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Role of hepatic stellate cell (HSC)-derived cytokines in hepatic inflammation and immunity

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ABSTRACT

In their quiescent state, Hepatic stellate cells (HSCs), are present in the sub-endothelial space of Disse and have minimal interaction with immune cells. However, upon activation following injury, HSCs directly or indirectly interact with various immune cells that enter the space of Disse and thereby regulate diverse hepatic function and immune physiology. Other than the normal physiological functions of HSCs such as hepatic homeostasis, maturation and differentiation, they also participate in hepatic inflammation by releasing a battery of inflammatory cytokines and chemokines and interacting with other liver cells. Here, we have reviewed the role of HSC in the pathogenesis of liver inflammation and some infectious diseases in order to understand how the interplay between immune cells and HSCs regulates the overall outcome and disease pathology.

1. Background

Hepatic stellate cells (HSCs) were first identified in 1876 using gold impregnation technique by von Kupffer, who described them as 'Sternzellen' [1]. However, in 1898, he mistakenly concluded these cells to be liver macrophages based on India ink staining. It was Ito and Nemto who unequivocally showed that stellate cells were different from macrophages and sinusoidal endothelial cells [2,3].

2. Origin

HSCs have been thought to be of embryologic or neural crest origin. Their embryologic origin is supported by localization of these cells in the septum transversum mesenchyme during liver development [4] and by having a common endoderm origin with hepatoblasts [5]. Neural crest origin is supported by their specific markers such as, glial fibrillary acidic protein (GFAP), nestin, neurotrophins and synaptophysin [6].

3. Cellular structure

HSCs are resident non-parenchymal cells present in the sub-endothelial space of Disse, between the basolateral surface of hepatocytes and the antiluminal side of sinusoidal endothelial cells [7]. They comprise approximately one-third of the non-parenchymal cell population, ~10-15% of the total number of liver resident cells and ~1.5% of total liver volume in normal human liver [8].

Through their star like dendritic cytoplasmic processes, HSCs are in direct contact with other cell types including other HSCs, hepatocytes, endothelial cells, and Kupffer cells. This diverse cell-cell contacts together with their specialized location allows intercellular transport of soluble mediators and cytokines permitting its diverse effects on the liver functions and immune physiology [9]. Moreover, the proximity of stellate cells to the nerve endings also allows its neurohormonal responsiveness [10–12].

HSCs in normal liver store vitamin A (retinoid) droplets as retinyl palmitate in their cytoplasm [13], which gives the cells a characteristic fading blue-green auto-fluorescence [14]. These retinoid droplets in stellate cells had a diverse distribution, which depended on the intralobular position of the cells. They are more concentrated in the periportal than in the pericentral regions [6]. Broadly speaking, there are two types of retinoid droplets [15]: (i). Small (up to 2 μm) and membrane bound Type I droplets that are derived from multivesicular bodies [16], and (ii). Large (up to 8 μm) Type II droplets that are not membrane bound. However, the functional difference between these two retinoid droplets is unclear [9].

4. Quiescent and activated hepatic stellate cells (HSC)

HSCs occur in two different physiologic states, quiescent or activated. Quiescent HSCs in normal liver are present in the subendothelial space of Disse, between the basolateral surface of hepatocytes and the antiluminal side of sinusoidal endothelial cells. Since the different compartments of the liver are intact in a normal state, HSCs do not come in contact with red blood cells (RBCs) or leucocytes (for example:

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Table 1
Characteristics and functional differences of quiescent and activated HSCs.

Quiescent HSCs/HSCs in Normal liver	Activated HSCs/HSCs in injured liver	Reference
Store 80–90% of liver vitamin A in the form of retinyl esters in cytoplasmic lipid droplets which consist of ~50–80% of total retinoid of the body	Lose lipid droplets	[6,18,163]
Decrease fibrogenesis	Increase fibrogenesis	[163]
Have round appearance with autofluorescence	Have large flat appearance	[163,187]
Proliferate less	Proliferate more via inducing PDGF-β, VEGF and FGF	[9]
Reduced ECM production	Increased ECM production	[9,188]
Express transcription factors that maintain HSC quiescence (PPAR-γ, FXR, PXR, LXR, RXR)	Express transcription factors that regulate inflammation and apoptosis (NF-κβ), ECM deposition, collagen expression and fibrogenesis (SMAD2, SMAD3, SMAD4, NF-1, AP-2), proliferation and α-SMA expression (AP-1, PPARβ)	[1639,30,189]
Are involved in vasoregulation through endothelial cell interactions	Transdifferentiate into α-SMA expressing contractile myofibroblasts, which contribute to vascular alterations and increased vascular resistance	[30]
Maintain immune tolerance via storing vitamin A and producing TGF-β	Produce intensified inflammation and immune regulation responses	[8,67,190]
Express high levels of surface class I MHC and low levels of T cell costimulatory molecules (CD40, CD80, and CD86)	Express high levels of class II MHC, adherent markers (ICAM-1 and VCAM) and programmed cell death markers (PD-L1 and Fas-L)	[191]
Are vital in development of intrahepatic bile ducts during development	Increased autophagy to induce fibrogenesis via lipid droplet mobilization, liberation of FFAs, and mitochondrial β-oxidation	[62,192]
Promote maturation of hepatic progenitors through cell-cell contact in culture		[193,194]

