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Abstract

Progressive liver fibrosis is a major health issue for which no effective treatment is available, leading to cirrhosis and orthotopic liver transplantation. However, organ shortage is a reality. Hence, there is an urgent need to find alternative therapeutic strategies. Cellbased therapy using mesenchymal stem cells (MSCs) may represent an attractive therapeutic option, based on their immunomodulatory properties, their potential to differentiate into hepatocytes, allowing the replacement of damaged hepatocytes, their potential to promote residual hepatocytes regeneration and their capacity to inhibit hepatic stellate cell activation or induce their apoptosis, particularly via paracrine mechanisms. The current review will highlight recent findings regarding the input of MSC-based therapy for the treatment of liver fibrosis, from in vitro studies to pre-clinical and clinical trials. Several studies have shown the ability of MSCs to reduce liver fibrosis and improve liver function. Howe...

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Use of mesenchymal stem cells to treat liver fibrosis: Current situation and future prospects

Silvia Berardis, Prenali Dwisthi Sattwika, Mustapha Najimi, Etienne Marc Sokal

Silvia Berardis, Prenali Dwisthi Sattwika, Mustapha Najimi, Etienne Marc Sokal, Laboratory of Pediatric Hepatology and Cell Therapy, Institut de Recherche Expérimentale et Clinique, Cliniques Universitaires St Luc, Université Catholique de Louvain, 1200 Brussels, Belgium

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Correspondence to: Silvia Berardis, MD, Laboratory of Pediatric Hepatology and Cell Therapy, Institut de Recherche Expérimentale et Clinique, Cliniques Universitaires St Luc, Université Catholique de Louvain, Avenue Hippocrate 10, 1200 Brussels, Belgium. silvia.berardis@uclouvain.be

Telephone: +32-2-7645285

Fax: +32-2-7648909

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their immunomodulatory properties, their potential to differentiate into hepatocytes, allowing the replacement of damaged hepatocytes, their potential to promote residual hepatocytes regeneration and their capacity to inhibit hepatic stellate cell activation or induce their apoptosis, particularly *via* paracrine mechanisms. The current review will highlight recent findings regarding the input of MSC-based therapy for the treatment of liver fibrosis, from *in vitro* studies to pre-clinical and clinical trials. Several studies have shown the ability of MSCs to reduce liver fibrosis and improve liver function. However, despite these promising results, some limitations need to be considered. Future prospects will also be discussed in this review.

Key words: Liver fibrosis; Cirrhosis; Mesenchymal stem cells; Cell therapy; Hepatic stellate cells

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Core tip: Liver fibrosis is a major public health issue for which no treatment is available. Cell therapy and, in particular, mesenchymal stem cells (MSCs), represent a promising strategy, based mainly on their immunomodulatory properties and differentiation capacity. In the current review, we discuss the rationale to propose cell therapy and, in particular, MSCs to treat liver fibrosis, overview of the current knowledge in this field and highlight future prospects.

Abstract

Progressive liver fibrosis is a major health issue for which no effective treatment is available, leading to cirrhosis and orthotopic liver transplantation. However, organ shortage is a reality. Hence, there is an urgent need to find alternative therapeutic strategies. Cell-based therapy using mesenchymal stem cells (MSCs) may represent an attractive therapeutic option, based on

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LIVER FIBROSIS: A MAJOR HEALTH ISSUE

Liver fibrosis refers to the excessive accumulation of extracellular matrix into the liver parenchyma in response to chronic injury. Injuries may result from viral, autoimmune, cholestatic, toxic or metabolic disease, including nonalcoholic steatohepatitis. Chronic fibrosis progresses from fibrosis to cirrhosis characterised by septa formation and rings of scar tissue surrounding nodules of surviving hepatocytes^[1]. Epidemiological data suggest that cirrhosis affects hundreds of millions people worldwide^[1]. It represents the 14th most common cause of death in adults worldwide (resulting in 1.03 million death per year) but the fourth in central Europe^[2]. In the European population, less than 1% (approximately 0.1%) of the population is affected by cirrhosis, corresponding to 14–26 new cases per 100000 inhabitants per year or an estimated 170000 deaths per year^[3].

CLINICAL ASPECTS

Although mild fibrosis remains largely asymptomatic, its progression towards cirrhosis is a major cause of morbidity and mortality. Fibrosis and distorted vasculature lead to portal hypertension and related complications, namely upper gastrointestinal bleeding from ruptured gastro-oesophageal varices, portal hypertensive gastropathy, ascites, renal dysfunction, and hypersplenism leading to thrombocytopenia and hepatopulmonary syndrome^[4]. Furthermore, cirrhosis is associated with hepatocellular insufficiency, impaired metabolic capacity and dysfunction of other organs such as the gastrointestinal tract^[5] and kidneys^[6], as well as the cardiovascular^[7], respiratory^[8] and skeletal systems^[9]. Cirrhosis can lead to hepatocellular carcinoma^[10].

HISTOLOGY OF LIVER FIBROSIS

Following acute injury, liver parenchymal cells regenerate and replace the necrotic damaged cells. During this process, an inflammatory response is observed accompanied by limited deposition of extracellular matrix in the liver parenchyma. In the case of persistence of the injury, the regenerative capacity of parenchymal cells is impaired and dead hepatocytes are replaced by an abundant accumulation of the extracellular matrix, mainly secreted by activated hepatic stellate cells^[11]. The pattern of fibrosis is related to the pathogenic mechanism of the underlying disease. In chronic viral hepatitis, autoimmune hepatitis and chronic cholestatic disorders, the fibrotic tissue will initially be located in the periportal areas. However, in alcohol-induced liver disease, the pericentral and perisinusoidal areas represent the initial localisation of extracellular matrix deposition^[12], most likely because alcohol is mainly metabolised in these regions.

Following disease progression, the collagen fibres will progressively evolve to bridging fibrosis, leading finally

to cirrhosis. Cirrhosis is defined histologically as a diffuse process characterised by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules^[13].

In the advanced stages of fibrosis, the liver contains approximately 6 times more extracellular matrix deposition levels than a normal liver, including collagens (types I, III and IV), fibronectin, undulin, elastin, laminin, hyaluronan and proteoglycans^[11]. The accumulation of extracellular matrix in the liver parenchyma results from both increased synthesis and decreased degradation by matrix metalloproteinases.

