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REVIEW

Decoding Fibrosis

A tough job: ion channels, transporters, and pumps during organ fibrosis

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Abstract

Fibrosis plays a crucial role in a range of chronic diseases, including cancer. Emerging evidence suggests that ion channels, transporters, and pumps—the transportome—have an essential share in fibrogenesis and fibrosis by regulating fibroblast and myofibroblast activity. This review bridges current knowledge gaps by integrating insights from multiple diseases affecting the heart, lungs, pancreas, kidney, and liver, as well as cancer. Thereby, we reveal shared molecular mechanisms of how the transportome modulates fibroblast activation, extracellular matrix deposition, tissue stiffness, and remodeling. We focus on the roles of various ion transport proteins, including PIEZO1, transient receptor potential (TRP), K^+, and cystic fibrosis transmembrane regulator (CFTR) channels; the Na^+/H^+ exchanger NHE1; and the Na^+/K^+-ATPase. By comparing analogous pathways across different fibrotic diseases such as Ca^{2+} signaling and transforming growth factor β1 (TGF-β1) and Wnt/β-catenin pathways, we highlight the druggable potential of these ion transport proteins and suggest novel concepts for therapeutic intervention.

epithelial-mesenchymal transition; inflammation; mechanotransduction; membrane potential; tumor microenvironment

INTRODUCTION

Fibrosis contributes in varying degrees to ∼35% of all global fatalities, putting it on par with leading risk factors such as smoking or high blood pressure. Yet, unlike these well-known determinants, fibrosis remains less discussed as a global health burden. The pathological fibrotic scarring process diverges from the physiological wound healing process by excessively accumulating extracellular matrix (ECM) and connective tissue. Instead of merely filling the void in a diseased tissue and rendering it palpably stiff, fibrosis stealthily progresses to destroy organ architecture and impair parenchymal functions (1).

Almost every organ system can be affected by fibrosis through both tissue-specific and shared pathophysiological mechanisms. This review focuses on diseases where fibrosis substantially contributes to mortality, including chronic diseases of the heart, lungs, pancreas, kidneys, liver, and solid tumors. Despite their clinical diversity, these diseases exhibit similar pathophysiological patterns. These involve, among others, sustained parenchymal injury, transformation of fibroblasts to myofibroblasts, and complex cellular cross talk between immune, endothelial, and parenchymal cells (2–5). These processes are orchestrated by a seemingly well-characterized network of molecular mediators such as growth factors, cytokines, and transcription factors. However, often overlooked is that these signaling networks rely on more fundamental cellular mechanisms such as mechanosensation, pH regulation, and Ca^{2+} homeostasis, all of which converge on the broader machinery of cellular ion homeostasis. This highlights a vast but underappreciated class of molecules in the context of fibrosis: ion transport proteins.

Encompassing ion channels, transporters, and pumps, ion transport proteins are remarkably versatile in modifying the pericellular microenvironment and sensing and responding to a wide range of physical and chemical cues. For example, increased environmental stiffness caused by accumulated connective tissue can be sensed by mechanosensitive ion channels such as PIEZO1 (see *Mechanotransduction*). However, these molecular sensors and transducers do not act alone: ion transport proteins form a dynamic functional network mutually influencing and regulating each other—the so-called "transportome" (6, 7). For instance, PIEZO1-mediated Ca^{2+} influx is often amplified by other ion channels, such as transient receptor potential (TRP) channels TRPV4 or TRPC1 (8). Moreover, ion transport proteins can form physical signaling hubs and have functions beyond their canonical conductive properties by physically interacting with a large number of other proteins, as recently shown for $K_{ir}2.1$, $K_V1.3$, or $K_{Ca}3.1$ channels (9–11). Through such interactions, the transportome can not only sense even minuscule environmental cues but also efficiently transduce them to robust fibrosis-relevant responses such as fibroblast migration and myofibroblast differentiation (12–14).

This review introduces the concept that the transportome contributes to fibrosis by acting as a modifier, sensor, and

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transducer in the fibrotic processes. First, we examine fundamental mechanisms related to ionic homeostasis that accompany and drive fibroblast activation and extracellular matrix deposition. Next, we critically evaluate the evidence for key ion channels, transporters, and pumps playing specific roles in fibrotic pathologies. We continue by mapping shared and organ-specific intersections between the transportome and canonical mediators of fibrosis, with the aim of bridging the existing gap between the disciplines of fibrosis research and electrophysiology. Finally, we discuss the rationale of treating fibrotic diseases by targeting the transportome to guide future therapeutic efforts.

ION TRANSPORT PROTEINS AS SENSORS AND DRIVERS OF FIBROSIS

It is increasingly clear that ion transport proteins play an active role in coordinating complex fibrotic processes by complementing and sometimes enabling the action of growth factors, cytokines, and transcriptional regulators. This section will outline some basic concepts by which ion channels and transporters may operate during fibrosis. Specifically, we will focus on mechanosensation, electrochemical integration, immune cross talk, and metabolic stress response.

Mechanotransduction

Fibrosis, at its core, can be seen as a biomechanical process (15–17). Its defining feature is excessive ECM deposition that inevitably transforms the architecture and mechanical properties of tissues. Specifically, fibrosis increases tissue stiffness, elevates osmotic and interstitial fluid pressure, and applies compressive stress on surrounding cells (18–24). In the fibrotic tissue of pancreatic ductal adenocarcinoma (PDAC), for example, tissue stiffness can reach values of 5–10 kPa, which is up to five times higher than in normal pancreatic tissue (25, 26). Altered mechanical properties of the fibrotic tissue are not only epiphenomena of the disease but also active contributors of its progression. For instance, in a rat model of liver fibrosis, tissue stiffening preceded overt fibrosis, suggesting that mechanical changes can initiate cellular remodeling (27). Similar observations were made in other fibrotic organs, such as the heart (28), the lung (29), or the skin (30); increased ECM stiffness can activate PIEZO1 channels and initiate myofibroblast differentiation before significant matrix deposition. Thereby, fibrosis creates a biomechanical environment that is both a consequence and a catalyst of its own progression. At the cellular level, this increased tissue stiffness translates to a greater resistance for cells when they attempt to deform, spread, or migrate. Cells sense and transmit these forces, among others, through cell-ECM adhesions (e.g., through collagens or fibronectin acting as tethers for integrins), actomyosin contractions, and cytoskeletal tension, ultimately influencing cellular signaling and function (31–33). Mechanosensitive ion channels are another essential class of sensors (21) that contribute to fibrosis. Here, we focus on their role in pathological fibrotic remodeling.

We propose a feed-forward model of how cells in a fibrotic microenvironment may respond to mechanical stress based on an analogy to desmoplastic solid tumors (34). We can distinguish between outside-in, inside-in, and inside-out signaling events, also applicable to fibrotic processes. First, the altered mechanical landscape in fibrotic tissues is sensed by the cellular transportome via an "outside-in" mechanism. Many pathways converge on increased intracellular [Ca^{2+}] ([Ca^{2+}]$_i$) either through direct influx, e.g., through TRP and PIEZO channels. [Ca^{2+}]$_i$ could also be indirectly affected by (mechanosensitive) K^+ channels, e.g., K_{2P} and K_{Ca} channels, that provide the electrical driving force for Ca^{2+} influx. As a second messenger, Ca^{2+} drives changes in transcriptional programs ("inside-in") (20, 21, 28), influencing cell phenotype and triggering "inside-out" effects, typically increasing ECM production or exerting increased force onto the surrounding ECM. This would drive further mechanical remodeling and sustain the pathological feedback loop. Thus, in addition to transducing mechanical cues from the fibrotic tissue, the transportome may ultimately modify its mechanical properties.

The proposed feed-forward mechanism is far from being simply circular, as it involves the coordinated action of multiple transport proteins. For instance, PIEZO1 often acts as the primary mechanosensor, with other channels (e.g., TRPC1, TRPV4, or P_2X_7) supporting downstream effects (9, 35). Notably, ion channel activity in fibrogenesis is tightly linked with cell adhesion. Macrophages physically interact with fibroblasts via integrins, which activate PIEZO1 and induce a rapid Ca^{2+} influx into fibroblasts. This Ca^{2+} signaling promotes fibroblast contraction and myofibroblast marker expression even in the absence of soluble transforming growth factor β1 (TGF-β1) (36). Subsequently, macrophages maintain this activated state by adhering to myofibroblasts via cadherin-11 and serving as a local source of TGF-β1 (37).

Membrane Potential

During fibrosis, changes in the expression and activity of ion channels and transporters alter the membrane potential, creating what can be described as electrophysiological remodeling. This concept, originally introduced in the context of atrial fibrillation (38), proposes that cardiac fibrosis is associated with increased membrane potential heterogeneity of cardiomyocytes and decreased electrical conductivity. Since then, evidence has revealed the involvement of mechanosensitive ion channels in the altered membrane potential in atrial fibroblasts (39, 40).

The electrical properties of different cell types fundamentally affect the mechanisms of Ca^{2+} influx. In excitable cells, including neurons, cardiomyocytes, and other muscle cells, membrane depolarization opens voltage-gated Ca^{2+} channels, allowing rapid Ca^{2+} entry (41). Conversely, nonexcitable cells such as fibroblasts, endothelial cells, and immune cells rely on membrane hyperpolarization that enhances the driving force for Ca^{2+} influx through cation channels, including TRP channels and stromal interaction molecule (STIM)/Orai complexes (42).