T lymphocytes and Macrophages) and therefore remain in their quiescent form [17,18]. In contrast, activated HSCs are prevalent during conditions or states that result in liver injury or inflammation. During inflammatory conditions associated with liver injury, the hepatocytes and sinusoidal endothelial cell layers that surround HSCs become damaged and consequently the resident HSCs come in contact with leucocytes that enter the space of Disse [17]. This cell-cell contact (i.e HSC-macrophage or HSC-T cell) and the cytokine milieu (i.e. IFN-γ, IL-10, TGF-β and IL-2) that is produced by different cell types in the space of Disse allows for activation of HSCs [19]. Activated HSCs change their shape and assume a large flat appearance. This activation process leads to loss of lipid droplets, increased proliferation and extracellular matrix (ECM) production by HSCs, which ultimately results in fibrosis.

The number, phenotype and cytokine profile of quiescent and activated HSCs in the liver are altered in different phases and conditions of liver injury. Generally, there are fundamental differences between quiescent HSCs and activated HSCs in normal and injured liver and these have been summarized in Table 1.

The activation of quiescent HSCs is the primary step that precedes their transdifferentiation into myofibroblasts. This process is facilitated through autocrine and paracrine stimulation of different mediators produced by several liver resident cell types and migratory inflammatory cells within the hepatic environment. Some of these cells and their produced mediators include, hepatocytes (producing IGF, ROS, TGF-β), KCs (producing TNF-α, ROS, TGF-β), existing myofibroblasts (producing TGF-β, PDGF), sinusoidal endothelial cells (producing VEGF, ICAM-1, TGF-β), $CD8^+$ T cells, neutrophils (producing ROS) and platelets (producing PDGF, EGF, and TGF-β) [8,20]. In addition to these mediators, potentially new molecules have also emerged from a microarray-based study. This study has identified novel genes such as CXCL14, survivin, septin 4, osteopontin, PRX1, LMCD1, GPR91, leiomodin, and anillin that are involved in diverse functions such as immunity, cell signaling and cellular dynamics [21].

Vitamin D receptor (VDR) expressed by quiescent HSCs, is downregulated upon activation [22]. Studies have shown that activation of HSCs can be negatively regulated by p62, a signaling adaptor and autophagy substrate protein, via the vitamin D receptor (VDR). p62 directly cooperates and enhances the heterodimerization of VDR and RXR (retinoid X receptor), which is essential for VDR:RXR target gene recruitment. There is impaired suppression of fibrosis and inflammation by VDR agonists following loss of p62 in HSCs [23].

MicroRNA (miRNA) levels change in HSCs during activation [24,25] and a recent microarray analysis of human quiescent HSCs showed 47 downregulated and 212 upregulated miRNAs [26]. Among these, let7A and let7B miRNAs have been shown to regulate HSC activation in response to LPS and TGF-β [27]. Overexpression of let7A and let7B suppressed myofibroblastic activation of HSCs as evident by downregulation of ACTA2, COL1A1, TIMP1 and FN1 [27] Similarly, there was increased expression of miR-27a and-27b in activated HSCs, and their downregulation led to reduced HSC proliferation and increase in lipid droplets suggesting that miR-27a and-27b may play key role in HSC quiescent phenotype [28]. It has also been shown that miR-27a and-27b directly targeted the 3′ -UTR of RXRα to inhibit its expression in HSCs leading to decrease in DNA synthesis and subsequent growth arrest [29,30].

5. Markers

HSCs can be identified through a variety of markers such as those from ectoderm origin (e.g. glial fibrillary acidic protein (GFAP), nestin, neurotrophins and their receptors, nerve growth factor (NGF), brain-derived neurotrophic factor, synaptophysin and N-CAM); and mesoderm origin (vimentin, desmin, α-SMA and hematopoietic markers) and Lecithin retinol acyltransferase (LRAT) [30].

