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Review

Liver Cirrhosis: An Overview

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Abstract

Liver cirrhosis is a common sequel to diverse chronic liver injuries of different etiologies and represents an elevating cause of morbidity and mortality worldwide. Identification and characterization of cell populations contributing to the myofibroblastic pool and production of extracellular matrix (ECM) in liver fibrosis, as well as the increasing knowledge about natural course, many of the intricate cellular and molecular mechanisms underlying liver fibrogenesis and its progression, and contributions of the genetic regulation, inflammatory and immuno-mediators, neuroendocrine factors, and oxidative stress, have provided important data upon which the design of effective and targeted antifibrotic pharmacological strategies, aiming at halting the progression to decompensated cirrhosis or even reversing the liver fibrogenesis, can be based. This review summarizes recent progresses in understanding the pathogenesis of liver fibrosis and some new experimental therapeutic interventions.

Keywords: Provide minimum of five keywords

INTRODUCTION

The chronic activation of the tissue repair mechanisms that follows reiterated liver injury leads to progressive deposition of collagen and other components of the ECM, and the subsequent hepatic cirrhosis. Liver cirrhosis is an elevating cause of morbidity and mortality, being the 14th most common cause of death in adults worldwide and the fourth in central Europe. It is the main indicator for 5500 liver transplants in Europe every year (Tsochatzis *et al.,* 2014). In the United States, cirrhosis is the most common non-neoplastic cause of death among hepatobiliary and digestive diseases, accounting for approximately 30,000 deaths per year (Rockey and Friedman, 2012). Globally, liver cirrhosis was the reason for a million deaths in 2010, 33% more than in 1990, roughly equally attributable to hepatitis B virus (HBV), hepatitis C virus (HCV), and alcohol abuse(Lozano *et al.,* 2012). It is difficult to ascertain the precise prevalence of liver cirrhosis and probably it is higher than reported because cirrhosis is often clinically silent, whereas the initial stages are always asymptomatic, which make the disease undiagnosed (Tsochatzis *et al.,* 2014). Rates of cirrhosis vary widely across countries, with Egypt having the highest level (about 10-fold higher than that in other countries) (Cuadros *et al.,* 2014). The number of Egyptians estimated to be chronically infected with HCV is 9.8%, in addition to about more than 500,000 new infections annually (Miller and Abu-Raddad, 2010). In addition to schistosomiasis, 50% of Schistosoma mansoni-infected population in Egypt is co-infected with HCV (Van-Lume *et al.,* 2013). Concomitant HCV and S. mansoni infection contributes to a higher incidence of hepatic cirrhosis, hepatocellular carcinoma, and a much higher liver related mortality rate (Kamal *et al.,* 2004 and2006).

Definition

The term cirrhosis is credited to René Laënnec and derived from the Greek word kirrhos; meaning orange or tawny, while osis; meaning condition (Cheney et al., 2012; Guha and Iredale, 2007). Progressive deposition of a qualitatively altered ECM (scar) that is highly enriched in type I and III fibrillar collagens as well as the decreased matrix remodeling lead to hepatic fibrogenesis and ultimately to cirrhosis; a case histologically defined

by diffuse fibrosis and conversion of normal lobular organization of liver into structurally abnormal regenerative nodules, causing remarkable distortion of the hepatic vasculature that increases resistance to portal blood flow and hence results in portal hypertension and hepatic synthetic dysfunction (Mallat and Lotersztajn, 2013b; Saffioti and Pinzani, 2015).

Fibrosis and cirrhosis are not synonymous words. Fibrosis may be noticed in zone one as in bile duct obstruction and congenital hepatic fibrosis; or zone two as in granulomatous liver disease; or acinar zone three as in heart failure, but without nodularity. Formation of nodules without fibrosis, as in nodular regenerative hyperplasia, is not cirrhosis, as well (Cheney *et al.,* 2012; McCormick, 2011).

Etiology and risk factors

Both fibrosis and cirrhosis are the consequences of a sustained wound healing response to chronic liver injury from a range of different etiologies (Table 1). In developed countries the leading causes of liver cirrhosis are alcohol abuse, non-alcoholic liver disease, and viral infection, in particular HCV. The principal causes in developing countries are HBV and HCV, whereas the most common cause in sub-Saharan Africa and most parts of Asia is infection with HBV (Tsochatzis *et al.,* 2014; Wells, 2011). Following infection with HCV, cirrhosis may develop within an average of 20-30 years in some patients while in others, the rate of progression is faster, and cirrhosis may develops after 10-15 years. Patients with chronic HBV infection and detectable hepatitis B envelope antigen have a higher risk of developing cirrhosis than those without hepatitis B envelope antigen. In patients co-infected with HBV and hepatitis delta virus, hepatic fibrosis progresses rapidly to cirrhosis (Bataller and Brenner, 2009).

The risk of developing cirrhosis from several etiologies may also depend on a number of factors such as age older than 50 years, gender of the patient, duration of the disease, immunological status, alcohol misuse, insulin resistance, systemic hypertension, and high levels of triglyceride. Obesity (body mass index > 28 kg/m2) correlates with severity of fibrosis and risk of cirrhosis (Schuppan and Afdhal, 2008). Necroinflammatory activity with alanine aminotransferase's (ALT) values more than two times normal levels and/or aspartate aminotransferase (AST)/ALT ratio> 1 also represents a risk factor (Rockey and Friedman, 2012). Herbal medications should be considered in patients with liver fibrosis (Bataller and Brenner, 2009).

Routine laboratory tests and findings in cirrhosis

Changes in the laboratory parameters depend on the stage of the disease and the cause of cirrhosis (Dancygier, 2010) as summarized in the next Table 2.