As fibroblasts become "activated" and acquire a myofibroblastic phenotype, their electrophysiological properties change depending on the tissue context and species model. A striking example is the de novo expression of the voltage-gated sodium

channel $Na_V1.5$ in atrial fibroblasts during differentiation into myofibroblasts (43). The induction of $Na_V1.5$ channel expression, driven by profibrotic stimuli such as TGF-β1 and mechanical stress, contributes to membrane depolarization, proliferation, and motility (44).

The resting membrane potential of fibroblasts is mainly shaped by K^+ channels, primarily inwardly rectifying K_{ir} channels (45–48). Moreover, $K_{2P}2.1$ (also known as TREK1; encoded by *KCNK2*) regulates the resting membrane potential of hepatic and pancreatic stellate cells. The impact of the channel, however, depends on environmental factors such as pH and ambient pressure (49, 50). The abovementioned K^+ channels only function properly provided the Na^+/K^+-ATPase maintains the necessary ionic gradients and supports electrical stability. Notably, the Na^+/K^+-ATPase pump contributes a modest (∼5–10 mV) but significant amount to hyperpolarizing the resting membrane potential of fibroblasts (51). In cardiac fibrosis, both in vitro and in vivo studies have demonstrated that the dysfunction of the Na^+/K^+-ATPase contributes to membrane depolarization and fibroblast activation (52, 53).

The resting membrane potential typically, however not always, becomes less negative during fibroblast activation (12, 54). Pancreatic stellate cell activation leads to the opposite effect. The membrane depolarization hyperpolarizes when cells are activated, which, in turn, also modulates Na^+/Ca^{2+} exchanger (NCX) activity and migration capacity (50). However, the actual values of resting membrane potentials vary considerably from study to study (55–57). Notably, even within a single tissue type, resting membrane potential values of individual fibroblasts can be observed to ranging from −5 to −70 mV (58, 59). Thus, the membrane potential of fibroblasts and its phenotypic consequences remain unclear, primarily due to differences depending on cell origin, activation status, and measurement techniques.

Inflammation

Sustained inflammation is a hallmark of fibrosis in nearly all affected organs (60). Numerous immune cells, including macrophages, T cells, and mast cells, engage in a continuous cross talk with fibroblasts to drive fibrosis (4, 61). It is well-established that ion channels, pumps, and transporters are essential for orchestrating immune responses, as reviewed elsewhere (62). A critical ion channel mediating inflammatory fibrosis is P_2X_7, a purinergic ATP-gated cation channel (63, 64). Pannexin-dependent ATP release from damaged cells can be sensed by P_2X_7 in macrophages, facilitating inflammasome activation and cytokine (e.g., IL-1β) release (65, 66). In addition, P_2X_7 in fibroblasts has been associated with the progression of lung, liver, and kidney fibrosis (63, 64).

A loss-of-function mutation of the Cl^- channel cystic fibrosis transmembrane regulator (CFTR) is a compelling example for how a malfunctioning ion channel drives an inflammatory response. The absence of functional CFTR channels in airway epithelia leads to impaired mucociliary clearance, which, in turn, results in a persistent inflammatory state dominated by neutrophils. Recurrent infections and the associated release of IL-8, oxidative stress, and fibroblast activation ultimately lead to lung scarring and fibrosis (67). In the absence of functional CFTR, the epithelial sodium channel (ENaC) becomes hyperactive, resulting in excessive cellular Na^+ influx. Besides its epithelial role, ENaC is also expressed in immune cells such as macrophages, where it contributes to a dysfunctional proinflammatory state. The disturbed sodium influx activates the NLRP3 inflammasome, leading to increased IL-1β and IL-18 secretion and perpetuating neutrophilic inflammation (68).

In hepatic stellate cells, TRPV1 disturbs NF-κB signaling and keeps them in a quiescent state. During hepatic stellate cell activation, *Trpv1* is downregulated, and complete deletion enhances liver fibrosis in mice (69). In contrast, knockdown of TRPV3 reduces proinflammatory LOX-1 protein in hepatic stellate cells and mRNA levels of interleukins IL-1β and IL-6 and tumor necrosis factor α (TNFα) in a carbon tetrachloride (CCl_4)-induced hepatic fibrosis mouse model (70). In the murine PDAC model, adjuvant treatment with a Na^+/H^+ exchanger 1 (NHE1) inhibitor increased immune cell recruitment and reduced fibrosis (71).

Fibrometabolism

The concept of fibrometabolism refers to the set of metabolic adaptations that fibroblasts and stromal cells undergo in response to sustained stress (72). As fibrosis progresses and vascular density declines, oxygen and nutrient delivery deteriorate (73). These metabolic changes may be initiated or shaped by ion channels and transporters.

How a capillary network develops (or fails to develop) around fibrotic tissue shapes the onset and persistence of fibrosis. Hypoxia and mechanical stresses present in fibrotic tissue act synergistically to reprogram endothelial cells toward a profibrotic phenotype. In hepatic stellate cells, hypoxia stabilizes hypoxia-inducible factor 1α (HIF-1α), which interacts with the Notch intracellular domain, and upregulates *TRPC6* expression. This, in turn, activates the calcineurin–nuclear factor of activated T-cells (NFAT) pathway and results in increased expression of profibrotic genes and enhanced ECM production (74). Moreover, TRPC6 is also an effector of hypoxia response in pancreatic stellate cells, where this channel regulates cell migration, Ca^{2+} signaling, and cytokine secretion upon hypoxia (75). Also, under hypoxia, pannexins release ATP into the extracellular space, where it functions as a paracrine danger signal. In models of systemic sclerosis, ATP binds to P_2Y_2 receptors of dermal fibroblasts, triggering Ca^{2+} influx (76).

Once initiated, the reduction in vascular density can feed back to further promote fibrogenesis, among others, by hypoxia. However, in other contexts, especially in later stages of fibrosis or certain organs, fibrosis is accompanied by excessive or dysregulated neovascularization. In a sheep model of bleomycin-induced pulmonary fibrosis, fibrotic lung areas displayed increased capillary density and VEGF expression, both of which were attenuated by blockade of the $K_{Ca}3.1$ channel using senicapoc (77). In parallel, this inhibition reduced ER stress markers such as GRP78 and CHOP, leading to decreased epithelial apoptosis and attenuated fibrosis (78). These findings indicate that ion channels can influence fibrogenesis through direct signaling and by modulating stress-related metabolic responses (77).

TRANSPORTOME-SPECIFIC INSIGHTS INTO FIBROSIS

This section aims to provide an overview of what happens during fibrosis upon perturbing individual ion transport proteins. Fibrosis is typically quantified by measuring the extent of ECM deposition, fibroblast activation, and tissue remodeling. In research settings, histological staining techniques are commonly used to visualize collagen accumulation, whereas gene and protein expression analyses of markers like α-smooth muscle actin (α-SMA), collagen I, or fibronectin reflect myofibroblast differentiation or "activation." Moreover, assessing the fibrosis master-regulator TGF-β1 and its canonical signaling pathway, e.g., Smad phosphorylation, is also commonly used. Clinically, fibrosis assessment varies by organ: cardiac fibrosis is typically evaluated via MRI or echocardiography; liver fibrosis is staged using elastography or biopsy; and pulmonary fibrosis is monitored by high-resolution computed tomography (CT) scans and lung function tests. In the following section, we will highlight those ion transport proteins, whose involvement in fibrotic diseases is strongly validated, optimally by both genetic and pharmacological means in in vitro and in vivo fibrotic disease models.

Ca^{2+}-Permeable Channels

Voltage-gated Ca^{2+} channels.

There is increasing evidence that voltage-gated Ca^{2+} channel (Ca_V) function has a direct impact on fibrotic conditions, particularly in pulmonary fibrosis. A recent epidemiological study from the Korean National Health Screening Cohort found that individuals using Ca^{2+} channel blockers, commonly prescribed for cardiovascular diseases, have a significantly lower risk of interstitial lung disease and idiopathic pulmonary fibrosis (IPF) compared with never-users (79). Two independent studies focusing on pathophysiological features of IPF showed in vivo that the dihydropyridines nifedipine and felodipine prevent fibrotic changes, including lung stiffness and ECM deposition (79, 80). The observed effects were not primarily through inhibition of lung inflammation, as immune cell counts and IL-6 levels remained largely similar (80). On a cellular level, TGF-β1-induced Ca^{2+} oscillations in lung fibroblasts were substantially reduced by nifedipine and other blockers.

Orai channels.

The role of store-operated Ca^{2+}-entry (SOCE), mediated by interactions between ORAI channels (ORAI1-3) and STIM proteins (STIM1-2), in fibrosis is best described in pancreatic fibrosis, although involvement in other organs has also been reported (81, 82). However, current evidence predominantly focuses on ORAI1, which appears to be an important profibrotic mediator of SOCE-related processes. In models of acute and chronic pancreatitis, ORAI1 expression and function are upregulated in both acinar and stellate cells (83, 84), promoting Ca^{2+}-dependent cytokine (mainly TNF-α, IL-1β, and TGF-β1) and ECM (mainly collagen I) secretion. Both genetic interference with ORAI expression using siRNA and pharmacological ORAI inhibition (e.g., using CM4620) prevent pancreatitis progression and fibrosis by blocking pancreatic stellate cell activation, proliferation, and migration (84). A similar notion is supported by our study where we found Orai1-positive cancer-associated fibroblasts to be enriched in the fibrotic PDAC stroma (85). Moreover, ORAI1 siRNA or its inhibitor Synta-66 reduced ECM deposition by pancreatic stellate cells.