PHYSIOPATHOLOGY OF LIVER FIBROSIS

Cellular effectors: Extracellular matrix producing cells

Extracellular matrix is mainly produced by hepatic stellate cells (HSCs), located in the space of Disse between the hepatocytes and sinusoids. Following liver injury, HSCs are “activated” and evolve to myofibroblast-like cells following paracrine and autocrine signalling. This activation is characterised by an increase in cell proliferation and extracellular matrix protein deposition, loss of vitamin A droplets and acquisition of contractile features. HSC activation has been well identified as a key event in the fibrotic response to liver injury. Proliferating activated HSCs are typically located in the regions of greatest injury. This phenomenon is preceded by an influx of inflammatory cells and is associated with extracellular matrix accumulation^[14].

Initiation represents the first activation phase and refers to early changes in gene expression and phenotype. HSCs are stimulated by paracrine signals, including exposure to lipid peroxides and products released from damaged hepatocytes as well as biochemical signals from Kupffer and endothelial cells. In the perpetuation phase, the activated phenotype is maintained, and fibrosis is generated. Autocrine as well as paracrine loops are implicated. Resolution refers either to the reversion to a quiescent phenotype or to clearance through apoptosis^[14]. At the structural level, activated HSCs lose their large vitamin A-containing lipid droplets and up-regulate the expression of cell adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), promoting the recruitment of inflammatory cells to the injured liver. The up-regulation of adhesion molecules expression has been studied *in vitro* and *in vivo*^[15]. The expression of α -smooth muscle actin is also up-regulated and the secretion of pro-inflammatory cytokines is increased^[14,16]. During fibrosis, the enhanced expression of the cytoskeletal protein alpha-smooth muscle actin (α -SMA) confers a contractile potential to HSCs, that is a determinant of increased portal resistance^[14]. High expression level of α -SMA correlates with an extent of disease progression. Some particularities have been documented as in kidney. Indeed, renal fibrosis progression (in experimental glomerulonephritis model) was enhanced in mice lacking

this protein in myofibroblasts, while tissue fibrosis was ameliorated by forced expression of α -SMA in renal interstitial myofibroblasts^[17]. These data suggest that α -SMA expression could play a role in moderating chronic organ fibrosis.

In addition to HSCs, other cellular sources contributing to extracellular matrix accumulation have been identified. These cells include portal fibroblasts (mainly implicated in biliary fibrosis)^[18], circulating fibrocytes, and bone-marrow derived cells^[19], as well as fibroblasts derived from epithelial-mesenchymal transition (EMT) of hepatocytes and bile duct epithelial cells^[20]. EMT is characterised by the loss of cell adhesion, repression of E-cadherin expression and increased cell mobility. Transforming growth factor beta (TGF β) induces the acquisition of a fibroblastoid phenotype by hepatocytes and their expression of proteins characteristic for EMT and fibrogenesis. After EMT, hepatocytes will contribute to the population of myofibroblasts and consequently, participate to fibrogenesis^[21]. This phenomenon represents an attractive target for liver fibrosis treatment.

Other cellular sources involved in fibrogenesis

Biliary progenitor cells: In biliary fibrosis, the proliferating biliary progenitor cells secrete several factors that attract and activate HSCs into proliferative and extracellular matrix-producing cells. This phenomenon is amplified by several molecules secreted by the surrounding myofibroblasts and by inflammatory cells, such as interleukin (IL)-6 and fibroblast growth factor^[22].

Liver sinusoidal endothelial cells: In perisinusoidal fibrosis, liver sinusoidal endothelial cells (LSECs) are activated and proliferate. LSECs contribute to extracellular matrix production and secrete cytokines and growth factors [such as TGF β and platelet-derived growth factor (PDGF)] that activate HSCs as well as factors contributing to intrahepatic vasoconstriction. Myofibroblasts activate LSECs *via* the secretion of angiogenic factors such as vascular endothelial growth factor (VEGF) and angiopoietin-1^[23].

Inflammatory cells: CD4⁺T cells with Th2 polarization also promote fibrogenesis. These cells secrete IL-4 and IL-13, which can stimulate the differentiation of fibrogenic myeloid cells and macrophages^[24]. Th17 cells, induced by TGF- β 1 and IL-6, secrete IL-17A, which activates myofibroblasts directly and indirectly by stimulating TGF- β 1 release by inflammatory cells^[25]. Regulatory T cells can either favour or inhibit fibrogenesis by secreting TGF- β 1 (profibrotic) or IL-10 (anti-fibrotic)^[22]. CD4⁺ Th1 cells have an anti-fibrotic effect^[22].

NK cells can reduce fibrosis by killing activated HSCs and by producing interferon γ ^[26]. Monocytes play a key role in inflammation and fibrosis. They are precursors of fibrocytes, macrophages and dendritic cells^[27]. Macrophages are fibrogenic during fibrosis

progression and fibrolytic during its reversal^[22].

Key factors

Factors involved in HSC proliferation: PDGF- β signaling is one of the best characterised pathways involved in the HSC activation process. After PDGF- β binding to its receptor, several intracellular pathways are activated (including the Ras-MAPK, PI3K-AKT/PKB and PKC pathways) supporting cellular proliferation. In early HSC activation, a rapid induction of PDGF- β receptor is observed^[28,29].

Even if PDGF is the most potent mitogen towards HSC, other growth factors such as TGF α , epidermal growth factor and VEGF can also stimulate HSC proliferation^[30].

Fibrogenic molecules: TGF β 1 is derived from both autocrine and paracrine sources and represents the most potent fibrogenic cytokine in the liver. TGF β 1 recruits Smad2/3, leading to its phosphorylation and stimulation of fibrogenic gene expression^[31]. Leptin also has a pro-fibrotic action through suppression of peroxisome proliferator-activated receptor- γ (PPAR γ)^[32]. Connective tissue growth factor, secreted by HSCs, is also fibrogenic.

Chemokines: The migration of HSCs to the site of injury is promoted by several chemokines (such as CCL5) secreted by HSCs which express the respective receptors^[30].

