Acta Pharmacologica Sinica

www.nature.com/aps

REVIEW ARTICLE

Mesenchymal stem cells in fibrotic diseases—the two sides of the same coin

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Fibrosis is caused by extensive deposition of extracellular matrix (ECM) components, which play a crucial role in injury repair. Fibrosis attributes to ~45% of all deaths worldwide. The molecular pathology of different fibrotic diseases varies, and a number of bioactive factors are involved in the pathogenic process. Mesenchymal stem cells (MSCs) are a type of multipotent stem cells that have promising therapeutic effects in the treatment of different diseases. Current updates of fibrotic pathogenesis reveal that residential MSCs may differentiate into myofibroblasts which lead to the fibrosis development. However, preclinical and clinical trials with autologous or allogeneic MSCs infusion demonstrate that MSCs can relieve the fibrotic diseases by modulating inflammation, regenerating damaged tissues, remodeling the ECMs, and modulating the death of stressed cells after implantation. A variety of animal models were developed to study the mechanisms behind different fibrotic tissues and test the preclinical efficacy of MSC therapy in these diseases. Furthermore, MSCs have been used for treating liver cirrhosis and pulmonary fibrosis patients in several clinical trials, leading to satisfactory clinical efficacy without severe adverse events. This review discusses the two opposite roles of residential MSCs and external MSCs in fibrotic diseases, and summarizes the current perspective of therapeutic mechanism of MSCs in fibrosis, through both laboratory study and clinical trials.

Keywords: fibrotic diseases; mesenchymal stem cells; myofibroblasts; liver cirrhosis; pulmonary fibrosis

Acta Pharmacologica Sinica (2022) 0:1–20; https://doi.org/10.1038/s41401-022-00952-0

INTRODUCTION

Many types of tissue injury trigger serial cellular and molecular cascades that lead to tissue fibrosis. Fibrosis is a disease characterized by scarring and sclerosis of tissues, which can affect many organs, including the liver, bone marrow, lung, kidney, gastrointestinal tract, skin, eyes, and myocardial intima, ultimately leading to cellular dysfunction and organ failure [1]. Fibrotic diseases attribute to ~45% of all deaths worldwide [1, 2]. For instance, liver fibrosis is one of leading causes of liver cancer which is increased rapidly and causes estimated 750,000 deaths per year [3, 4]. Moreover, there are millions of hepatitis B virus (HBV) and hepatitis C virus (HCV) carriers globally, which might attribute to the millions of people affected by pulmonary fibrosis [5]. However, despite the huge morbidity and mortality, there are only very limited approved anti-fibrosis therapies [6]. Therefore, there is an urgent need to develop new anti-fibrosis therapies for the treatment of fibrotic diseases. Moreover, understanding the cellular mechanisms behind fibrosis is of great importance for improving the therapeutic outcomes and discovering new therapeutic approaches.

Mesenchymal stem cell (MSC) refers to a stem cell population with demonstrable progenitor cell functionality of self-renewal and differentiation, as clarified by International Society for Cell & Gene Therapy (ISCT) Mesenchymal Stromal Cell (ISCT MSC) committee [7]. The classic minimal criteria to define human MSCs is through its phenotype, which includes positive expression of CD105, CD73, and CD90, and negative of hematopoietic and endothelial markers, such as CD45, CD34, CD14, CD19, and human leukocyte antigen-DR isotype (Fig. 1). Similarly, a typical mouse MSC is positive of CD105, CD29, CD44, and stem cell antigen 1 (SCA-1), and negative of CD45, CD31, and lymphocyte antigen 76 (Ly76) (Fig. 1). Besides, MSCs shall be multipotent and capable of trilineage differentiation into adipocyte, chondrocyte, and osteoblast [8] (Fig. 1). MSCs widely existed in mesenchymal tissues and can be harvested from bone marrow, umbilical cord, cord blood, placenta, adipose tissue, muscles, dermal tissue, amniotic fluid, menstrual blood, and urine [9–15].

Based on the conventional understanding of multipotent stem cells, MSCs were believed to have promising application in reconstructive therapy due to their self-renewal and multipotent properties [16, 17]. Surprisingly, greater therapeutic potential of MSCs was discovered as more complex functional mechanisms of these cells were revealed over the decades, including its immunomodulatory capabilities [18], autocrine and paracrine effects [19], and the abilities to escape from the innate immune system and counteract the complement system [20]. Therefore, the clinical application of MSCs has been extensively attempted for various diseases, such as osteoarthritis [21], rheumatoid arthritis [22], tissue repair [23–25], diabetic foot ulcer [26], diabetes [27], female infertility [28], autoimmune diseases [29],

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Received: 19 February 2022 Accepted: 29 June 2022
Published online: 27 July 2022

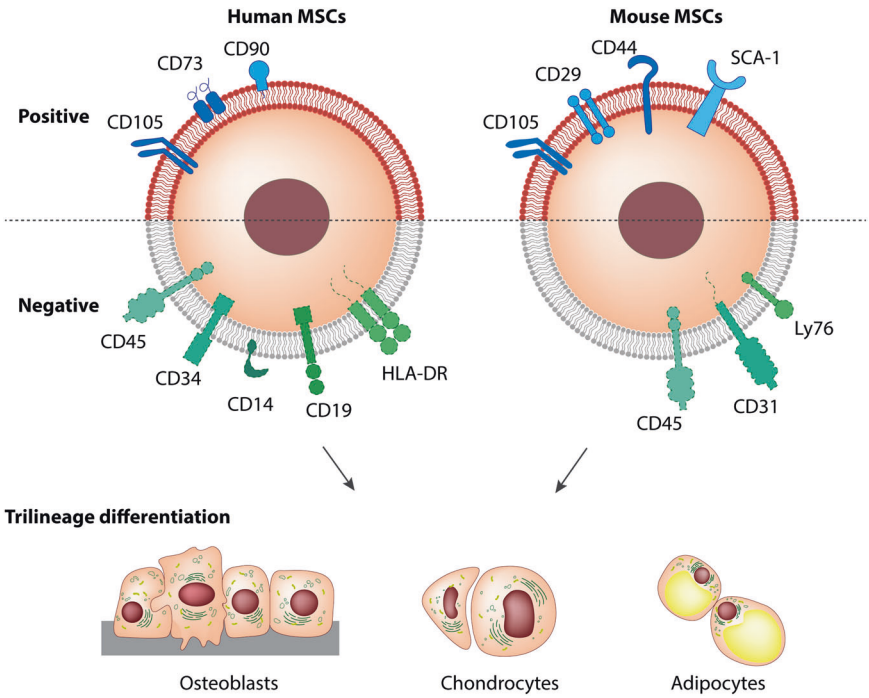

Fig. 1 Cellular markers and trilineage differentiation of MSCs. The standardized phenotype of MSCs was proposed by the International Society for Cellular Therapies (ISCT). A typical human (h)MSC positively expresses CD105, CD73, and CD90 membrane markers, but negative with CD45, CD34, CD14, CD19, and HLA-DR on its surface. Comparably, the positive membrane markers for mouse (m)MSCs include CD15, CD29, CD44, and SCA-1, but negative with CD45, CD31, and Ly76. According to ISCT, MSCs all share the classical trilineage differentiation potential in vitro, i.e., MSCs can differentiate into osteoblasts, chondrocytes, and adipocytes in culture.

cardiovascular diseases [30], neurodegenerative diseases [31], graft versus host disease (GvHD) [32], COVID-19 patients [33], and different types of fibrotic diseases [34–36].

With current technical advances in cell lineage tracing, imaging, and phenotyping, many cell fate mapping studies revealed that the sources of fibrotic cells come from residential MSCs which differentiate and participate in the progress of fibrosis. Together with the beneficial effects of MSCs infusion in both preclinical and clinical trials, these studies suggest potential dual roles of MSCs in the pathogenesis and treatment of fibrosis. Here in this review we summarized the causal factors and mechanisms in fibrosis, discussed the diverse roles of MSCs in the development and treatment of fibrosis, and finally listed current ongoing clinical MSC trails in fibrotic diseases.

FIBROTIC DISEASES: PATHOGENESIS AND MECHANISM

Tissue fibrosis is characterized as the extensive deposition of extracellular matrix (ECM) components, which plays a crucial role in injury repair. At the initial stage of fibrogenic process, the organ will undergo an activation of local effector cells such as fibroblasts and myofibroblasts. The stimulation of tissue injury is followed by the reconstruction of the extracellular matrix, during which inflammatory factors are secreted and ECM components such as collagen and fibronectin are synthesized [6]. These changes initiate and propagate wound healing response. In a short term, fibrosis exhibits adaptive characteristics, showing that once the normal organizational structure of the tissue is restored, the ECM will be reshaped with little effect on organ function. However, when severe or recurrent injury happens, the excessive deposition of ECM components accelerates the progression of fibrosis and ultimately leads to terminal organ failure. The pathologic matrix-producing cells are activated fibroblasts, called myofibroblasts in different organ and tissue fibrosis [37]. Myofibroblasts are characterized with pronounced rough endoplasmic reticulum and large nucleolus, as well as high synthetic and proliferative capability [37]. The extensive proliferation, differentiation, and ECM deposition of myofibroblasts are triggered by a variety of cytokines and growth factors, such as transforming growth factor β1 (TGF-β1) and platelet-derived growth factor (PDGF), derived from adjacent stimulated tubular epithelial cells, endothelial cells, leukocytes or from fibroblast themselves [38]. According to our current understanding of fibrosis, one important way to find new treatment for fibrosis is to decipher the cellular sources of myofibroblasts.