PIEZO channels.

There is ample evidence that PIEZO1 is crucial for fibrotic processes in various organs (Table 1) (89, 90, 92, 93, 98, 99). In the pancreas, PIEZO1 is functionally expressed in pancreatic stellate cells (35, 100). It senses ductal hypertension, triggers fibrotic gene programs, and promotes pancreatic stellate cell migration. When activating PIEZO1 using Yoda1, the Ca^{2+} signal leads to upregulated TGF-β1, fibronectin, and collagen I expression (35, 91, 94, 97, 100). These responses are abolished by the PIEZO1 blocker GsMTx4 or genetic *PIEZO1* deletion (35, 91, 94). Importantly, PIEZO1 requires a certain amount of TRPV4 activity: pancreatic stellate cells from TRPV4-knockout (KO) mice are similarly resistant to pressure-induced activation, so that *Trpv4*-KO mice are protected from duct-ligation-induced pancreatic fibrosis (35). Besides TRPV4, PIEZO1 also cooperates with TRPC1 in regulating stiffness-directed cell migration, i.e., durotaxis of pancreatic stellate cells (8).

PIEZO1 expression is elevated in different liver fibrosis models (96, 97), both in hepatic stellate cells and in cells of the myeloid lineage (97). Accordingly, macrophage-specific PIEZO1 deletion attenuates hepatic fibrosis progression by reducing profibrotic cytokine (TNFα, IL-1β, and IL-6) and cathepsin-S release. On the other hand, PIEZO1 activation in macrophages on a stiff ECM can promote anti-inflammatory behavior via Rac1 signaling (96). This points to context-dependent effects of PIEZO1 activation. In liver sinusoidal endothelial cells, cyclical stretch engages integrin/Notch-PIEZO1 signaling to induce CXCL1 secretion and neutrophil recruitment (102). This ultimately contributes to sinusoidal thrombosis and portal hypertension, putatively mediating hepatic fibrosis. Thus, PIEZO1 and its downstream effectors link mechanical stress to organ fibrosis in multiple cell types. In addition, PIEZO2 has been identified as a mechanoreceptor in lung fibrosis that contributes to myofibroblast differentiation, suggesting that both PIEZO channels may play important roles in fibrotic disease progression (99).

TRP channels.

As indicated in Table 2, various members of the TRP superfamily have been associated with both pro- and antifibrotic roles, with evidence reported for TRPV (123–127, 129, 130, 134–137), TRPM (1115–121), TRPC (106–114, 130), and TRPA (103, 105). For instance, in hepatic fibrosis, decreasing TRPV1 function by genetic or pharmacological means exacerbates hepatic fibrosis leading among others to increased α-SMA and collagen III expression (130). In contrast, TRPC6 is upregulated in the fibrotic liver and gut, in TGF-β1-stimulated hepatic stellate cells and myofibroblasts (110, 114). TRPV3 is also functionally upregulated in activated hepatic stellate cells in fibrosis. It promotes an inflammatory response in the liver by inducing an increased expression of TNF-α, IL-1β, and IL-6 (70). Similar profibrotic functions have been associated to TRPM7 across multiple organs (138). TRPM7 mediates TGF-β1-induced ECM production through predominantly Smad-dependent pathways in

Table 1. *ORAI and PIEZO channels in fibrosis modulation*

Protein Name	Organ	Species	Model/Investigated Cell Type	Exp. in Fibrosis	Effect of Channel Activity	Applied Channel Modulation	Refs.
ORAI1	Heart (left ventricle)	Human	Human left ventricular tissue, ventricular fibroblasts	↑	Collagen ↑	YM58483 (blocker)	(81)
ORAI1	Pancreas	Human, mouse	Human PS-1 cells; murine PDAC (KPfC) samples; murine PSC, cerulein mouse model, human pancreas tissue, RLT human activated PSC cell lines	↑	Proinflammatory cytokine Tnfa, IL-1b, TGF-β1 ↑, AKT activation ↑ pancreatitis ↑, immune cell infiltration ↑, PSC activation, proliferation, and migration ↑ collagen release from PSC under TGFβ/Vitamin C stimulation ↑	CM5480 (blocker), Synta-66 (blocker); *ORAI1* knockdown, si*ORAI1*	(84–86)
STIM/ORAI	Pancreas	Mouse, rat	Primary mouse and rat pancreatic acini, immortalized mouse pancreatic stellate cells, mouse pancreatitis model		TGFβ1, COL1A1 ↑, NFAT and NF-κB signaling ↑, myeloperoxidase activity ↑, inflammatory cytokines ↑	CM4620 (blocker)	(87)
ORAI1	Kidney	Human, mouse,	Mouse kidney fibrosis model (high-fat diet and by UUO), human tissue, human proximal tubule epithelial cells (HK2)	↑	Fibronectin, α-SMA, TGF-β1, collagens I/III/IV ↑, TGF-β1-induced intracellular Ca^{2+} influx and p-smad2/3 ↑, EMT ↑	*ORAI1* knockdown (sh*ORAI1*), SKF96365 (blocker)	(82)
ORAI3	Heart	Mouse	Mouse cardiomyocytes, mouse TAC		Normal heart function ↑, cardiomyocyte cell death ↓	Cardiac-specific *Orai3*$^{-/-}$	(88)
PIEZO1	Heart	Human, mouse	Cardiac hypertrophy (TAC model), epithelial cells	↑	COL1A1 and COL3A1 ↑, TIMP1 ↑, pressure overload induced cardiomyocyte hypertrophic growth ↑, stretch induced hypertrophy ↑, calcineurin- and calpain-related signaling ↑	*Piezo1*$^{-/-}$, Yoda1, Dooku1 (activators), GsMTx4 (blocker)	(89–91)
PIEZO1	Lung	Human	Human lung epithelial cells, lung injury mouse model		EMT ↑	Yoda1 (activator), GsMTx4 (blocker), PIEZO1$^{-/-}$ (in lung epithelial cells)	(92)
PIEZO1, TRPV4	Pancreas	Human, mouse	Piezo1$^{GFAP-/-}$ mice; Trpv4$^{-/-}$ mice, mouse PSC, human PSC		PIEZO1: Fibronectin ↑, collagen I ↑ TRPV4: PSC activation ↑	*Trpv4*$^{-/-}$ mice, *Piezo1*^{GFAP}*-KO* mice (PSC); Yoda1 (activator), GsMTx4 (blocker), HC067047 (TRPV4 activator)	(35)
PIEZO1	Kidney	Human, mouse	UUO mouse model, human tissue, human HK2 cells and primary cultured mouse proximal tubular cells, mouse model Piezo1 specific knockout in myeloid cells, TCMK-1 mouse renal tubular cell line, human tissue	↑	Calpain activation ↑ macrophage infiltration and activation ↑, EMT ↑ cell apoptosis and mitochondrial dysfunction↑	Yoda1 (activator), GsMTx4 (blocker), Myeloid-specific deletion	(93–95)

Continued

Table 1.— *Continued*

Protein Name	Organ	Species	Model/Investigated Cell Type	Exp. in Fibrosis	Effect of Channel Activity	Applied Channel Modulation	Refs.
PIEZO1	Liver	Mouse, human	Piezo1$^{fl/fl}$ Lyz2^{Cre} (depleted Piezo1 in myeloid cells); mouse fibrosis model, primary mouse BMDMs; Kupffer cells, human data base	↑	Efferocytosis function ↑, reprogramming macrophages into an anti-inflammatory phenotype ↑, liver injury and fibrosis ↓, neutrophil infiltration ↓, fibrosis-related genes ↓	Yoda1 (activator), Piezo1$^{fl/fl}$ (myeloid cells)	(96)
PIEZO1	Liver	Human, mouse	C57BL/6J bile duct ligation, CCl4 injection; human tissue; LX-2 cells (human hepatic stellate cells)	↑	Collagen I and III, vimentin, fibronectin, α-SMA, TGF-β ↑, inflammation (TNF-α, IL-1β, IL-6, and NOS2) ↑	Yoda1 (activator), Piezo1$^{fl/fl}$, Piezo1$^{\Delta LysM}$ (myeloid specific)	(97)
PIEZO1	Skin	Human, mouse	Mouse model, human dermal fibroblasts; human tissue	↑	Fibroblast activation ↑, fibroproliferative phenotype ↑, skin stiffness ↑, Wnt2/Wnt11 pathway ↑	PIEZO1 knockdown (siPIEZO1), AAV-mediated PIEZO1 knockdown	(30)
PIEZO1		Human	Human adipose-derived stem cell		Collagen synthesis ↓, PIEZO1 regulates collagen synthesis in hASCs in a manner that is sensitive to substrate architecture	Yoda1 (activator), GsMTx4 (blocker), knockdown (siPIEZO1)	(98)
PIEZO2	Lung	Human, mouse	Human tissue from IPF patients; bleomycin mouse model; primary human lung fibroblasts	↑	α-SMA, fibronectin ↑, myofibroblast differentiation ↑	Knockdown (siPIEZO2); D-GsMTx4 (blocker)	(99)

α-SMA, α-smooth muscle actin; BMDM, bone marrow-derived macrophage; EMT, epithelial-to-mesenchymal transition; Exp., expression; IPF, idiopathic pulmonary fibrosis; PSC, pancreatic stellate cell; Ref.: reference; TAC, transverse aortic constriction; UUO, unilateral ureteral obstruction.

