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Dopamine receptors and organ fibrosis

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ABSTRACT

Organ fibrosis, considered as a major global health concern, is a pathological condition often occurring after tissue injury in various organs. The pathogenesis of fibrosis involves multiple phases and multiple cell types. Dopamine is involved in various life activities by activating five receptors (D1, D2, D3, D4, D5). Activation or loss of function of dopamine receptors has been reported to be associated with the fibrosis of several organs, such as ocular, lung, liver, heart, and kidney. In this paper, we review dopamine receptors' potential roles in organ fibrosis and mechanisms by which organ fibrosis develops or decreases when dopamine receptors function is activated or perturbed.

1. Introduction

Fibrosis is an outcome of the tissue healing response to chronic damage in various organs. It is a disease state characterized by an abnormal increase in extracellular matrix (ECM) components like fibronectin and collagen. When damage is minor, there is only a transient increase in the deposition of ECM components and facilitating the restoration of functional tissue architecture. However, when the injury is severe, ECM components continue to accumulate, It can result in tissue architecture disruption, organ dysfunction, and eventual organ failure [1]. To some extent, fibrosis is a major global health concern, and it has been reported that up to 45 % of all deaths in developed countries are caused by fibrotic tissue responses [2]. The pathogenesis of fibrosis involves multiple phases and multiple cell types, along with the release of cytokines and growth factors caused by platelet aggregation and degranulation, proliferation and effector cell activation, and finally, ECM deposition and remodeling. The complex interactions among mesenchymal cells, epithelial cells, vascular endothelial cells, and cells related to inflammation are regulated by various soluble mediators in the microenvironment [3–5].

In recent years, researches have demonstrated the role of dopamine receptors (DRs) in regulating fibrosis in tissues such as in the lung, liver and kidney. To some extent, this is not surprising, because dopamine (DA), a catecholamine neurotransmitter, plays a role in the central nervous system and inflammation [6]. Dopamine exerts its effects through five receptors: dopamine D1 receptor (D_1R), dopamine D2 receptor (D_2R), dopamine D3 receptor (D_3R), dopamine D4 receptor (D_4R), and dopamine D5 receptor (D_5R). DRs belong to the rhodopsin family/class A G protein-coupled receptors (GPCRs). DRs are located within many tissues, including the brain, spinal cord, eye, heart, kidney, and gastrointestinal tract [7–9].

In this review, we summarized the data on DA and DRs and their roles in organ fibrosis. We describe 1) the basic structure, distribution, and signal transduction mechanisms of DA and DRs and 2) the experimental and clinical evidences for the effects of DRs on organ fibrosis. These may strengthen our understanding of the role of dopamine and its receptors in organ fibrosis and highlight their potential as antifibrotic agents.

2. Dopamine, dopamine receptors and their signaling pathways

DA is synthesized from the nonessential amino acid L-tyrosine in the cytoplasm of noradrenergic and dopaminergic nerves, as well as non-neural tissues like the kidney and gastrointestinal tract [10]. After being produced, DA is moved into secretory vesicles for storage. Upon stimulation, DA-containing vesicles fuse with the cytoplasmic

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membrane and release DA into the synaptic cleft via exocytosis. DA works through binding to specific cell surface receptors and activating DA signaling. These receptors belong to the rhodopsin-like family and are characterized by having seven transmembrane domains and linkages to heterotrimeric G proteins, which consist of a, b, and g subunits. According to ligand recognition properties and physiological effects on cAMP production, DRs are initially divided into two pharmacological families [11]:D1-like and D2-like receptors. D_1R and D_5R are D1-like receptors which coupled to Gs and Golf proteins and then stimulating adenylyl cyclase (AC) and cAMP production, while D_2R, D_3R, and D_4R are D2-like receptors which coupled to Go and Gi proteins and then inhibiting AC, resulting in a

Decrease in cytosolic cAMP levels. The roles of DA and DRs in the central nervous system (CNS) have been extensively studied [12,13]. DRs have also been identified outside the brain in various organs and tissues, comprising the immune cells, vascular beds, heart, gastrointestinal tract, eyes, kidney, and the pancreas [14,15]. DRs can act as monomers or form dimeric and/or oligomeric complexes through the combination of either a single species (homodimers or homomers) or distinct species (heterodimers or heteromers) [16,17]. Various dopamine-associated behaviors and functions are induced and regulated through dopamine signals and dopamine receptors. The main signaling pathways associated with dopamine include cAMP/PKA signaling, ERK signaling, Akt/GSK-3 signaling, phospholipase signaling and Ca^{2+} channel signaling [18]. D1-like receptors or D2-like receptors can activate or inactivate these signaling pathways by phosphorylating/dephosphorylating key enzymes [19–26].