Neurotransmitters: Following chronic liver injury, the local neuroendocrine system is up-regulated, and HSCs express different receptors, including those regulating cannabinoid signalling, and secrete endogenous cannabinoid. The activation of CB1 receptor is pro-fibrogenic, but the CB2 receptor is anti-fibrotic. Opioid and serotonin pathways, as well as thyroid hormones, have a pro-fibrotic effect^[30].

Inflammatory pathways: Finally, inflammatory pathways are also involved in the HSC activation process. HSCs secrete inflammatory chemokines and interact directly with immune cells through the expression of adhesion molecules, including ICAM-1 and VCAM-1^[33]. Moreover, apoptotic hepatocyte DNA can interact with Toll-like receptor 9 expressed on HSCs, repressing HSC migration and increasing collagen production^[34].

CURRENT THERAPEUTIC APPROACHES

Anti-fibrotic drugs

Liver fibrosis is a dynamic process that may undergo reversal^[35]. The best aim of anti-fibrotic therapy is to eliminate the underlying disease process. For chronic viral hepatitis, anti-viral treatment efficacy has been recently documented to improve liver fibrosis. In the context of chronic hepatitis B, prevention of developing cirrhosis and fibrosis regression has been demonstrated

for entecavir and tenofovir, two third-generation nucleotide analogues. Chang *et al.*^[36] firstly documented histological improvements and reversal of fibrosis/cirrhosis in patients with chronic hepatitis B treated with entecavir for a period of at least 3 years. More recently, Marcellin and colleagues reported regression of fibrosis and cirrhosis among patients with chronic hepatitis B infection treated for 5 years with tenofovir disoproxil fumarate. Seventy-four percent of the patients with cirrhosis were no longer cirrhotic at year 5^[37]. With respect to chronic hepatitis C, significant regression of fibrosis has been shown among patients presenting mild-to-moderate fibrosis after treatment with Peginterferon alpha-2a or alpha-2b plus ribavirin during 24 or 48 wk, depending on genotype^[38]. However, beyond the strict enrolment criteria of the studies, the long term efficacy and safety of these anti-viral treatments have to be confirmed with older patients presenting several comorbidities and treated with other medications.

In the case of impossibility to treat the underlying process, anti-fibrotic therapy would be ideal. Currently, there is no anti-fibrotic drugs available in a clinical setting^[1,39,40]. Although specific agents are under investigation, none has been approved as anti-fibrotic therapy.

The use of anti-fibrotic drugs has been reported in preclinical and clinical studies. This approach targets several aims^[41-43], such as: (1) downregulation of HSC activation^[44-51]; (2) neutralisation of the proliferative, fibrogenic, and contractile responses of HSCs^[52-58]; (3) promotion of HSC apoptosis^[59,60]; (4) promotion of matrix degradation^[61,62]; (5) reduction of inflammation^[63-68]; and (6) inhibition of collagen I cross-linking^[69], as shown in Table 1. Overall, anti-fibrotic agents have been shown to be highly effective in animal models and represent potential anti-fibrotic drugs. Several anti-fibrotic agents that have been transitioned to clinical studies are PPAR- γ agonist^[45,46], interferon γ (IFN- γ)^[48,49], angiotensin II antagonist^[55], colchicine^[57], interleukin 10 (IL-10)^[64], anti-tumour necrosis factor alpha (TNF- α)^[66], ursodeoxycolic acid^[68], and antioxidants^[51].

Given the supportive preclinical data, however, the data in human are mixed. Moreover, most of these studies were performed in small numbers of patients over a short period of time, but fibrosis is a long lasting, slowly progressive event. Human studies have examined the effect of PPAR- γ agonist^[45] and IFN- γ ^[48] in patients with liver fibrosis. In addition to the promising results in small-scale studies^[45,48], longer and larger studies have failed to demonstrate any beneficial effect^[46,49].

Compared with preclinical studies, clinical studies of several anti-fibrotic agents have been shown to yield dramatically different results^[51,57,64] that may be due to several reasons. In animal models, anti-fibrotic drugs were investigated against the development of fibrosis. On the other hand, in real clinical settings, and in most clinical trials, patients had advanced fibrosis. The potential of collagen degradation also differs between

the rodent model and humans because of difference in the cross-linking of ECM. Compared with human fibrosis, which requires years to develop, fibrosis in rodents occurs over weeks or months and contains less chemical cross linking. In addition, differences in the pharmacokinetics of anti-fibrotic drugs between animal models and humans contribute to the different results^[42].

Furthermore, a crucial issue that remains to be investigated is how to translate the preclinical evidence of other potential anti-fibrotic agents into a benefit for patients. In general, the development of anti-fibrotic drugs in humans meets several obstacles^[41]. First, liver fibrosis is a slowly progressive event, most likely requiring several years of follow up to establish efficacy. Second, the gold-standard tool to evaluate fibrosis remains to be histology. Patients and physicians may be reluctant to perform repeated biopsies due to possible adverse events^[70]. Moreover, sampling error in liver biopsy and inter-observer variability may interfere with the results^[71]. For all of these reasons, noninvasive diagnostic tools would be highly desirable, ranging from physical examination, laboratory investigation, radiographic testing, to specific serum markers^[42]. Transient elastography has also been developed to measure liver stiffness using ultrasound principles^[72].

Orthotopic liver transplantation

Currently, orthotopic liver transplantation (OLT) remains the most effective treatment for this condition. Over time, the survival rate after OLT has progressively increased, reaching currently 83% after 1 year. Liver cirrhosis remains the main indication for OLT in Europe (59%) (EASL 2013). In children, a survival rate above 80% has been reported 10 years after OLT^[73]. However, over the last 10 years, the annual number of OLTs has stopped growing because organ donation has not kept up with demand, leading to increased mortality and morbidity^[74]. Moreover, some limitations such as operative risk, post-transplant rejection, recurrence of the pre-existing liver disease and high costs must be considered^[75]. Moreover, fibrosis often develops in the liver grafts as early as one year after transplantation. One year after paediatric OLT, portal fibrosis is present in 31% of liver grafts^[76].

The prevalence of fibrosis increases to 65% five years after OLT and to 71% at 10 years, with 29% of severe fibrosis^[77].

Cell-based therapy

Cell-based therapy has been proposed as a less invasive potential alternative to OLT. The rationale is mainly based on the ability of several cells to: (1) improve the hepatic inflammatory microenvironment; (2) inhibit the activation or induce apoptosis of HSCs; (3) replace damaged hepatocytes; and (4) promote the regeneration of residual hepatocytes.