Table 2. *TRP channels in fibrosis modulation*

Protein Name	Organ	Species	Model/Investigated Cell Type	Exp. in Fibrosis	Effect of Channel Activity	Applied Channel Modulation	Refs.
TRPA1	Heart	Human, mouse	Trpa1$^{-/-}$ mice, myocardial infarction model, neonatal WT cardiac fibroblasts	↑	Differentiation and Ca^{2+} signaling of cardiac fibroblasts ↑, TGF-β-dependent signaling ↑	*Trpa1*$^{-/-}$, knockdown (siTRPA1), overexpression, HC-030031, TCS-5861528 (blockers)	(103)
TRPA1	Intestine	Human, mouse	Murine chronic colitis model; intestinal myofibroblast cell line (InMyoFibs); human intestinal biopsies	↑	TGF-β1–induced stress-fiber formation and collagen ↓, inflammation ↓	*Trpa1*$^{-/-}$, HC-030031 (blocker)	(104)
TRPA1	Pancreas	Human, mouse	Human PSCs, mouse pancreatitis model	↓	Ethanol-induced Ca^{2+} influx ↑, cell death ↑	HC-030031 (blocker), *TRPA1* silencing (siRNA)	(105)
TRPC3	Heart	Human, rat, mouse, dog, goat	Aged and spontaneous hypertensive rats, primary murine, goats, dogs and human cardiac tissues, primary rat, goat, murine (also *Trpc3*$^{-/-}$ mice) and human, rats and mouse cardiac fibroblasts and cardiomyocytes, iPSC derived cardiomyocytes	↑	TGF-β1, collagens I/III, CTGF, ACE, periostin, TGF-β2, TGF-β3 ↑, AngII induced migration and proliferation, Ca^{2+} transient ↑, NFATc3 activation	Pyr3, gadolinium, (blockers), *Trpc3*$^{-/-}$, knockdown (sh*TRPC3*)	(106–109)
TRPC6	Intestine	Human Intestinal myofibroblast cell line (InMyoFibs); human intestinal biopsies		↑	α-SMA and stress fiber formation ↑, COL1A1, IL-10, -11 ↑ SMAD-2, ERK1/2, p38-MAPK Signaling ↑	Knockdown (si*TRPC6*); dominant-negative *TRPC6* mutants	(110)
TRPC6	Heart/kidney	Human, mouse	Human right ventricular cardiac fibroblasts, Endoglin (Eng)$^{+/-}$ mice, Sugen + Hypoxia treated Wt and Eng$^{+/-}$ mice	↑	Collagens I/III, TGF-β1, fibronectin, MMP2, TIMP2 ↑ TGF-β1-mediated calcineurin and α-SMA ↑	*TRPC6* silencing (si*TRPC6*), BI 749327 (blocker)	(111, 112)
TRPC6	Kidney	Human, mouse	UUO mice models; TEC; HEK293 cells	↑	Collagen I, CTGF, α-SMA, MMP-2, MMP-9 ↑	*TRPC6*$^{-/-}$, BTP2 (blocker)	(113)
TRPC6	Liver	Human, mouse	Human hepatic stellate cell line (LX-2) and bile duct ligation-induced hepatic fibrosis	↑	↑ TGF-β1-induced LX-2 cell activation and proliferation via the PI3K/AKT/p70S6K signaling pathway ↑	SAR7334 (blocker); knockdown (sh*TRPC6*), *TRPC6*$^{-/-}$ mice	(114)
TRPM4	Heart	Human, mouse	Primary human atrial and ventricular fibroblasts (failing and non-failing hearts), TRPM4$^{-/-}$ atria	↑	↑ Ca^{2+} current, fibroblast growth, α-SMA	9-phenanthrol (blocker), knockdown (sh*TRPM4*), *TRPM4*$^{-/-}$	(115, 116)
TRPM7	Heart	Human, mouse, rat	*Trpm7*$^{+/\Delta kinase}$ mice, rat fibroblasts; human atrial fibroblast isolated from atrial fibrillation and normal sinus rhythm patients	↑	Collagen, fibronectin, TGF-β1, p-Smad3 ↑, TNFα, IL-12, IL-10, $CD45^{+}$ cells, F4/$80^{+}CD206^{+}$ macrophages, CD3 +, CD8 + T cell ↑ p-Stat 1, calpain II activity ↑	*Trpm7*$^{-/-}$, silencing (si*TRPM7*, sh*TRPM7*); SB431542 (TGF-β1 receptor blocker)	(117–119)
TRPM7	Liver	Rat	HSC-T6 cells (rat HSC line); rat model treated with CCl4	↑	TGF-β1-induced expression of α-SMA, COL1A1↑, MMP13 ↓, p-Smad2/3 ↑, PDGF-BB-induced cell proliferation, α-SMA and COL1A1↑, cyclin D1, PCNA and CDK4 ↑; p-ERK and p-AKT ↑	2-APB (non-specific blocker); knockdown (si*TRPM7*)	(120, 121)
TRPM7	Pancreas	Human	PS-1 and RLT-PSC PSC cell lines, cancer-associated fibroblasts	↑	PSC activation ↑, Cell cycle progression (G1-S transition) ↑, through p53 expression ↓ and PI3K/Akt ↑	NS8593 (blocker); knockdown (siTRPM7)	(122)

Continued

Table 2.— *Continued*

Protein Name	Organ	Species	Model/Investigated Cell Type	Exp. in Fibrosis	Effect of Channel Activity	Applied Channel Modulation	Refs.
TRPV1	Heart	Human, mouse	Checked myofibroblasts in tissue, *Trpv1*$^{-/-}$ mice	↑	TGF-β1, VEGF, MMP-2, Smad2, recruitment of myofibroblasts, collagen deposits ↑ COL1A1, COL3A1, macrophage infiltration, TNFa, IL-6 ↑	*Trpv1*$^{-/-}$	(123, 124)
TRPV1	Liver	Human, mouse	Human tissue, *Trpv1*$^{-/-}$ mice; human and mouse primary HSCs; CCl4 treated mice	↓	Collagens IV/V ↓, HSC activation ↓, NF-kB-mediated inflammatory HSC ↓, proinflammatory signaling ↓	*Trpv1*$^{-/-}$	(69)
TRPV3	Heart	Rat	Abdominal aortic constriction (AAC) /pressure overload rat hearts, cardiac fibroblasts from neonatal rats	↑	G1/S transition, collagen I/III, cyclin E, EDK2 complex, TGF-β1 ↑	Carvacrol (blocker), ruthedium red (Ca^{2+} channel blocker), TRPV3 silencing (siRNA)	(125)
TRPV3	Liver	Human, mouse	Hepatic stellate cells; human liver cirrhosis specimen; mice liver CCl4 treated	↑	LOX-1 protein ↑, IL-1β, TNF-α, IL-6 ↑, HSC proliferation ↑	Drofenine (activator); forsythoside B (blocker); knockdown (si*TRPV3*)	(70)
TRPV3	Heart	Human, rat, mouse, pig	Diabetic rats, Cardiac fibroblasts, *Trpv4*$^{lox/lox}$, and *Trpv4*^{ECKO}, human heart tissues, Trpv4$^{-/-}$ mice, Neonatal rat ventricular myocytes, porcine valvular Interstitial Cell	↑	Collagen I, TGF-β1, p-Smad3, IL-1β, IL-6, TNF-α, MIP-2, MCP-1, p-CaMKII, p-NFκB ↑ cardiomyocyte apoptosis ↑, YAP/TAZ fibroblast activation ↑ VEGFR2, Rho/Rho kinase activation, AngII/PE-induced Ca^{2+} overload ↓	HC06704, GSK2193874 (blockers), GSK1016790A (activator), *Trpv4*$^{-/-}$, knockdown (si*TRPV4*)	(126–128)
TRPV3	Kidney	Rat	Control versus spontaneously hypertensive rats, rat kidney interstitial fibroblast cells (NRK-49F)	↑	TGF-β1 ↑, Smad 2/3 ↑, CTGF ↑	RN-1734 (blocker), lactate	(129)
TRPV4	Liver	Human, rat	HSC-T6 cells; human liver tissue; rat fibrosis model; hepatic stellate cells, HSC-T6 cell line	↑	TGF-β1-induced HSC-T6 cell proliferation, α-SMA, COL1A1 ↑ HSC apoptosis ↓, autophagy ↑	Ruthenium red (blocker); knockdown (si*TRPV4*)	(130, 131)
TRPV4	Lung	Human, mouse	*Trpv4*$^{-/-}$ mice, bleomycin-induced pulmonary fibrosis *Trpv4*$^{-/-}$ mice, lung tissues from patients, primary human lung fibroblast,	↑	Ca^{2+} signaling, fibroblast differentiation and airway remodeling, TGFβ1, ROS signaling through NOX4 ↑	RN1734 (selective blocker)	(101, 132)
TRPV4	Pancreas	Rat	Primary PSC rat; high fat alcohol-fed rats	↑	Ca^{2+} mobilization ↑	4aPDD (activator)	(133)
TRPV4	Skin	Human, mouse	Myofibroblasts, skin tissues of patients with SSc; mouse model of SSc	↑	Collagen deposition ↑	*Trpv4*$^{-/-}$	(134)
TRPV4	Fibroblast	Human, mouse	GD25 cells, NIH 3T3 cells, human breast cancer MCF7 cells, human gingival fibroblasts		DDR1 ↑, cell spreading linked to elevated Ca^{2} influx via TRPV4, collagen compaction ↑	GSK1016790A (activator); RN-1734 (blocker)	(135)
TRPV6	Pancreas	Human, mouse	Human database; *Trpv6*$^{mut/mut}$ mice	↓	Protection against pancreatitis ↑, acinar to ductal metaplasia ↓	*Trpv6*$^{mut/mut}$	(136)

Exp., expression; HSC, hepatic stellate cell; PSC, pancreatic stellate cell; Refs., references; ROS, reactive oxygen species; UUO, unilateral ureteral obstruction.

hepatic stellate cells and atrial fibroblasts and promotes fibroblast proliferation and differentiation via PI3K/ERK signaling (117–122). Moreover, TRPV4 inhibition in hepatic stellate cells by both siRNA and blocker lowers profibrotic cytokine (TNFα, IL-1b, and IL-6) release and suppresses hepatic stellate cell proliferation and viability (131).