Fibrosis is a highly dynamic process which could be seen as the outcome of multiple types of tissue injury in the course of chronic inflammation. In fact, wound healing of injured tissues requires recruiting a large number of cell types coordinated at the space-time level to sustain tissue homeostasis [39]. Studies have shown that immature tissue can heal without fibrotic scars before the inflammatory response, suggesting the role of inflammation on fibrosis [40–42]. When tissue is subjected to sustained injury, the substantial chronic injury could lead to uncontrolled myofibroblast activation and excessive accumulation of ECM, which results in a chronic inflammatory environment infiltrated by macrophages, lymphocytes, eosinophils, and other immune cells [43]. In addition, genetic changes in organs also participate in the progress of fibrosis, such as Mucin 5B (MUC5B) in pulmonary fibrosis and Myosin Heavy Chain 7 in cardiac fibrosis [44, 45]. These specific mutations associated with fibrosis suggest that some non-fibroblast types are involved upstream of the pathogenesis of fibrosis, highlighting the importance of multicellular interactions in this disease.

The causal factors of fibrotic diseases

Fibrotic diseases are driven by typical cellular and molecular mechanisms. Much of our understanding of fibrotic diseases has been derived from the elucidation of the basic physiologic and pathologic processes of fibrosis in evidence from experimental

Table 1. Animal models utilized in the study of fibrotic diseases.

Fibrotic diseases	Transgenic animal models	Surgical/drug-induced animal models
Cardiac fibrosis	*FAK* knockout mice [275]; SR-BI/apoE double KO mice [276]; *EC-SOD* overexpressing mice [277];	Myocardial ischemia model [278]; Transverse aortic constriction(TAC) model [279]; ISO (Isoproterenol) induced mice [280]; Angiotensin II mice [281];
Skin fibrosis	*TSK* mutant mice [282, 283]; MRL/lpl/IFNγ receptor null mice [284]; Mutant kinase deficient type II *TGF-β* receptor transgenic mice [285];	Radiation ulcers [77]; Bleomycin-induced skin fibrosis [286]; Skin wound healing models [287]: Vinyl chloride induced model [288];
Liver fibrosis	*TbRIIDk* transgenic mice [289]; *HBV* transgenic mice [290];	CCl_4 mouse model [291]; Diethylnitrosamine (DEN) rat model [104]; Bile duct ligation (BDL) model [292];
Lung fibrosis	*TNF-* overexpressing mouse [293]; *TGF-β-* overexpressing mouse [294]; *IL-1*-overexpressing mouse [295];	Bleomycin-induced mice model [296]; Silica aerosolized model [297]; FITC induced model [298]; Irradiation-induced pulmonary fibrosis [299]; Human fibroblasts transplantation in immunodeficient mice [300];
Renal fibrosis	*Bradykinin B1* receptor deficient mice [301]; *TGF-β-* overexpressing rat [302]; *Nep25* transgenic mice [303]; *AT1* receptor-deficient mice [304]; *Coll-GFP* mice [305];	Drug induced models [306]: ($HgCl_2$, Vanadate, Adriamycin, Uranyl nitrate, Folic acid etc.); Surgical induced models: Ureteral obstruction (UUO) rodent model [307]; kidney ischemia mice [308];
Myelofibrosis (bone marrow)	*TPO*(Thrombopoietin)-overexpressing mice [309]; $GATA\text{-}1^{low}$ mice [310]; $Calr^{del52}$ mice [311]; *Abi-1* knockout mouse [312];	$JAK2^{V617F}$ murine bone marrow transplantation model [313]; MPL^{W515L} murine bone marrow transplantation model [314];
Cystic fibrosis (airway)	PTEN-long–deficient mice ($Ptenl^{-/-}$) [115, 125]; $Cftr^{\Delta F508}$ mutation mice [315];	Ovalbumin-exposed mice [316];
Intestinal fibrosis	*IL-10* KO mice [317]; *TGF-β1-* overexpression mice [318];	Organoid-based epithelial to mesenchymal transition (OEMT) model [319]; Trinitrobenzene sulfonic acid (TNBS) model [320]; Salmonella typhimurium models [321]; Radiation-Induced rat model [322];
Pancreatic fibrosis	*R122H* transgenic mice [323];	DBTC induced model [324]; Caerulein-induced model [325]; Oleic acid-induced model [326]; Cerulein-induced model [327];

animal models. Table 1 outlines the typical transgenic and inducible (drug or surgical induced) animal models that have been widely used in the study of fibrotic diseases. Based on the observations and studies over these models, it is now well-accepted that different fibrotic diseases are tightly associated with diverse casual factors. Here we summarize some causal factors and current treatment for common fibrotic diseases.

Cardiac fibrosis. Cardiac fibrosis implicates abnormalities in myocardial function and cardiac metabolism, resulting in heart failure, arrhythmias, and other heart diseases. Cardiovascular diseases, such as hypertension, ischemic heart disease, dilated cardiomyopathy, viral myocarditis, and diabetic cardiomyopathy, can be observed in varying degrees of myocardial fibrosis [46]. There are several pathological factors involved in the cardiac fibrosis, such as pressure overload, endothelial loss, or ischemic injury, during which myocardial fibroblasts and cardiomyocytes cause collagen deposition and lead to interstitial fibrosis in the fibrotic heart [5]. After myocardial injury, the pathological basis of myocardial fibrosis is associated with excessive and continuous deposition and composition changes of ECM. During the process, the expression of different types of collagens causes collagen deposition and fibrotic scar formation. Increased expression of type I and type III collagen significantly promoted the proliferation of cardiac fibroblasts, which was mediated by extracellular signal-regulated protein kinases 1 and 2 [47]. Type V and VI collagen have been reported to interact with α-Integrin receptors in cardiac fibroblasts and promote the differentiation of myofibroblasts [48, 49]. Decreased secretion of type V collagen increased the expression of αvβ3 and αvβ5 Integrins, which could change the scar size through the activation of Integrin-mediated feedback pathway [49].

Besides ECM changes, reported studies showed that several genes are tightly associated with cardiac fibrosis. For example, gene mesenchyme homeobox 1 (Meox1) is activated in stress-induced fibroblasts and stimulates fibrosis, which is correlated with the activation of cardiac fibroblasts in mice with heart failure [50]. When these mice were treated with bromodomain and extra-terminal domain inhibitors, the levels of Meox1 decreased dramatically [50], indicating that blocking this gene may prevent fibrosis of heart and other organs. Moreover, bromodomain-containing protein 4 (BRD4), as an epigenetic regulator, plays an important role in regulating cardiac fibroblast. Chemical inhibitors that target BRD4 can effectively block cardiac fibroblast activation [51]. These studies indicate that the status of cardiac fibroblasts may be a feasible target for therapeutic intervention.

Although the pathogenesis of cardiac fibrosis remains to be further studied, continuous inflammatory response and fibroblast activation are the key factors causing cardiac fibrosis. A large number of studies have shown that cytokines and immune cells promote fibrosis through the interaction with fibroblasts [52]. Cardiac fibroblasts transform into activated myofibroblasts and

release inflammatory factors in response to pathological stress and rapidly regulate ECM turnover. During myocardial infarction (MI), yes-associated protein (YAP) is involved in the regulation of macrophage-mediated pro-inflammatory responses and interacts with the Hippo pathway which is essential to cardiac repair [53]. YAP also enhanced the sensitivities of cardiac fibroblasts to the pro-fibrotic activity of TGF-β1 [54]. Under MI or ischemia, cardiac remodeling is regulated by Ca^{2+}/calmodulin-dependent protein kinase II, which is activated by reactive oxygen species (ROS) in the inflammatory environment and modulates the pro-inflammatory nuclear factor kappa-B (NF-κB) [55]. ROS can also directly regulate the secretion of ECM by regulating the expression of matrix metalloproteinases (MMPs) [42]. Endoplasmic reticulum (ER) stress is related to the pro-inflammatory responses during fibrosis and stress-induced cardiac fibrosis can be attenuated by 4-phenylbutyric acid through interfering with the process of cardiac apoptosis and cardiac rupture [56, 57]. Besides inflammatory pathways, metabolic dysfunction can also trigger cardiac fibrosis. For instance, in models of type 1 or type 2 diabetes, cardiac fibroblasts, macrophages, and other cell types are involved in the process of pro-fibrosis effects, during which cardiac fibroblasts are induced by high glucose, transformed into myofibroblasts, and stimulates the deposition of ECM through interacting with TGF-β/Smad pathway [58]. In addition, leptin is one of the factors that stimulate ECM accumulation in the myocardium and interacts with aldosterone receptor, which triggers endothelial dysfunction and the development of cardiac fibrosis [59]. Therefore, the various signaling molecules involved in the cardiac fibrosis can provide therapeutic targets that may attenuate fibrotic responses.

Skin fibrosis. Skin fibrosis is a serious global health problem which manifests in many forms, such as systemic sclerosis (SSc), GvHD, nephrotic fibrodermatitis, connective tissue disease, sclerosing edema, hypertrophic scars, and keloids [60]. Skin fibrosis is caused by external environmental factors, inflammation, or autoimmune mechanisms [61]. Moreover, skin injury, infection, and radiation can promote the process of skin fibrosis [60]. The underlying cause of skin fibrosis is the excessive accumulation of ECM, which leads to thickening of normal tissue and induces skin pain or dysfunctions [62].