Isolated hepatocytes: Hepatocyte transplantation has

Table 1 Preclinical and clinical studies representing the development of anti-fibrotic strategies

Antifibrotic drug	Preclinical/clinical results	Disease model	Ref.
Downregulation of hepatic stellate cell (HSC) activation			
Peroxisomal proliferator-activated receptor gamma agonist (pioglitazone)	Inhibition of HSC activation and amelioration of hepatocyte necroinflammation in rats after 8 wk	Carbon tetrachloride (CCl ₄)-induced liver fibrosis	[44]
	Reduction of steatosis, but not fibrosis compared to placebo, in patients with NASH after 6 mo (26 pioglitazone; 21 placebo)	Nonalcoholic steatohepatitis (NASH)	[45]
	No benefit of pioglitazone over placebo in term of steatosis and fibrosis in patients with NASH after 96 wk (80 pioglitazone; 83 placebo)	NASH	[46]
Interferon gamma (IFN- γ)	Inhibition of the activation of HSC and extracellular matrix production	CCl ₄ -induced liver fibrosis	[47]
	Improvement of fibrosis scores in patients with chronic hepatitis B virus (HBV) infection after 9 mo (54 IFN- γ ; 29 control)	Chronic HBV infection	[48]
Antioxidant (vitamin E)	No reversion of fibrosis in patients with advanced liver disease after 1 yr (IFN- γ 1b 100 μ g 169; IFN- γ 1b 200 μ g 157; placebo 162)	Chronic hepatitis C virus (HCV) infection	[49]
	Protective effects against liver damage and cirrhosis in rats	CCl ₄ -induced liver fibrosis	[50]
	No benefit on liver function tests in patients with mild to moderate alcoholic hepatitis after 1 yr (25 vitamin E, 26 placebo)	Alcoholic hepatitis	[51]
Neutralization of proliferative, fibrogenic and contractile responses of HSC			
Anti-transforming growth factor beta (TGF- β)	Suppression of fibrosis in rats after 3 wk	Dimethylnitrosamine-induced liver fibrosis	[52]
Short interference RNA	Inhibition of the expression of TGF- β 1 and attenuation of liver fibrosis in rats	High-fat diet and CCl ₄ -induced model of liver fibrosis	[58]
Endothelin antagonist	Nonpeptide endothelin-A receptor antagonist, LU 135252, reduced collagen accumulation in rats after 6 wk	Secondary biliary fibrosis	[53]
Angiotensin system inhibitor	Olmesartan, an angiotensin II type 1 receptor blocker, decreased expression of collagen genes and attenuated liver fibrosis in rats after 15 wk	Methionine-choline-deficient rat model of NASH	[54]
	Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor-1 blocker (ARB) did not retard the progression of liver fibrosis in patients with advanced liver fibrosis after 3.5 yr (66 ACEi/ARB, 126 non-ACEi/ARB, 343 no antihypertensive medication)	Chronic hepatitis C	[55]
Colchicine	Colchicine and colchicine (metabolite of colchicine) prevented the increase in collagen synthesis and increased the intracellular degradation of collagen rats	CCl ₄ -induced liver fibrosis	[56]
	Colchicine improved fibrosis marker expression, but not histological finding, in patients with hepatic fibrosis after 12 mo (21 colchicine; 17 control)	Liver fibrosis of various etiologies	[57]
Promotion of HSC apoptosis			
Gliotoxin	Morphologic alterations typical of HSC apoptosis <i>in vitro</i> (activated rat and human HSCs) and reduction of the number of activated HSCs in rats	CCl ₄ -induced liver fibrosis	[59]
Sulfasalazine	Induction of activated HSC apoptosis, by inhibiting nuclear factor kappa B-dependent gene transcription, both <i>in vitro</i> (activated rat and human HSC) and <i>in vivo</i>	CCl ₄ -induced liver fibrosis	[60]
Promotion of matrix degradation			
Matrix metalloproteinase (MMP) inducer	Urokinase-type plasminogen activator, an initiator of the matrix proteolysis cascade, induced collagenase expression and reversal of fibrosis rats	CCl ₄ -induced liver fibrosis	[61]
Tissue inhibitor of matrix metalloproteinase (TIMP) inhibitor	Polaprezinc, a zinc-carnosine chelate compound, attenuated fibrosis by inhibiting TIMP expression during a later phase, thus promoting fibrinolysis, in mice after 10 wk	Dietary methionine and choline deficient (MCD)-induced NASH	[62]
Reduce inflammation			
Interleukin 10	Inhibition of HSC activation and decrease of the expression of TGF- β 1, MMP-2, and TIMP-1 in rats	CCl ₄ -induced liver fibrosis	[63]
	Anti-inflammatory effect, but increased HCV viral burden <i>via</i> alterations in immunologic viral surveillance, in patients (30 subjects for 3-dose trial)	Chronic hepatitis C	[64]
Anti-tumour necrosis factor- α	Infliximab decreased necrosis, inflammation, and fibrosis in rats	Dietary MCD-induced NASH	[65]
	Infliximab improved Maddrey's score in patients after 28 d (20 subjects)	Alcoholic hepatitis	[66]
Ursodeoxycholic acid (UDCA)	Reversion of liver damage in rats	CCl ₄ -induced liver fibrosis	[67]
	Reduction of periportal necroinflammation and, if initiated at the earlier stages I-II of the disease, delay of the progression of histologic stage in patients after 2 yr (200 UDCA, 167 placebo)	Primary biliary cirrhosis	[68]

Inhibition of collagen I cross-linking Anti-Lysyl oxidase-like-2	Reduction of liver fibrosis, decrease in the number of myofibroblasts and lower p-Smad3 signal	CCL4-induced liver fibrosis	[69]
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provided the proof-of-concept that cell therapy could be used to treat some liver diseases such as metabolic disorders and acute liver failure^[78-80]. A decrease in liver fibrosis and restoration of phospholipid secretion were also observed in a mouse model of progressive familial intrahepatic cholestasis type III after hepatocyte transplantation^[81]. The feasibility and safety of this technique are supported by the numerous clinical trials performed with hepatocytes.