3. Dopamine receptors in organ fibrosis

3.1. Dopamine receptors and ocular fibrosis

Ocular fibrosis causes visual loss in millions of people worldwide [27]. It has been reported that retinal pigmented epithelial (RPE) cells can synthesize both L-DOPA and dopamine [28,29]. DA and dopaminergic signaling in the retina have been thoroughly investigated. In Gao's study [30], compared with D_1R, D_3R, and D_4R, D_2R and D_5R were prominently expressed in RPE cells. D_5R expression in RPE cells rose after 24-h exposure to transforming growth factor beta (TGF-β), but this increase did not continue with further incubation, while D_2R mRNA expression remained higher than that of D_5R. According to Gao'study, because D_2R and D_5R are prominently expressed in RPE cells, so they focused on the relationship between these two DRs and ocular fibrosis. In the absence of profibrotic stimuli by TGF-β, loxapine (a D_2R antagonist) and Fenoldopam (a D_5R agonist) inhibited fibrotic activity in RPE cells. No matter Fenoldopam or Loxapine exerted their effects through interactions with DRs. Moreover, D_2R is the dominant recipient of autocrine dopamine signaling in RPE cells exposed to TGF-βstimuli. When adding exogenous dopamine alone to the cells, adding loxapine or fenoldopam in the absence of TGF-β also had no effect in the fibrotic process. Another latest research also showed that besides loxapine, other D_2R antagonists, for example, Fluphenazine exhibited anti fibrotic effects [31]. So far, there have been no studies reported changes in fibrosis after activation or antagonism of these three DRs (D_1R、D_3R、D_4R), so the relationship between these three DRs and ocular fibrosis is still unclear.

3.2. Dopamine receptors and cardiac fibrosis

All DRs except for D4R are present within the heart in animals such as mice, or rats [32–34]. Furthermore, evidence links age-related cardiac fibrosis with the loss of functional D_3R in D_3R knockout mouse, leading to the over-accumulated collagen in the heart's interstitial space [35]. Another recent study suggested that pramipexole,a D3R agonist, could prevent morphine-induced hypertrophy, a state which may develop to cardiac fibrosis in C57BL/6 male mice [36]. D_1R, the most abundant DR present in the CNS, is also expressed in various other organs [37,38]. The D_1R in H9C2 cardiac myoblasts is more highly expressed compared to other cells and markedly increased following intervention with doxorubicin (DOX). Evidence suggested that A-68930, a specific D_1R-specific agonist, could reduce cardiac damage and fibrosis in mice treated with DOX via the inhibition of the nucleotide-binding domain-like receptor protein 3 (NLRP3) inflammasome in the heart [39]. Previous studies have suggested that D_1R and D_3R participate in crosstalk in human and mice, but the question of functionality is still unclear [40]. However, considering the excitatory characteristics of D_1R and its inhibitory effects on D_3R, the combined effects of these two receptors on the heart may explain the mechanisms of cardiac fibrosis and heart failure. This finding will lead to identifying targets for halting the pro-fibrotic effects of these receptors.

