Mechanistically, Se deficiency upregulates Wnt5a, which activates Dvl1, increasing free β-catenin levels and driving aberrant Wnt/β-catenin signaling. This cascade leads to excessive ECM deposition,

 doi:10.20944/preprints202501.1657.v1

altered matrix metalloproteinase (MMP) activity, and epithelial-mesenchymal transition (EMT). Dvl1's scaffold function organizes and amplifies Wnt/β-catenin components, promoting fibrosis.

Another study identified a regulatory axis involving lncRNA6524, miR-92a-2-5p, and Dvl1, where lncRNA6524 upregulation in renal fibrosis models relieved miR-92a-2-5p inhibition of Dvl1, enhancing Wnt/β-catenin signaling[130]. This activation of Dvl1 promotes β-catenin accumulation and nuclear translocation, further driving ECM deposition. Targeting lncRNA6524 or disrupting its interaction with miR-92a-2-5p offers a novel therapeutic approach to prevent Dvl1 activation. These findings highlight Dvl1 as a potential target for mitigating renal fibrosis, particularly through modulation of Wnt/β-catenin signaling.

JAK2 plays a key role in kidney fibrosis through cytokine signaling and its scaffold function in stabilizing receptor complexes[131]. In a mouse model of chronic kidney disease (CKD) leading to heart failure with preserved ejection fraction (HFpEF), retinol-induced activation of the JAK2/STAT5 pathway was identified as a major driver of myocardial hypertrophy and fibrosis. JAK2 mediates STAT5 phosphorylation, contributing to fibrosis, while its scaffold function supports the integrity of the interferon-gamma receptor complex. Inhibition of STAT5 phosphorylation with AC-4-130 effectively reduced fibrosis, suggesting JAK2-STAT5 signaling as a potential therapeutic target for CKD-related fibrosis. Additionally, JAK2 overexpression reversed liver fibrosis inhibition caused by CXCL14 knockdown in vivo, further underscoring its role in fibrotic diseases[132].

LGALS3 (Galectin-3) plays a critical role in kidney fibrosis, especially in IgA nephropathy (IgAN), a common glomerulonephritis that often progresses to kidney failure[133]. Elevated Gal-3 expression in IgAN patients and preclinical models correlates with disease severity. As a multifunctional scaffold protein, Gal-3 facilitates pro-fibrotic and pro-inflammatory pathways by enhancing NLRP3 inflammasome activation, promoting Th17 cell differentiation, and suppressing autophagy. Gal-3 knockout models show significant improvements in proteinuria, kidney function, histopathological damage, and reduced neutrophil infiltration, Th17 differentiation, and NLRP3 activity. Additionally, competitive Gal-3 inhibitors, such as 6-de-O-sulfated, N-acetylated low-molecular-weight heparin, restored kidney function and attenuated fibrosis in IgAN models. These findings highlight LGALS3 as a key regulator and therapeutic target in kidney fibrosis, with its scaffolding functions central to the inflammatory and fibrotic processes in renal pathology.

PDZK1, a scaffold protein in renal tubular cells, mitigates kidney fibrosis by inhibiting epithelial-mesenchymal transition (EMT) and oxidative stress[134]. Its expression is downregulated in fibrotic kidneys, correlating with TGF-β1 levels. TGF-β1 reduces PDZK1 via p38 MAPK and PI3K/AKT activation, while inhibiting these pathways restores PDZK1 and alleviates fibrosis. PDZK1 downregulation worsens TGF-β1-induced EMT, while overexpression enhances antioxidants like carnitine and ergothioneine, protecting against fibrosis. PDZK1's role in regulating signaling pathways positions it as a promising therapeutic target for chronic kidney disease and other fibrotic conditions, such as hypertensive myocardial fibrosis[154].