GFAP was originally identified as a protein expressed by astrocytes and essential for restoring the blood-brain barrier following brain injury [31]. It is also expressed by HSCs and participates in remodeling the vasculature of damaged hepatic tissues during liver fibrosis [32]. GFAP is used both as a marker for quiescent HSCs [33] or as an early marker of HSC activation [34]. Desmin, originally known as muscle-specific type III intermediate filament, is expressed at low levels during early development of muscle cells and in higher levels as the cells near terminal differentiation [35]. Although reports indicate the presence of desmin positive HSCs around blood vessels in fetal liver [36], *trans*-differentiation of HSCs into myofibroblast has also been shown to be associated with increased desmin synthesis and formation of desmin-containing intermediate filaments in a vimentin dependent manner [36]. α-SMA, which is an actin isoform, was originally known to be a specific marker for smooth muscle cell differentiation [37]. However, activation and transdifferentiation of HSCs into myofibroblasts require enhanced expression of α-SMA and hence this molecule has been used as a marker for activated HSCs [38,39]. However, a recent report have argued for their specificity in activated HSCs and have demonstrated that α-SMA can also be a marker of quiescent HSCs in normal liver by using very sensitive detection techniques [40]. Lecithin retinol acetyl transferase (LRAT) is a physiological retinol esterification enzyme that incorporates retinol into the retina and adjusts its concentration to maintain visual function [41]. It also plays a role in storing systemic retinoid in rodent and human liver [42]. Recently, this marker has successfully been used to specifically identify liver HSCs by different

authors [42,43]. Synaptophysin is a plasma membrane protein primarily associated with neural tissues and is responsible for release and/or uptake of neurotransmitters in the synapse [44]. In both human and rodent liver, synaptophysin is expressed on the surface of activated HSC derived myofibroblasts [45]. Its extracellular domain can be internalized via endocytic vesicles. This property has been utilized to specifically target depletion of activated HSCs using human gliotoxin coupled with recombinant single-chain antibody (scAb termed C1-3 [46]) that targets the extracellular region of synaptophysin [47]. This has dramatically enhanced the specificity of HSC depletion because the use of only gliotoxin has been shown to stimulate the apoptosis of liver myofibroblasts [48] and to a lesser degree the apoptosis of hepatocytes and KCs [49,50].

6. Biological functions of HSCs

HSCs have varied functions in normal liver homeostasis ranging from liver regeneration and development, retinoid metabolism, extracellular matrix homeostasis, secretion of mediators, drug metabolism to detoxification of noxious substances and metabolites [18]. HSCs that express α-SMA, desmin, and vimentin, have been shown to promote maturation of hepatic progenitors [51,52]. Factors secreted by HSC such as epimorphin and pleiotrophin, promote liver organogenesis and regeneration and bile duct epithelial morphogenesis [53,54]. In addition, stellate cell precursors express hepatocyte growth factor (HGF), CXCL12, and homeobox transcription factors that support their role in liver development and hematopoiesis [55,56]. Other than retinoids, HSCs droplets also contain triglycerides, phospholipids, cholesterol, free fatty acids and proteins (perilipins) [57–60]. These lipid droplets regulate activation and possibly trigger autophagy in HSCs [61,62].

HSCs in the space of Disse produce ECM components like collagen 1, laminin, collagen III and IV [30,63]. Additional factors that regulate the development of ECM such as matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) are also produced by HSCs [64,65]. A Disintegrin and Metalloproteinase-domain proteins (ADAMs) that prevent TIMP action and contribute to trans- (TGF-β) activation [66], are also produced by HSCs and contributes to collagen I deposition and fibrosis [67,68]. Interestingly, a recent study in LRAT deficient mice showed that retinoids are not essential for fibrosis [69].

Besides participating in hepatic fibrosis, HSC-derived molecules are also critical in preserving liver homeostasis and promoting regeneration. Expression of VEGF by inactive stellate cells [70] is critical in communication and liver homeostasis. NGF, brain-derived neurotrophin, neurotrophin 3 and neurotrophin 4/5 are all expressed by HSCs [10] and contribute to HSC activation and tissue repair [10,55,71]. HSCs express both alcohol- and acetaldehyde- dehydrogenases and different isoforms of cytochrome p450 [72]. The production of different isoforms of cytochrome p450 by HSCs is downregulated during cellular activation [73]; and this might be important in xenobiotic detoxification and oxidant stress response [30].