Besides its association with PIEZO1 (see *PIEZO channels*), TRPV4 is also implicated in pulmonary and dermal fibrosis (131, 139). *Trpv4*-KO mice show less α-SMA-positive myofibroblasts and decreased collagen deposition (132). In the intestinal context, TRPA1 has been linked to fibrosis progression through potential antifibrotic effects (104). Specifically, in Crohn's disease, its expression is elevated in stenotic regions. In murine colitis models, *Trpa1*-deficient mice develop more severe intestinal fibrosis and respond poorly to steroid therapy, suggesting that TRPA1 activity contributes to the antifibrotic effects of glucocorticoids. Mechanistically, TRPA1 activation suppresses TGF-β1-induced expression of collagen I, α-SMA, and HSP47 in myofibroblasts and antagonists such as HC-030031 block steroid-induced Ca^{2+} influx. Similarly, activated pancreatic stellate cells downregulate *TRPA1*. In this way, they become resistant to toxic Ca^{2+} overload and continue to deposit matrix despite ongoing damage and inflammation (105).

K^+ Channels

K^+ channels also have a well-established link to fibrosis (Table 3) (140–142). The intermediate conductance Ca^{2+}-activated K^+ channel $K_{Ca}3.1$ is a key profibrotic mediator in many organs. $K_{Ca}3.1$ channels have been linked to maintaining Ca^{2+}-induced Ca^{2+} influx (e.g., via TRP channels) by hyperpolarizing the membrane potential of fibroblasts, ultimately promoting cell proliferation and ECM production (143). $K_{Ca}3.1$ is upregulated in fibrotic kidneys, pancreas, lungs, liver, and heart, and its blockade (genetic knockout or inhibitors such as TRAM-34 and senicapoc) generally attenuates fibrosis (144–153). For example, $K_{Ca}3.1$ expression rises markedly in a mouse model of renal fibrosis induced by unilateral ureteral obstruction (144). Global $K_{Ca}3.1$ channel knockout in these mice or TRAM-34 treatment has reduced myofibroblast accumulation and collagen deposition in the kidneys. In diabetic nephropathy models, TRAM-34 lowers collagen, fibronectin, and α-SMA expression and limits inflammatory cell infiltration (154). Similar antifibrotic effects of $K_{Ca}3.1$ inhibition are seen in lung fibrosis models: $K_{Ca}3.1$ is upregulated in bleomycin- or paraquat-induced pulmonary fibrosis, and TRAM-34 or senicapoc treatment reduces collagen and α-SMA, myofibroblast proliferation, and inflammation (77, 143). Mechanistically, $K_{Ca}3.1$ blockade impairs TGF-β1-induced Smad2/3 phosphorylation and downstream ERK signaling in fibroblasts and suppresses the expression of ICAM-1 and the proinflammatory cytokine monocyte chemoattractant protein 1 (MCP-1) (155). In the liver, however, $K_{Ca}3.1$ shows a more nuanced role. Hepatic stellate cells upregulate $K_{Ca}3.1$ during activation, and TRAM-34 can reduce cell proliferation and type-I collagen and α-SMA expression in vitro (145). Yet, $K_{Ca}3.1$ also appears hepatoprotective: $K_{Ca}3.1^{-/-}$ mice subjected to CCl_4 have worsened liver injury and fibrosis, with more hepatocyte DNA damage and apoptosis (147). In contrast, the $K_{Ca}3.1$ inhibitor senicapoc treatment reduced fibrosis in a thioacetamide-induced hepatotoxic liver injury model (146). This suggests that depending on the original trigger $K_{Ca}3.1$ may have a dual role in cirrhosis, promoting hepatic stellate cell fibrogenesis in the thioacetamide model but safeguarding hepatocytes upon carbon tetrachloride exposure.

As opposed to the predominantly profibrotic channel $K_{Ca}3.1$, another channel in the family, large-conductance K_{Ca} channel, $K_{Ca}1.1$, acts in an antifibrotic way. $K_{Ca}1.1$ is downregulated in renal and hepatic fibrosis, whereas channel activation decreases fibrotic responses (156). In models of renal fibrosis induced either by unilateral ureteral obstruction or folic acid treatment, $K_{Ca}1.1$-KO mice show exaggerated fibrosis with higher fibronectin, vimentin, α-SMA, and collagen expression (157). Conversely, pharmacological $K_{Ca}1.1$ openers attenuate fibrosis via inhibiting TGF-β1/Smad2/3 signaling (157). Similar principles apply to hepatic fibrosis: $K_{Ca}1.1$ overexpression in hepatic stellate cells reduces migration and collagen I, α-SMA levels, while channel knockdown results in opposite effects (156).

The mechanosensitive $K_{2P}2.1$ is yet another K^+ channel with strong links to fibrosis (158). $K_{2P}2.1$ expression and function are induced in the heart, lung, pancreas, and liver fibroblasts upon primarily mechanical triggers. Importantly, cardiac-specific $K_{2P}2.1$ deletion protects against pressure-overload fibrosis, decreasing ECM deposition and fibrosis gene expression (159). $K_{2P}2.1$ fosters fibroblast activation by modulating membrane potential and Ca^{2+} dynamics that activate c-Jun *N*-terminal kinase (JNK) and focal adhesion kinase (FAK) signaling. In bleomycin-triggered pulmonary fibrosis, $K_{2P}2.1$ becomes upregulated (160). In the same model system, $K_{2P}2.1$ knockdown or inhibition (e.g., with fluoxetine) reduces α-SMA, fibronectin, and collagen I expression, reversing the myofibroblast phenotype, likely via suppression of FAK and ERK pathways. In human hepatic stellate cells, $K_{2P}2.1$ knockdown similarly diminishes collagen I and PDGF-BB expression (49, 50). Thus, similar to $K_{Ca}3.1$, $K_{2P}2.1$ drives fibrogenesis by sustaining profibrotic signaling cascades.

Cl^- Channels

CFTR is a well-studied example of Cl^- channels in fibrosis (161). Specifically, CFTR is downregulated and internalized in murine renal fibrosis induced by unilateral ureteral obstruction and in human fibrotic kidneys. Loss of CFTR function (e.g., by the pathognomonic ΔF508 mutation) unleashes aberrant Wnt/β-catenin signaling and epithelial-to-mesenchymal transition (EMT) in myofibroblasts. CFTR normally binds Dishevelled2 to restrain β-catenin signaling. In contrast, CFTR dysfunction leads to unbalanced β-catenin activation and enhanced fibrosis. Overexpressing CFTR in injured kidneys can reverse these fibrogenic changes, highlighting an antifibrotic role for CFTR. As mentioned in *Inflammation*, CFTR downregulation in epithelia (e.g., lung and pancreas) similarly promotes local inflammation and fibroblast activation (144, 145, 161, 162).

Other Cl^- channels may have profibrotic roles. There is accumulating evidence that the Cl^- channel ClC-3 promotes cardiac and lung fibrosis and hypertrophic scar formation

(163–165). ClC-3 contributes to cardiac myofibroblast differentiation by modulating Cl^- currents (166). Moreover, knockdown or pharmacological inhibition of ClC-3 reduces renal and dermal fibroblast migration, collagen I/III synthesis, and TGF-β1 signaling, suggesting that ClC-3 promotes fibrosis by enhancing fibroblast activation and matrix deposition (164, 165).

There seems to be a tissue-specific role of the Ca^{2+}-activated Cl^- channel anoctamin1 (ANO1, encoded by *TMEM16A*) in fibrosis. For instance, ANO1 inhibits cardiac fibrosis after myocardial infarction via TGF-β/Smad3 pathway in rats (167). In contrast, another study in rats showed profibrotic effects. For instance, after ANO1 knockdown, the expressions of angiotensin II type 1 receptor (AT1R) and cell nuclear proliferation antigen were markedly reduced, and the phosphorylation levels of MEK and ERK1/2 were decreased (168). Another study showed that ANO1 also contributes to renal fibrosis through increased intracellular Cl^- concentration and TGF-β1-dependent pathways (169). This indicates that ANO1 regulates fibrosis differentially through the TGF-β/Smad3 pathway and the AT1R-mediated MAPK signaling pathway.

