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Review:

Current status and future prospects of mesenchymal stem cell therapy for liver fibrosis*

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Abstract: Liver fibrosis is the end-stage of many chronic liver diseases and is a significant health threat. The only effective therapy is liver transplantation, which still has many problems, including the lack of donor sources, immunological rejection, and high surgery costs, among others. However, the use of cell therapy is becoming more prevalent, and mesenchymal stem cells (MSCs) seem to be a promising cell type for the treatment of liver fibrosis. MSCs have multiple differentiation abilities, allowing them to migrate directly into injured tissue and differentiate into hepatocyte-like cells. Additionally, MSCs can release various growth factors and cytokines to increase hepatocyte regeneration, regress liver fibrosis, and regulate inflammation and immune responses. In this review, we summarize the current uses of MSC therapies for liver fibrosis and suggest potential future applications.

Key words: Liver fibrosis, Cell therapy, Mesenchymal stem cells
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1 Introduction

Liver fibrosis is a pathologic process that occurs between liver injury and liver cirrhosis. After liver injury, several processes occur including cell apoptosis, inflammation, and scarring, resulting in the deposition of the extracellular matrix (ECM). In the early stages, the ECM deposition can be hydrolyzed by proteolytic enzymes such as matrix metalloproteinases (MMPs). However, continuous damage will ultimately lead to excessive matrix deposition and the alteration of the normal liver structure (Lichtinghagen *et al*., 2001).

Liver fibrosis can be triggered by viruses, alcohol abuse, drug abuse, and auto-immunity, among other conditions. When liver fibrosis is not well controlled, it can develop into liver cirrhosis, which is the end-stage of liver disease. Currently, liver transplantation is the main effective therapy for liver cirrhosis, but this treatment method is associated with many problems, such as immunological rejection, donor shortages, surgical complications, and high costs (Eom *et al*., 2015). Therefore, finding new therapeutic strategies for liver fibrosis is essential.

In addition to liver transplantation, cell therapy is a common treatment method for liver disease. For instance, hepatocyte transplantation can be used to restore liver function because of the regeneration abilities of these cells. However, the utility of this treatment is limited because hepatocytes easily lose their viability and function when they are cultured in vitro or when they are preserved cryogenically (Eom *et al*., 2015). Thus, other types of cells have been explored in an effort to find an ideal treatment for liver diseases. Such research has shown that stem cell transplantation is an effective therapy for liver fibrosis

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(Kakinuma *et al*., 2009; Kharaziha *et al*., 2009). Among the different types of stem cells, mesenchymal stem cells (MSCs) in particular have obvious advantages in regenerative repair because of their high potential for multipotent differentiation, capacity for self-renewal, and low immunogenicity (Jang *et al*., 2014). MSCs are fibroblast-like and plate-adhering cells, which have the ability to self-renew and to differentiate into adult cells from different germ layers, such as neurocytes from ectoderm, osteoblasts and myocytes from mesoderm, and hepatocyte-like cells from endoderm (Chan *et al*., 2014). Recently, MSCs have been isolated from a variety of tissues including umbilical cord blood, adipose tissue, liver, lung, dermis, amniotic membrane, and menstrual blood (Erices *et al*., 2000; Campagnoli *et al*., 2001; Jiang *et al*., 2002; de Ugarte *et al*., 2003; Mou *et al*., 2013). Additionally, MSCs can secrete a series of cytokines and signaling molecules, such as hepatocyte growth factor (HGF), interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-α), epidermal growth factor (EGF), nitric oxide, prostaglandin E2 (PGE2), and indoleamine 2,3-dioxygenase (Ortiz *et al*., 2007; Kiss *et al*., 2008; Puglisi *et al*., 2011), which can regulate inflammatory responses, stimulate hepatocyte proliferation, and maintain hepatocyte function (Lin *et al*., 2011; Sharma *et al*., 2014) (Fig. 1).

In general, MSC therapy for liver fibrosis is effective and promising, and many studies have been performed in this field. Thus, in this review, we discuss the current research regarding the mechanisms and uses of MSC therapy for liver fibrosis and the associated limitations, and we suggest some potential future applications of this therapy.