Pathogenesis of liver cirrhosis

Cell types involved in the pathogenesis of liver fibrosis

Recent investigations have revealed that during chronic liver injury accumulation of ECM is driven by a heterogeneous population of cells (liver fibrogenic cells; myofibroblasts; MFs), which plays a major role during fibrogenesis (Elpek, 2014). Their origin has been extensively studied, and at least three cellular populations act as main precursors of the hepatic MFs have been identified (Xu et al., 2014):

Hepatic stellate cells (HSCs)

In adult mammalian liver, about 50-80% of the body retinoids are stored in the cytoplasmic droplets of these cells (Pinzani, 2007). Different experimental models of liver injury as well as genetic cell lineage-tracing experiments in mouse models have firmly established resident activated HSCs as the major source of MFs in liver fibrosis independent of its etiology (Iwaisako *et al.,* 2014; Mederacke *et al.,* 2013; Michelotti *et al.,* 2013). Many studies have reported that HSCs are derived from mesodermal-derived multipotent mesenchymal progenitor cells, which also give rise to neural cells and other mesenchymal cells (Geerts, 2001; Tsukamoto *et al.,* 2011). Supporting this finding, under physiological conditions, adult HSCs exhibit a quiescent phenotype and express neural markers like glial fibrillary acidic protein, nestin, synemin, synaptophysin, and p75 neurotrophin receptor, as well as, mesenchymal markers such as vimentin and desmin (Koyama *et al.,* 2015; Tsukamoto *et al.,* 2011). Recent advances in liver fibrosis based upon the fundamental dogma that upon activation, HSCs orchestrate an intricate and tightly regulated network of cellular and molecular responses resulting in an accumulation of ECM and hepatic fibrosis (Hasegawa *et al.,* 2015).

Portal fibroblasts

Portal fibroblasts (PFs), the resident fibroblasts of the portal tract, are a heterogeneous population found in the mesenchyme surrounding the bile ducts (Wells, 2014).In almost all types of chronic liver injury, fibrosis develops mainly in the portal area and appears to progress from this area, even if the injury targets intralobular hepatocytes. This observation suggests that PFs may contribute to liver fibrosis more than generally assumed

Table 1. Causes of liver fibrosis and/or cirrhosis

Chronic viral infection
Hepatitis B
Hepatitis C
Hepatitis D
Autoimmune diseases
Autoimmune hepatitis
Primary biliary cirrhosis
Primary sclerosing cholangitis
Overlap syndromes
Graft versus host disease
Metabolic/Inherited diseases
Non-alcoholic fatty liver disease (e.g., non-alcoholic steatohepatitis; NASH)
Copper overload (e.g., Wilson's disease)
Iron overload (e.g., hereditary hemochromatosis)
α_1-antitrypsin deficiency
Glycogen storage diseases (e.g., type IV glycogenesis)
Fructosemia
Galactosemia
Tyrosinemia
Urea cycle disturbances
Byler's disease
Wolman's disease
Long-term parenteral nutrition
Lipid abnormalities (e.g., Gaucher's disease, abetalipoproteinemia)
Progressive familial intrahepatic cholestasis syndromes
Autosomal recessive polycystic kidney disease
Cystic fibrosis
Porphyria
Mucopolysaccharidosis
Biliary diseases
Secondary biliary cirrhosis (results from common bile-duct stones, bile-duct or head-of-the-pancreas carcinoma, biliary-tract infections or strictures)
Biliary atresia
Intrahepatic obstruction
IgG_4-associated cholangitis
Ischemic cholangiopathy
Alagille's syndrome
Caroli's disease
Vascular diseases
Chronic right-sided heart failure
Hepatic venous outflow block (e.g., Budd-Chiari syndrome, sinusoidal obstruction syndrome (veno-occlusive disease), congenital web)
Tricuspid insufficiency
constrictive pericarditis
Inferior vena cava thrombosis
Hereditary hemorrhagic telangiectasia
Hepatotoxic agents
Alcohol
Drugs: methotrexate, α-methyldopa, amiodarone, isoniazid, halothane, aflatoxin, diclofenac, dantrolene, arsenic, troglitazone, CCl_4, others
Hypervitaminosis A
Granulomatous hepatitis
Sarcoidosis
Mycobacterial infections
Schistosomiasis
Miscellaneous
Malnutrition
Congenital hepatic fibrosis
Indian childhood cirrhosis
Post-intestinal bypass surgery
Ischemia
Syphilis
Cryptogenic

Table 2. Laboratory findings in patients with liver cirrhosis modified from (Dancygier, 2010; Schuppan and Afdhal, 2008)