Na^+ Channels

Na^+ channels may not act as central mediators of fibrosis across organs. However, organ-specific roles for fibrotic processes are emerging for some channels. $Na_V1.5$ in the heart is the best-studied example, with studies converging on the notion that $Na_V1.5$ appears to exert divergent effects on TGF-β signaling depending on the cardiac region. Nearly 50% of all human atrial myofibroblasts exhibit inward Na^+ currents driven mainly by $Na_V1.5$, together with $Na_V1.2$ and $Na_V1.9$ (43, 170, 171). Functionally, $Na_V1.5$ inhibition with a specific antibody ($Na_V1.5$-E3) boosts TGF-β1 secretion. This is in contrast to ventricular fibroblasts, in which increased $Na_V1.5$ activity stimulates the TGF-β1 pathway (172). Whether this apparent contradiction reflects spatial specificity (atria vs. ventricles) of signaling or fibroblast heterogeneity remains unresolved. Nevertheless, the study described a gain-of-function $Na_V1.5$ mutation causing long QT syndrome type 3 (LQT3) (172). Here, the authors observed increased fibroblast proliferation, resulting in an excessive number of fibroblasts in vivo. As a potential mechanism, the authors pointed out that $Na_V1.5$ in ventricular fibroblasts might cooperate with the Na^+/Ca^+ exchanger NCX.

Another potential candidate for organ-specific fibrosis is the epithelial Na^+ channel ENaC. It is well-established that there is a functional balance between CFTR-directed secretion and ENaC-mediated absorption of NaCl and H_2O in healthy airways (173). In cystic fibrosis, loss of CFTR function disrupts the normal balance between Cl^- secretion and Na^+ absorption, resulting in airway surface liquid dehydration and mucus plugging. Mice with airway-specific overexpression of the β-subunit of ENaC (βENaC-Tg) have been generated. They mimic this key pathogenic feature with mucus hyperconcentration and lung disease resembling cystic fibrosis (174, 175). Although targeting the interplay between CFTR and ENaC seems a plausible therapeutic strategy in cystic fibrosis, ENaC inhibitors such as BI 1265162 have not yet shown a clear clinical benefit (176, 177).

Ion Transporters

Secondarily active transporters of the solute carrier (SLC) superfamily are also involved in fibrotic processes. The best-studied transporter in fibrosis is the Na^+/H^+ exchanger NHE1 (encoded by *SLC9A1*) (71, 178), which seems to act largely in a profibrotic manner. NHE1 is a major regulator of the intra- and extracellular pH homeostasis. The local pH landscape is crucial in the context of fibrosis. Extracellular acidification triggers ECM remodeling, by initial degradation via enzymes such as matrix metalloproteases, which cleave the latent TGF-β complex into its active form and promote profibrotic signaling (179). A recent study shows that pharmacological NHE1 inhibition disrupts the pH homeostasis in human lung fibroblasts and abrogates TGF-β-induced α-SMA upregulation, stress fiber formation, and profibrotic cytokine (TGF-β1, IL-6, and IL-8) secretion (178). In vivo, a rat lung fibrosis model treated with the NHE1 inhibitor rimeporide showed reduced fibrosis and smaller collagen-positive areas (180). Similarly, in a rat model of liver fibrosis, treatment with the NHE1 inhibitor cariporide significantly reduced fibrosis, correlating with decreased hepatic stellate cell activation, proliferation, and collagen deposition (181). Moreover, our data show that NHE1 contributes to myofibroblastic phenotype and cell motility of pancreatic stellate cells, thereby promoting fibrosis in a murine pancreatic cancer model (71).

The Na^+/Ca^{2+} exchanger (NCX) is yet another interesting ion exchanger in fibrosis. NCX can operate in two modes: the "forward" mode (extruding Ca^{2+}) and the "reverse" mode (mediating Ca^{2+} influx), reviewed elsewhere (54, 182). Nakamura et al. (183) demonstrated NCX expression in activated rat hepatic stellate cells both in vitro and in vivo following CCl_4-induced injury, inducing activation markers such as α-SMA. In hypertensive rodent models, elevated endogenous digitalis-like factors were reported to promote NCX-mediated Ca^{2+} influx in cardiac fibroblasts, activating p42/44 MAPKs and enhancing collagen synthesis. Pharmacological inhibition of NCX with SEA0400 reduced collagen deposition, lowered left ventricular stiffness, and improved survival (184).

Magnesium, iron, and manganese transporters and the regulation of the homeostasis of these ions also appear to be relevant in the development of fibrosis across various organs. A recent machine-learning-driven genome-wide association analysis revealed that metal ion transporters, prominently *SLC30A10* (ZNT10), *SLC39A8* (ZIP8), *HFE*, and *SLC41A1*, are closely linked to fibrotic diseases across multiple organs (185). They have been genetically linked to fibrotic processes across organs, potentially through modulation of inflammatory and oxidative pathways. Indeed, the relevance of SLC39A8 is underlined by its direct impact on epithelial renewal and lung fibrosis (186). Furthermore, a study on angiotensin II-induced cardiac fibrosis revealed that $[Ca^{2+}]_i$ is influenced by extrusion of intracellular Mg^{2+} by SLC41A1 in cardiac fibroblasts (187). However, the functional relevance of these ion transport proteins remains to be confirmed by further mechanistic studies.

Ion Pumps

Beyond its classical role in maintaining the concentration gradients of intra- and extracellular Na^+ and K^+ ions, the Na^+/K^+-ATPase has notable effects on fibrosis signaling, as

already reviewed by Orlov et al. (188). The Na^+/K^+-ATPase forms a large protein complex with Src kinase, triggering downstream cascades such as ERK, PI3K/Akt, and reactive oxygen species (ROS) generation (52, 53, 189–194). Hence, the effects of the Na^+/K^+-ATPase on fibrosis may be at least partly exerted through its nonconductive properties, in that it acts as a signaling hub. Mainly, this pump can act in a profibrotic manner in cardiac and pulmonary fibrosis and in cancer-associated fibroblasts. In rat cardiac fibroblasts, inhibition of the Na^+/K^+-ATPase by cardiotonic steroids like ouabain decreases antifibrotic miRNA (miR-29b-3p) expression and enhances collagen synthesis via a Src-dependent mechanism (189). However, inhibition of Na^+/K^+-ATPase-related Src signaling with pNaKtide prevented collagen accumulation induced by partial nephrectomy in mice (52). Similar profibrotic effects were observed for lung fibroblasts, where low-dose ouabain infusion markedly attenuated bleomycin-induced pulmonary fibrosis in mice by attenuating TGF-β1 signaling (194).

A similar role in regulating fibrosis has emerged for the V-type H^+-ATPase, a proton pump critical for acidifying intracellular organelles such as lysosomes. Beyond pH regulation, the V-type H^+-ATPase modulates key fibrotic processes such as collagen degradation and myofibroblastic differentiation (195–198). In kidney and peritoneal fibrosis models, V-type H^+-ATPase inhibition with bafilomycin A1 suppresses TGF-β1 signaling and epithelial-to-mesenchymal transition, preserving epithelial integrity and reducing α-SMA expression (196, 197). In hepatic stellate cells, pharmacological inhibition or genetic perturbation of this pump restores AMPK activity and decreases proliferation and ECM gene expression (199). These findings highlight V-ATPase as a regulator of fibrotic remodeling and a potential target for antifibrotic intervention.

DECODING COMMON AND ORGAN-SPECIFIC SIGNALING PATHWAYS AFFECTED BY THE TRANSPORTOME IN FIBROTIC DISEASES

The previous section outlined that the functional expression pattern of ion transport proteins is remarkably similar across different fibrosis entities and organs. Analogous to the profibrotic cytokine TGF-β1, which can be seen as a master regulator, there seem to be ubiquitously expressed, largely profibrotic transportome players, prominently PIEZO1, $K_{Ca}3.1$, and NHE1. Conversely, mainly antifibrotic functions were associated with TRPV1, $K_{Ca}1.1$, and CFTR across different organ systems. This is remarkable considering the vast heterogeneity of fibroblasts across tissues, with at least 18 different subtypes (200).

Importantly, the abovementioned sets of ion transport proteins are not exclusive to fibroblasts in the fibrotic niche, as these are shared with other cell types. In cardiomyocytes, activation of PIEZO1 (91) or upregulation of TRPC6 (88), as a compensatory effect of lacking ORAI3, may lead to Ca^{2+}-dependent hypertrophy and remodeling through the calcineurin signaling pathway. Similarly, hyperactive ENaC stiffens endothelial cells, increases vascular permeability, impairs nitric oxide signaling and may be linked to cardiac fibrosis (201). Moreover, as detailed in *Inflammation*, immune cells are also equipped with multiple players of the transportome that partake in fibrotic processes.