Although there is no general consensus on the etiology of skin fibrosis, several studies have identified series of cytokines and growth factors that drive scar formation. It is clinically formulated that skin injury or inflammation is a prerequisite for abnormal sustained wound healing and subsequently keloid formation [63]. Genetics have been noted to be involved in keloid development and single nucleotide polymorphisms are thought to influence scar severity [64]. In addition, the immune system plays an important role in regulating wound repair and tissue regeneration following initial trauma [65]. The inflammatory environment formed following injury significantly increases the numbers of neutrophils and macrophages which secrete varies of growth factors, such as TGF-β, vascular endothelial growth factor (VEGF), PDGF to participate in the skin fibrosis [66–68]. Moreover, T Helper 2 (Th2) cell cytokine is involved in wound healing and fibrotic processes. When Th2 cytokine responses become hyperactive or uncontrolled, they will trigger "over repair" mechanisms which lead to fibrosis [69, 70]. IL-4 and IL-13 secreted by Th2 cells are related to the pathogenesis of fibroproliferative disorders [43, 69]. During wound healing, the continuous activation of IL-4 and IL-13 related pathways, such as JAK/STAT6 (Janus kinase/signal sensor and transcriptional activator protein 6), promotes fibroblast proliferation, myofibroblast differentiation, and the production of collagen and ECM turnover [43, 71, 72]. IL-4 in skin fibroblasts of SSc patients was significantly elevated and stimulated collagen synthesis [73, 74], whereas IL-4 expression was decreased after the wound was healed in murine models [75]. IL-13 can activate the proliferation and differentiation of fibroblasts, as well as the expression of type I collagen and α-SMA [76]. In addition to inflammatory factors, metabolic abnormalities persist in patients with skin fibrosis. For example, the level of fatty acid oxidation is reduced and glycolysis is elevated in fibrotic skin with abundant ECM [77]. Activation of peroxisome proliferator-activated receptor signaling or inhibiting glycolysis could lead to decreased ECM gene transcription and increased ECM degradation [77]. Furthermore, ECM accumulation in skin fibrotic mice can be effectively reduced by upregulating the expression of fatty acid transporter CD36 [77]. These studies provide new therapeutic molecular targets for the treatment of skin fibrosis.

Liver fibrosis. Liver fibrosis is a pathological process of abnormal hyperplasia of connective tissue in the liver caused by a variety of pathogenic factors. Liver fibrosis could develop into liver cirrhosis and even hepatocellular carcinoma in serious conditions. The most studied liver disease is nonalcoholic steatohepatitis (NASH), the risk factors of which are either obesity, high cholesterol, or metabolic syndrome [78]. Moreover, there are a variety of potentially preventable causes for liver fibrosis, including HBV and HCV infections, obesity, alcohol abuse, and aflatoxins [79].

Myofibroblasts are activated in response to liver injury, which is the main source of ECM in fibrotic liver [4]. The sources of hepatic myofibroblasts can be identified as hepatic stellate cells (HSCs), liver-resident cells, portal fibroblasts, and bone MSCs [4, 80–82]. Among them, HSCs seem to be the main source of ECM formation [83]. Toxic liver injury can promote the activation of HSCs, while cholestatic liver fibrosis activates both HSCs and portal fibroblasts [82, 84]. Physiologically, HSCs exhibit a quiescent phenotype, but are activated in response to the chronic injury and further upregulate the expression of α-SMA, and persistently secrete ECM to induce the formation of fibrous scar [85]. Moreover, extensive studies in animal models reveal that the depletion of activated HSCs by genetic or pharmacological ways can limit the progression of liver fibrosis [86, 87]. The activation of HSCs is also regulated by the pro-inflammatory cytokines (e.g., IL-6, IL-1β, TNF, and TGF-β) [88, 89].

The key molecular mechanisms of liver fibrogenesis have been revealed using transgenic mice models [90, 91]. Genes that related with fibrogenesis interact with environmental factors in liver and coordinate the progression of the fibrosis and the immune response to the hepatic injury [92, 93]. Death receptor-mediated genes (e.g., TRAIL, Bcl-xL, Fas), the pro-apoptotic pathways (e.g., Caspase 3), and natural killer cells regulate hepatocyte apoptosis which is a key initial event that responds to the hepatic damage in liver fibrosis [94–97]. During liver damage, the process of oxidative stress leads to the production of ROS which is mediated by NADPH oxidases and regulates HSC activation [98, 99]. The inflammation and oxidative stress also lead to hepatocyte apoptosis and contribute to the development of NASH [100]. Studies have shown that there is a high level of oxidative stress response in NASH [101]. Moreover, the application of agonists of transcription factors PPARγ could improve the inflammation responses in liver fibrosis [102]. Increased IL-17 level was found in the intestinal flora of NASH patients [103]. In addition, studies showed that spleen tyrosine kinase (SYK) could promote liver fibrosis, which could be a possible target of anti-fibrosis treatment. SYK antagonist effectively inhibited liver fibrosis by inhibiting the activation of HSCs, and reduced the occurrence of obstructive jaundice, and hepatocellular carcinoma in cell and animal models [104]. The therapeutic strategies that target HSCs and inflammatory cells to mediate liver repair are needed to further study.

Pulmonary fibrosis (PF). Pulmonary fibrosis is a heterogeneous end-stage interstitial lung disease characterized by parenchyma destruction, ECM deposition, and inflammatory injury [105]. It is the most common form of idiopathic interstitial pneumonia which

is associated with a number of causes, including systemic sclerosis, infection, chemotherapy, environmental exposures, or unknown etiologies [106].

Idiopathic pulmonary fibrosis (IPF) is a progressive lung disorder that affects the health of over 5 million people worldwide [6]. IPF is highly related to some co-morbidities and complications [107]. According to the pathogenesis of IPF, genetic mutations, epigenetic factors, environmental and microbial factors contribute to the development of pulmonary fibrosis. The dysfunction of alveolar epithelial cells (AECs) is considered to be the driver during the initiation of IPF [108]. The mutations in the surfactant protein C (*SFTPC*) gene and the surfactant protein A2 (*SFTPA2*) are associated with the development of IPF by affecting the protein trafficking and folding in AECs [109, 110]. Toll interacting protein (*TOLLIP*) expressed in AECs and telomerase expressed in stem cells and progenitor cells are also reported to be associated with IPF [44, 111]. Tumor suppressor phosphatase and tensin homolog (*PTEN*) also plays a key role in lung infections and fibrosis. Dysfunctional epithelia and AEC injury lead to a lower level of *PTEN* expression in IPF patients, which activates the NF-κB pathway and triggers the deposition of collagen in fibroblasts [112]. During AEC injury, epithelial cells and macrophages release a variety of chemokines (e.g TGF-β, PDGF, IL-1, TNF-α) and activate the related signaling pathways, leading to fibroblast proliferation, and differentiation [113].

In addition, evidence of lung tissue from IPF patients, mouse models, and cultured lung fibroblasts have shown that drugs targeted at cell metabolism could reverse pulmonary fibrosis. Metformin, a widely used drug to treat non-insulin-dependent diabetes, could reverse lung fibrosis and affect the mechanism of the disease [114]. In addition, amphotericin (AmB) has been currently approved as a candidate drug for the treatment of pulmonary fibrosis. AmB helps to restore the function of lung cells and avoid chronic bacterial pulmonary infection [115]. Genome-wide association studies have shown that genetic variants of *MUC5B* which is expressed in bronchiolar epithelium can slow down the disease progression [44, 116]. The better understanding of IPF pathogenesis is important for providing references of treatment approaches to increase the life expectancy of patients with pulmonary fibrosis.

Cystic fibrosis (CF). Cystic fibrosis (CF) is a genetic disease that could affect multiple organs, including lung, intestine, airway, etc. [117]. There are more than 100,000 CF patients worldwide who continue to suffer from serious complications throughout their lives [118]. CF is caused by mutations and dysfunction of cystic fibrosis transmembrane conductance regulator (*CFTR*) gene [119]. According to the physiology functions of CFTR protein, the mutations of *CFTR* gene can be classified into six classes: Class I mutations cause no protein production; Class II mutations (e.g., Phe508del) cause the misfolded CFTR protein retained at the endoplasmic reticulum; In class III, CFTR can be transported to cell surface but has a defective channel regulation; Class IV mutations reduce the channel conductance; Class V mutations decrease the synthesis of CFTR; In class VI, mutations have a short half-life and a lower stability compared to intact CFTR protein [120].

A better understanding about the pathophysiology of CF can facilitate the development of novel therapies targeting this disease. Reported study showed that the prevalence of pancreatitis increases in people with mutations of classes IV and V [121]. In CFTR-related chronic pancreatitis, pancreatic ducts secrete the fluid with neutral-acidic pH which can be alkalinized through CFTR-mediated chloride and bicarbonate secretion [122]. In the airway, CFTR mutations block Cl^- transporter, resulting in impaired mucus clearance, increased viscosity of airway mucus, and inflammatory infection [123]. In CFTR-related lung disease, lungs continued exposure to the inflammatory microenvironment which is generated by the impaired microorganisms clearance and pro-inflammatory microenvironment [124]. In addition to *CFTR* gene, *PTEN* also plays a critical role in the development of CF. *PTEN* deficiency stimulates mitochondrial activity and inhibits succinate dehydrogenase activity, resulting in the increased release of succinate and mitochondrial ROS [125]. This environment promotes the colonization of *Pseudomonas aeruginosa* in airway and stimulates anti-inflammatory response dominated by the immune response gene 1 and itaconate [125]. Moreover, there are antibiotic and anti-inflammatory therapies for cystic fibrosis [126]. A novel drug testing of CF patients uses a combination of multiscale differential dynamic microscopy and a video analysis algorithm to evaluate ciliary beat frequency [127]. In addition, a new potential single-molecule therapy which is based on Thymohormone α1 (Tα1) could not only correct genetic defects in CF patients, but also significantly reduces pro-inflammatory NF-κB activity and promotes expression of the anti-inflammatory cytokine IL-10 [128]. This treatment could potentially correct the genetic defects that cause cystic fibrosis in patients and help reduce inflammatory response in the body.