SPAG9 (JLP), a multifunctional scaffolding protein, protects against kidney fibrosis by inhibiting TGF-β1-driven profibrotic pathways[100]. In normal kidneys, JLP is expressed in renal tubular epithelial cells (TECs), but its expression is downregulated in fibrotic kidneys, correlating with increased fibrosis. JLP inhibits TGF-β1-induced EMT, ECM production, apoptosis, and autophagy by regulating Beclin-1 and disrupting profibrotic signaling. In mouse models, TEC-specific JLP overexpression mitigates fibrosis, while its deficiency worsens it. JLP also forms a negative feedback loop with TGF-β1 and FGF-2, where TGF-β1 suppresses JLP expression, amplifying fibrosis. These findings position JLP as a key antifibrotic factor and therapeutic target for kidney fibrosis. Additionally, bioinformatics analyses suggest JLP's involvement in liver fibrosis[155].

p62 (SQSTM1), a key autophagy receptor and scaffold protein, regulates renal fibrosis by mediating autophagy and epithelial-mesenchymal transition (EMT). In TGF-β-induced fibrosis, autophagy, including mitophagy, mitigates fibrotic changes. Lycopene (LYC) alleviates fibrosis by inhibiting AKT signaling, activating mitophagy, and downregulating TGF-β/SMAD signaling[135]. LYC reduces p62, PINK1, and PRKN, enhances MAP1LC3-II expression, and restores mitochondrial

 doi:10.20944/preprints202501.1657.v1

function, decreasing ECM deposition and EMT markers. Inhibition of autophagy with bafilomycin A1 or chloroquine reverses LYC's effects, highlighting the role of active autophagy. Molecular studies confirm LYC stabilizes the AKT active site, repressing its signaling. These findings suggest p62 and autophagy as potential therapeutic targets for chronic kidney disease.

MyD88 regulates kidney fibrosis through the MyD88/p38 MAPK pathway, especially in Alport syndrome caused by COL4A3 mutations[156]. These mutations impair type IV collagen secretion, leading to ER stress (ERS) and activation of the MyD88/p38 MAPK pathway, driving inflammation and fibrosis. In a Col4a3 mutant mouse model, tauroursodeoxycholic acid (TUDCA) inhibited ERS, restored collagen secretion, and suppressed MyD88/p38 MAPK activation, reducing proinflammatory cytokines and fibrotic markers, improving kidney function. These findings highlight MyD88 as a therapeutic target in fibrotic kidney diseases. Additionally, maslinic acid targets MyD88 to protect kidneys in a unilateral ureteral obstruction model[157].

SH2B3 (LNK) regulates kidney fibrosis through cytokine modulation, particularly in hypertension-related inflammation. The rs3184504 SNP (R262W) promotes hypertension and exacerbates renal damage[137]. In Trp/Trp mice, higher blood pressure, renal injury, and fibrosis were seen after angiotensin II infusion. Trp-encoding SH2B3 reduced IL-12 signaling inhibition in CD8+ T cells, enhancing Stat4 phosphorylation and IFNγ production, driving inflammation and fibrosis. These results suggest targeting SH2B3 or IFNγ signaling as a therapeutic strategy for hypertension-related kidney fibrosis, especially in individuals with the rs3184504 minor allele.

RACK1, a classic scaffold protein, plays a pivotal role in kidney fibrosis by stabilizing key proteins and facilitating signaling pathways that drive fibroblast-to-myofibroblast transition (FMT)[138]. c-Abl stabilizes RACK1 at focal adhesions, enhancing its interaction with FAK and activating cell adhesion and migration pathways. In knockout mouse models, c-Abl deletion reduced RACK1 levels, disrupted FMT, and alleviated fibrosis. The c-Abl-RACK1-FAK axis may also induce microtubule depolymerization, worsening fibrosis. These results suggest targeting the c-Abl-RACK1-FAK axis as a therapeutic strategy for kidney fibrosis. Additionally, Neuropilin 1 promotes renal fibrosis via RACK1 in renal tubular epithelial cells[139].

TP6V0C, a scaffold protein in V-ATPase, is essential for lysosomal acidification and autophagosome-lysosome fusion in kidney fibrosis[140]. In UUO models, impaired TFEB regulation of ATP6V0C disrupts autophagy, leading to G2/M arrest and ECM deposition. TFEB binds the ATP6V0C promoter to facilitate fusion via SNARE proteins, crucial for ECM turnover. TFEB silencing in fibrotic kidneys, caused by DNMT3a-mediated hypermethylation, is reversed by 5A-za, restoring autophagy and reducing fibrosis.