During fibrosis, the initial profibrotic signals often come from injured parenchymal cells. Upon stress, they release ATP, protons, reactive oxygen species, and cytokines such as TGF-β. Some of these signals are directly mediated by ion channels and transporters, as detailed for P_2X_7 (see *Inflammation*). These early responses converge on fibroblasts, which then undergo differentiation. Indeed, numerous studies detailed in this review boil down to a limited number of mechanisms by which the transportome alters fibroblast differentiation. The transportome can achieve this by

1) Amplifying intracellular Ca^{2+} signaling, which acts as a master integrator of fibrotic stimuli (202). Transient Ca^{2+} bursts may support normal repair, but prolonged oscillations can reprogram cell fate. Ca^{2+} serves as a second messenger, initiating pathways related to adhesion, inflammation (87), fibrosis itself, or TGF-β1 (94).
2) Reinforcing the canonical TGF-β signaling pathway (203). TGF-β induces the expression of transportome members, including PIEZO1 [up to threefold in human proximal tubule cells (94), ORAI1 (86), and TRPC6 (114)]. Higher expression of ion channels establishes a feedback loop where signaling enhances sensitivity to subsequent stimuli. In turn, these channels can contribute to TGF-β1 upregulation, which then directly increases the expression of multiple ECM proteins (97).
3) Interfacing with broader canonical fibrotic pathways (185). Beyond TGF-β, PIEZO1 and CFTR modulate Wnt/β-catenin signaling (30, 161, 204). Zhang et al. (205) proposed a model in kidney fibrosis involving TGF-β, Wnt, and angiotensin II as interconnected drivers. The angiotensin II/AT1R pathway also promotes cardiac fibrosis via $K_{Ca}3.1$ activation (153). PIEZO1 activity is also involved in the NF-κB pathway and subsequent NLRP3 inflammasome activity (68, 206, 207).

This response may not be pathological by default—at the same time, fibroblasts also signal back to support the repair of parenchymal and endothelial cells (Fig. 1). However, under sustained stress, the same signals build up ECM stiffens and cells begin to sense the new mechanical environment. Despite different sources of stress, such as hypoxia in the liver or pressure overload in the heart, the transportome appears to serve as a shared mediator of detection and response across organs.

In addition to cross-organ fibrotic pathways, ion transport proteins also take part in tissue-specific processes. Indeed, it seems that not only the presence of a given protein matters but also its functional context and interactions. TRPV4 suppresses angiogenesis in the heart by downregulating *VEGFR2* (128), whereas in the liver it promotes autophagy in stellate cells through AKT signaling (114). In the pancreas, TRPV4 works with PIEZO1 to activate stellate cells (35). Despite this diversity, all effects of TRPV4 contribute to the progression of fibrosis in a tissue-specific manner. Context matters also within a given organ, as observable for the differential function of $Na_V1.5$ in the cardiac atrium versus ventricle, which was discussed in more detail in *Na^+ Channels*.

Many of the ion transport proteins associated with fibrosis, whether pro- or antifibrotic, are also central to basic cellular

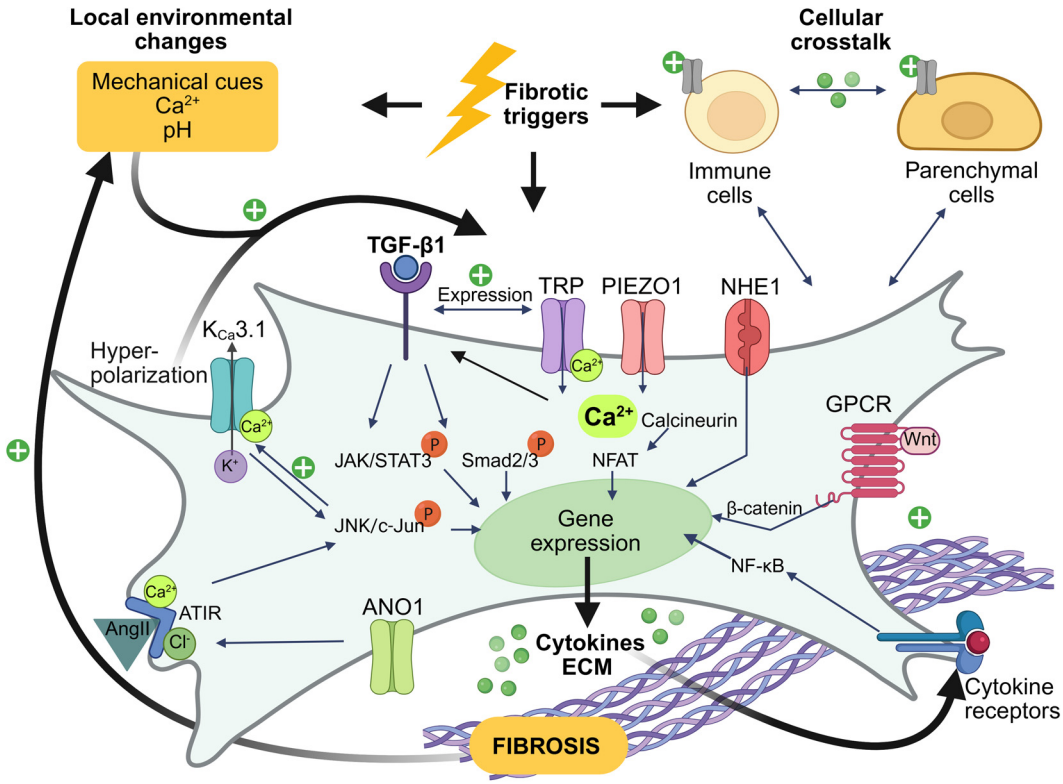

Figure 1. The contribution of ion channels and transporters in sustaining fibrosis. Fibrotic triggers, such as chronic injury, inflammation, or cancer, disrupt the local microenvironment and initiate a profibrotic cross talk. These signals converge on myofibroblasts (center), which express a range of ion channels and transporters. Channels like PIEZO1 and TRP mediate Ca^{2+} influx, whereas K^+ channels such as $K_{Ca}3.1$ maintain a hyperpolarized membrane potential to support sustained Ca^{2+} signaling. The transportome further amplifies fibrosis by modulating pathways including TGF-β, AngII, NF-κB, and Wnt. These intracellular signals drive gene expression and profibrotic phenotypes, such as extracellular matrix (ECM) production and cytokine release, which feedback to myofibroblasts via autocrine and paracrine loops, reinforcing fibrosis. Figure 1 was created with a licensed version of BioRender.com.

homeostasis. In uninjured tissues, they are often expressed constitutively at baseline. The fibrotic transportome is not defined by the presence or absence of specific channels per se, but rather by their use-dependent regulation: once activated by mechanical stress, ionic imbalance, or inflammatory cues, these molecules begin to amplify their own functions through feedback mechanisms. One important, yet underexplored aspect of this response is pH regulation. On the one hand, the function of ion channels and transporters such as $K_{2P}2.1$, NHE1, and NCX is linked to cellular pH of myofibroblastic cells (49, 54, 71). On the other hand, it is underexplored in which way environmental acidosis, a hallmark of chronically inflamed, cancerous or fibrotic tissues, affects the transportome (208). Thus, despite its relevance, the precise role of pH dynamics in fibrosis remains poorly understood and deserves closer investigation in future studies. An additional layer of mechanistic complexity is added by the fact that some families of ion channels can form heteromers and are extensively spliced in specific organs. This means that, e.g., TRP channels such as TRPC3 can form heteromers with TRPC6 that could eventually lead to even more nuanced tissue-specifically defined fibrotic responses.

Beyond acquired defects in ion channel function, inherited ion channel mutations, i.e., channelopathies, can also contribute to fibrotic disease development. The most prominent example for this is cystic fibrosis, caused by loss-of-function mutations in CFTR. Moreover, as noted for $Na_V1.5$, channelopathies in its encoding gene (*SCN5A*) can lead to long-QT-syndrome associated with a fibrotic cardiac phenotype (172). On a similar notion, inherited loss-of-function of $K_{Ca}1.1$ can not only cause pronounced neurological symptoms but also prominent connective tissue phenotypes that remain to be fully characterized (157). These examples highlight how defects in antifibrotic ion channel function can ultimately converge on fibrotic phenotypes.

Regeneration is a controlled and self-limiting process. Following injury, transient activation of inflammatory and mechanical signals promotes repair, after which the process slows as healing completes. At some point, however, this regenerative system crosses a threshold. Ca^{2+} signaling, initially transient, becomes sustained (*Ca^{2+}-Permeable Channels*). Mechanical feedback loops grow stronger, gradually detaching from the original injury. Meanwhile, antifibrotic regulators such as CFTR are lost, removing brakes within the system (209–211). In this altered state, the transportome no longer supports repair, it begins to drive pathology and favors chronicity. Among activated fibroblasts, a subpopulation may enter senescence. Premature senescence in fibroblasts and epithelial cells can be caused by elevated stiffness (212). Senescent fibroblasts present increased $[Ca^{2+}]_i$ and secrete proinflammatory and profibrotic factors [TGF-β, IL-6, and matrix metalloproteinase (MMPs)] (213, 214). Loss of TRPC3 in lung fibroblasts drives senescence through mitochondrial Ca^{2+} overload