The molecular mechanisms of the fibrotic pathogenesis

Fibrosis is considered as the hallmark of pathological tissue remodeling in many clinical diseases. It is tightly associated with radiation, chronic infection, toxins, or other congenital or autoimmune factors, and also related to a large number of bioactive factors, including proteolytic enzymes, cytokines, growth factors, and angiogenic factors [6]. The molecular mechanisms that drive fibrosis are complex. Fibrosis is a highly dynamic process which has strong plasticity, and many key molecules are involved in the regulation of fibrosis. Several important signaling pathways that involved in the fibrotic pathogenesis have been summarized in the following paragraphs.

Transforming growth factor-β (TGF-β). Transforming growth factor-β is the main factor leading to fibrosis, which may serve as a potential anti-fibrosis target. In response to tissue injury, fibroblasts need to release TGF-β and other factors to coordinate the local inflammation and myofibroblast activation processes. These cells secrete collagen and fibronectin to participate in wound healing and ECM remodeling to restore tissue integrity and promote parenchymal replacement [129, 130]. Extensive evidence has shown that inhibition of TGF-β activity can ameliorate the development of tissue fibrosis. Bioactive TGF-β acts through two types of cell surface receptors with transmembrane serine/threonine kinases activity (TβRI and TβRII) to regulate fibroblasts activation and immune responses during fibrotic process [131].

TGF-β family signaling is thought to be mediated by Smad- or non-Smad pathways [131]. During liver fibrosis, macrophages-derived TGF-β coordinates with other pro-fibrotic factors (e.g., PDGF, MMPs) and promotes inflammatory response and scarring through TGF-β1-Smad signaling or PI3K-Akt signaling pathway [4, 132, 133]. Specific inhibition of canonical TGF-β–Smad2/3 signaling in cardiac fibroblasts significantly reduces myofibroblast differentiation and cardiac hypertrophy [134]. However, continued systemic inhibition of TGF-β1 has been found to have strong side effects, such as the development of systemic autoimmunity in TGF-β1 knockout mice and the carcinogenic effect of pan-TGF-β blocker [129]. Additionally, based on extensive preclinical data, Integrin-mediated TGF-β activation that regulates tissue and immune homeostasis could serve as another potential therapeutic target. TGF-β signaling pathways also coordinate with other transcription factors to regulate fibrosis. For example, transcription factor PU.1 is involved in regulating the process of fibroblast pro-fibrosis in various fibrotic diseases [135–138]. PU.1 expression is upregulated in various fibrotic diseases and induces the expression of pro-fibrotic related genes in fibroblasts which produce excessive ECM [136]. Moreover, angiotensin-II (AngII) induced cardiac fibrosis can be attenuated by PU.1 inhibition

through TGF-β1/Smad pathway. Inactivation of PU.1 gene disrupts the fibrotic network and reprograms fibroblasts into quiescent fibroblasts, leading to reprogramming and regression of fibrosis in multiple organs [139]. These works have uncovered the molecular mechanism by which TGF-β activation leads to fibrotic disease and may provide a new strategy for antifibrotic treatment in the future [139].

Interleukins. Cytokines are also reported as another important inducer of fibrosis. Several synergistic mechanisms drive the activation of TGF-β signaling pathways that promote fibrosis. Notably, IL-17 signaling plays an important role of multiple tissue fibrosis, including lung, liver, kidney, heart, and skin [140, 141]. In SSc-associated organ fibrosis, either cirrhosis, lung, skin, cardiac, or renal, there is a higher level of the cytokine IL-17 detected [142–145]. IL-17 is secreted by $CD4^+$ T lymphocytes from SSc patients which can be stimulated by IL-27 and further results in the production of ECM proteins [146]. In cardiac fibroblasts, IL-17 promotes the expression of MMP-1 through RANKL/OPG (receptor activator of nuclear factor-κB ligand/osteoprotegerin) pathway, which can result in myocardial fibrosis [143, 147]. Notably, there is a paradoxical role of increased IL-17 during renal fibrosis. Knocking down the expression of IL-17 in mouse interstitial fibrosis model promotes fibrotic process and the ECM accumulation through upregulating TGF-β-induced phosphorylation of p38MAPK and AKT [148]. However, in diabetic nephropathy, IL-17 treatment suppresses the accumulation of collagen and α-smooth muscle actin through IL-6/STAT3 (signal transducer and activator of transcription 3) signaling during interstitial fibrosis [149, 150].

Moreover, IL-13, IL-4R, or IL-13Rβ1 deficient in mice showed reduced fibrosis after multiple types of tissue injury [151, 152]. IL-4 serves as a pro-fibrotic mediator secreted by T helper 2 (Th2) cells. Th2 cytokines/STAT6 pathway is mediated by IL-4 receptor α, which could promote the inflammatory responses of macrophages during wound repairing and tissue remodeling [43, 153, 154]. As another Th2 cytokine, IL-13 shares same receptor and signaling pathways as IL-4 and significantly increases the synthesis of collagen in fibroblasts of keloids [72, 155]. During intestinal tissue healing, the upregulation of IL-13 triggers the formation of fibrosis [156]. IL-13 induces pulmonary fibrosis and requires the activation of TGF-β, which is regulated by MMP-9-dependent mechanism [157]. IL-13 also promotes fibrosis independently of TGF-β, which is partially through directly targeting stromal and parenchymal cells, like epithelial cells and collagen-producing fibroblasts [158]. Gp130, a cytokine receptor that regulates IL-6 and IL-11 proteins, is upregulated in patients with Crohn's disease who have failed to respond to anti-TNF (tumor necrosis factor) therapy. Using Gp130 inhibitor bazedoxifene could reduce fibrosis-associated gene expression [34]. Recently, a study has shown that patients with inflammatory bowel disease have an increased serum level of IL-24, which induced the production of fibrosis-associated factors (e.g., TGF-β1, MMP-2, COL1A1, PDGFβ) [35]. These findings led to new insights into the potential role of interleukins as therapeutic targets of fibrosis.

Integrins. Integrin-mediated cell-ECM interactions have been extensively studied. Integrins transform extracellular signals into a variety of cellular behaviors, including changes in cell adhesion, migration, proliferation, differentiation, and apoptosis [159]. As transmembrane receptors, Integrins couple external ECM to internal cytoskeleton of the cells. The Integrin family has 24 different heterodimers composed of different α and β subunits in humans [160]. Several synergistic mechanisms between Integrin signals, TGF-β pathways, and ECM proteins drive the activation of fibrosis. Integrins can activate TGF-β1 signaling to regulate myofibroblast differentiation and promote fibrosis [48]. Before activation, TGF-β exists as a complex of latency-associated protein (LAP) and latent TGF-β binding protein [49]. The Integrins bind to these inactive forms can mediate the activation of TGF-β. The αvβ1 Integrin that is widely expressed on the fibroblasts can bind to the LAP of TGF-β, resulting in the TGF-β activation and inducing pulmonary fibrosis [50]. The αvβ6 Integrin activates TGF-β through binding to the LAP of TGF-β1 gene, which is involved in the fibrosis of liver, renal, and lung [38, 40, 51]. Therefore, studies showed that the blockage of αvβ6 Integrin protects against pulmonary fibrosis by decreasing the activation of TGF-β [161]. Moreover, suppressed αvβ6 Integrin in epithelial cells can mitigate the development of chronic wounds [162] and inhibit advanced renal fibrosis by reducing the TGF-β activity [163]. In addition, α8β1 and α11β1 are significantly increased in hepatic stellate cells, which promote liver fibrosis through TGF-β activity and YAP-1 pathways [164, 165].

There is an Integrin–ECM connection during tissue repair process. Collagen-binding Integrins such as α1β1, α2β1, and α11β1 have been found to contribute to fibroblast function in wound healing [43, 44]. The α1β1 Integrins expressed in fibroblasts can bind with collagens and mediate ECM accumulation during wound repairing [45, 46]. The type I collagen-binding α2β1 Integrins can promote myofibroblast differentiation and accelerate wound closure [46, 47]. Moreover, MMPs that mediate the degradation of ECM components can interact with Integrins and participate in the activation of downstream signals [52–54]. The αvβ8 Integrin binds the LAP of TGF-β1 by recognizing RGD motif and it selectively coordinates with membrane-type 1 (MT1)-MMP to mediate TGF-β1 activation [55]. The αvβ3 Integrin can interact with MMP-2 whereas αvβ3 Integrin does not participate in the activation of TGF-β1 [55, 56]. These studies provide new insights into the mechanisms underlying organ fibrosis.

Microbiome. Recent studies suggest that there are close relationships between the microbiome and fibrosis development. Microbial dysbiosis is believed to be a key driving force of the pathogenesis of inflammatory bowel disease, including Crohn's disease and ulcerative colitis [166]. For Crohn's disease, the main complication is the intestinal stenosis and the formation of fibrotic intestinal wall, which eventually requires surgical intervention [42]. As a microbial sensor, variants of nucleotide-binding oligomerization domain containing 2 (*NOD2*) gene exist in patients with Crohn's disease which could narrow the intestines [167, 168]. Intestinal inflammation and fibrosis are also modulated by tumor necrosis factor-like cytokine 1A (TL1A) and Tl1a-mediated intestinal inflammation, which is reported to be affected by the intestinal microbiome through pro-inflammatory cytokines such as IL-1 or TNFα on the epithelial cells [169]. In addition, intestinal microbiota-induced intestinal fibrosis has a higher level of TGF-β1 and collagen deposition. Clearance of the anaerobic bacteria can disrupt the profibrotic effects of TGF-β-mediated fibrosis [170].