However, the efficacy of hepatocyte transplantation seems to have a limited durability, with a progressive decrease in the observed effects^[82]. Moreover, hepatocytes are poorly resistant to cryopreservation, which can be limitative as fresh hepatocytes are not always available^[83]. Moreover, hepatocytes are rare materials and cannot be expanded *in vitro*. Therefore, finding a new and readily available cell source was primordial.

Stem/progenitor cells: Stem/progenitor cells have progressively emerged as an attractive alternative to hepatocytes in the context of cell-based therapy. Stem/progenitor cells can proliferate in culture, are resistant to cryopreservation and have three interesting characteristics: plasticity, migration and engraftment.

Embryonic stem cells and induced pluripotent stem cells

Pluripotent embryonic stem cells (ESCs) are derived from the inner cell mass of blastocyst embryos. Several *in vivo* studies have revealed the potency of ESCs to differentiate into hepatocyte-like cells and reduce induced liver fibrosis. Mouse ESC-derived green fluorescent protein⁺ cells injected into CCl₄-injured mice^[84], undifferentiated mouse ESCs injected into CCl₄-treated mice^[85,86], and human differentiated ESCs transplanted into CCl₄-injured SCID mice^[87] showed hepatic differentiation, integrated into the liver parenchyma, and reduced liver fibrosis without evidence of tumorigenicity. The result of these studies should be further confirmed, however, because teratoma formation was observed in other studies. Splenic teratomas were formed in mice with induced hepatocellular injury 35 d after the administration of undifferentiated mouse ESCs and 60 d after the transplantation of mouse ESC-derived alpha-fetoprotein-producing cells^[88]. Injection of undifferentiated mouse ESCs into the spleen of immunosuppressed nude mice also gave rise to splenic teratomas^[89]. Although ESCs have the ability to differentiate into hepatocytes, their malignant potential and ethical issues remain the major obstacles to develop ESC treatment in clinical settings. Moreover, there may be genetic/epigenetic changes and immune rejection problems when ESCs are transplanted, due to their allogeneic nature^[90].

To avoid these issues, new technologies have enabled tissue cells to become induced pluripotent stem cells (iPSCs). Along with the development in the field of stem cell reprogramming, iPSCs represent promising stem cells in cell-based liver therapy. Song and colleagues provided evidence of hepatocyte differentiation of human iPSCs for the first time^[91]. At various differentiation stages, human iPSC-derived hepatic cells from different organs repopulated the liver of mice with induced liver cirrhosis. The engraftment potential of differentiated iPSCs was comparable to that of human hepatocytes and was higher than that of undifferentiated human ESCs or iPSCs^[92]. iPSCs provide an unlimited source for regenerative medicine since patient-specific cells produce no ethical issue and problem of cell rejection. Despite the promise of iPSCs, the potential risk of genetic manipulation and mutagenesis should be considered before any clinical application. Other issues that remain to be addressed in recruiting iPSCs are (1) the source of iPSCs, whether patient-specific iPSCs should be derived from the diseased tissue portion; (2) the directed hepatic differentiation protocol; and (3) extensive characterisation of hepatic differentiation^[93].

Mesenchymal stem cells

Mesenchymal stem cells (MSCs) have extensively been investigated as potential therapeutic options for the treatment of various degenerative diseases and immune disorders, mainly because of their differentiation potential and immunoregulatory properties^[94]. The MSC secretion profile also represents an attractive property, as MSCs are known to secrete several anti-fibrotic molecules such as hepatocyte growth factor (HGF)^[95]. Compared with embryonic stem cells, MSCs do not cause ethical problems and have a safer profile in terms of oncogenicity^[96].

The different properties of MSCs make them an attractive therapeutic tool in the context of liver fibrosis, a topic that will be discussed in the following paragraphs.

PROPERTIES OF MSCs AND THEIR POTENTIAL USE IN REGENERATIVE MEDICINE

General features

In 2006, the International Society for Cellular Therapy proposed minimal criteria to define human MSCs^[97]. First, MSCs must be plastic-adherent when maintained under standard culture conditions. Second, $\geq 95\%$ of the MSC population must express CD105, CD73 and CD90, and lack the expression ($\leq 2\%$ positive) of CD45, CD34, CD14 or CD11b, CD79 α or CD19 and HLA class II

surface molecules. Third, MSCs must differentiate into osteoblasts, adipocytes and chondroblasts under standard *in vitro* differentiating conditions^[97].

MSCs are spindle-shaped fibroblast-like cells and have the ability of self-renewal. They can be isolated and expanded with high efficiency^[98].

Differentiation potential

The high degree of plasticity of MSCs has widely been described during the last decade^[99-102].

MSCs have been shown to differentiate into various mesodermal cell lineages (including adipocytes, osteoblasts, chondroblasts, myocytes and cardiomyocytes) and into non-mesodermal cells (such as hepatocytes and neurons), depending on their microenvironment^[103].

In particular, *in vitro* models have provided evidence of the differentiation potential of MSCs into hepatocyte-like cells with functional properties such as albumin and urea production, glycogen storage, LDL uptake and phenobarbital-induced cytochrome p450 expression^[104,105].

Moreover, the *in vivo* hepatic differentiation of MSCs has been demonstrated in rats^[106,107], mice^[108], sheep^[109] and humans^[110].

In comparison with extra-hepatic MSCs, adult-derived human liver stem/progenitor cell, a subtype of MSCs derived from the adult human liver, has a preferential hepatocyte differentiation pattern^[111,112].

This hepatic differentiation potential is essential for MSC-based therapies in the context of chronic liver diseases in which the injured hepatocytes cannot regenerate^[74].

Immunomodulatory properties

The ability of MSCs to modulate the immune response has attracted great interest, in the context of cell-based therapy and allogeneic transplantation.

It is well known that MSCs suppress the activity of cells from both adaptive and innate immunity. Indeed, MSCs can inhibit the proliferation of CD8⁺ cytotoxic lymphocytes and increase the relative proportion of CD4⁺ T helper-2 lymphocytes and CD4⁺ regulatory T lymphocytes^[113,114]. This effect on T lymphocytes indirectly suppresses the function of B lymphocytes because their activation is mainly T cell dependent. Moreover, MSCs can modulate B cell functions by inhibiting their proliferation, differentiation into antibody-secreting cells and chemotaxis. Soluble factors such as transforming growth factor β 1, hepatocyte growth factor, prostaglandin E2 and indoleamine 2,3-dioxygenase seem to be implicated in this immunosuppressive activity^[115].