Laboratory tests	Description
Parameters of hepatocellular injury (aminotransferases: AST, ALT)	• Often normal or moderately raised due to leakage from damaged hepatocytes • Viral cirrhosis: AST/ALT ratio is less than one • Alcoholic cirrhosis: AST/ALT ratio is greater than one
Parameters of cholestasis (alkaline phosphatase; ALP, γ-glutamyl transpeptidase; γ-GT, bilirubin)	• **ALP**: Increases by less than threefolds, except in primary biliary cirrhosis and primary sclerosing cholangitis • **γ-GT**: More specific for liver than ALP • **Bilirubin**: Raises in advanced stage of cirrhosis, later than γ-GT and ALP, due to cholestasis as well as decreased hepatocyte and renal excretory function; important predictor of mortality • Biliary cirrhosis: ↑ALP, ↑γ-GT,↑bilirubin • Alcoholic cirrhosis: ↑γ-GT
Parameters of the synthetic capacity of the liver (albumin, choline esterase, prothrombin time)	• **Albumin:** decreases in advanced stage of cirrhosis due to decreased hepatic production and sequestration into ascites and interstitium • **Choline esterase:** decreases in advanced stage of cirrhosis • **Prothrombin time:** is prolonged in advanced stage of cirrhosis and does not return to the normal with vitamin K therapy
Immunoglobulins	• Serum levels increase due to poor reticuloendothelial function and shunting of portal venous blood carrying intestinal antigens to lymph tissues with resultantstimulation of plasma cells • Autoimmune hepatitis: γ-globulins increase in all patients • Primary biliary cirrhosis: ↑ IgM • Alcoholic cirrhosis: ↑ IgA • Viral cirrhosis: ↑ IgG
Ammonia	• Serum levels increase in advanced stage of cirrhosis, but do not correlate with signs and symptoms of hepatic encephalopathy
Electrolytes	• Sodiumimbalance (hyponatremia) arises due to inability to excrete free water via kidneys due to increased activity of antidiuretic hormone
Branched-chain amino acids	• Serum levels decrease in advanced stage of cirrhosis
Aromatic amino acids	• Serum levels increase in advanced stage of cirrhosis
Hematology (Blood count)	• There is usually a mild normocytic to macrocytic, normochromic anemia due to folate deficiency, hypersplenism, direct toxicity (alcohol), and gastrointestinal blood loss (e.g., via esophageal varices) • Leukopenia and thrombocytopenia arise due to hypersplenism, dysfibronogenemia, and reduced hepatic thrombopoietin production • ↑ plasma cells
Urine analysis	• If the patient is jaundiced, urobilinogen and bilirubin will be detected • The urinary sodium excretion is diminished in the presence of ascites, and in severe cases less than 5 mmol is passed daily

(Lemoinne et al., 2013).After liver injury, PFs undergo activation, increasing the expression of α-smooth muscle actin (α-SMA), proliferation, and secretion of type I collagen, like HSCs (Iwaisako et al., 2012). The activated PFs display more prominent rough endoplasmic reticulum and Golgi complexes than normal PFs (Tang et al., 1994).

Fibrocytes

Bone marrow-derived mesenchymal cells such as fibrocytes and circulating mesenchymal cells may also contribute to the hepatic MFs pool (Iwaisako *et al.,* 2014; Mederacke *et al.,* 2013). Fibrocytes have dual

characteristics of fibroblasts (due to expression of collagen type I, fibronectin, and vimentin) and hematopoietic cells (due to CD45, CD34, MHC class II, and others) (Abe *et al.,* 2001; Bellini and Mattoli, 2007; Quan *et al.,* 2004). Under physiological conditions, fibrocytes appear spindle in shape, however, in response to injury or stimulation by transforming growth factor-β (TGF-β), they proliferate, migrate to the injured organ, down regulate expression of hematopoietic markers, and rapidly undergo differentiation into α-SMA positive MFs (Bellini and Mattoli, 2007; Quan and Bucala, 2007; Scholten *et al.,* 2011). The number of recruited fibrocytes has been reported to vary from 25% in lung fibrosis to about 3-5% in liver fibrosis (e.g., bile duct ligation and CCl_4), of the collagen type I expressing cells, suggesting that the magnitude of their differentiation into MFs depends on the organ and the type of injury (Brenner *et al.,* 2012).

Recent studies have proposed that hepatocytes, cholangiocytes, and endothelial cells can be minor contributors to the fibrogenic cells pool through epithelial-to-mesenchymal transition (Choi and Diehl, 2009; Kalluri, 2009) or endothelial-to-mesenchymal transition (Piera-Velazquez *et al.,* 2011; Zeisberg *et al.,* 2008), respectively.

Hepatic stellate cells' activation

Following liver injury of any etiology, HSCs undergo activation, which is a dynamic programmed event during which quiescent vitamin A-laden HSCs transdifferentiate into fibrogenic, proliferative, and contractile MFs. Activated HSCs do not only respond to signals but also generate them causing a complex bidirectional signaling network of cells and mediators, which culminates in an accumulation of ECM and hepatic fibrogenesis. The activation process of HSCs can be divided into two major stages: initiation (also referred to as pre-inflammatory) and perpetuation. Regression (resolution), a third phase may follow depending upon the nature and course of the liver injury (Hasegawa et al., 2015).

Initiation

Refers to a range of early genetic and phenotypic changes that render the HSCs more responsive to spectrum of other cellular and cytokines stimuli; thus can be considered a priming step(Friedman, 2008c). In the early stage of liver injury, HSCs receive paracrine stimulation from neighboring damaged cells including: hepatocytes, Kupffer cells (KCs), sinusoidal endothelial cells (SECs), leukocytes, and platelets (Elpek, 2014).

Hepatocytes

In response to liver injury, damaged hepatocytes release reactive oxygen species (ROS), lipid peroxides, and apoptotic bodies; all of them are potent mediators for the activation of quiescent HSCs (Hasegawa *et al.,* 2015). Oxidant stress can perturb homeostasis in endoplasmic reticulum, which increases autophagy in HSCs, which in turn provides the energy required for initiating and perpetuating the activation of HSCs, following injury (Hernández-Gea and Friedman, 2012; Hernández-Gea *et al.,* 2013). In NASH and HCV, steatosis directly correlates with the increased HSCs' activation and fibrogenesis; may be because fats represent an enhanced source of lipid peroxides (Rockey and Friedman, 2012). There are two common mechanisms by which apoptotic hepatocytes can induce hepatic fibrosis: 1) engulfment (phagocytosis) of apoptotic bodies of hepatocyte by HSCs triggers their profibrogenic activation and liver fibrosis (Canbay *et al.,* 2003a); 2) apoptotic hepatocytes can release profibrogenic mediators (Guicciardi and Gores, 2010). The magnitude of hepatocellular apoptosis correlates with the severity of hepatic fibrosis and inflammatory activity in NASH (Feldstein *et al.,* 2003), and with the progression of fibrosis in patients transplanted for HCV (Meriden *et al.,* 2010). Takehara *et al.* (2004)illustrated that hepatocyte-specific disruption of Bcl-xL,in vivo, resulted in persistent apoptosis of hepatocytes that was sufficient to induce fibrotic responses. On the other hand, however, experimental studies using culture and some rodent models of liver fibrosis have demonstrated that either blockage of hepatocellular apoptosis (Canbay *et al.,* 2004; Canbay *et al.,* 2002) or selective induction of apoptosis in HSCs (Anan *et al.,* 2006; Wright *et al.,* 2001) could be a therapeutic strategy for the resolution of fibrosis in many liver diseases, these approaches carry a high risk of unwanted side effects in clinical trials (Schuppan and Kim, 2013).