2 Mechanisms of fibrogenesis in the liver

The mechanisms of liver fibrosis are complex and involve a variety of cytokines, growth factors, and signaling pathways. Although many studies have been performed, the exact mechanisms of fibrogenesis remain unknown. It has been established that an imbalance between ECM production and degradation is the precipitating cause of liver fibrosis (Ek *et al*., 2007). However, how the imbalance happens is unclear.

The universally accepted key mechanism involved in ECM accumulation is the activation of transforming growth factor beta (TGF-β)/Smad signaling (Wrana, 1999; Berardis *et al*., 2015), which is mediated by transmembrane serine/threonine kinase receptors including type I and type II. In the injured liver, the microenvironment promotes the activation of Kupffer cells, which in turn exert proinflammatory

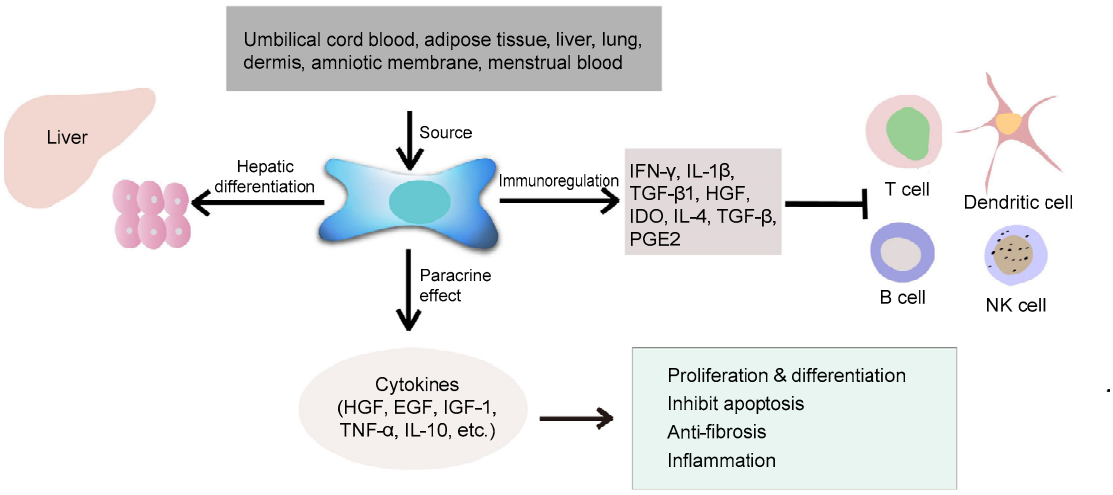

Fig. 1 Sources and function of mesenchymal stem cells (MSCs)

The sources of MSCs are abundant, including umbilical cord blood, adipose tissue, liver, lung, dermis, amniotic membrane, and menstrual blood, among others. MSCs can differentiate into hepatocytes, secrete various cell factors, and participate in immunoregulation. IFN-γ: interferon gamma; IL: interleukin; TGF: transforming growth factor; HGF: hepatocyte growth factor; IDO: indoleamine 2,3-dioxygenase; PGE2: prostaglandin E2; EGF: epidermal growth factor; IGF: insulin-like growth factor; TNF: tumor necrosis factor; NK cells: natural killer cells

cytokines such as TNF-α, TGF-α, TGF-β, and platelet-derived growth factor (PDGF), among others. The increased TGF-β, combined with the type II receptor, activates the type I receptor and forms a complex. Then, the complex phosphorylates, for the downstream signal transduction molecules Smad2/3, are translocated into the nucleus where they regulate transcriptional responses such as collagens.