Table 3. *K^+ channels in fibrosis modulation*

Protein Name (Gene)	Organ	Species	Model/Investigated Cell Type	Exp. in Fibrosis	Effect of Channel Activity	Applied Channel Modulation	Refs.
$K_{Ca}1.1$ (*KCNMA1*)	Kidney	Mouse, rat, human	$K_{Ca}1.1^{-/-}$ mice, UUO and FAN mouse models, HK-2; normal rat kidney fibroblast and proximal tubular epithelium-like cell line; and HEK-293T	↓	Collagen I/III, fibronectin, α-SMA ↓, TGF-β1/Smad pathway ↓, degradation of TGF-β receptors↑	$K_{Ca}1.1^{-/-}$, NS1619, BMS191011 (activators)	(157)
$K_{Ca}1.1$ (*KCNMA1*)	Liver	Rat, human	Rat model of liver fibrosis, rat HSC, human hepatic stellate cell line LX2	↓	HSC migration ↓, collagen expression ↓, TGFβ1/SMAD3 and JAK/STAT3 signaling pathways ↓	Paxilline (blocker), rottlerin (activator), overexpression/ knockdown (siKCNMA)	(158)
$K_{Ca}3.1$ (*KCNN4*)	Heart	Rat	Rat model, rat atrial fibroblasts	↑	Remodeling, αSMA, collagens ↑	TRAM-34 (blocker), knockdown (sgRNA-Cas9), overexpression	(153)
$K_{Ca}3.1$ (*KCNN4*)	Lung	Human, rat, sheep	Rat model of paraquat poisoning, primary pulmonary fibroblasts, tissue explants	↑	Inflammation ↑, lung compliance ↓, ECM, collagen I, α-SMA ↑, (myo)fibroblast proliferation ↑, wound healing ↑, p-Smad2/3 and nuclear translocation ↑	TRAM-34, senicapoc (blockers)	(143, 148–150, 152)
$K_{Ca}3.1$ (*KCNN4*)	Kidney	Human, mouse	Human kidney biopsies, diabetic nephropathy model, unilateral urinary obstruction model, human proximal tubular cells (HK2), mouse kidney fibroblasts	↑	Fibroblasts proliferation ↑, MCP-1, ICAM1, F4/80, collagens, fibronectin ↑, TGF-β1, TβRII, p-Smad2/3, p38 and ERK1/2 MAPK ↑, TGFβ1-induced MCP1 ↑	TRAM-34 (blocker), $K_{Ca}3.1^{-/-}$, knockdown (siKCNN4)	(142, 144, 151, 155)
$K_{Ca}3.1$ (*KCNN4*)	Liver	Rat, human	Rat liver fibrosis models (biliary obstruction, high-fat diet, bile duct ligation, thioacetamide), primary rat HSC, HepG2 cells human liver cancer cell line	↑	Steatosis ↑, HSC proliferation ↑, TGF-β1, collagen, α-SMA ↑	TRAM-34, senicapoc (blockers)	(145, 146)
$K_{Ca}3.1$ *KCNN4*)	Liver	Human, mouse, rat	Human liver specimen, mouse fibrosis model (CCl4), $K_{Ca}3.1^{-/-}$ mice, rat liver fibrosis models (biliary obstruction, CCl4, thioacetamide), primary rat HSC and hepatocytes	↑	Protective role for hepatocytes ↑, collagen, α-SMA ↓, HSC activity ↓	$K_{Ca}3.1^{-/-}$, senicapoc, TRAM-34 (inhibitors)	(147)
$K_{2P}2.1$ (*KCNK2*)	Heart (left ventricle)	Mouse	$K_{2P}2.1^{-/-}$ and TAC mice, cardiac fibroblasts, cardiomyocytes	↑	Fibroblast dysfunction ↑, JNK ↑, pressure overload–induced cardiac dysfunction ↑	Global $K_{2P}2.1^{-/-}$, conditional $K_{2P}2.1^{-/-}$ in cardiomyocytes or cardiac fibroblasts	(159)
$K_{2P}2.1$ (*KCNK2*)	Lung	Mouse	Bleomycin-induced lung fibrosis mouse model, macrophages, fibroblasts	↑	macrophage M2 phenotype ↑, fibroblast activation, differentiation via TGF-β1 ↑, FAK/p38/YAP signaling↑	$K_{2P}2.1^{-/-}$, fluoxetine (blocker), overexpression	(160)
$K_{2P}2.1$ (*KCNK2*)	Liver	Human	Human HSCs, LX-2		Collagen I ↑, platelet-derived growth factor ↑, HSC proliferation ↑	Knockdown (siKCNK2), arachidonic acid (activator), tetrapentylammonium (blocker)	(49)

Continued

Table 3.— *Continued*

Protein Name (Gene)	Organ	Species	Model/Investigated Cell Type	Exp. in Fibrosis	Effect of Channel Activity	Applied Channel Modulation	Refs.
$K_{ir}2.1$ (*KCNJ2*)	Heart (left atria)	Dog	Dog chronic heart failure model, cardiac fibroblasts	↑	Fibroblast KCNJ2 expression ↑, hyperpolarizing RMP, Ca^{2+} entry ↑, atrial fibroblast proliferation ↑	Overexpression, knockdown	(141)
$K_v1.3$ (*KCNA3*)	Kidney	Human, mouse	HEK293T cells, iBMDM (immortalized), Primary BMDMs, UUO surgery mice	↑	Collagen I, fibronectin, α-SMA, TGF-β1 ↑, macrophage M2 polarization (Arg1, Mrc1, and Ym1) ↑, p-STAT6 ↑, leukocyte infiltration ↑	$K_v1.3^{-/-}$, PAP-1 (blocker)	(140)

α-SMA, α-smooth muscle actin; BMDM, bone marrow-derived macrophage; Exp., expression; FAN, folic acid nephropathy; HSC, hepatic stellate cell; MMP, matrix metalloproteinase; PSC, pancreatic stellate cell; Refs., references; UUO, unilateral ureteral obstruction.

and oxidative stress (215). Upregulation of CLIC-3 in bleomycin-induced lung injury leads to mitochondrial dysfunction, DNA damage, and senescence-associated secretory phenotype (216). Fibrosis and senescence are frequently observed together; however, the role of the transportome at this intersection remains ill-defined. This shifts the view of ion transport from a secondary effect to a process that actively enhances and prolongs fibrotic signaling.

THERAPEUTIC PERSPECTIVES AND CONCLUSIONS

The evidence compiled in this review highlights that fibrotic conditions can be modulated by targeting several players of the transportome. Notably, a current clinical trial explores the potential of ENaC inhibitors in cystic fibrosis. Targeting ion transport proteins may offer an attractive antifibrotic strategy, as a complete lack of fibrosis can be detrimental. Eliminating the fibrotic barrier in cancer can facilitate tumor invasion and metastasis (34, 217). Likewise, a scar in the heart, as imperfect as it is, may be lifesaving by sealing off structural defects. Thus, a growing number of preclinical or associated studies indicate that modulating rather than abolishing fibrosis would often be the therapeutic ideal.

Numerous clinically available drugs already target members of the transportome and have shown efficacy in preclinical models to reduce fibrosis, or they are supported by epidemiological data. Especially Ca^{2+} and K^+ channels and NHE1 represent promising targets for antifibrotic therapy. Patients taking Ca^{2+} channel blockers experience less fibrosis, as shown for idiopathic pulmonary fibrosis (218), suggesting a clinically relevant link worth of mechanistic exploration. Moreover, the pharmacological blockade of $K_{Ca}3.1$ with selective, well-tolerated small molecule inhibitors such as senicapoc attenuates fibrosis in numerous models (*K^+ Channels*; Table 3) (148, 150). Similar effects were elicited by inhibiting NHE1 with cariporide in a genetically engineered mouse model of pancreatic ductal adenocarcinoma: NHE1 inhibition prevented the activation of quiescent pancreatic stellate cells and attenuated fibrosis of the tumor stroma. Notably, both senicapoc and cariporide are candidate compounds for repurposing since they had already been tested in phase 3 clinical trials for sickle cell anemia and cardiac reperfusion-ischemia injury, respectively (219, 220).

Studying mechanosensitive channels including PIEZO1 also shows great promise, as it contributes to fibrosis in multiple ways (94, 95). The major issue with targeting PIEZO1 is currently the lack of specific modulators. Therefore, it may be more practicable to target players of the transportome that rather amplify and fine-tune primary mechanical signals and are well-druggable, such as TRPV4. Indeed, TRPV4 antagonists (and even agonists) disrupt the sensing of matrix stiffness that drives myofibroblast differentiation and function in pulmonary and pancreatic fibrotic processes (132, 133).

This review aimed at showcase future areas of transportome-related fibrosis research. In our view, understanding the complex network of signaling cascades between different ion channels is a priority. It is a prerequisite for developing effective combination therapies (12, 14). Here, the heterogeneity of fibroblasts across different organs and disease states presents both a challenge and an opportunity (221). Better

characterizing organ-specific and disease-specific ion transport protein signatures, their pathophysiological relevance and their related signaling networks could enable more targeted therapeutic approaches. This includes an exploration of the temporal dynamics of ion channel expression during fibrotic disease progression to define the optimal windows for therapeutic intervention and identify players of the transportome as biomarkers for fibrosis.

In conclusion, this review underscores three major insights into the role of transportome in fibrosis. First, ion transport proteins are crucial for fibrosis by regulating cellular signaling pathways including Ca^{2+} signaling, pH regulation, and direct effects on TGF-β signaling pathways. Second, there is remarkable conservation of ion channel involvement across different fibrotic conditions, suggesting broadly applicable therapeutic approaches despite considerable fibroblast heterogeneity between organs. Third, the druggability of numerous members of the transportome and their context-dependent activity make them compelling targets for future antifibrotic interventions.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

W.W., C.M.L., and Z.P. prepared figures; W.W., R.S., C.M.L., and Z.P. drafted manuscript; W.W., R.S., C.M.L., A.S., and Z.P. edited and revised manuscript; W.W., R.S., C.M.L., A.S., and Z.P. approved final version of manuscript.

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