Kupffer cells

KCs are the resident macrophages populating the hepatic sinusoids (Jaeschke, 2007). In liver injury and hepatocellular necrosis, activated KCs are a major source of inflammatory mediators including cytokines [interleukin (IL)-1, IL-6, IL-10, tumor necrosis factor-α (TNF-α), interferon-α, interferon-β, TGF-β1], ROS, nitric oxide, eicosanoids, chemokines, and lysosomal as well as proteolytic enzymes (Laskin, 1990; Winwood and Arthur, 1993). In vitro studies have revealed that KCs can induce expression of platelet-derived growth factor's (PDGF) receptors on HSCs, thus enhancing their proliferation and matrix production (Friedman and Arthur, 1989). KCs-derived TGF-β1 has been suggested to trigger the activation of HSCs and induce their production

of collagen and proteoglycans (Meyer et al., 1990). Moreover, hydrogen peroxide generated by KCs may enhance the production of type I collagen by HSCs through its participation in modulating the transactivation of both COL1A1 and COL1A2 promoters (Nieto, 2006). TNF-α and IL-1 exhibit a mitogenic effect on HSCs (Matsuoka *et al.,* 1989). KCs release 95 kDa type IV collagenase that has degradative activity against gelatin as well as native types IV and V collagens; this enzyme may cause local disruption of the subendothelial matrix, creating conditions that disturb hepatocellular functions and promote activation of HSCs (Winwood and Arthur, 1993). In experimental model of cholestatic liver injury, engulfment of apoptotic bodies by KCs stimulated expression of cytokines and death ligands (including Fas ligand and TNF-α), which in turn promoted hepatic inflammation and fibrogenesis (Canbay *et al.,* 2003b).

Hepatic sinusoidal endothelial cells

In liver fibrosis, SECs by virtue of their close proximity to both HSCs and the blood supply of the liver, are likely to play two important roles, particularly in the early stages before the myofibroblastic differentiation of HSCs (Wells, 2008). First, capillarization of the sinusoids, which is characterized by loss of typical SECs' fenestrations and formation of an organized subendothelial basement membrane in the space of Disse, has been recognized as a major contributor to hepatic failure and as one of the hallmarks of liver fibrosis since it was first described by Schaffner and Popper (1963) (Braet and Wisse, 2002; Wells, 2008). The second role attributed to SECs is the production of a splice variant of cellular fibronectin called fibronectin extra domain A, a fetal isoform of fibronectin expressed primarily during development and in response to injury (Wells, 2008). In vitro studies have elegantly shown that fibronectin extra domain A is necessary to mediate the myofibroblastic differentiation of HSCs (Jarnagin *et al.,* 1994; Serini *et al.,* 1998), and that TGF-β acts on SECs to rapidly upregulate the production of fibronectin extra domain A (George et al., 2000), thus linking TGF-β, SECs, and HSCs' activation (Wells, 2008). Recent study has reported that, pharmacological modulation that restores the differentiated endothelial cell phenotype accelerates regression and prevents progression of fibrosis via promoting reversal of activated HSCs to quiescence (Xie *et al.,* 2012).

Leukocytes

Cells of innate immunity, including neutrophils, macrophages, natural killer T (NKT) cells, natural killer (NK) cells, and mast cells, and from the adaptive immune response, like T- and B-lymphocytes, contribute to the fibrogenesis process (Duval *et al.,* 2015).

In co-culture system, the release of ROS (particularly superoxide anion) by activated neutrophils contributed, through the induction of lipid peroxidation and the generation of reactive aldehydic end-products, to synthesis of collagen by human HSCs and the subsequent development of liver fibrosis associated to alcoholic hepatitis (Casini *et al.,* 1997). Moreover, neutrophils can produce IL-17A, which appears to induce liver fibrosis through multiple mechanisms in mice (Meng *et al.,* 2012). In a mouse model of NASH, the neutrophil-derived human neutrophil peptide-1 enhanced the hepatic fibrosis by inducing the proliferation of HSCs (Ibusuki *et al.,* 2013).

The function of NKT cells in the pathogenesis of liver fibrosis is more complex and probably mediates diverse actions due to five reasons: first, there are several types of NKT cells that play diverse and sometimes opposing immunologic functions in the liver (Notas *et al.,* 2009; Santodomingo-Garzon and Swain, 2011). Second, upon activation, the detection of NKT cells becomes more difficult than that of NK cells due to the rapid downregulation of NKT cell's markers and/or apoptosis (Eberl and MacDonald, 1998; Harada *et al.,* 2004). Third, the mechanisms by which NKT cells are activated, in vivo, by endogenous ligands and cytokines are still largely unknown (Venkataswamy and Porcelli, 2010). Fourth, NKT cells become tolerant and non-responsive to subsequent stimuli upon activation (Jung et al., 2012; Parekh *et al.,* 2005). Eventually, activated NKT cells can produce large amounts of both antifibrotic (e.g., interferon-γ) and profibrotic (e.g., IL-4, IL-13, hedgehog ligands, and osteopontin) cytokines as well as many other mediators that can differentially regulate liver fibrogenesis (Gao and Radaeva, 2013)

Although still controversial, mast cells seem to be involved in the fibrotic response to chronic inflammation and parasitic infection of the liver (Franceschini et al., 2006). The mast cells' chymase has been linked with the production of angiotensin II and the development of myocardial and renal fibrosis (Franceschini *et al.,* 2006), while human mast cells' tryptase induces proliferation, migration, and synthesis of collagen type I by fibroblasts (Cairns and Walls, 1997; Gruber *et al.,* 1997). Furthermore, mast cells can be considered key element in the process of sinusoidal capillarization (Grizzi *et al.,* 2003).