STAP2 promotes renal fibrosis by modulating HSP27 phosphorylation and activating the PI3K/AKT pathway[141]. Elevated STAP2 expression was found in fibrotic kidneys of human patients and mouse models induced by UUO, IRI, cisplatin, and LPS-stimulated HK-2 cells. STAP2 knockout or knockdown reduced EMT, inflammation, and collagen deposition, while overexpression worsened fibrosis. Mechanistically, STAP2 interacts with HSP27 to drive PI3K/AKT signaling, crucial for fibroblast activation and ECM deposition. Targeting STAP2 offers a novel strategy to alleviate fibrosis and prevent AKI progression to CKD.

Tissue transglutaminase (TG2) promotes kidney fibrosis by inducing M2 macrophage polarization via ALOX15 upregulation[142]. In renal fibrosis models, TG2 knockout or inhibition reduced M2 macrophages and fibrosis. Bone marrow experiments confirmed TG2-mediated M2 polarization worsens fibrosis. Targeting TG2 and ALOX15 offers potential therapies for macrophage-driven fibrosis.

7. Therapeutic Applications of Scaffold Proteins in Treating Fibrotic Diseases of Visceral Organs

Recent research has highlighted the versatile therapeutic potential of synthetic scaffold proteins across various applications. These include facilitating catalytic reactions [158], enabling programmable control of cellular behavior[159], reprogramming iPSCs into NPCEC-like cells[160],

 doi:10.20944/preprints202501.1657.v1

targeting MHCII antigens for immune modulation[161], enhancing antitumor immunity [136], and promoting DNA repair mechanisms to confer drug resistance[162]. Notably, scaffold proteins have also been successfully employed in tissue repair strategies [163,164]. The scope of scaffold protein applications in fibrotic diseases is expanding, particularly in visceral organs in lung fibrosis[165], heart fibrosis[166], heptic fibrosis[83] and kidney fibrosis[167]. Specifically, BRD4 [168,169], CARMA3 [170], Cav1, [171] and TG2[172] have been reported in fibrotic diseases. Given the multifaceted roles of scaffold proteins in cellular signaling and structural support, their therapeutic potential in fibrosis is grounded in the mechanisms detailed in prior sections. This overview focuses on selected applications, demonstrating how these proteins can be strategically harnessed to treat fibrotic diseases. By understanding their interactions and mechanisms, novel therapeutic strategies can be developed to address the complexities of fibrotic conditions.

Table 2. Applications for fibrotic diseases by regulating scaffold proteins.

Therapies/reagents	Intervention	Effect	References
Galectin-3 inhibitor	Reducing ECM deposition, suppressing TGF-β signal	Decreasing fibrosis.	[173]
TULP3	Regulating profibrotic WNT and TGF-β signaling pathways.	Restoring functions and mitigating fibrosis.	[174]
The SLC15A3-p62 axis	Linking autophagy and oxidative stress.	Reducing oxidative stress-induced fibrosis and promoting intracellular clearance.	[31]
TOLLIP	Interacting with IRAK-1 and LC3, suppressing inflammatory pathways.	Restoring tissue homeostasis.	[175]
Monoclonal antibodies targeting TG2	Inhibiting transamidase activity and ECM deposition.	Inhibiting fibrosis progression.	[176]
TG2 inhibitors	Inhibiting irreversible cross-linking of ECM proteins.	Inhibiting fibrosis progression.	[177]
NUDT21	Inhibiting collagen cross-linking.	Reducing fibrosis in silicosis models.	[178]
Cav1-derived peptides	Inhibiting epithelial apoptosis, reducing ECM accumulation, improving lung function.	Inhibiting fibrosis progression.	[29,121]
Circtada2a	Upregulating Cav1 and Caveolin-2.	Countering fibrotic progression.	[29]
Cav1	Suppressing NF-κB signaling.	Mitigating inflammation and fibrosis.	[121]
BA	Downregulating Wnt target genes.	Preventing fibrosis.	[179,180]
ARV-825	Modulating chromatin remodeling and reducing the expression of profibrotic genes.	Preventing fibrosis.	[181]
C75	Promoting β-catenin degradation.	Reducing fibroblast activation.	[35]
The AAV6-based CasRx system	Enhancing β-catenin stabilization.	Promoting alveolar regeneration and	[36]