MSCs also exert inhibitory effects on monocytes, dendritic cells, macrophages and NK cells, which belong to the innate immune system. MSCs inhibit the maturation of monocytes into dendritic cells, which play a role in antigen presentation to naïve T-cells. MSCs also inhibit the secretion of TNF- α , INF- γ and interleukin-12 by dendritic cells and increase their secretion of IL-10, reducing their proinflammatory potential^[116,117]. This

inhibitory effect exerted by MSCs seems to be mediated by soluble factors, including prostaglandin E2 (PGE2)^[118]. MSCs can also suppress NK cell's proliferation, cytolytic activity and secretion of cytokines. The role of PGE2 and indoleamine 2,3-dioxygenase has been established^[119].

Because of all these characteristics, MSCs have generated a great interest for their potential use in regenerative medicine.

In summary, although having less potential to differentiate into endodermal cells compared with ESCs and iPSCs, MSCs can be readily obtained and expanded into large quantities. Moreover, MSCs are resistant to cryopreservation and maintain a stable phenotype following passages in culture^[120]. Furthermore, the use of MSCs sidesteps many obstacles for conducting human trials, such as ethical concerns, the risk of rejection, and teratoma formation. Considering the unrelieved concerns regarding safety and efficacy, there has not been a clinical trial using human ESCs and iPSC-derived hepatocytes for liver regeneration.

Homing and engraftment

MSCs have the potential to migrate to the injured site and thereafter to engraft into the concerned organ. This involves their ability to migrate across the endothelial cells and to integrate the organ.

It is well known that injured tissues express several receptors and ligands (such as CXCR4 and SDF-1) that facilitate the migration of MSCs to the damaged sites. Furthermore, chemokines are released following injury, creating a gradient followed by MSCs^[121]. This represents a key mediator of the trafficking of MSCs to the site of injury. Finally, MSCs also express some integrins, selectins and chemokine receptors involved in the adhesion and migration of leucocytes^[122,123].

The advantage of this property is that MSCs can participate in liver regeneration and ensure continued delivery of trophic signal molecules. However, follow-up studies are necessary to assess the long-term engraftment rate of MSCs.

Therapeutic significance of the MSC secretome

Soluble factors secreted by MSCs have been described to play an important role in liver regeneration and to protect hepatocytes from cell death. It has been demonstrated that bone marrow MSC conditioned medium has anti-apoptotic and pro-mitotic effects on cultured hepatocytes. Moreover, systemic infusion of MSC conditioned medium could inhibit hepatocyte cell death and enhance liver regeneration *in vivo*, in a D-galactosamine-induced rat model of acute liver injury^[124]. Zhang and colleagues demonstrated that human umbilical cord matrix stem cells provide a significant survival benefit in mice with CCl₄-induced acute liver failure, through paracrine effects, by stimulating endogenous liver regeneration^[125].

In addition to liver regeneration, the MSC secretome has also been described to have anti-fibrotic properties. Li *et al.*^[126] demonstrated that transplantation of exosomes

derived from human umbilical cord MSCs could alleviate CCl₄-induced liver fibrosis by inhibiting EMT and by protecting hepatocytes.

MSC-BASED THERAPY FOR LIVER FIBROSIS TREATMENT: FROM *IN VITRO* STUDIES TO CLINICAL TRIALS

Over the past few years, an increasing number of studies have evaluated the anti-fibrotic potential of MSCs. *In vivo* studies have highlighted the ability of MSCs to reduce liver fibrosis in animal models. *In vitro* studies have been aimed to elucidate the underlying mechanisms by which MSC could modulate HSC activation. Finally, clinical trials have evaluated the efficiency of MSC transplantation for the treatment of liver fibrosis in humans.

Preclinical studies

Several *in vivo* studies were performed to evaluate the therapeutic potential of mesenchymal stem cells in the context of liver fibrosis (Table 2)^[127-135].

In most of the studies, liver fibrosis was induced by intraperitoneal or subcutaneous injection of CCl₄. This model has the advantage of being the best characterized model with respect to histological, biochemical, cellular and molecular changes associated with the development of liver fibrosis. Moreover, it can reproduce the pattern of most of the diseases observed in human fibrosis. However, this model has some limitations. First, it is not a suitable model to study all types of liver fibrosis, such as biliary fibrosis. Second, it cannot provide a perfect simulation of a human disease because there are large species differences in immune reactions, gene expression/regulation, and metabolic, pharmacological and tissue responses^[136].

The most studied MSCs are those from the bone marrow. These cells have been reported to be beneficial in the prevention of pulmonary fibrotic lesions^[137]. However, aspiration of the bone marrow remains an invasive procedure. The bleeding tendency of cirrhotic patients and their general condition may represent an obstacle for autologous cell transplantation.

Alternative sources of MSCs such as adipose tissue and umbilical blood cord have subsequently been proposed but the number of studies in the context of liver fibrosis treatment remains limited, such as studies using human MSCs in animal models. Most of the cell sources used in the *in vivo* studies are murine MSCs. To our knowledge, tissue based MSCs and bone marrow-derived MSCs have not been compared in terms of efficacy for liver fibrosis treatment until now. The beneficial effects were observed regardless of the origin of MSCs, even if the superiority in terms of immunomodulation has been demonstrated *in vitro* for adipose tissue-derived MSCs in comparison with bone marrow-derived MSCs^[138].

The results of the *in vivo* studies are promising because they report a decrease in the liver fibrosis with frequent improvement of hepatic functions. Most of the time, these results are observed 4 wk after cell infusion. Long-term studies would be of great interest to evaluate whether the observed anti-fibrotic effect persists over time. However, the CCl₄ injections need to be continued after MSC injection to avoid a regression of liver fibrosis. This represents an obstacle to long-term studies, because animals can hardly support CCl₄ injections over a long period of time. In addition to an improvement in liver fibrosis and liver function, one study reported an improvement in liver microcirculation after MSC injection^[128]. In two other studies, the decrease in the collagen deposition was correlated to a decrease in α -SMA expression, a classical marker of activated stellate cells^[133,135].