The activated hepatic stellate cells (HSCs), which can transform into myofibroblast-like cells, also play a critical role in the production of ECM (Berardis *et al*., 2015). When stimulated by lipid peroxides, products from injured hepatocytes, or biochemical signals from Kupffer cells, HSCs can become activated and exhibit the following: high expression of alpha smooth muscle actin (α-SMA), tissue inhibitors of metalloproteinases (TIMPs)-1/2, the secretion of collagen-1, and increased proliferation ability (Iredale *et al*., 1992; Friedman, 1993; Benyon *et al*., 1996). The activation can occur through autocrine and paracrine signaling pathways; one of the main pathways is the PDGF-β signaling pathway. The PDGF-β signaling pathway can activate other pathways, such as the Ras-mitogen-activated protein kinase, phosphoinositide 3-kinase-AKT/protein kinase B, and protein kinase C pathways, resulting in HSC proliferation (Kelly *et al*., 1991). In addition to HSCs, other cell types, such as circulating fibrocytes, portal fibroblasts, and bone marrow-derived cells, are believed to contribute to ECM deposition (Forbes *et al*., 2004; Wells *et al*., 2004).

Recent studies have shown that the development of liver fibrosis is accompanied by the expression of MMPs (Lichtinghagen *et al*., 2001). MMPs are critical for the regression of fibrogenesis in which they can degrade collagens and are involved in the early stages of tissue remodeling (Milani *et al*., 1994; Benyon *et al*., 1996). Moreover, TIMPs, which can be produced by activated HSCs, are believed to induce ECM deposition by slowing the breakdown of collagens (Arthur, 1995; 1997). It is known that the expression of TIMPs is mainly induced by inflammation responses. Inflammation factors like IL-1β and TNF-α can promote TIMP expression. Thus, the expression level and activity of TIMPs can be used as indicators to measure the disease process. In general, the balance between MMPs and TIMPs plays an important role in liver fibrosis (Böker *et al*., 2000).

Thus, it is clear that the TGF-β/Smad signaling pathway plays a critical role in ECM accumulation. When this pathway is activated, the downstream factors notably increase, which induces the expression of fibrosis-related genes including the genes for collagen-1, α-SMA (a surface marker of HSCs), and TIMPs. As a result, the number of activated HSCs increases, whereupon the degradation cannot match the production of ECM, resulting in liver fibrosis (Fig. 2).

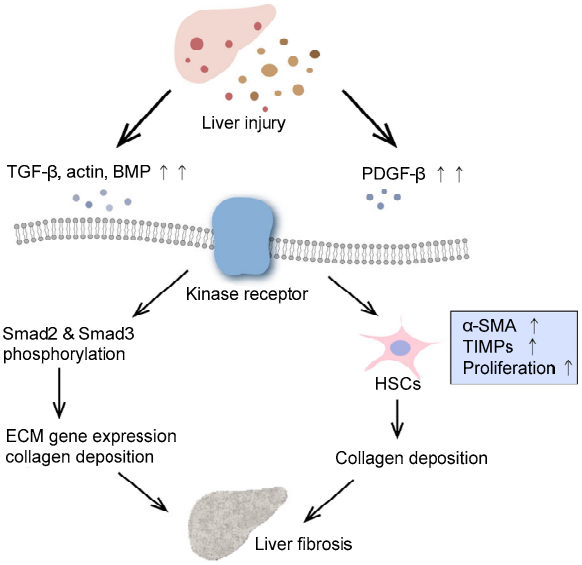

Fig. 2 Signaling pathway of liver fibrogenisis
The injured liver produces various cell factors, which can activate transforming growth factor beta (TGF-β) and platelet-derived growth factor beta (PDGF-β), and bone morphogenetic protein (BMP). Through the TGF-β signaling pathway, Smad2/3 are phosphorylated and activate downstream molecules such as extracellular matrix (ECM) genes, resulting in the deposition of collagen. Hepatic stellate cells (HSCs) are greatly increased through the PDGF-β pathway and they induce the secretion of collagens and tissue inhibitors of metalloproteinases (TIMPs). Thus, the degradation of collagens decreases and the secretion increases, leading to the deposition of collagens, which results in worsened liver disease. α-SMA: alpha smooth muscle actin

3 Differentiation ability of MSCs

It is known that MSCs have the capacity to differentiate into various progenitor cells from different cell lines, including hepatic progenitor cells. Indeed, a variety of studies (Banas *et al*., 2007; Ishii *et al*., 2008; Kakinuma *et al*., 2009; Puglisi *et al*., 2011; Hang *et al*., 2014) have demonstrated the ability of MSCs to

differentiate into hepatocyte-like cells by examining the expression of specific hepatocyte markers such as albumin, α-fetoprotein, and cytokeratin-19, among others.