CD8+ T-lymphocytes increase in fibrotic livers and are thought to play a role in promoting not only liver injury but also the fibrogenic response (Muhanna *et al.,* 2008; Safadi *et al.,* 2004). CD4+ T-lymphocytes may induce fibrogenesis by secreting cytokines, including TNF-α and IL-2 (Gressner and Bachem, 1990; Marra *et al.,* 2009). Muhanna et al. (2008)reported that activation of HSCs after phagocytosis of disease-associated lymphocytes is a novel and potentially important pathway regulating the impact of lymphocytes on the course of hepatic fibrogenesis. Recent study demonstrated that T helper

type 2-dominant splenic lymphocytes migrate into the liver and induce liver fibrosis by shifting the cytokine balance towards T helper type 2 dominance (Tanabe *et al.,* 2015). In study by Novobrantseva et al. (2005), following six weeks of CCl4 administration, B cell-deficient mice showed markedly reduced collagen deposition than wild-type mice. They also established that B cells have an impact on fibrosis in an antibody- and T cell-independent way. Moreover, B cells produce the profibrotic cytokine IL-6, which may induce the differentiation of HSCs into MFs, proliferation of fibroblasts, and synthesis of collagen as well as tissue inhibitors of metalloproteinases (Bhogal and Bona, 2005).

Platelets

In injured liver, platelets are a major source of the potent HSCs' mitogen PDGF-B, as well as the production of TGF-β1 and epidermal growth factor (Puche *et al.,* 2013). A recent study by Yoshida *et al.* (2014) supported the involvement of platelets in promoting fibrogenic pathways by the following evidences: (1) levels of PDGF-β protein in fibrotic mice can be lowered to normal using an anti-platelet antibody, suggesting that they are a dominant source of this mitogen; (2) in fibrotic areas, platelets tend to localize in close proximity to activated HSCs; and (3) depletion of platelets reduces the circulating and hepatic levels of PDGF-β and significantly leads to a reduction in α-SMA and expression of genes that promote fibrosis. By contrast, other studies suggested that platelets may block the activation of HSCs, based of evidences such as: (1) in culture, the activation of human HSCs is suppressed by platelet-derived adenosine 5′-triphosphate via adenosine- cyclic adenosine 5′-monophosphate signaling pathway (Ikeda *et al.,* 2012); (2) hepatocyte growth factor released by activated platelets plays a critical role in inhibiting type I collagen gene expression in cultured HSCs (Kodama *et al.,* 2010); (3) transgenic mice with thrombocytopenia develop exacerbated liver fibrosis in response to cholestasis (Kodama *et al.,* 2010); and (4) platelet transfusion can improve the liver function of patients with chronic liver disease and cirrhosis (Kurokawa *et al.,* 2015).

Perpetuation

If the initial insult is sustained, ongoing paracrine signaling from neighboring cells and the surrounding ECM, as well as autocrine signals generated by HSCs themself, collectively, will perpetuate and amplify the activation of HSCs. Perpetuation of HSCs' activation is an organized process including number of functional outcomes that can conceptually be divided into: (1) proliferation; (2) contractility; (3) fibrogenesis; (4) chemotaxis; (5) matrix turnover; (6) retinoid loss; and (7) inflammatory and immuno-regulation (Friedman, 2008a; Puche et al., 2013).

Proliferation

An increase in the number of HSCs is a hallmark of hepatic fibrosis (Rockey and Friedman, 2012). HSCs proliferate in response to a host of molecules such as PDGF, which is considered the most potent mitogen towards HSCs (Borkham-Kamphorst *et al.,* 2007; Elpek, 2014). Other compounds with mitogenic activity towards HSCs and with a potential role in fibrogenesis include thrombin and its receptor, epidermal growth factor, vascular endothelial growth factor, TGF-α, basic fibroblast growth factor, keratinocyte growth factor, endothelin-1, and insulin growth factor, among others (Friedman, 2008a; Friedman, 2008b; Li et al., 2008). Vascular endothelial growth factor is a central mediator of both proliferation of HSCs and hepatic angiogenesis during development of liver fibrosis (Zhao *et al.,* 2012). Angiogenesis supports the proliferation of HSCs by providing important nutrients and vascular fibrous septa in which the HSCs will reside (Hasegawa *et al.,* 2015).

Contractility

Activation of HSCs is accompanied by an increase in expression of proteins that are characteristic of contractile cells such as the cytoskeletal protein α-SMA (Elpek, 2014; Iizuka *et al.,* 2011). The force generated by the contraction of activated HSCs contributes to modulating the blood flow via sinusoidal constriction (Rockey, 2001; Thimgan and Yee, 1999) and to hepatic fibrosis (Melton et al., 2005). The mechanism by which HSCs become contractile is mediated by both Ca2+-dependent and Ca^{2+}-independent pathways (Iizuka *et al.,* 2011; Melton *et al.,* 2005; Saiman *et al.,* 2013). Endothelin-1 and nitric oxide are the major inducers of HSCs' contraction and relaxation, respectively, although several other mediators have been implicated (Friedman, 2008a; Puche *et al.,* 2013). During liver injury, endothelin-1 is overproduced by HSCs, while endothelial cell-derived nitric oxide production is reduced (Rockey, 2001). Disruption of the normal hepatic architecture, primarily through remodeling of the hepatic sinusoids and development of fibrous septa replete with contractile HSCs, contributes to the increased intrahepatic vascular resistance that is the primary cause of portal hypertension during liver fibrosis, which in turn leads to a cascade of further clinical complications (Hasegawa *et al*., 2015). Therefore, modulation of the HSCs' contractility is an evolving treatment concept for the intrahepatic portal hypertension (Fallowfield *et al.,* 2014; Rockey, 2001).