Intestinal microbiome disorders may also affect the progression of liver fibrosis. In patients with chronic liver disease, bacteria and their products are often transported across the intestinal barrier that has been disrupted [171]. Blocking Toll-like receptor 4 (TLR4) signaling in mice and reducing liver exposure to intestinal microbes by using antibiotics decelerate the development of liver fibrosis [172]. During Salmonella-induced colitis, the expression of myeloid differentiation primary response gene *(MyD)88* increases and promotes fibrotic responses [173]. TLR4 regulates the activities of HSCs through TGF-β-induced signals which is affected by MyD88-NF-κB-dependent pathway [174]. In the liver, gut dysbiosis also triggers innate immune responses to inflammasomes (e.g., NLRP3) and proinflammatory cytokine production, which activates HSCs and produces ECM leading to fibrosis [175, 176]. Moreover, in patients with nonalcoholic fatty liver disease, fibrosis severity is associated with the changes in gut microbiome (e.g., *Enterobacteriaceae, Veillonellaceae*, and

Ruminococcaceae) [177]. In addition, cirrhotic patients have abundant gut microbiota which is associated with membrane transport and endotoxin production [178]. People with CF have diverse airway microbial communities, which are affected by age, antibiotics, and lung disease progression [179–181]. Antibiotic therapy used in CF can also regulate the inflammatory microenvironment which is affected by CFTR modulators through pro-flammatory cytokine IL-18 [182]. These studies reveal the role of the microbiome regulating the progression of fibrotic diseases and facilitating the therapeutic approaches targeting the microbiome.

Until now, it is still not fully understood the mechanism through which tissue repair process goes wrong in fibrotic diseases. Despite great advances in the understanding of the pathology and molecular biology of fibrosis, a large gap remains between the identification of anti-fibrosis targets and effective anti-fibrotic therapies.

MSCS IN FIBROTIC DISEASES

Stem cells are unspecialized cells with great potential to accomplish self-renew for long period and differentiate into various specialized cell types under certain physiological or experimental conditions [183]. Due to the ethical concerns of embryonic stem cells and the potential teratoma formation of induced pluripotent stem cells, great attention has been put on mesenchymal stem cells (MSCs) for preclinical experiments and clinical applications in regenerative medicine. MSCs were first reported with isolation and characterization by Friedenstein et al. from bone marrow in 1968 [184]. Ever since then, these cells have been extensively characterized regarding their origins, stemness, and differentiation capability. MSCs originate from the mesoderm, posse high self-renewal ability and multipotent capability into mesoderm lineage cells (including chondrocytes, osteoblasts, adipocytes, and skeletal muscle cells) [185], ectodermic cells (such as neurons, skin cells, and sweat glands) [186] and endodermic cells (such as endothelial cells) [187]. Among all the types of cells MSCs could differentiate into, their trilineage differentiation into adipocyte, chondrocyte, and osteoblast is commonly used as a criteria for their identification [8] (Fig. 1).

MSCs have been found in almost all tissue types, including bone marrow, adipose tissue, fetal liver, the umbilical cord, muscle, dental tissue, lung umbilical cord and placenta, peripheral blood, and endometrial tissue. Among them, MSCs can be successfully isolated and expanded from several common sources [188], i.e., bone marrow-derived stem cells (BMSCs), adipose tissue-derived stem cells (ADSCs), dental stem cells, and perinatal tissues. Even though MSCs derived from above tissues show good self-renew and differentiation capability, their cellular markers and therapeutic potentials are not idential, accompanied with different isolation procedure, yield amount, and cytokine secretion etc. [188]. Inspired by their tremendous healing ability in various disease backgrounds, MSCs are widely used for treating different types of fibrotic diseases. However, current achievements from cell lineage tracing studies showed that the cellular sources of myofibroblasts could be partially originated from the residential progenitor or multipotent stem cells during many fibrotic diseases' development. Therefore, it is crucial to understand the different roles and functions of residential/internal MSCs in disease pathogenesis and external MSCs in the treatment of fibrotic diseases.

Internal MSCs as one major source of myofibroblasts

Unlike the micro-environment of many other diseases, such as degenerative diseases and inflammations, one of the characterizations of fibrotic diseases is aberrant myofibroblast accumulation [189, 190]. Myofibroblasts are the major ECM-depositing cells that are positive of alpha-smooth muscle actin ($ACTA2^+$/α-SMA) marker. Because there is no single marker specifically for all myofibroblasts, the cellular source of myofibroblasts in fibrosis is controversial [37]. Current advancements in cell phenotyping, transplantation, lineage tracing, and imaging allow fate mapping of the cell sources of myofibroblasts in the progress of fibrosis in different disease conditions [190]. Depending on the disease and tissue backgrounds, these myofibroblasts were reported to be originated from various cell types, including the residential fibroblasts, residential epithelial and endothelial cells, residential MSC-like cells, arteries, and arterioles, and some circulating bone marrow (BM)-derived cells [37, 190, 191]. Among these cells, the local residing MSCs, circulating BM-derived MSCs, perivascular MSCs and epithelial–mesenchymal transition (EMT)-transformed cells have been considered as the major contributors for massive myofibroblast accumulation, extensive ECM deposition, and the causes of organ failure, which have been reported in many fibrotic diseases [192, 193] (Fig. 2).

Evidence shows that the major origin of myofibroblasts varies in different fibrotic tissue background. For example, idiopathic pulmonary fibrosis-associated myofibroblasts originate from multiple cell sources [194]. It seems that resident mesenchymal cells, rather than epithelial or BM-derived cells, were the main source for the formation of lung myofibroblasts in pulmonary fibrosis [195]. Moreover, 35% of renal myofibroblasts are derived from circulating BM-derived MSCs during renal fibrosis [196]. Another study showed that renal myofibroblasts originate from kidney resident $Gli1^+$ cells, which label a subset of MSCs from the perivascular niche [197]. Genetic lineage tracing analysis showed that this tissue-resident, but not circulating, $Gli1^+$ cells have been proved to differentiate into myofibroblasts during tissue injury in kidney, lung, liver, and heart [197]. Moreover, during bone marrow fibrosis (BMF), genetic fate tracing studies showed that the fibrosis-driving myofibroblasts derived from $Gli1^+$ MSCs are recruited from the endosteal and perivascular niche and cause BMF and finally bone marrow failure [191].

The EMT process is a critical process of cellular conversion from epithelial cells to mesenchymal phenotypes. According to the different biological contexts, EMT process is classified into three subtypes [198]: type I EMTs occur during embryo formation, organ development, and other related normal biological process; type II EMTs refer to the transition of epithelial or endothelial cells into resident tissue fibroblasts during wound healing, tissue regeneration, and organ fibrosis; type III EMTs are related to metastatic invasion in neoplastic cells. During type II EMTs, epithelial cells gradually lose their epithelial markers, such as E-cadherin and cytokeratin, translocate β-catenin signals into nuclei, and de novo express some mesenchymal markers typically α-SMA, vimentin, and fibroblast specific protein 1 in mesenchymal myofibroblast cells [192]. During the development of scarring and fibrosis, the matrix-producing myofibroblasts arise from epithelial lineage cells that underwent EMT process [193, 199]. Moreover, in kidney fibrosis, EMT of polarized epithelial cells into mesenchymal myofibroblast cells is mediated by upregulated MMP-9 induced by TGF-β signaling [192]. In addition, TGF-β signaling can act on multiple cell types that drive kidney fibrosis, suggesting that TGF-β is an alternative therapeutic target for renal fibrosis [200].

In short conclusion, published results suggest that myofibroblasts responsible for fibrotic development in various tissues partially come from internal MSCs. Targeting these MSCs and terminating their proliferation, differentiation, and secretion abilities could be a way to reduce fibrogenic development. However, the underlying mechanism of the transition from normal MSCs into myofibroblast-forming MSCs is still not clear; how to differentiate these two types of MSCs still be a crucial challenge for researchers.

The roles of external MSCs in fibrotic diseases

Unlike the residential MSCs, implantations of external MSCs are reported with effective and protective functions in the treatment

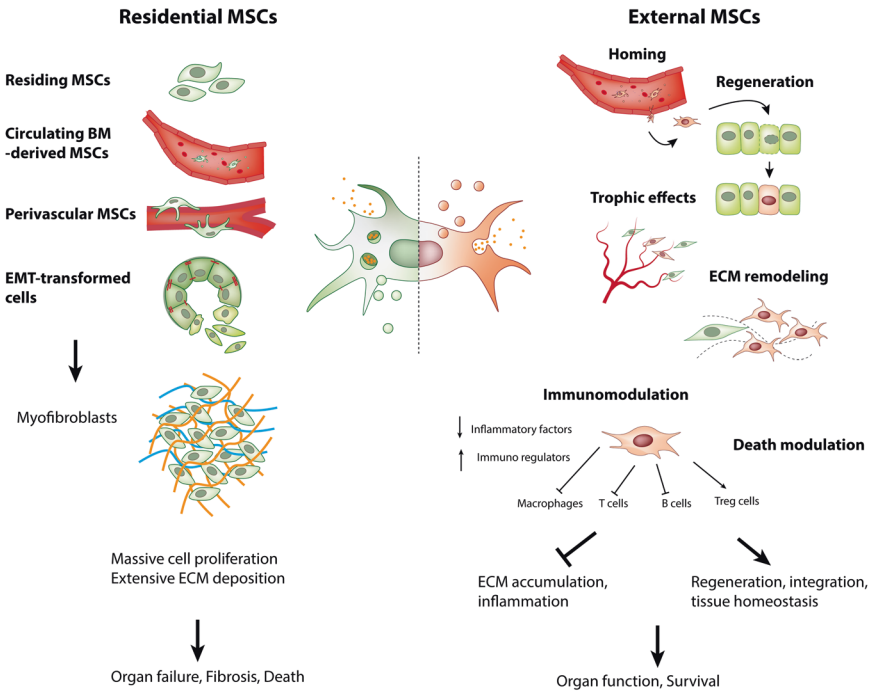

Fig. 2 Dual functions of MSCs in fibrotic diseases. On one hand, organ residential MSCs are reported as one major cellular source of myofibroblasts in fibrosis development. The residing MSCs, circulating BM-derived MSCs, perivascular MSCs and EMT-transformed cells are potential origins for myofibroblasts in many fibrotic diseases. On the other hand, external MSCs administrations show significantly beneficial contributions in the treatment of fibrosis in different organs. These MSC contributions include homing, regeneration, trophic effects, ECM remodeling, immunomodulation, and death modulation.