The ability of MSCs to differentiate into hepatocyte-like cells makes them an ideal alternative method for treating liver fibrosis. Therefore, many studies have examined the mechanisms underlying the differentiation ability of MSCs. Several recent studies (Yoshida *et al*., 2007; Ishii *et al*., 2008; Liu *et al*., 2015) have demonstrated that Wnt/β-catenin signaling plays an important role in regulating the hepatic differentiation of human MSCs. Upon Wnt signaling activation, β-catenin will translocate into the nucleus and coactivate downstream transcription factors to regulate the differentiation of MSCs. Furthermore, mesenchymal-epithelial transition and the reverse, epithelial-mesenchymal transition are critical developmental processes that play fundamental roles in the differentiation of multiple tissues (Hay, 2005). Epigenetic modifications, such as DNA methylation and histone acetylation, have also been shown to participate in the differentiation of MSCs (Snykers *et al*., 2007).

Additionally, some studies have tried to enhance the efficiency of MSC differentiation, since during regular differentiation, MSCs have low metabolic activity and low expression of functional proteins (Ek *et al*., 2007). For instance, Mohsin *et al*. (2011) demonstrated that pretreating MSCs with injured liver tissue enhances their differentiation ability owing to the growth factors and cytokines that are released by the injured tissue, such as HGF, insulin-like growth factor (IGF), EGF, and basic fibroblast growth factor (bFGF), among others (Liu *et al*., 2015).

While it is clear that MSCs have multi-differentiation abilities including the ability to differentiate into hepatocyte-like cells, it remains unclear whether MSCs can adopt a mature hepatic fate, as no reliable and detailed results of mature hepatocytic gene expression have been reported. Many researchers believe that MSCs can become hepatocytes both morphologically and functionally. For instance, Banas *et al*. (2007) and Yin *et al*. (2015) demonstrated that adipose tissue-derived MSCs could be induced into transplantable and mature hepatocyte-like cells both in vivo and in vitro. Moreover, these studies showed that differentiated MSCs express hepatocyte-specific markers including albumin and α-fetoprotein and share liver functions such as low-density lipoprotein uptake, glucose storage, and ammonia detoxification.

In contrast, other researchers have opposed the opinion that MSCs can adopt a mature hepatic fate by claiming that only early specific markers have been detected and noting that little credible data on the detection of mature hepatocyte markers exist. Campard *et al*. (2008) conducted a study to detect the differentiation ability of umbilical cord matrix stem cells; the results showed that the differentiated umbilical cord matrix stem cells exhibited hepatocyte-like morphologies, specific liver markers (e.g., albumin, α-fetoprotein, cytokeratin-19, connexin-32), and some hepatic functions including glucose storage, low-density lipoprotein uptake, and urea production. However, the cells did not express hepatocyte nuclear factor 4 or HepPar1, two specific hepatic makers. In addition, the differentiated MSCs still contained some MSC-specific makers. Collectively, these findings suggested that the differentiated MSCs did not express enough markers of mature hepatocytes, implying that MSCs cannot fully become hepatocytes. Lian *et al*. (2006) demonstrated that bone marrow (BM) hematopoietic stem cells expressed several hepatic markers but could not be efficiently converted into hepatocyte-like cells, as one of the mature hepatic markers (anti-trypsin) was not detected. Another study (Hengstler *et al*., 2005), based on drug metabolism, showed that it is unlikely that MSCs fully differentiate into hepatocytes, and it has also noted that the use of different protocols for hepatic differentiation and different detection methods are problematic. Therefore, specific criteria are needed to define hepatocyte-like cells derived from MSCs. It has been suggested that the definition should not only be based on qualitative analyses but also on quantitative analyses including analyses of enzyme activity.