Fibrogenesis

HSCs induce fibrosis not only by proliferation, but also by increasing production and secretion of matrix per cell (Lee and Friedman, 2011). Overproduction of type I collagen is a common hallmark of fibrosis in various organs including the liver (Inagaki and Okazaki, 2007). TGF-β, mainly produced by monocytes and macrophages, is the most potent cytokine in stimulating the transcription of type I collagen gene (Hernández-Gea and Friedman, 2011; Inagaki and Okazaki, 2007). HSCs express little amounts of TGF-β, however, once stimulated by fibrogenic stimuli, HSCs are the only cells that respond by expressing augmented amounts of the all three different isoforms of this cytokine (Inagaki and Okazaki, 2007). Once activated, TGF-β transmits signals via its cognate receptors to intracellular Smad proteins, which induce the transcription of target genes, including procollagen I and III (Breitkopf et al., 2006; Inagaki and Okazaki, 2007). It also regulates expression of matrix metalloproteinases as well as their inhibitors, and modulates inflammatory responses by influencing T cell's functions (Inagaki and Okazaki, 2007).

CCN2 (connective tissue growth factor), is another well-characterized fibrogenic growth factor-matricellular protein (Puche *et al.,* 2013). Its levels elevate in liver injury and promote a range of profibrotic activities mediated by a G protein-coupled receptor (Gressner and Gressner, 2008; Huang and Brigstock, 2012). It may be a useful serum biomarker for assessment of liver fibrosis, as it significantly correlates with fibrosis in patients with chronic HCV infection (Kovalenko *et al.,* 2009).

Leptin, a circulating adipogenic hormone, is a profibrogenic cytokine in the liver, as some evidences indicate.Mechanisms underlying its profibrogenic effect most likely involve: (1) induction of TGF-β1 in SECs as well as KCs, (2) increasing the proliferation and collagen promoter activity of HSCs, (3) modulating the production and action of cytokines involved in wound repair (Ikejima *et al.,* 2007; Leclercq *et al.,* 2002), (4) suppression of peroxisome proliferator-activated receptor-γ, an antifibrogenic nuclear receptor that can reverse HSCs' activation and maintain its quiescence (Zhou *et al.,* 2009), and (5) decreasing the activity of norepinephrine, which in turn, promotes the depletion of hepatic NKT cells, and thereby attenuates the release of additional profibrogenic cytokines (Li *et al.,* 2004). In patients with HCV-genotype 4, serum adiponectin correlates with the different stages of liver injury (Khattab et al., 2012). Circulating resistin has also been reported to increase in patients with liver cirrhosis, along with the severity of disease (Kakizaki *et al.,* 2008; Yagmur *et al.,* 2006).

Following liver injury, activated HSCs express specific G protein-coupled receptors (cannabinoid type 1 receptor and cannabinoid type 2 receptor), which are components of the endocannabinoid system that plays a part in regulating the fibrogenic cascade (Giannone *et al.,* 2012; Mallat *et al.,* 2013; Trebicka *et al.,* 2011). Data indicate that activation of cannabinoid-1 receptor promotes profibrogenic effects, whereas cannabinoid-2 receptor triggers antifibrogenic responses (Caraceni *et al.,* 2009; Mallat *et al.,* 2013). In chronic liver diseases, the profibrogenic signal of cannabinoid-1 receptor prevails on the antifibrogenic signal of cannabinoid-2 receptor, therefore, regression of fibrosis can be achieved by the pharmacological blockade of cannabinoid-1 receptor even in an advanced stage of the disease (Giannone et al., 2012). Opioid signaling stimulates proliferation and production of collagen in HSCs in a paracrine manner (De Minicis *et al.,* 2008). Serotonin synergizes with PDGF to stimulate proliferation of HSCs (Ruddell et al., 2006). Thyroid hormones enhance activation of HSCs in rats through increased expression of p75 neurotrophin receptor and activation of Rho, thereby accelerating development of liver fibrosis (Zvibel *et al.,* 2010).

Osteopontin, an ECM cytokine expressed by HSCs, can drive fibrogenesis by modulating the HSCs' profibrogenic phenotype and expression of type I collagen via engagement of integrin α(V)β(3) and activation of the PI3K/pAkt/NF-κB signaling cascade (Urtasun *et al.,* 2012). IL-17 induces liver fibrosis through multiple mechanisms in mice, therefore, blockade of this cytokine has been proposed as a potential strategy for treatment of patients with cirrhosis, recently (Meng *et al.,* 2012).

The role of microRNAs in the activation of HSCs and progression of fibrosis is being clarified (Noetel *et al.,* 2013; Ogawa et al., 2012). MicroRNA-29b is involved in the activation of HSCs and regulation of liver fibrosis and is part of a signaling nexus involving TGF-β- and NF-κB-dependent downregulation of micro RNA-29 family members in HSCs with subsequent upregulation of ECM genes (Roderburg et al., 2011; Sekiya *et al.,* 2011). MicroRNAs could be explored as novel markers for the diagnosis or monitoring of the progression of liver fibrosis (He *et al.,* 2012).