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		reducing fibrosis.	
VCAM1-VNT-LPS platform	Delivering BCL-2 inhibitors.	Reducing fibrosis, suppressing migration of fibroblasts into foci, and enhancing drug accumulation in fibrotic lungs.	[182]
AAV1.SERCA2a gene therapy	Restoring calcium homeostasis and modulating critical signaling pathways.	Reducing fibrotic progression.	[183]
SKI	Suppressing TGF-β1 signaling.	Mitigating cardiac fibrosis.	[184]
Cav1	Modulating NF-κB signaling.	Suppressing cardiac inflammation and ECM deposition.	[69,185]
Periostin	Reducing interaction with collagen and fibronectin.	Reducing fibrosis.	[186]
Carvedilol	Antagonizing β-arrestin2-biased.	Mitigating cardiac remodeling and fibrosis.	[187,188]
XSB	Downregulating β-arrestin 1 and fibrosis markers.	Preventing fibrosis.	[189]
BRD4 inhibitor	Modulating inflammatory and profibrotic gene expression.	Mitigating fibrosis and improve cardiac function.	[190–192]
Alamandine	Downregulating Cav-1.	Impairing glycolysis and suppressing fibrosis.	[193]
ISL	Suppressing GPX4 and upregulating TFR and DMT1.	Reducing fibrosis.	[194]
XHH2	Disrupting the Gal-3/integrin-β1 interaction.	Suppressing HSC activation and fibrosis.	[195]
Numb	Ubiquitinating and degrading Notch.	Modulating HSC differentiation.	[196]
Hic-5 antisense oligonucleotides	Targeting Hic-5.	Inhibiting advanced hepatic fibrosis.	[99,197,198]
Salvianic acid A	Downregulating BRD4 to suppress HMGB1 translocation.	Alleviating alcoholic liver disease.	[99,197,198]
Spiroganodermaines	Enhancing IRS1 phosphorylation, promoting glucose uptake and suppressing fibrotic markers.	Inhibiting renal fibrosis.	[199]
ZLD2218	Inhibiting BRD4 to inhibit TGF-β/Smad3 signaling and reduce α-SMA and collagen.	Reducing fibrosis in UUO models.	[200]
Xylitol	Reducing BRD4 levels.	Mitigating renal fibrosis.	[201]
AD-114	Disrupting CXCR4-mediated signaling, reducing macrophage infiltration and cytokine expression.	Reducing renal fibrosis.	[202]

 doi:10.20944/preprints202501.1657.v1

8. Lung Fibrosis

Galectin-3, a carbohydrate-binding scaffold protein, orchestrates ECM remodeling and inflammatory signaling in fibrosis. Its inhibitors reduce ECM deposition, suppress TGF-β signaling, and attenuate fibroblast activation, highlighting their broad-spectrum antifibrotic potential [173]. TULP3, an adaptor protein critical for ciliary trafficking, regulates profibrotic WNT and TGF-β signaling pathways. Deficiency in TULP3 leads to disrupted ciliary composition, impaired DNA damage repair, and fibrotic diseases such as fibrocystic kidney disease and liver fibrosis. Therapeutic interventions targeting TULP3, such as gene editing and cell-based therapies, hold promise for restoring its functions and mitigating fibrosis [174]. The SLC15A3-p62 axis links autophagy and oxidative stress, critical in IPF. Modulating this axis reduces oxidative stress-induced fibrosis and promotes intracellular clearance [31]. TOLLIP (Toll-interacting protein) offers dual roles in regulating inflammation and autophagy. TOLLIP suppresses NF-κB-mediated inflammatory pathways by interacting with IRAK-1 and facilitates autophagosome-lysosome fusion via LC3. Genetic studies link TOLLIP to IPF susceptibility, emphasizing its clinical relevance. By modulating TOLLIP activity, cell-based therapies can restore tissue homeostasis, offering a novel antifibrotic approach[175].