Overall, MSCs have the potential to differentiate into immature hepatocyte-like cells that exhibit some early specific hepatic markers and functions. Regardless, MSCs are an optimal choice for treating liver fibrosis because of their paracrine effects and immunologic regulation in addition to their multi-differentiation potential.

4 Paracrine effect of MSCs

MSCs have the ability to migrate into injured tissues via chemotaxis due to cytokines that are released from the injured organ or tissues (Golzar *et al*., 2015; Lourenco *et al*., 2015). Under stimulation of the microenvironment in injured tissue, like some inflammation factors, MSCs can release various growth factors and cytokines, which promote the proliferation of endogenous hepatocytes, reduce hepatocyte apoptosis, enhance liver function, and repress inflammatory responses (Zhou *et al*., 2009; Lin *et al*., 2011).

Research shows that MSCs secrete cytokines, such as HGF, EGF, IL-6, and TNF-α, which can stimulate hepatocyte proliferation and enhance liver function, as indicated by the high levels of albumin and urea secretion. For instance, Kim *et al*. (2014) overexpressed HGF by transducing MSCs with an adenovirus vector carrying the HGF gene. Their results showed a decrease in collagen and lower mRNA levels of the fibrogenic cytokines PDGF-bb and TGF-β1, suggesting that MSCs that overexpress HGF are effective in the treatment of liver fibrosis. Additionally, MSCs can release other cytokines such as IGF-1, stromal cell-derived factor-1 (SDF-1), and a vascular endothelial growth factor (VEGF), which inhibit cell apoptosis mainly by regulating the SDF-1/CX chemokine receptor-4 (CXCR-4) axis (Lin *et al*., 2011). IGF-1 is an important factor in body metabolism, and has been demonstrated to be anti-apoptotic to hepatocytes and increase the secretion of HGF in the cirrhotic liver (Bonefeld and Møller, 2011). Fiore *et al*. (2015) used a recombinant adenovirus overexpressing IGF-1 in BM-MSCs to ameliorate liver fibrosis in mice. The application of BM-derived AdIGF-I-MSCs resulted in the reduced activation of HSCs, increased IGF-I and HGF expression, reduced fibrogenesis, and increased hepatocyte proliferation.

Moreover, researches (Siller-López *et al*., 2004; Snykers *et al*., 2007) have demonstrated that MSCs overexpressing MMPs promote the regression of liver fibrosis. MSCs have the potential to reverse the fibrotic process by inhibiting collagen deposition through high levels of MMPs including MMP-8, MMP-9, and MMP-13. MMPs have been shown to degrade the ECM directly in order to balance the increased TIMPs that are induced by activated HSCs, thus contributing to the regression of fibrogenesis (Lin *et al*., 2011). In addition, the blockades of MSC-derived IL-10 and TNF-α exhibit minimal inhibitory effects on HSC proliferation and collagen synthesis, demonstrating the anti-fibrogenic effects of IL-10 and TNF-α (Parekkadan *et al*., 2007).

It is known that cytokines are important factors that participate in inflammation, as they can mediate inflammatory responses and prevent inflammatory effects. TNF-α, IL-1, and IL-6 are familiar proinflammatory factors that play critical roles in activating immunocytes and in regulating tissue metabolism (Liu *et al*., 2013; Huang *et al*., 2015). In injured tissue, TNF-α is one of the first factors to be released, which then activates neutrophil granulocytes and lymphocytes and induces the secretion of other inflammation factors. In a lung injury model, MSCs have been shown to express an IL-1 receptor antagonist that blocks the release of TNF-α from activated macrophages, thus preventing tissue damage (Ortiz *et al*., 2007).