3.3. Dopamine receptors and lung fibrosis

Lung fibrosis is a kind of lung disorder marked by the progressive and irreversible damage to alveolar epithelial architecture, which ultimately leads to respiratory failure. Idiopathic pulmonary fibrosis (IPF) globally occurs among about 3 million people [41]. Dopamine and DRs are reported to be expressed in lung tissue; D1-like receptors (D_1R, D_5R) are present in nerve fibers in pulmonary nerve trunks, and D2-like receptors (D_2R, D_3R, D_4R) are present in pulmonary trunks [42]. D_1R was also reported to be expressed predominantly in fibroblasts, and D_1R agonism could reduce lung collagen abundance after bleomycin (BLM)-trigged lung injury in mouse and stimulation of D_1R prompted fibroblasts to present a pro-resolution phenotype by enhancing expression of matrix degrading enzymes and promoting fibroblasts to produce a less stiff ECM in vitro [43]. Dihydrexidine, one kind of D_1R agonist, can inactivate YAP (Yes-associated protein)/TAZ (transcriptional coactivator with PDZ binding motif) in fibroblasts [44] and stimulate cathepsin K [45], a gene related to collagen I degradation and clearance [46], thereby reducing the expression of ECM, and TGF-β-stimulated collagen I accumulation. In a BLM-induced pulmonary fibrosis mouse model, the use of spiperone and pegylated hyaluronidase (pegHYAL) represents a novel strategy for treating pneumofibrosis. Spiperone is a selective D_2R antagonist and the pegHYAL can block D_2R and subsequent changes in the hyaluronan matrix [47]. When administered singularly and in combination with pegHYAL, spiperone could reduce hydroxyproline and total collagen levels compared with monotherapy in mice. Despite the opposing functions of D1-like receptors and D2-like receptors, findings from Mou's study demonstrated that a selective D_1R agonist (Fenoldopam, FNP) and a selective D_2R agonist (sumanirole, SMR) protected mice from BLM-induced pulmonary fibrosis. They achieved this by blocking TGF-β1/Smad2 signaling to inhibit fibroblast-to-myofibroblast differentiation, thereby decreasing the levels of fibrotic markers both in vitro and in vivo [48]. These DR agonists could be a promising treatment option for patients with IPF in clinical practice.

3.4. Dopamine receptors and liver fibrosis

Liver injury can stimulate hepatic stellate cells (HSCs) to transition from a quiescent state to a fibrogenic, proliferative, and myofibroblastic phenotype. This transformation is crucial for the collagen progressive accumulation, which ultimately leads to liver fibrosis [49]. Liver fibrosis is a chronic and lethal complication of liver disease, and there is no effective treatment for this condition. It have been reported that sympathetic nervous system inhibitors could help in reducing liver fibrosis in CCl4 treated Wistar rats [50]. In another mice model, HSC was demonstrated it could express key enzymes for catecholamine biosynthesis, and produce norepinephrine and other catecholamines. Moreover, HSC could use catecholamines to autoregulate their growth. It suggested that HSCs could act as both a direct target and a source of norepinephrine [51]. This finding helps us better understand the mechanisms involved in the development of liver fibrosis due to

catecholamines. It also indicates that targeted interruption of catecholamine signaling in HSCs could serve as a potential treatment strategy to inhibit the fibrogenic reaction to liver damage [52]. This inspire us that DA as a catecholamine neurotransmitter and DRs may play a role in the liver fibrosis. In Zhao's study, D_2R expression was significantly upregulated in diabetic livers and HG-treated HSCs, which can lead to liver oxidative damage and inflammation, eventually resulting in hepatic fibrosis [53]. Recently, another study confirmed that immune cells play a role in liver fibrosis. Levels of YAP in macrophages were elevated in the livers of both humans and mice affected by liver fibrosis. Macrophage-specific YAP deficiency attenuated liver fibrosis. D_2R antagonists could selectively block YAP expression within in macrophages and prevent liver fibrosis in murine models [54]. These results confirmed the association between D_2R and liver fibrosis. Further research is needed to explore whether other DRs are also involved in the process of liver fibrosis.

3.5. Dopamine receptors and renal fibrosis

The renal dopaminergic system plays a crucial role in preserving normal renal function and blood pressure, as well as in regulating inflammatory reactions and tissue injury [55]. DA-mediated protection against renal inflammation and tissue injury is partly derived by D_2R, for disruption of the D_2R gene (D22/2) was associated with increased production of reactive oxygen species (ROS) [56]. Jiang's study showed that the existence of certain single nucleotide polymorphisms (SNPs) in the D_2R gene (namely, rs6277, rs6276, and rs1800497) caused a decrease in the expression of D_2R in renal proximal tubule cells. This decrease led to a pro-inflammatory phenotype, characterized by elevated levels of cytokines, chemokines, and TNF-α, as well as a pro-fibrotic phenotype, characterized by heightened TGF-β1 expression [57]. D_1R is also expressed in glomerular mesangial cells and plays an important physiological role. According to recent study, there was a decrease in the production of H_2S, the expression of D_1R and cystathionine-γ-lyase (CSE) in the renal tissues of diabetic mice and mesangial cells exposed to high levels of glucose. However, SKF38393 (a D_1R agonist) and NaHS (an exogenous H2S donor) reversed the pro-inflammatory and pro-fibrotic effects of high glucose. The positive impacts of SKF38393 were comparable to those of the $ERK_{1/2}$ inhibitor PD98059 in this study. As per the findings, activating the D_1R-CSE/H_2S pathway can reduce diabetic mesangial cell proliferation and ECM deposition in renal [58].