In vivo studies highlight the controversy that remains concerning the exact mechanisms by which MSCs exert their beneficial effect. Indeed, some studies have mentioned the differentiation of MSCs into hepatocyte-like cells^[127,131] and/or the expression of metalloproteinases by MSCs^[131,132,135]. The promotion of hepatocyte proliferation and modulation of inflammation have also been proposed^[130].

The question of the ideal route of MSC administration remains one of the main unsolved issues regarding efficient injection of MSCs. Even if the tail vein seems to be the most often used administration route in animals, the portal vein^[128,131] and intrahepatic injections^[129] also seem to be efficient. The optimal doses of cells also need to be evaluated because there are significant variations among studies in terms of the number of cells injected per animal.

In vitro studies

As mentioned above, following liver injury, hepatic stellate cells (HSCs) are activated into proliferative, α -smooth muscle actin positive, myofibroblast-like and extracellular matrix-producing cells^[14]. Hence, activated HSCs represent an attractive target for antifibrotic therapy.

Several *in vitro* studies have demonstrated the ability of MSCs to modulate HSC activation indirectly *via* paracrine mechanisms and directly through cell-cell contacts. The use of *in vitro* models is supported by the ability of HSC activation to be mimicked *in vitro*, when HSCs are in contact with the plastic culture dishes^[14].

Paracrine mechanisms: Using indirect co-culture systems, Parekkadan *et al.*^[139] showed that human bone marrow-derived MSCs could inhibit collagen synthesis in activated HSCs from rats and, to a lesser extent, in immortalized human HSCs, as demonstrated by a significant reduction in the procollagen type I C-peptide secretion level. Moreover, MSCs could inhibit HSC's proliferation and induce their apoptosis, even if HSCs did not revert to a quiescent state. The underlying

Table 2 *In vivo* studies using mesenchymal stem cells to treat liver fibrosis

Species	Fibrosis induction	Administration route	MSC source	Number of cells injected/ animal	Results	Anti-fibrotic mechanisms proposed	Ref.
Rats	CCl ₄ IP	Tail vein	Human umbilical cord blood	1 × 10 ⁶	Liver fibrosis alleviated 4 wk post-infusion Improvement of liver function	Differentiation into hepatocyte-like cells	[127]
Rats	CCl ₄ IP	Portal vein	Rat adipose tissue	2 × 10 ⁶	Improvement of liver functional tests, histological findings and microcirculation 6 wk post-infusion	Not mentioned	[128]
Mice	CCl ₄ IP	Intrahepatic	Murine bone marrow	1 × 10 ⁶	Reduced fibrosis and apoptosis 30 d post-infusion Improvement of liver function	Not mentioned	[129]
Mice	CCl ₄ IP	Tail vein	Murine bone marrow	1 × 10 ⁶	Thinner fibrotic areas and decreased collagen depositions 4 wk post-infusion Improvement of liver function	Promotion of hepatocyte proliferation and modulation of inflammation	[130]
Rats	CCl ₄ SC	Portal vein	Human bone marrow	1 × 10 ⁶	Reduced fibrosis 4 wk post-infusion Improvement of liver function	Differentiation into hepatocyte-like cells expression of MMPs by MSCs	[131]
Mice	CCl ₄ IP	Tail vein	Murine bone marrow	1 × 10 ⁶	Decrease in liver fibrosis 4 wk after transplantation	Increased expression of MMPs	[132]
Rats	CCl ₄ SC/DMN IP	Intravenous	Rat bone marrow	3 × 10 ⁶	Decrease in collagen deposition and of α -SMA expression Improvement of liver function	Not mentioned	[133]
Rats	CCl ₄ SC	Tail vein	Rat bone marrow	3 × 10 ⁶	Decrease in collagen deposition Elevation of serum albumin	Not mentioned	[134]
Mice	CCl ₄ IP	Tail vein	Human bone marrow	5 × 10 ⁵	Reduction in fibrosis 4 wk after cell infusion	Enhanced expression of MMP-9 and decreased expression of α -SMA, TNF α and TGF β	[135]

MSC: Mesenchymal stem cell; DMN: Dimethylnitrosamine; MMP: Matrix metalloproteinase; α -SMA: Alpha-smooth muscle actin; TNF α : Tumour necrosis factor- α ; TGF β : Transforming growth factor beta.

mechanisms in the modulation of HSC activity by MSCs were attributed to IL-10, TNF α and HGF. IL-10 and TNF α secretion by MSCs seemed to inhibit synergistically the collagen secretion and the proliferation of HSCs but MSC-derived HGF induced apoptosis in activated HSCs, as demonstrated by antibody-neutralisation studies.

Adipose tissue derived human MSCs could also indirectly inhibit murine HSC proliferation. This growth inhibition is partially mediated by TGF- β 3 and HGF, which are secreted by MSCs. Neutralisation of both cytokines synergistically decreased the percentage of cells in the G0/G1 cell cycle phase. A decrease in the phosphorylation of extracellular signal-regulated kinase 1/2 by MSCs seemed to be partially involved in the suppressive effect of MSCs on HSCs. Gene expression of collagen type I and III was also inhibited by MSCs^[140].

NGF released from human bone marrow-derived MSCs may also represent an important paracrine loop by which human HSC activation can be modulated. Using indirect co-culture systems, Lin and colleagues demonstrated that NGF could inhibit HSC proliferation and promote their apoptosis. The same effect was reproduced using recombinant NGF. NF- κ B and its target gene, Bcl-xl, seem to participate in the regulation of this process^[141].

Cell-cell contacts: Other studies have evaluated the

effects of direct interplay and juxtacrine signaling between MSCs and HSCs.

Rat bone marrow-derived MSCs were shown to significantly inhibit rat HSC proliferation and reduce their α -SMA expression level, through a cell-cell contact mode. The Notch pathway, known to induce cell cycle arrest, is activated following MSC-HSC contact. This signalling pathway may participate in the inhibition of HSC proliferation. In addition, the PI3k/Akt pathway seems to be involved in the growth inhibition of HSCs by the Notch pathway^[142].