5 MSC therapy and immunoregulation

It has been established that MSCs possess remarkable immunosuppressive properties that inhibit the proliferation and function of immune cells from both the adaptive and innate immune systems (Shi *et al*., 2011). The immunomodulatory effects of MSCs are mediated through both a cell-cell contact and secreted factors such as PGE2, nitric oxide, and TGF-β. MSCs can also inhibit the proliferation of T lymphocytes through cell contact (Tse *et al*., 2003; Sotiropoulou *et al*., 2006) and through soluble cytokines such as HGF, IL-1β, TGF-β1, interferon gamma (IFN-γ), and indoleamine 2,3-dioxygenase (di Nicola *et al*., 2002; Meisel *et al*., 2004; Groh *et al*., 2005; Krampera *et al*., 2006), which is indicated by an increase in the number of cells in the G0/G1 phase (Glennie *et al*., 2005) and by the up-regulated expression of p27 (Krampera *et al*., 2003). Further, MSCs can inhibit CD_4^+ T cells, CD_8^+ T cells (Glennie *et al*., 2005), T-helper lymphocytes (Th1/Th17) (Aggarwal and Pittenger, 2005; Zappia *et al*., 2005), and cytotoxic T cells (Potian *et al*., 2003; Rasmusson *et al*., 2003). The suppression effect of MSCs on T

cells can indirectly act on B lymphocytes because B cell activation mainly depends on T cells. Additionally, MSCs can directly inhibit the proliferation of B lymphocytes, the production of antibodies, and chemotaxis when co-stimulating with anti-immunoglobulin antibodies, anti-CD40L and IL-4 in humans (Corcione *et al*., 2006).

MSCs also have suppression effects on cells belonging to the innate immune system, including natural killer (NK) cells, dendritic cells (DCs), monocytes, and macrophages. Studies have shown that MSCs can only partially suppress the proliferation of activated NK cells. Some cell factors such as TGF-β1 and PGE2 are believed to participate in the suppression of NK cell proliferation (Rasmusson *et al*., 2003; Krampera *et al*., 2006). In addition, MSCs can affect the production of DCs by inhibiting the differentiation of monocytes, as MSCs can block the maturation signals and co-stimulatory molecules (Zhang *et al*., 2004; Jiang *et al*., 2005; Nauta *et al*., 2006). On the other hand, MSCs reduce the proinflammatory ability of DCs by decreasing the secretion of TNF-α, IFN-γ, and IL-12 and increasing IL-10 secretion (Zhang *et al*., 2004; Jiang *et al*., 2005).

In summary, the ability of MSCs to regulate immune responses is an important advantage for cell therapy and allogeneic transplantation. It is known that MSCs have low immunogenicity because they lack human leukocyte antigen class II and co-stimulatory molecules such as CD80, CD86, and CD40 in the cytomembrane (Reinders *et al*., 2013). In addition, the sources of MSCs are various and abundant. MSCs also have direct migration abilities and a high differentiation capacity. Considering all of these characteristics, MSCs are the ideal transplant donors in regeneration diseases.

6 MSC therapy and CRISPR/Cas9

Currently, genome editing is widely used in studies involving functional genomics, transgenic animals, and gene therapy. Genome editing is based on programmable and highly specific nucleases, which generate site-specific cleavage and subsequently induce cellular DNA repair (Zhang *et al*., 2014). Multiple artificial nuclease systems have been developed for genome editing, including zinc-finger nucleases, transcription activator-like effector nucleases, and clustered regularly interspaced short palindromic repeats (CRISPR) and the CRISPR-associated (Cas) protein 9. Zinc-finger nucleases and transcription activator-like effector nucleases, based on protein-DNA interactions, are more complex and time-consuming compared with CRISPR/Cas9, which is easier and more efficient when using guide RNA (gRNA) and DNA targeting.

CRISPR/Cas9 is widely used in genetic modification, transcription regulation, and gene therapy studies. Researches have demonstrated that CRISPR/Cas9 can be used to conduct genomic editing in many organisms, including in bacteria (Jiang *et al*., 2013), drosophila (Gratz *et al*., 2013), zebrafish (Hruscha *et al*., 2013), mice (Wang H. *et al*., 2013), *Caenorhabditis elegans* (Friedland *et al*., 2013), and *Bombyx mori* (Wang Y. *et al*., 2013). Furthermore, in terms of the development of stem cell therapy, CRISPR/Cas9 has been widely applied in the accurate and complex genetic manipulation of stem cells to enhance their reprogramming, differentiation, and other functions. Mandal *et al*. (2014) successfully silenced the expression of the genes *B2M* and *CCR5* in human hematopoietic cells using CRISPR/Cas9 with minimal off-target mutagenesis. Additionally, Wettstein *et al*. (2016) transfected two paired CRISPR single guide RNAs (sgRNAs)-Cas9 plasmids into mouse embryonic stem cells, which resulted in the knock-out of the targeted gene.