Transglutaminase 2 (TG2) plays a central role in ECM remodeling by catalyzing irreversible cross-linking of ECM proteins like collagen and fibronectin, driving fibrosis progression. Monoclonal antibodies targeting TG2's catalytic core have shown nanomolar efficacy in inhibiting transamidase activity and ECM deposition in fibrosis models[176]. In parallel, TG2 inhibitors, such as LDN 27219, provide additional antifibrotic strategies [177]. Lysyl oxidase-like protein 2 (LOXL2), another ECM regulator, facilitates collagen cross-linking and fibrosis[203]. Its regulation by NUDT21 and therapeutic targeting through siRNA-loaded liposomes have significantly reduced fibrosis in silicosis models, highlighting its potential for antifibrotic interventions[178].

Caveolin-1 (Cav1), a critical scaffold protein, regulates TGF-β signaling and fibroblast activation. Cav1-derived peptides, like CSP7, inhibit epithelial apoptosis, reduce ECM accumulation, and improve lung function in murine models of pulmonary fibrosis [29,204]. CircTADA2A acts as a competing endogenous RNA, sponging miR-526b and miR-203 to upregulate Cav1 and Caveolin-2 (Cav2), respectively. By stabilizing Cav1-mediated signaling, circTADA2A effectively counters fibrotic progression, positioning Cav1 as a pivotal player and a potential target in IPF treatment strategies[29]. In silicosis, a debilitating occupational disease, Cav1 mitigates inflammation and fibrosis by suppressing NF-κB signaling. Cav1 deficiency exacerbates silica-induced lung injury, highlighting its therapeutic potential in silicosis management[204]. Betulinic acid (BA), a natural pentacyclic triterpenoid, targets Dishevelled 2 (DVL2) in the Wnt/β-catenin pathway. BA inhibits fibroblast activation, downregulates Wnt target genes, and prevents ECM accumulation, showcasing its antifibrotic efficacy in IPF models [179,180]. **ARV-825**, a BRD4 degrader, demonstrates antifibrotic efficacy by modulating chromatin remodeling and reducing the expression of profibrotic genes.[181].

Axin1, a Wnt/β-catenin signaling regulator, has emerged as a potential target in pulmonary fibrosis. The inhibition of fatty acid synthase (FASN) with C75 treatment increases Axin1 expression, promoting β-catenin degradation and reducing fibroblast activation. In vivo studies have shown that C75 alleviates pulmonary fibrosis, emphasizing the therapeutic value of targeting Axin1 [35].The AAV6-based CasRx system, designed for precise RNA knockdown, targets Axin1 in lung epithelial cells. This strategy enhances β-catenin stabilization in alveolar stem cells, promoting alveolar regeneration and reducing fibrosis. The transient nature of this system minimizes potential safety concerns while offering a robust antifibrotic effect [36].

The VCAM1-VNT-LPS platform, a selective delivery system targeting VCAM1-expressing myofibroblasts, delivers BCL-2 inhibitors with minimal off-target effects. This nanotechnology-based approach significantly reduces fibrosis and enhances drug specificity [182]. In a bleomycin-induced mouse model of lung fibrosis, VCAM1-VNT-LPS demonstrated superior therapeutic efficacy by reducing fibrosis, suppressing migration of fibroblasts into foci, and enhancing drug accumulation in fibrotic lungs compared to non-targeted LPS or free VNT. Importantly, safety profiles confirmed no significant systemic toxicity. This selective delivery mechanism, grounded in scaffold protein-

 doi:10.20944/preprints202501.1657.v1

targeted nanotechnology, underscores the potential of VCAM1-VNT-LPS as a transformative intervention for idiopathic pulmonary fibrosis, warranting further validation in advanced humanized models. In the context of lung fibrosis, AAV1.SERCA2a gene therapy emerges as a promising treatment strategy. It not only restores calcium homeostasis but also modulates critical signaling pathways such as STAT3/FOXM1 and the SNON/SKI axis, effectively reducing fibrotic progression[183].

9. Cardiac Fibrosis

SKI, a multifunctional transcriptional regulator and scaffold protein, mitigates cardiac fibrosis by deactivating myofibroblasts and reducing excessive extracellular matrix (ECM) deposition. It forms inhibitory complexes with R-Smads, suppressing TGF-β1 signaling, a major driver of fibrosis. Studies in myocardial infarction (MI) models confirm SKI's role in improving cardiac remodeling by inhibiting fibroblast activation and interacting with additional signaling pathways, such as β-catenin and integrins, within the ECM niche [184]. Caveolin-1 (Cav1), a membrane-associated scaffold protein, exhibits antifibrotic and anti-inflammatory effects by modulating NF-κB signaling. Overexpression of Cav1 suppresses cardiac inflammation and ECM deposition in diabetic cardiomyopathy models, emphasizing its therapeutic potential [69,185].