of fibrotic diseases in both pre-clinical and clinical studies [36, 190, 201, 202]. These MSCs are in vitro amplified either from autologous (cells derived from the same individual) or allogeneic (cells derived from the same species but not the same individual) sources (Fig. 2). Interestingly, studies showed that autologous MSCs seem have more effective functions than allogeneic MSCs in the treatment of acute kidney injury animals [203]. In general, there are two major methods commonly used for MSC delivery in current pre-clinical and clinical applications (Fig. 3): one is the systematic infusion of MSCs into the vascular circulation, such as intravenous or intradermal administration; the other is a direct application of these therapeutic cells locally to the wounds [204]. These administered external MSCs display multiple functionalities in modifying the fibrotic environment and influencing the damaged cells though both direct and indirect approaches. Here, we summarized six major reported regenerative features that external MSCs applied, i.e., homing ability, tissue regeneration capacity, ECM remodeling, tropic effects, paracrine effects, as well as death modulation in the process of preventing fibrotic diseases [205, 206] (Fig. 2).

Homing ability. Even though the administration of MSCs may not be directly applied to the defective sites in fibrotic diseases, external MSCs can sense and migrate to wounded sites through their homing ability [207]. Homing ability is the starting point for MSC-mediated regenerative effects in fibrosis. For example, in a treatment of age-associated skin morphologic disgraces and structural deficits, ADSCs can be rapidly recruited into the wounded sites [208]. In a drug-induced liver fibrosis model, fluorescence-labeled BMSCs were captured under microscopy in the fibrotic livers [209]. In addition, in vivo live imaging system showed that transplanted Luc-GFP(green fluorescence protein)-MSCs in a chronic kidney disease model can be detected in damaged kidney tissue from 3 days to 14 days after transplantation, with an improved treatment for the renal interstitial fibrosis [210].

Since it is still debated whether the clearance of MSCs from circulation into particular damaged tissues is an active transmigration mechanism or a passive entrapment and clearance, the homing mechanism is not well documented [211]. Moreover, the homing efficiency is not optimistic in MSC-based therapies [207, 212]. A variety of factors, such as the donor age and the number of cellular passages, in vitro culture conditions, the delivery approaches, as well as the fibrotic disease itself, can influence the homing efficiency of MSCs [213]. Studies showed that the homing capacity seems to be highly correlated to external culture conditions. For example, the primary/uncultured MSCs show significant higher efficient homing capacity than 24 h cultured MSCs to bone marrow and spleen [214]. Moreover, pre-conditioning of MSCs with various factors could also influence their homing ability. In a carbon tetrachloride (CCl_4) induced liver fibrosis model, nitric oxide (NO) and interleukin-6 (IL-6) can enhance MSCs homing to damaged liver tissue with a better outcome of anti-fibrosis [209, 215]. In another study with induced liver fibrosis, BMSCs pretreated with 5 μM melatonin, a hormone to improve sleep disorders, had significant improved homing capability than untreated BMSCs [216]. Thus, improving the MSC's homing capacity is necessary for better treatment of fibrosis.

Regenerative capacity. MSCs not only migrate to the wounded sites, but also proliferate, differentiate into targeted tissues, replace, and regenerate the damaged tissues. In a chronic skin wound model, injection of BMSCs around the wound significantly accelerated the healing process of excisional wound [217]. These allogeneic BMSCs were pre-tagged with GFP^+ and differentiated into epithelial cells with keratinocyte-specific protein keratin marker [217]. As a satisfactory alternative to dermal fibroblasts, BMSCs can develop into skin substitute in epidermis development and skin wound healing [218]. Moreover, ADSCs in the treatment of skin defects can differentiate into multiple cell types, including dermal fibroblasts, endothelial cells, and keratinocytes in damaged sites [208]. During the regeneration process, VEGF is one of the principal

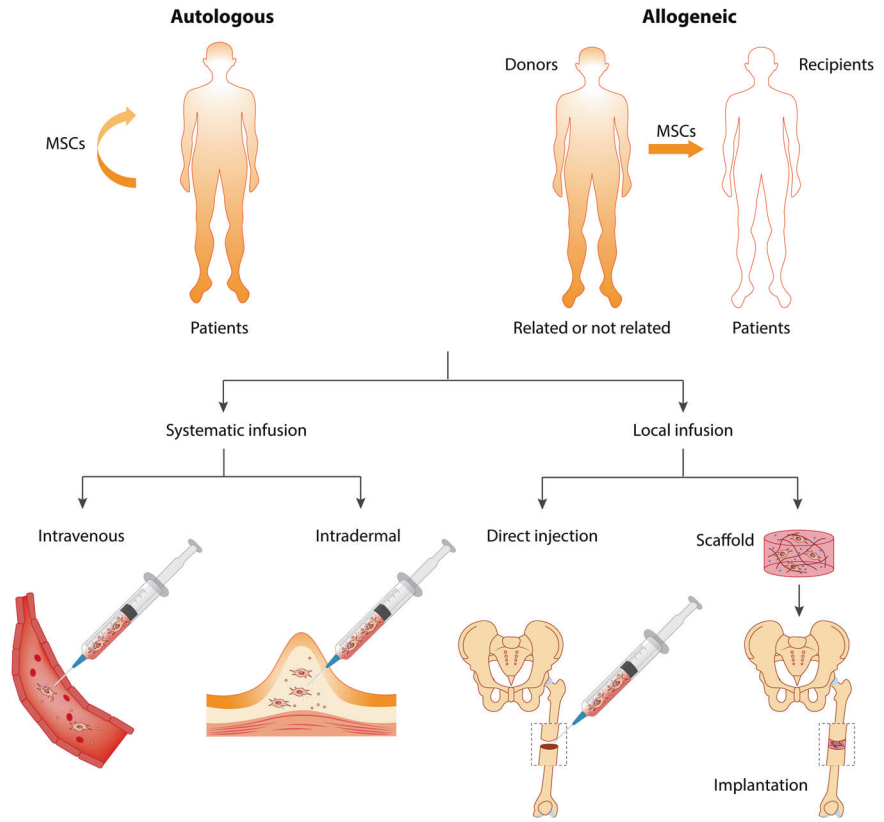

Fig. 3 Applications of MSCs in the treatment of fibrotic diseases. For pre-clinical and clinical trials of MSCs treatment, patients can either receive their own MSCs in an autologous way, or MSCs from related or not-related donors in an allogeneic way. Purified and amplified MSCs can be infused back into patients either systematically or locally. Systematic infusion includes intravenous injection (MSCs and MSC-derived factors are delivered in vein through circulation) and intradermal injection (MSCs and MSC-derived factors are delivered into the dermis, just below the epidermis). Local infusion can be achieved with direct injection of MSCs and MSC-derived factors into the sites of injury (for example, femur fracture), or transplantation of engineered MSC scaffolds to the sites of injury.

paracrine mediators of renoprotection of MSCs. In an acute kidney injury model, MSCs with VEGF knockdown by small-interfering RNA reduced the effectiveness and survival of MSCs [203].

Trophic effects. Besides these direct contributions from MSCs mentioned above, these cells can indirectly enhance tissue recovery through producing a large variety of bioactive trophic factors that stimulate neighboring parenchymal cells to repair damaged tissues in the treatment of fibrotic diseases [219]. These bioactive trophic factors can enhance angiogenesis, prevent apoptosis, stimulate cellular survival, proliferation, and differentiation of residential cells in wounded tissues [219]. Angiogenesis is a typical trophic effect of MSC administrations in skin diseases. On one hand, MSCs can directly differentiate into endothelial cells and/or pericytes in promoting angiogenesis in wound healing [220]. On the other hand, conditioned medium from cultured BMSCs which enriched with MSC-released proangiogenic factors, such as VEGF and angiopoietin-1, has promoting effects in endothelial cell tube formation in skin would closure [217]. Moreover, ADSCs also secrete pro-angiogenic growth factors in the treatment of non-healing wounds [221]. In addition to angiogenesis, ADSCs promote epidermal stem cells proliferation, resulting in epithelialization and increased epidermal thickness [222]. In an autologous bone marrow cell infusion therapy to liver cirrhosis, bone marrow cells (BMCs) activated the proliferation of hepatic progenitor cells and hepatocytes, which further promoted the restoration of liver functions [223].

ECM remodeling. During the pathogenesis of organ fibrosis, the massive accumulation of disorganized and stiff ECM is a diagnostic biomarker, which takes the center stage for malfunction and failure of damaged tissues [224]. MSCs have been shown with anti-fibrotic effects in reducing fibrotic ECM accumulation. In SSc, a rare chronic autoimmune disease with progressive fibrosis, MSCs treatment provides anti-fibrotic effects with reduced skin and lung fibrosis in various SSc animal models [225]. In a mouse model of cutaneous scar formation, MSCs can suppress the cellular proliferation and fibrotic formation of co-cultured fibroblasts [226]. Moreover, in a rat model of radiation-induced pulmonary fibrosis, infusion of human ADSCs triggered the secretions of hepatocyte growth factor (HGF) and prostaglandin E2 (PGE2), but decreased TNF-α and TGF-β1 levels in hosts [227]. As a consequence, the human MSCs successfully limit pulmonary fibrosis through inhibition of fibroblast activation and collagen deposition, and prevention of the EMT process of type II alveolar epithelial cells at the damaged sites [227]. Moreover, in vitro studies showed that conditioned medium from human ADSCs significantly suppressed the α-SMA translation and transcription induced by TGF-β treatment in murine muscle, myoblast cell line C2C12 [228]. Similarly, conditioned medium from ADSCs decreased the expression of *Col1* and *Col3* in hypertrophic scars (HS) tissues, and thinner and orderly arranged collagen fibers were examined in HS tissues cultured with ADSC-conditional medium [229]. Together, these results suggest that MSCs have anti-fibrotic effects in the potential application to prevent organ fibrosis.