3.6. Mechanism by which dopamine receptors affect organ fibrosis

As previously mentioned, DR agonists or antagonists can alleviate fibrosis. Studies with an association proven between DRs and organ fibrosis are summarized in Table 1. According to the available experimental models of organ fibrosis, the mechanisms by which DRs affect organ fibrosis regression mainly include three aspects: 1. inhibition of chronic tissue injury; 2. deactivation a nd elimination of myofibroblasts; and 3. degradation of the ECM. Fig. 1 illustrates the effects of DRs on the regulation of organ fibrosis.

3.7. Inhibiting chronic tissue injury

DA or agonists of DRs have been documented to regulate the progression of inflammation through interaction with its receptors [59,60]. There are five subtypes of DRs (D_1R–D_5R). However, only D_1R has been shown to mediate the DA-induced suppression of NLRP3 inflammasome activation [61]. NLRP3 inflammasome activation is a cytosolic protein complex consisting of NLRP3, ASC, and caspase-1, and its activation promotes the maturation and release of some pro-inflammatory cytokines [62]. A specific D_1R-specific agonist called A-68930 can suppress the NLRP3 inflammasome in the heart via the D_1R/cAMP signaling axis [38]. A-68930 interfered with the inflammatory cascade in DOX-treated

Table 1
Summary of Dopamine Receptors and experimental species.

Year published	Species studied	Organ system	Results summary	References
2022	human retinal pigmented epithelial cells (hRPECs)	Ocular	A potential advantage of fenoldopam (D_5R agonist) and loxapine (D_2R antagonist) in selectively inhibiting fibrotic activity in profibrotic RPE cells	[30]
2013	mouse	cardiac	Loss of functional D_3R in mice resulted in an excessive accumulation of collagen within the interstitial space of the heart.	[35]
2020	mouse	cardiac	Activation of D_3R signaling could protect against morphine-induced cardiac fibrosis.	[36]
2021	mouse	cardiac	A-68930, a specific D_1R-specififfic agonist, could reduce cardiac injury and fibrosis in a Doxorubicin treated mouse model	[39]
2015	mouse	lung	Spiperone, selective D_2R antagonist, instillation separately or together with pegHYAL reduced the MSC-like cells considerably, which considered as a new strategy in treatment of pneumofibrosis.	[47]
2019	mouse	lung	D_1R agonist selectively inhibits YAP/TAZ function in mesenchymal cells and shifts their phenotype from profibrotic to fibrosis resolving, reversing in vitro extracellular matrix stiffening and in vivo tissue fibrosis in mouse models.	[44]
2020	primary normal human lung fibroblasts; mouse	lung	D_1R agonist played an important role in fibrosis resolution in vitro and in vivo by mediating collagen clearance.	[45]
2021	human; mouse	lung	Fenoldopam (a selective D_1R agonist) and sumanirole (a selective D_2R agonist) exerted potent antifibrotic effects in BLM-induced pulmonary fibrosis by attenuating the differentiation and proliferation of fibroblasts.	[48]
2021	Mouse	Liver	D_2R inhibition can reduce diabetic HSCs oxidative damage and fibrotic proliferation partly via the TGF-β1/Smads and NFκB pathways.	[53]

(*continued on next page*)

Table 1 (*continued*)