CRISPR/Cas9 provides us with a more efficient way to optimize MSC therapy for liver fibrosis. We can transform MSCs using different aspects to enhance their vitality and function, including their proliferation and differentiation ability, chemotaxis for injured tissue, and anti-inflammatory capacity. To aid in this, Schmidt *et al*. (2015) successfully built an arrayed sgRNA library that can target one critical exon of almost every protein-coding gene in humans. Therefore, by using the sgRNA library, we can find genes related to the various characteristics of MSCs, and then knockout the specific gene to optimize the MSC function.

It is also possible to take advantage of homologous recombination to overexpress targeted genes through CRISPR/Cas9. As mentioned above, genetically engineered MSCs that overexpress certain genes such as the genes for HGF and IGF-1 have therapeutic effects on liver fibrosis. However, it is

unclear how we can overexpress specific genes stably without affecting the MSC function or the expression of other genes. This problem is critical. Currently, the use of recombinant virus infection is fervent, including the use of non-integrating viruses like RNA viruses, modified lentiviruses, and integrating adenoviruses (Seah *et al*., 2015). The efficiency of virus infection and the level of gene expression are both high; however, there are still some problems with this method. Non-integrating viruses will not integrate into the cell genome; therefore, the heterologous gene will not be stably expressed as cell proliferation. Thus, integrated adenoviruses are a good vector for targeted gene overexpression. However, adenoviruses, lentiviruses, and RNA viruses are all viruses, meaning that they are associated with pathogenic risks in clinical treatments. Therefore, finding a new method is necessary.

CRISPR/Cas9 is a promising tool that may allow us to transform MSCs in order to overexpress targeted genes. Currently, our lab is performing some related experiments. We have constructed a donor vector that contains the targeted gene, and next we will transfect it with the CRISPR sgRNAs-Cas9 plasmid into MSCs. Taking advantage of homology-direct repair, targeted genes can be combined into the genomic DNA of the MSCs and stably expressed through proliferation (Fig. 3). Our goal is to obtain the targeted gene in a stably expressed cell line, which can then be used to treat liver fibrosis. However, the transfection efficiency is not high; hence, additional research is needed to improve the efficiency.

In general, CRISPR/Cas9 can be used to reform stem cells. Additionally, stem cell therapy combined with genomic editing will be a promising method for many diseases in the future.

7 Current problems and future prospects

The transplantation of MSCs for the treatment of liver fibrosis is an effective and promising method, considering the targeted migration ability, release capacity, and low immunogenicity of MSCs. MSCs can directly interact with the fibrogenic liver by differentiating into hepatocyte-like cells or by fusing with hepatocytes. Additionally, MSCs have the potential to release different growth factors and