Immunomodulatory effects. One essential trophic mediator of MSCs is their ability in attenuating inflammation at the site of injury [230–232]. MSCs can produce a vast spectrum of paracrine factors, including TGF-β, PGE2, HGF, IL-10, IL-6, indoleamine

2,3-dioxygenase, NO, and human leukocyte antigen G etc. [233]. With these factors, MSCs are capable of modulating large numbers of different immune cells, such as natural killer (NK) cells, dendritic cells, neutrophils, macrophages, B cells, and T cells [202, 233]. Studies demonstrated that MSCs altered T lymphocyte phenotypes increased the frequency of $CD4^+CD25^{high}CD45RA^+$ T_{reg}s, and modulated the associated cytokine production [234]. Moreover, activating MSCs' autophagy can enhance the immunosuppression of $CD4^+$ T cells, which is mediated by TGF-β1 pathway [231]. Moreover, MSCs facilitate monocyte to macrophage transition, shift inflammatory M1 macrophages to an anti-inflammatory M2 activation stage in a PGE2-dependent manner [235, 236]. Studies also showed that MSCs can downregulate macrophages in a liver fibrosis model [237]. Interestingly, the MSCs-derived exosomes display similar effective immunomodulatory properties and anti-inflammatory abilities as MSCs [238]. Moreover, the effects of MSCs derived from bone marrow and from adipose tissues show comparable immunomodulatory effects on both innate and acquired immunity of cells [239]. Based on the beneficial effects of MSCs in anti-inflammation and immunomodulation, large attention has been attracted to the application of MSCs therapy for immune and inflammatory diseases [240–243], including allergic diseases, osteoarthritis, and immune-dysregulating infectious diseases such as the novel coronavirus disease 2019 (COVID-19) [244, 245].

Death modulation. In addition to the functions listed above, MSCs can modulate cellular death of stressed cells in fibrotic conditions [246]. This death modulation by MSCs is mediated through both direct cell-cell contact and indirect paracrine secretion on the third-part cells affected by apoptosis, necroptosis, and pyroptosis [246]. On one hand, MSCs can facilitate the endogenous progenitors' survival and differentiation; on the other hand, MSCs can enhance the clearance of damaged cells and restore tissue homeostasis. For example, in chronic liver injuries, MSCs can reduce hepatocyte apoptosis and increase hepatocyte regeneration, which further reverse liver fibrosis and enhance liver functionality [206]. Recently, in a CCl_4-induced liver fibrosis model, BMSCs experienced and underwent apoptosis in damaged liver with massive production of apoptotic bodies, which stimulated macrophages to release MMP-12 and accelerate ECM degradation in mice [247]. Moreover, in a murine diabetic wound model, MSCs subcutaneously injected around the wound can contribute to the clearance of apoptotic cells by enhancing the phagocytosis of apoptotic cells and suppressing the number of apoptotic cells in wounds [248].

Importantly, these functioning features listed above are not exclusive from each other, and MSCs have been reported with multiple functions at one treatment in many cases. For example, in a mouse chronic liver fibrosis model, MSCs infusion and MSCs-CM treatment decreased hepatocellular death by promoting liver regeneration and inhibiting hepatocyte apoptosis, and suppressed necroinflammation by increasing Th2 and Treg cells and reducing Th17 cells at the same time [237]. With all the beneficial contributions of MSCs, MSC-based treatments have shown promising results of therapies for the preventing or reversing process of fibrosis.

MSCs and their microenvironment

It is intriguing how do MSCs from internal and external populations behave differently in the development of fibrosis in various tissue backgrounds. The key to answer this question could be the microenvironment that the internal MSCs entrapped in damaged tissue during the disease progress and that the external MSCs directly experienced during circulation or in the fibrotic tissues after cell administration. Evidence showed that the microenvironment of fibrotic tissues is detected with a high level of ROS [249], increasing alternations and stiffness of ECMs [250], accompanied with a pre-inflammatory environment featured with increasing NK cells and regulatory T cells [251, 252]. Clinical samples were enriched with secreted TGF-β1, IL-1β, and TNF-α in HBV patients with advanced fibrosis, which could induce a profibrotic cascade and proinflammatory responses in human stellate cell line LX-2 in vitro [253]. Those physical, chemical, and biological environment changes bring different stimulations to MSCs and further influence their functioning features. To study the influence of pro-inflammatory microenvironment on MSCs, in vitro studies were applied in cell culture systems. Pro-inflammatory cytokines, such as IL-1β, IL-6, and IL-23, had no effect on MSCs morphology and immunophenotype, but upregulated the expression of CD45, associated with enhanced adipogenic and osteogenic differentiation capacity in both human BMSCs and ADSCs [254]. Moreover, another inflammatory condition with TNFα and IFNγ increased the gene expression of adhesion molecules whereas migration-related genes were down-regulated in equine BMSCs [255]. These observations further suggest the complex microenvironment that MSCs experiences, and the diversity of the environmental cues could lead to totally different behaviors of these cells.

CLINICAL TRIALS OF MSCS IN FIBROTIC DISEASES

Although the therapeutic roles of MSCs have been studied in various types of fibrotic diseases in vitro and in animal models, clinical trials of using MSCs for fibrosis treatment were mainly focused on pulmonary fibrosis and liver cirrhosis. We did a systematic search in ClinicalTrial.Gov database and PubMed by searching the keywords "mesenchymal stem cell" and "fibrosis or cirrhosis" and found 75 registered clinical trials in ClinicalTrial.Gov database. However, among these trials, many of them were opaque with their status or the follow-up searches showed no clue for any actual conduction of the trials. Therefore, these registrations without clear status or clues for actual practice are excluded from this review. Table 2 listed all the registered or published clinical studies using MSCs to treat fibrotic diseases with ongoing or completed status.

MSCs are widely utilized to treat the patients with liver cirrhosis in clinical trials across the world (Table 2). In 19 registered clinical trials, 9 used autologous stem cell sources from bone marrow (8) and adipose tissue (1); and 10 used allogeneic sources from umbilical cord (8), adipose tissue (1), and menstrual blood (1). The dosage of MSC administration ranges from 0.5 million to 50 million per kg body weight per dose in different studies (estimated as 20 million to 400 million per dose), and multiple doses may give to the patients in some studies with each dose given after 1-week to 1-month intermission. The dosage of cells is mainly dependent on preclinical study, source of the cells, and safety concerns [20]. In a study conducted in 2006, 30–50 million autologous bone marrow-derived MSCs were injected into peripheral or the portal vein of liver cirrhosis patients, and the results showed that the cells were well tolerated by all patients and the liver function was improved. The disease score decreased from 17.9 ± 5.6 to 10.7 ± 6.3 ($P < 0.05$) and prothrombin complex decreased from international normalized ratio 1.9 ± 0.4 to 1.4 ± 0.5 ($P < 0.05$). Serum creatinine decreased from 114 ± 35 to 80 ± 18 μmol/L ($P < 0.05$) [256]. In another study, an average of 31.73 million autologous bone marrow-derived MSCs were infused systematically to patients with decompensated liver cirrhosis, and the results showed that the disease score was decreased and the quality of life of all four treated patients was improved with no adverse events observed [257].

Another target indication of MSCs therapy for fibrotic diseases is pulmonary fibrosis and seven related clinical trials were found in the reviewed 15 studies (Table 2). For lung diseases, allogeneic MSCs were more preferred and five out of seven studies used allogeneic cell sources from umbilical cord, bone marrow, and