Year published	Species studied	Organ system	Results summary	References
2022	Human; Mouse; Minipig	Liver	D_2R antagonist selectively targeted YAP-dependent fibrogenic crosstalk between macrophages and $CTGF^+VCAM1^+$ vascular niche, promoting liver regeneration over fibrosis in both rodent and large animal models.	[54]
2014	Mouse renal proximal tubule cells	Kidney	Single-nucleotide polymorphisms of the D_2R increase inflammation and fibrosis in Human Renal Proximal Tubule Cells.	[57]
2022	Mouse Glomerular mesangial cell; Mouse	Kidney	D_1R-CSE/H_2S pathway activation attenuated diabetic mesangial cells proliferation and extracellular matrix deposition by down-regulating the $ERK_{1/2}$ signaling pathway.	[58]

H9C2 cardiac myoblasts by decreasing the levels of NLRP3 protein and subsequently reducing the initiation and progression of IL-1β and caspase-1 in a time- and dose-dependent manner. Finally, it mitigated DOX-induced cardiac damage and myocardial fibrosis. The TGF-β1/Smad signaling pathway plays a role in regulating liver fibrosis [63]. Increases in the expression of D_2R, NOX-5, proteins associated with inflammation (TNF-α and IL-6), and proteins associated with fibrosis (MMP-2/9, CO–I/III/IV, TGF-β1, and fibronectin) were observed in a high glucose-treated rat model. Following the use of haloperidol (an inhibitor of D_2R) and n-acetyl-L-cysteine (NAC, an active oxygen scavenger), these changes were reduced. Haloperidol and NAC negatively regulated the expression of TGF-β1 and phosphorylated Smad2 and the phosphorylation of NFκB-p65 and IκBα [53]. Inhibition of D_2R can mitigate diabetic HSC-mediated oxidative injury and fibrotic proliferation in some cases via the TGF-β1/Smad and NFκB pathways. At present, there are no literature reported on other DRs and renal fibrosis.

3.8. Deactivation and elimination of myofibroblasts

Elevated expression of D_1R and D_2R can be observed in myofibroblasts found in lung tissue of individuals with IPF. FNP and SMR promoted fibroblast differentiation by adversely influencing the TGF-β1/Smad signaling pathway and decreasing the levels of *p*-Smad2 and *p*-Smad 3. These proteins play a crucial role in the differentiation of fibroblasts in response to TGF-β1 [64]. YAP and TAZ are transcriptional coactivators that play pathological roles in mesenchymal cell activation and fibrosis [65,66]. YAP and TAZ are involved in many mechanical and biochemical signals related to fibrosis, such as metabolic reprogramming, matrix stiffness, TGF-β expression, myocardin-related transcription factor, along with WNT signaling [67]. GPCRs are linked to effector proteins of four primary categories of G proteins: Gαs, Gαi/o, Gαq/11, and Gα12/13. A study showed that the activation of receptors coupled to Gα12/13, Gαq/11, and Gαi/o stimulated YAP/TAZ nuclear translocation and transcriptional activity; moreover, receptors coupled to Gαs inhibited YAP/TAZ nuclear localization and activity by increasing cAMP [68]. DRs are members of the GPCR superfamily. D_1R selectively couples to Gαs to promote an increase in cAMP [69] and overrides various profibrotic stimuli that promote fibroblast activation, switching fibroblasts to a state that favors matrix degradation and softening. Taken together, these findings revealed that a fibroblast-selective D_1R agonist could reverse profibrotic phenotypes and promote matrix degradation by inhibiting YAP/TAZ nuclear localization in fibroblasts in experimental lung and liver fibrosis models [43].

3.9. Degradation of extracellular matrix

Imbalances in the deposition and resorption of ECM are the main characteristics of fibrotic diseases. The ECM is a complicated structure made up of collagen and fibronectin. This dynamic process is driven by the harmonized release and activation of cysteine cathepsins and matrix metalloproteases (MMPs), and the subsequent collagen internalization. Fibroblasts are responsible for classic ECM resorption, which involves internalization of collagen into lysosomes [70]. Cathepsin K is a key effector proteases involved in the degradation of both extracellular and intracellular collagen I [71], and is therefore related to collagen I