Human bone marrow-derived MSCs were also shown to inhibit the proliferation and activation of HSCs (LX-2 cell line) through cell-cell contact and through the secretion of HGF. This HSC modulation is mediated by an inhibition of the TLR4/NF- κ B signaling pathway^[143].

Taken together, these studies shed light on new insights regarding the mechanisms responsible for the anti-fibrotic effects of MSCs.

Clinical trials

Over the past few years, nine clinical trials using human MSCs to treat patients presenting liver fibrosis have been published (Table 3)^[144-152].

The endpoints of the studies were to evaluate the safety and efficacy of bone marrow and umbilical cord MSCs transplantation. The cells were mostly infused

Table 3 Clinical trials using mesenchymal stem cell to treat liver fibrosis

Cell source	Administration route	Number of cells infused	Patient population	Number of patients	Follow up period	Endpoints	Efficacy	Ref.
Umbilical cord	Intravenous	5×10^5 /kg, 3 times	Chronic hepatitis B	30 treatment 15 control	1 yr	Safety/efficacy	Improvement of liver function and MELD score Reduced ascites	[144]
Umbilical cord	Intravenous	5×10^5 /kg, 3 times	Chronic hepatitis B	24 treatment 19 control	48 or 72 wk	Safety/efficacy	Improvement of liver function and MELD score Increased survival rates	[145]
Umbilical cord	Intravenous	5×10^5 /kg, 3 times	Primary biliary cirrhosis	7	48 wk	Safety/efficacy	Decrease in serum alkaline phosphatase and γ -glutamyltransferase levels Alleviation of fatigue and pruritus Decrease of ascites	[146]
Bone marrow (autologous)	Intravenous	30×10^6 /patient	3 cryptogenic 1 autoimmune hepatitis	4	1 yr	Safety/efficacy	Improvement of MELD score	[147]
Bone marrow (autologous)	Intravenous (peripheral vein or portal vein)	30×10^6 - 50×10^6 /patient	4 chronic hepatitis B 1 chronic hepatitis C 1 alcoholic cirrhosis 2 cryptogenic	8	24 wk	Safety/efficacy	Improvement of liver function and MELD score	[148]
Bone marrow (autologous)	Hepatic artery	3.4×10^8 /patient	Chronic hepatitis B	53 treatment 105 control	192 wk	Safety/efficacy	Improvement of Alb, TBIL, PT and MELD score	[149]
Bone marrow (autologous)	Intravenous	1×10^6 /kg	Chronic hepatitis C	15 treatment 10 control	6 mo	Efficacy	Improvement of liver function and MELD score	[150]
Bone marrow (autologous)	Intrasplenic	10×10^6 /patient	Chronic hepatitis C	20	6 mo	Safety/efficacy	Decrease of TBIL, AST, ALT, PT and INR Increase of the albumin levels	[151]
Bone marrow (autologous)	Hepatic artery	5×10^7 /patient, twice	Alcoholic cirrhosis	12	12 wk	Efficacy	Histological improvements Improvement of Child-Pugh score Decrease of TGF- β 1, collagen type 1 and α -SMA	[152]

MELD: Model for end-stage liver disease; Alb: Albumin; TBIL: Total bilirubin; PT: Prothrombin time; TGF- β : Transforming growth factor beta; α -SMA: Alpha-smooth muscle actin; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; INR: International normalised ratio.

intravenously even if two studies reported infusions *via* the hepatic artery^[149,152]. Additionally, in one study, the cells were even injected into the spleen^[151]. There is a great variation in the number of cells infused per patient and in the frequency of injection in the different trials. The results of the studies seemed promising in terms of improvement of liver function and model for end-stage liver disease score. This score is based on objective variables (INR, serum albumin and serum bilirubin) and has been validated as a predictor of survival among patients with advanced liver disease^[153].

However, there is a lack of data regarding the evaluation of liver histology after cell transplantation, except in one study reporting histological improvements^[152].

Globally, the size of the samples is small in most studies and there is a lack of controls in five studies. The follow up period is quite short, except in one study with a 192-wk follow up. We believe that it is crucial to evaluate the long term efficacy, prognosis and safety before proposing this therapy routinely in the clinical practice. Using other types of MSCs and other patient populations could also be of great interest to evaluate the best therapeutic option for each pathology.

The use of MSCs in clinical practice is currently

hindered by the incapacity to monitor the transplanted cells in the patients and by the lack of standardised transplantation protocols. Standardised protocols providing information concerning the timing of cell injection following the stage of liver fibrosis, number of cells and administration route would be useful.

Only randomised controlled clinical trials can assess the potential clinical benefit of MSCs for patients affected by liver fibrosis. According to the clinical trials Website of the United States sponsored by the National Institutes of Health (<http://clinicaltrials.gov>), approximately 24 clinical trials are currently ongoing.

FUTURE PROSPECTS

MSCs may represent a clinically relevant solution for the treatment of liver fibrosis, given their interesting properties and the promising results of preclinical and clinical studies.

However, several issues need to be clarified before MSCs can be routinely proposed as a therapeutic option to treat liver fibrosis.

Over the past few years, concerns have been raised about the long-term effectiveness of MSC-based the-

rapy and the potential tumorigenic risk. Several lines of evidence have suggested that MSCs might promote tumour growth *in vivo*^[154-156]. On the other hand, because of their immunomodulatory properties, MSCs may have an antitumour effect, in relation with the modulation of the inflammatory environment that characterizes many tumours^[157-159]. MSCs can also interact with cancer cells and inhibit signalling pathways associated with tumour growth and cell division^[160,161].

Moreover, there is a lack of standardised protocols for MSC transplantation. The optimal MSC doses, timing and frequency of injection and administration route differ considerably among the different studies.

For all of these reasons, we believe that further studies, particularly randomised controlled trials, are needed to evaluate the long-term safety and efficacy of MSC-based treatment. Moreover, potency tests performed on MSCs before injection in patients could be useful.

CONCLUSION

Although considerable advances have been made in the past decade to better understand the cellular and molecular mechanisms underlying liver fibrogenesis, no efficient therapy is available so far to treat this serious condition.

Further investigations and efforts are currently being conducted to efficiently reverse liver fibrosis. MSC-based therapy has been shown to have a significant potential to decrease mortality and improve the quality of life of patients with liver fibrosis. However, a standardisation is needed before proposing this strategy routinely in clinical practice.

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