Periostin, an ECM protein, serves both as a structural scaffold and a modulator of ECM remodeling in heart fibrosis[186]. It stabilizes ECM architecture, contributing to tissue integrity, while also promoting fibrosis through ECM deposition and fibroblast activation. Periostin interacts with collagen and fibronectin to enhance fibrotic responses and alter the microenvironment, exacerbating tissue scarring. Its overexpression in pathological states underscores its role in heart fibrosis. Targeting periostin or its pathways may offer therapeutic potential, but its complex roles require further investigation.

In a high-fructose/high-fat diet (HFrHFD) mouse model, carvedilol, a β-arrestin2-biased agonist, alleviated cardiac fibrosis by reducing glucose, endothelin-1, DAG, and restoring β-arrestin2 and Akt levels[187,188]. These findings highlight β-arrestin2's role in fibrosis regulation, suggesting its therapeutic potential in diet-induced fibrosis. Similarly, Xin-shu-bao (XSB) downregulates β-arrestin1 and fibrosis markers in heart failure models, emphasizing β-arrestins' role in cardiac remodeling[189].

Galectin-3, implicated in inflammation and fibrosis, is a potential therapeutic target in cardiac remodeling. It promotes macrophage activation and ECM deposition. BRD4, a scaffold protein, regulates profibrotic gene expression, and its inhibition could mitigate fibrosis and improve cardiac function. Targeting both galectin-3 and BRD4 for myocardial infarction therapy has been suggested [190–192].

10. Heptic Firobisis

Cav-1 stabilizes phosphofructokinase liver type (PFKL) by competing with SQSTM1, preventing lysosomal degradation and sustaining glycolysis essential for hepatic stellate cell (HSC) activation. Knockdown of Cav-1 reduces glycolysis, alleviating fibrosis, while alamandine downregulates Cav-1 via ubiquitin-mediated degradation, impairing glycolysis and suppressing fibrosis[193]. Isoliquiritigenin (ISL), a bioactive compound derived from licorice, demonstrates significant potential in treating liver fibrosis by leveraging caveolin-1 (Cav-1)-mediated ferroptosis in hepatic stellate cells (HSCs)[194]. ISL targets Cav-1 to induce ferroptosis by suppressing GPX4 and upregulating TFR and DMT1, effectively reducing fibrosis in zebrafish and mouse models. These findings highlight Cav-1 as a critical scaffold protein in regulating glycolytic and ferroptotic pathways for antifibrotic therapies.

Gal-3 facilitates fibrosis via integrin-β1 and FAK signaling. XHH2, a rhamnogalacturonan-I-like polysaccharide, disrupts the Gal-3/integrin-β1 interaction, suppressing HSC activation and fibrosis[195]. In CCl4-induced mouse models, oral XHH2 reduces fibrosis markers without toxicity.

 doi:10.20944/preprints202501.1657.v1

XHH2 selectively targets Gal-3, effectively alleviating liver injury and fibrosis at doses as low as 2 mg/kg, positioning it as a promising anti-fibrotic agent.

Numb regulates HSC differentiation by promoting Notch degradation, favoring hepatocyte differentiation over biliary epithelial cells. In BDL-induced cholestatic liver fibrosis (CLF), BM-MSCs overexpressing Numb reduce inflammation and fibrosis, while Numb knockdown exacerbates fibrosis[196]. Numb's role as a scaffold protein and signaling regulator highlights its potential in CLF therapy, particularly through BM-MSC transplantation to reprogram HSC differentiation and suppress fibrosis progression.

Hic-5 antisense oligonucleotides (ASOs) inhibit advanced hepatic fibrosis by targeting Hic-5, while Salvianic acid A alleviates alcoholic liver disease by downregulating BRD4 to suppress HMGB1 translocation. These therapies highlight the promise of nucleotide-based interventions in liver fibrosis[99,197,198].