Chemotaxis

Chemotaxis is an important event in the formation of fibrotic septa by allowing the activated HSCs to align within regions of injury (Puche *et al.,* 2013). HSCs can migrate towards chemoattractant cytokines such as PDGF-BB (Fibbi et al., 2001; Kinnman *et al.,* 2000), vascular endothelial growth factor, angiopoietin-1 (Novo *et al.,* 2007), TGF-β1, epithelial growth factor (Yang et al., 2003), basic fibroblast growth factor (Fibbi *et al.,* 2001), monocyte chemotactic protein-1 (Marra *et al.,* 1999), and chemokine receptors such as cysteine-X-cystein receptor-3 (Bonacchi et al., 2001) and cysteine-X-cystein receptor-4 (Sawitza et al., 2009). Chemokine receptor-5 represents a potential mediator of migration and proliferation of culture-activated HSCs (Schwabe *et al.,*

2003). Intracellular generation of superoxide anion or hydrogen peroxide promotes directional migration of HSCs even in the absence of specific chemokines (Novo et al., 2011). Hypoxia is another activator of HSCs'migration via mitochondrial-dependent ROS-mediated activation of ERK1/2 and JNK1/2 pathways, followed by hypoxia-inducible factor-1α-dependent increased upregulation and release of vascular endothelial growth factor by stellate cells, promoting their mobility (Novo *et al.,* 2012). Matrix metalloproteinase-2 and type I collagen are able to mediate the migration of HSCs, further amplifying the fibrotic response (Yang *et al.,* 2003). Moreover, activated stellate cells use hyaluronic acid and its receptor, CD44v6, for migration (Kikuchi *et al.,* 2005).

Matrix turnover

As previously mentioned, fibrosis is a highly coordinated dynamic process reflecting a shift in balance between production and degradation of the matrix's components. Quantitative and qualitative changes in the activity of matrix metalloproteinases and their inhibitors, tissue inhibitors of matrix metalloproteinases, play a vital role in matrix's remodeling during liver fibrogenesis (Rockey and Friedman, 2012). Although quiescent HSCs are the major cellular source of matrix metalloproteinases in the onset of acute liver failure (Yan *et al.,* 2008), in chronic liver injury, the fully activated HSCs are incapable of expressing most matrix metalloproteinases (except matrix metalloproteinase-2) even under inflammatory stimulation (Han et al., 2004), a phenomenon that favors accumulation of the ECM (Qin and Han, 2010). In fibrotic livers, matrix metalloproteinase-9 and 13 are repressed at the level of chromatin (Qin and Han, 2010). Tissue inhibitor of metalloproteinase-1 and 2 are upregulated in progressive experimental liver fibrosis, which may explain the decreased degradation of the interstitial matrix observed in both experimental and human liver injury (Rockey and Friedman, 2012). Changes in the hepatic subendothelial matrix may stimulatethe matrix's production by HSCs and progression of the fibrotic process (Friedman *et al.,* 1989). Replating of activated HSCs on plates coated with matrix closely resembles the normal ECM of the space of Disse,inhibited the proliferation of these cells and progressively reduced their mRNA expression for type I procollagen and α-SMA (Gaça *et al.,* 2003). Recently, a specific phenotype of macrophages that express the surface marker Ly-6C has been characterized as the principle matrix metalloproteinase-expressing subset (Ramachandran and Iredale, 2012; Ramachandran *et al.,* 2012).

Retinoid loss

In response to, in vivo, fibrogenic stimuli or prolonged culture on uncoated plastic materials, HSCs start losing their lipid droplets and retinyl esters and concomitantly transform into highly proliferative and activated phenotype with high expression of ECM's genes and α-SMA (Bachem et al., 1992; Leo et al., 1993). Although disappearance of retinyl ester-containing lipid droplets is considered one of the traditional hallmarks of HSC's activation (Bataller and Brenner, 2005; Friedman, 2008a), it is not understood whether: (1) this dramatic loss affects the activation and differentiation of HSCs, (2) this loss is a cause or consequence of the HSCs' activation, and (3) it affects the hepatic response to chronic damage (Kluwe *et al.,* 2011). During activation of HSCs, retinoids release outside the cell in the form of retinol, suggesting that there is an intracellular hydrolysis of esters prior to export (Friedman *et al.,* 1993).

Autophagy participates in the HSC's activation via hydrolysis of retinyl esters,generating substrates that are essential for fueling the energy-intensive pathways of cellular activation (Friedman et al., 1993; Hernández–Gea et al., 2012;Thoen *et al.,* 2011). Recent studies have demonstrated that inhibition of autophagy downregulates the fibrogenic properties of HSCs, unveiling a potential new therapeutic strategy for liver fibrosis (Hernández-Gea et al., 2013; Hernández–Gea et al., 2012; Thoen *et al.,* 2011).

Inflammatory and immuno-regulation

Activated HSCs attract immune cells to the site of injury (Hasegawa *et al.,* 2015), secrete inflammatory chemokines, interact directly with various immune cells through expression of their adhesion molecules, including intercellular adhesion molecule-1 (Hellerbrand *et al.,* 1996) and vascular cell adhesion molecule-1 (Knittel et al., 1999) , and modulate the immunity through antigen presentation (Bomble *et al.,* 2010). As a result, a positive feedback loop exists in which fibrogenic and inflammatory cells stimulate each other in amplifying fibrogenesis (Lee and Friedman, 2011).