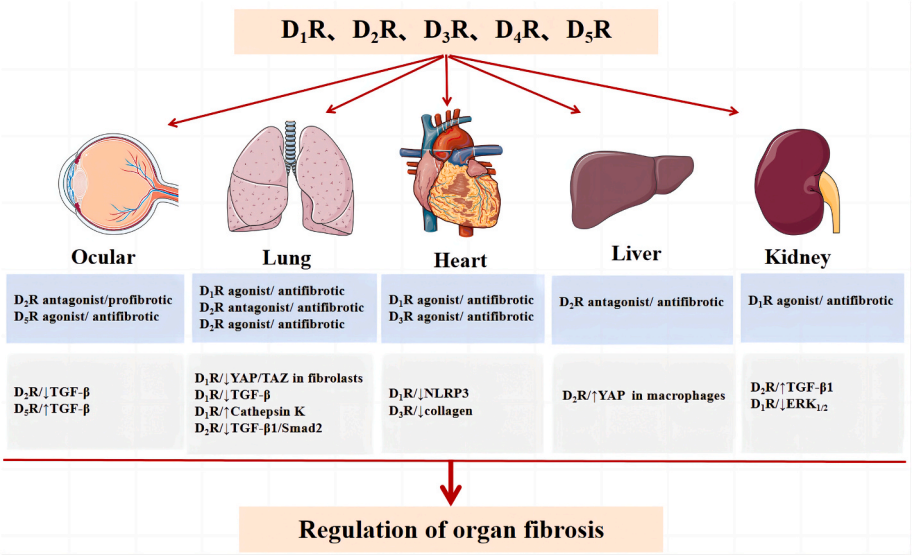

Fig. 1. Schematic diagram of dopamine receptors and organ fibrosis. D_1R, dopamine D1 receptor; D_2R, dopamine D2 receptor; D_3R, dopamine D3 receptor; D_4R, dopamine D4 receptor; D_5R, dopamine D5 receptor; TGF-β1, transforming growth factor-beta 1; YAP, Yes-associated protein; TAZ,transcriptional coactivator with PDZ binding motif; NLRP3, nucleotide-binding domain-like receptor protein 3.

clearance [72]. Dihydrexidine, a D_1R agonist, could promote fibroblast-mediated breakdown of collagen I originating from cells through the activation of cathepsin K by targeting D_1R.The primary pathological alterations linked to diabetic nephropathy involve the proliferation of glomerular mesangial cells (MC) and the ECM deposition. Under physiological conditions, MCs can proliferate abnormally and secrete significant quantities of ECM [73]. The CSE/H_2S pathway of D_1R activation hinders the collagen deposition caused by high glucose in MCs. D_1R could increase endogenous H_2S production by increasing Ca^{2+}, which inhibits the proliferation of MC, and attenuate ECM deposition through the downregulation of the $ERK_{1/2}$ signaling pathway [58].

4. Perspectives

Despite increasing evidence demonstrating that DA and its receptors may help to regulate organ fibrosis, challenges wait to be resolved to develop effective anti-fibrotic therapies. First, animal models and ex vivo cultures of primary human tissues should be developed to better translate new mechanisms to clinical use. Second, selecting patients for clinical trials is challenging due to patient heterogeneity and the slow progression of fibrosis. Organ fibrosis is considered a highly complex disorder. With more research focused on mechanisms that drive fibrosis progression, more approaches will be developed to provide effective antifibrotic therapies in the future.

CRediT authorship contribution statement

ZhongLi Liao: Writing – original draft. **XueFeng Tang:** Writing – original draft. **Bin Yang:** Supervision, Project administration. **Jian Yang:** Supervision, Conceptualization.

Declaration of generative AI and AI-assisted technologies in the writing process

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

ECM	extracellular matrix
DA	Dopamine
D_1R	dopamine D1 receptor
D_1R	dopamine D2 receptor
D_1R	dopamine D3 receptor
D_1R	dopamine D4 receptor
D_1R	dopamine D5 receptor
DRs	dopamine receptors
GPCRs	G protein-coupled receptors
CNS	central nervous system
RPE	retinal pigmented epithelial
TGF-β	transforming growth factor beta
DOX	doxorubicin
NLRP3	nucleotide-binding domain-like receptor protein 3
IPF	idiopathic pulmonary fibrosis
BLM	bleomycin
YAP	Yes-associated protein
TAZ	transcriptional coactivator with PDZ binding motif
pegHYAL	pegylated hyaluronidase
HSCs	hepatic stellate cells
CSE	cystathionine-γ-lyase
FNP	Fenoldopam
SMR	sumanirole

Data availability

No data was used for the research described in the article.

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