11. Renal Fibrosis

IRS1, a pivotal scaffold protein in insulin signaling, bridges metabolic regulation and anti-fibrotic effects. Spiroganodermaines, particularly (-)-spiroganodermaine G from *Ganoderma* species, enhance IRS1 phosphorylation, promoting glucose uptake while suppressing fibrotic markers (fibronectin, α-SMA) in TGF-β1-stimulated renal cells.This dual activity positions IRS1 as a key therapeutic target, and spiroganodermaines as promising agents for kidney fibrosis. Furthermore, other scaffold proteins may also serve as promising therapeutic targets for kidney fibrosis. For a detailed exploration of this topic, readers can refer to an excellent review on the subject[199].

BRD4, a scaffold protein involved in transcriptional regulation via chromatin remodeling, is a promising target for kidney fibrosis treatment. ZLD2218, a novel BRD4 inhibitor, significantly reduces fibrosis in UUO models by inhibiting TGF-β/Smad3 signaling and reducing markers such as α-SMA and collagen[200]. Similarly, xylitol, a natural intestinal metabolite, reduces BRD4 levels, offering an alternative strategy for mitigating renal fibrosis. These findings highlight BRD4's role in fibrotic signaling and its potential as a therapeutic target[201].

AD-114, a humanized single-domain i-body targeting CXCR4, effectively reduces inflammation, fibroblast activation, and ECM deposition in renal fibrosis models, including folic acid-induced nephropathy and UUO. It disrupts CXCR4-mediated signaling (p38 MAPK, PI3K/AKT/mTOR) while reducing macrophage infiltration and cytokine expression. AD-214, a second-generation i-body with enhanced pharmacokinetics, further validates these renoprotective effects, positioning these i-bodies as safe, effective alternatives to traditional CXCR4 antagonists[202].

Composite scaffolds designed for kidney tissue regeneration offer a novel approach, though the use of scaffold proteins for in vivo drug delivery requires further exploration. These advancements underscore the therapeutic potential of scaffold proteins in addressing kidney fibrosis[205].

12. Conclusions

Scaffold proteins are essential for pathway specificity and cross-talk integration, yet the mechanisms driving these processes are not fully delineated. Investigating how scaffold proteins coordinate signaling dynamics, particularly in tissue-specific contexts, could reveal critical insights into their roles in fibrosis. Advanced methods such as real-time imaging and computational modeling will be indispensable for capturing the transient interactions of scaffold proteins. Real-time imaging, single-cell transcriptomics, and advanced proteomics are critical for uncovering scaffold protein dynamics and interactions. Integrating these technologies with machine learning and computational tools will enable deeper insights and accelerate the discovery of novel scaffold protein regulators.

The transient and dynamic nature of scaffold protein interactions poses challenges for drug design. Developing small molecules, peptides, or biologics that selectively modulate scaffold protein function without disrupting normal cellular physiology is a critical need. High-throughput screening and rational drug design approaches will play pivotal roles in overcoming these challenges. The

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tissue-specific functions of scaffold proteins in fibrosis warrant further exploration. For instance, proteins like Cav-1 and BRD4 exhibit diverse roles in kidney, liver, and lung fibrosis, necessitating context-specific therapeutic strategies. Identifying and targeting the unique roles of scaffold proteins in various fibrotic tissues could enhance therapeutic precision and reduce off-target effects.

Scaffold proteins influence the interaction between fibroblasts, immune cells, and the extracellular matrix within the fibrotic niche. Understanding this interplay, particularly in conditions like silicosis and renal fibrosis, could inform the design of therapies that modulate immune-fibrotic cross-talk for better outcomes. Beyond therapeutic modulation, composite scaffolds mimicking scaffold protein functions may offer novel approaches for tissue regeneration in fibrotic organs. Such scaffolds could serve as drug delivery platforms or regenerative templates, bridging gaps in current treatment paradigms.

Declaration of interests: The authors declare no competing interests.

Funding: This work was supported by grants from the National Natural Science Foundation of China (No.82373547), and also supported by Jiangsu Province Science and Technology Plan Project 'Provincial Frontier Technology R&D Program' (BF2024054).

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