Table 2. Clinical trails of MSC treatment in fibrotic diseases

Disease type		Clinical trial info				MSC info		Reference	
Lesion	Indication	Phase	Country	Status	Year	Tissue Origin	Dose range	Clinical Trail database	Ref
Liver	Cirrhotic Patients With Pioglitazone	IIT Phase I	Iran	Completed	2011-2014	Autologous Bone marrow	Not specified	NCT01454336	
	Liver Cirrhosis	IIT Phase I	China	Completed	2011-2014	Allogeneic Menstrual Blood	1×10^6 cells/kg per dose, 4 doses	NCT01483248	
	Decompensated Liver Cirrhosis	IIT Phase II	India	Ongoing	2019-	Allogeneic Umbilical Cord	Not specified	NCT03945487	
	Decompensated Liver Cirrhosis	Phase I/II	Japan	Ongoing	2017-	Allogeneic Adipose	Not specified	NCT03254758	
	Liver cirrhosis	Phase I/II	Singapore	Ongoing	2018-	Autologous Bone marrow	$(0.5–1) \times 10^6$ cells/kg	NCT03626090	
	Decompensated liver cirrhosis	IIT Phase I	Iran	Completed	2007	Autologous Bone marrow	0.5×10^6 cells/kg	Not registered	[257]
	Liver cirrhosis	IIT Phase I	China	Completed	2010-2018	Allogeneic Umbilical cord	0.5×10^6 cells/kg	NCT01220492	
	Decompensated liver Cirrhosis	IIT Phase I	India	Completed	2020-2020	Autologous Bone marrow	Not specified	NCT04243681	
	Alcoholic Cirrhosis	Phase III	Korea	Ongoing	2020-	Autologous Bone marrow	7×10^7 cells/dose	NCT04689152	
	Liver Cirrhosis Patient Caused by Hepatitis B	IIT Phase I	Indonesia	Ongoing	2020-	Allogeneic Umbilical Cord	1×10^8 cells/dose	NCT03472742	
	Liver Cirrhosis	Phase I	Iran	Completed	2007-2009	Autologous Bone marrow	Not specified	NCT00420134	
	Hepatitis B liver cirrhosis	IIT Phase I	China	Ongoing	2019-	Allogeneic Umbilical Cord	6×10^7 cells/dose	NCT03826433	
	Liver Cirrhosis	Pilot	Japan	Completed	2010-2015	Autologous Adipose	Not specified	NCT01062750	
	Alcoholic liver cirrhosis	IIT Phase I	USA	Ongoing	2019-	Autologous Bone marrow	5×10^7 cells/dose	NCT03838250	
	Decompensated liver cirrhosis	IIT Phase I	China	Ongoing	2022-	Allogeneic Umbilical Cord	$(5–15) \times 10^7$ cells/dose	NCT05227846	
	Liver cirrhosis	IIT Phase I	Vietnam	Ongoing	2022-	Allogeneic Umbilical Cord	Not specified	NCT05331872	
	Liver cirrhosis	IIT Phase I	China	Ongoing	2021-	Allogeneic Umbilical Cord	1×10^8 cells/dose, 2 doses	NCT04541680	
	Decompensated alcoholic cirrhosis			Ongoing	2021-	Allogeneic Umbilical Cord	$(0.5–2) \times 10^6$ cells/kg	NCT05155657	
	Liver cirrhosis	IIT Phase I	Sweden	Completed	2006-2009	Autologous Bone marrow	5×10^7 cells/dose	Not registered	[256]
Lung	Idiopathic Pulmonary Fibrosis	IIT Phase I	Spain	Completed	2013-2018	Autologous Bone marrow	$(1–10) \times 10^7$ cells/kg	NCT01919827	[259]
	Radiation-induced Pulmonary Fibrosis	IIT Phase I	China	Completed	2014-2019	Allogeneic Umbilical cord	1×10^6 cells/kg	NCT02277145	
	Idiopathic Pulmonary Fibrosis	IIT Phase I	Australia	Completed	2011-2015	Allogeneic Placenta	$(1–2) \times 10^6$ cells/kg	NCT01385644	
	Idiopathic Pulmonary Fibrosis	IIT Phase I	USA	Completed	2013-2017	Allogeneic Bone marrow	$(2–20) \times 10^7$ cells/kg	NCT02013700	[258]
	Idiopathic Pulmonary Fibrosis	IIT Phase I	USA	Recruiting	2021-	Allogeneic Umbilical Cord	1×10^6 cells/kg	NCT05016817	
	Bleomycin Induced Pulmonary Fibrosis	Phase I/II	India	Ongoing	2014-	Autologous Adipose	2×10^6 cells/kg per dose, 3 doses	NCT02625246	
	Interstitial lung disease	IIT Phase I	Russia	Completed	2015-2018	Allogeneic Bone marrow	2×10^8 cells/kg	NCT02594839	
Systemic	Diffuse Cutaneous Systemic Sclerosis	IIT Phase I	Colombia	Ongoing	2020-	Allogeneic Wharton´s jelly	2×10^6 cells/kg	NCT04432545	
	Cystic Fibrosis	IIT Phase I	USA	Completed	2016-2020	Allogeneic Bone marrow	$(1–5) \times 10^6$ cells/kg	NCT02866721	

IIT Investigator initiated trials

placenta; while autologous MSCs from bone marrow and adipose tissue were used in another two registered clinical trials respectively. The cell dosage used in pulmonary fibrosis ranged from 1 million to 100 million cells per kg body weight (40–800 million cells per dose), higher than that in liver cirrhosis studies. In a study conducted in 2013, nine patients with IPF were dosed with a single intravenous infusion of 20, 100, or 200 million allogeneic bone marrow-derived MSCs. The study found no treatment-emergent serious adverse events, and by 60 weeks post-infusion, there was an average decline of 3.0% in predicted forced vital capacity (FVC, the amount of air that can be forcibly exhaled from lungs) and an 5.4% average decline in predicted diffusing capacity of the lungs for carbon monoxide [258]. Another study utilized 10 to 100 million autologous MSCs from bone marrow to treat 12 IPF patients, and revealed an initial mean FVC decline of 8.1% at 3 months. The number of patients without functional progression was six (46%) at 3 months and three (23%) at 12 months. No severe adverse events were found in this study either [259].

Compared with broad attempts in in vitro study and various animal tests, clinical trials using MSCs for fibrotic diseases are rather conservative. The registered clinical trials are mainly conducted on liver cirrhosis and IPF patients, while two studies out of 15 utilized allogeneic MSCs from bone marrow and Wharton's jelly to treat cystic fibrosis and diffuse cutaneous systemic sclerosis patients respectively. However, no available clinical data or publications were found about these two studies. Unlike studies designed in preclinical trails, no genetically modified MSCs were used during clinical trials, and in fact no intentional modifications (even induced differentiation) on MSCs were applied in the reported clinical trials. From safety perspective, it is encouraged to keep minimal manipulation and homologous use of the cell therapy products in clinical use [260].

CONCLUSIONS AND PERSPECTIVES

Growing attentions have been attracted to the applications of MSCs in fundamental and clinical researches, which lead to large numbers of studies focusing on the new areas of the applications of MSCs and MSCs-sourced bioactive factors to achieve optimal outcomes.

In the field of cellular sources, such as bone marrow and adipose tissues as traditional MSC sources, more sources of MSCs have emerged, including various umbilical cord tissue (Wharton's jelly), placenta, dental pulps, mobilized peripheral blood, and medical waste material from birth-derived tissues [261]. Importantly, MSCs derived from these non-traditional sources have been shown with comparable efficacy in the treatment of fibrotic diseases [262]. Furthermore, preconditioning of MSCs, including hypoxia, pharmacological agents, mechanical treatment, trophic factor administrations, etc., have been applied and studied in the improvement of MSC therapy in preclinical and clinical trials [263]. Moreover, cell-free products from MSCs, including exosomes, probiotics, MSC-derived ECM are largely involved in current studies. Results showed an accelerated healing and decreased scar formation were achieved with MSC-derived extracellular vesicles (EV) treatment in chronic skin ulcers [264]. MSC-EV had similar mechanisms, such as promoting angiogenesis, immunosuppression, and skin regeneration [264]. In addition, new combinations of MSCs and other treatment or engineering tools present promising therapeutic outcomes in preventing fibrotic diseases. Previously, MSCs treatment as a cell-based approach showed some defects in the direct injection, such as low cell viability, transient retention, and poor efficacy [265]. A bioactive hydrogel scaffold which provides MSCs with a physiologic microenvironment, including mechanical support and protection from native immune system is a promising method to improve the therapeutic effect through changing cell delivery [265]. In a mouse wound healing model, microspheres have been used to deliver MSCs into wound margins and significantly enhanced wound healing with reduced fibrotic activities [226]. Moreover, combined ADSCs and platelet-rich plasma therapy showed better healing outcome in diabetic wound healing model [222].

The microenvironment where MSCs originate and experience, i.e., the physical properties, chemical components, various soluble factors as well as neighboring cells, regulates their cellular proliferation, differentiation, and other important functions. Increasing studies support that MSCs display a dual role in the progress of fibrosis: On one hand, the internal/residential MSCs show a promoting role in the disease pathogenesis; On the other hand, the external MSCs exhibit a suppressive role in fibrosis and serve as a promising therapeutic option in the clinical applications for fibrotic diseases. Interestingly, this dual nature of MSCs is not unique to fibrosis. Published studies suggest that MSCs also present dual roles in cancer progress [266] and in inflammatory cascade [267]. In both cases, the microenvironment that MSCs face plays major contribution in switching their cellular behaviors and finally outcomes in disease development. The complex microenvironment that internal and external MSCs faced and encountered in fibrosis diseases could bring opposite outcomes for their functions. Based on this information, pre-conditioning strategies for MSCs have been encouraged to be used in preclinical and clinical trials, including physical and chemical pre-conditioning strategies such as hypoxic conditions, with inflammatory cytokines, or with different pattern recognition receptor ligands [268, 269].

With broader MSCs sources, MSCs and their derived bioactive factors, dynamic cellular modifications, and more efficient delivery for MSCs therapeutic applications are extensively used in disease conditions besides fibrosis, such as tumor growth [270], vascular diseases [271], degenerative conditions [272], neurological disorders [273], inflammation [241], and immune-related conditions [274]. The dual functions of MSCs in the development and treatment of fibrotic diseases arise great challenges for the fundamental research and clinical applications of MSCs in fibrosis. It is crucial to fully understand the difference between myofibroblast-forming MSCs and anti-fibrotic MSCs in cellular sources, cellular markers, and regulatory pathways. By knowing the differences of the two sides of MSCs in the pathogenesis and therapy of fibrotic diseases, we can extend our understanding about MSCs and their applications in more pathogenic conditions.

ACKNOWLEDGEMENTS

We acknowledge the assistance of Core Research Facilities of Southern University of Science and Technology (SUSTech). This research was funded by the National Key Research and Development Program of China Grants (2019YFA0906001), National Natural Science Foundation of China Grants (82022047, 81972100), Guangdong Provincial Science and Technology Innovation Council Grant (2017B030301018), and project of Huazhong University of Science and Technology Union Shenzhen Hospital (NY2021029, NY2021030, NY2021031).

ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

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