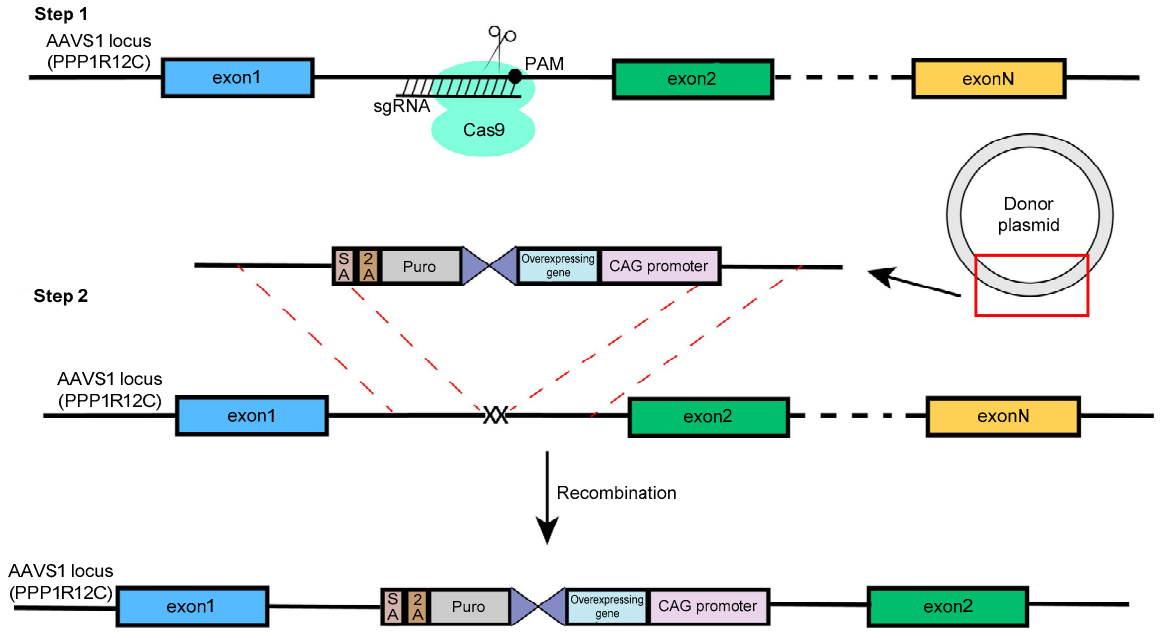

Fig. 3 Overexpressing gene in targeted site of genome through CRISPR/Cas9

The cleavage induced by CRISPR/Cas9 produces a double strand break, which will trigger cellular DNA repair processes, including non-homologous end-joining and homology-directed repairs. The AAVS1 locus is a safe harbor for insertion, and does not interfere with the expression of the inserted gene or other genes. We constructed a plasmid containing homologous arms of AAVS1 and inserted genes. Taking advantage of homology directed repair, we can insert certain genes into the specific site and obtain a stably expressed cell line

cytokines, which can regulate the microenvironment and immune system to enhance their therapeutic effects on liver fibrosis. MSCs can also be combined with gene engineering to create a new method that can obviously regress fibrogenesis, promote regeneration, and restore the liver function. Therefore, MSC therapy for liver fibrosis is an optimal choice. However, many issues with these methods still need to be resolved. For instance, several different types of MSCs exist, which each have their respective advantages and disadvantages. The isolation of BM-MSCs is strenuous and traumatic. In contrast, MSCs derived from adipose tissue-derived MSCs are abundant and easily obtained, but the therapeutic effect is inferior to that of BM-MSCs (Liu *et al*., 2015). Moreover, we still do not fully understand the mechanisms underlying the therapeutic effects of MSCs. Therefore, the oncogenic potential and the risks of using MSCs remain unknown. In addition, when combining MSCs with gene engineering, the transfection problem exists, which will require finding a better transfection condition to increase the efficiency. In general, there is still much for us to explore regarding the use of MSCs in the treatment of liver fibrosis.

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Compliance with ethics guidelines

Yang GUO, Bo CHEN, Li-jun CHEN, Chun-feng ZHANG, and Charlie XIANG declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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中文概要

题　目：间充质干细胞治疗肝纤维化的现况和前景

概　要：许多慢性肝病发展到终末阶段形成肝纤维化进而转变成肝硬化，严重威胁人们的健康。目前临床治疗肝纤维化的有效方法是肝移植，但由于供体缺乏、免疫排斥和治疗费用昂贵等诸多缺陷，这种疗法并不是一种理想的治疗途径。近些年细胞治疗研究火热，间充质干细胞作为一种来源广泛、可定向迁移和多向分化的治疗载体，在肝纤维化治疗上具有广阔的应用前景。本文对间充质干细胞治疗肝纤维化的现状进行归纳，并对其可行性、局限性及应用前景进行分析。

关键词：间充质干细胞；肝纤维化；细胞治疗