During late stages of fibrosis, there is an increased bacterial load delivery from the gut to the liver due to the increased intestinal permeability, causing an increase in the bacterial lipopolysaccharide and activation of Toll-like receptor 4 by HSCs (Puche *et al.,* 2013). Stimulation of HSCs with ligands of Toll-like receptor 4 enhances TGF-β signaling and production of proinflammatory and chemotactic cytokines, leading to a more profibrogenic response (Guo *et al.,* 2009; Seki *et al.,* 2007). In another interaction, activation of KCs increases the activity of NF-κB and the subsequent secretion of proinflammatory cytokines such as TNF-α and monocyte chemoattractant protein-1, which provoke the activation of HSCs (Liu *et al.,* 2010). In turn, HSCs respond to this stimulation by secreting macrophage colony-stimulating factor (Pinzani et al., 1992), monocyte chemoattractant protein-1 (Czaja

et al., 1994), IL-6 (Tiggelman *et al.,* 1995), chemokine CCL21 (Bonacchi *et al.,* 2003), RANTES, and chemokine receptor-5 (Schwabe *et al.,* 2003) causing an amplified acute phase response with further activation of macrophages. Finally, oxidant stress (Guimarães *et al.,* 2010) and apoptotic parenchymal cells (Jaeschke, 2002) are also strong inducers of the immune system.

Regression

The current understanding of the fate decisions for activated HSCs displays three mechanisms by which they may regress. These mechanisms are apoptosis, senescence, and reversion to an inactivated phenotype (Hasegawa *et al.,* 2015).

Apoptosis

In both models of cholestasis and toxic liver injury, in which the insult is removed after the development of fibrosis, there is resolution of injury and fibrosis within six weeks, and marked apoptosis of MFs (Iredale *et al.,* 1998; Issa et al., 2001). Although the mechanisms by which apoptosis is regulated are not entirely clear, several mediators and cell populations have been implicated: (1) NF-κB, which protects the HSCs from apoptosis (Watson *et al.,* 2008) and whose inhibition accelerates the resolution of fibrosis in CCl4-treated rodents (Oakley *et al.,* 2005); (2) nerve growth factor, which is secreted by hepatocytes, may promote the apoptosis via inhibition of NF-κB (Oakley *et al.,* 2003); (3) NK cells expressing NKG2D (natural-killer group 2, member D) and tumor necrosis factor-related apoptosis-inducing ligand (Radaeva *et al.,* 2006); (4) activated KCs, which can induce the apoptosis of HSCs by caspase-9- and receptor-interacting protein-dependent mechanisms(Fischer et al., 2002); (5) members of the heat-shock family of proteins, which protect against stress-induced apoptosis (Gabai *et al.,* 2000) and whose genetic ablation results in rapid regression of liver fibrosis and disappearance of activated HSCs in animal models (Kisseleva *et al.,* 2012); (6) endoplasmic reticulum stress (Huang et al., 2014; Zhu et al., 2014); (7) farnesoid X receptor-small heterodimer partner regulatory cascade (Fiorucci *et al.,* 2005); and (8) components of the ECM may also be involved, for example, disruption of the integrin α3β2 increased the ratio of Bax/Bcl2 as well asactivation of caspase-3, leading to apoptosis of human melanocytes (Gieling et al., 2008).

Senescence

Initial studies in cultured human HSCs suggested that as the cells reach their proliferative capacity, they adopt a more inflammatory and less fibrogenic phenotype that might modulate the chronic wound healing process (Schnabl *et al.,* 2003). Cellular senescence is mediated by progressive shortening of telomere and activation of a DNA damage response (Krizhanovsky *et al.,* 2008; Schrader et al., 2009). In addition to the lack of proliferation, senescent activated HSCs are characterized by expression of β-galactosidase; induction of p53, p21, and p16; reduced production of ECM's components; enhanced secretion of ECM-degrading enzymes; and upregulated immune surveillance (Krizhanovsky *et al.,* 2008). The p53 tumor suppressor can promote the cellular senescence and restrict the malignant transformation by triggering cell-autonomous programs of cell-cycle arrest or apoptosis (Lujambio et al., 2013). IL-22 also promotes the senescence of HSCs thereby ameliorating the liver fibrogenesis (Kong *et al.,* 2012). The immune system, especially NK cells, plays an important role in the clearance of senescent activated HSCs, thereby facilitating the resolution of fibrosis (Krizhanovsky et al., 2008).

Reversion to an inactivated HSCs phenotype

Until recently, reversion of activated HSCs to quiescence was only demonstrated in cultured cells (Puche et al., 2013). In one of these studies, fructose-1,6-bisphosphate induced quiescent phenotype in cultured HSCs via activation of peroxisome proliferator-activated receptor-γ (de Mesquita et al., 2013). According to two, in vivo, genetic fate mapping studies, activated HSCs may revert to an inactivated state following cessation of the experimental liver injury (Kisseleva *et al.,* 2012; Mallat and Lotersztajn, 2013a; Troeger *et al.,* 2012). Activated HSCs are able to escape apoptosis during regression of liver fibrosis, downregulate their fibrogenic genes, and acquire a phenotype similar to, but distinct from quiescent HSCs in their higher responsiveness to recurring fibrogenic stimulation (Kisseleva *et al.,* 2012; Troeger *et al.,* 2012).

CONCLUSION

Dramatic advances in the few past decades have advanced our understanding of the cellular and molecular biology of liver fibrogenesis. However, more basic and clinical research is still required in liver cirrhosis to eradicate being an irreversible process and an elevating cause of morbidity and mortality worldwide. In the clinical settings, patients at a high risk of progression to cirrhosis should be identified and the genetic determinants that influence progression of fibrosis should be uncovered. Any antifibrogenic strategy should selectively target the ECM-producing cell in a given tissue, without implying secondary effects on the biology of other cell types.

Although many new potential antifibrotic drugs are effective in the experimental models, their efficacy and safety in humans is still unknown. Clinical trials are still hampered by the lack of simple and reliable non-invasive techniques to screen for earlier stages of fibrosis and to monitor antifibrotic drug effects.

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