7. HSC and immune regulation

HSCs regulate the hepatic immune system by directly or indirectly interacting with immune cells and thus contribute to the outcome of liver inflammation and disease. There is a bidirectional interaction between HSCs and hepatic immune cells. HSCs receive signals from leukocytes within the hepatic environment, amplify these signals and produce molecules that in turn target and modulate leukocytes. Specifically, HSCs promote leukocyte chemotaxis and adherence, and may also regulate activation of leukocytes within the hepatic environment by secreting immunoregulatory cytokines [74]. HSCs regulate chemotaxis of immune cells like neutrophils, macrophages/monocytes, NK/NKT cells, by releasing a wide variety of chemokines such as CCL2 [75], CCL5 [76], CCL21 [77], CCL4 [78], CX3CL1 [78–80], and others [79]. Many of these chemokines are also capable of directly modulating the activation, differentiation, proliferation, survival and apoptosis of immune cells. Furthermore, activated HSCs specifically promote ICAM-1 and VCAM-1 dependent adhesion and migration of lymphocytes [81].

HSCs display properties of antigen presenting cells (APCs) as they express members of the MHC (MHC class I and MCH class II), lipid-presenting molecules (CD1b and CD1c), and costimulatory molecules involved in T-cell activation (including CD40, CD80 and CD86). In the context of human fibrogenesis, HSCs can act as APCs as they highly express HLA-II and CD40 in human cirrhotic livers. Furthermore, activated HSCs are also capable for internalizing macromolecules and modulate T cell proliferation [82]. Functional studies have shown that HSCs can activate T cell responses by presenting lipid and protein specific antigens to CD1-d, MHC-I-, and MHC-II-restricted T cells [83]. However, a recent study using highly purified HSCs showed that they upregulate MHC class II only in response to IFN-γ stimulation [84], suggesting that at steady state, HSCs may not be equipped with the antigen presentation and costimulatory abilities. Consistent with an insufficient APC function, HSC were unable to activate naive OT-II TCR transgenic $CD4^+$ T cells and only moderately activated a-galactosylceramide–primed invariant NKT cells [84]. It has also been shown that HSCs alone cannot present antigen to naïve T cells and require retinoic acid, DCs and TGF-β1 to induce functional (mostly regulatory $Foxp3^+$) T cells [85]. This observation highlights the regulatory function of HSCs in immunity. Indeed, HSCs greatly enhanced Foxp3 expression by OT-II TCR transgenic T cells primed by DCs, whereas they significantly restricted Th17 differentiation [84]. HSCs also suppress adaptive immune responses via their expression of B7-H1 (PDL-1) and B7-H4 receptors, by inhibiting T cell responses either by inducing T cell apoptosis via B7-H1/PD-1 ligation or by inhibiting early T cell activation resulting in anergy [86,87]. Similarly, high expression of CD54 in HSCs prevents the activation of naïve T cells by DCs by restricting IL-2 and IL-2R expression on T cells [88]. This property of HSCs to indirectly affect T cell response has been proposed as an alternate mechanism employed by HSCs to mediate T cell suppression and tolerance in the liver [88].

Interactions between monocytes/macrophages and HSCs are among some of the important events that drive liver fibrogenesis. Activated HSCs release proinflammatory chemokines that attract monocytes [78–80], mainly the inflammatory $Ly6C^+$ subset, from the periphery into the injured liver [89]. TGF-β produced by these inflammatory monocyte-derived macrophages, activates HSC [90]. Indeed, a subset of $CD14^+CD16^+$ monocyte from patients with hepatic fibrosis, release inflammatory cytokines, thereby efficiently activating HSCs [91,92]. Studies from co-cultures of human HSCs and peripheral blood monocytes, showed that activated HSC are capable of inducing $CD14^+$HLA-DR-/low cells that suppressed T-cell proliferation via arginase 1 in a manner akin to monocyte-derived suppressor cells" (MDSC) [93]. Indeed, HSC has been shown to activate MDSC and this has been proposed to be one of the immune suppressive pathways employed by HSCs to regulate liver inflammation.

Apart from monocytes/macrophages, HSCs also interact with other cells including dendritic cells and NK cells. Although interaction of DCs with HSCs do not lead to HSC activation in co-culture systems, it leads to activation of NF-κβ dependent genes through an IL-1 and TNF-dependent mechanism [94]. However, HSCs are critical in DC development [94]. DCs exposed to HSCs or their supernatants express low CD11c, CD86, and MHC class II molecules, resulting in an inferior allostimulatory respones [30,94]. In addition to DCs, liver lymphocytes also contain significant numbers of NK as well as NKT cells which are capable of regulating HSC in liver fibrosis. NK cells are capable of selectively clearing early or senescence activated HSCs via their activating receptor NKp46.[95,96]. Similarly, human NK cells can kill HSC via apoptosis, in a TRAIL-, FasL- and NKG2D-dependent manner [97]. Presence of activating signals like IFN-γ or inhibiting signals like TGF-β regulate the NK cell-mediated cytotoxicity in HSCs [95,98]. On the other hand, NKT cells activate HSC via osteopontin and hedgehog

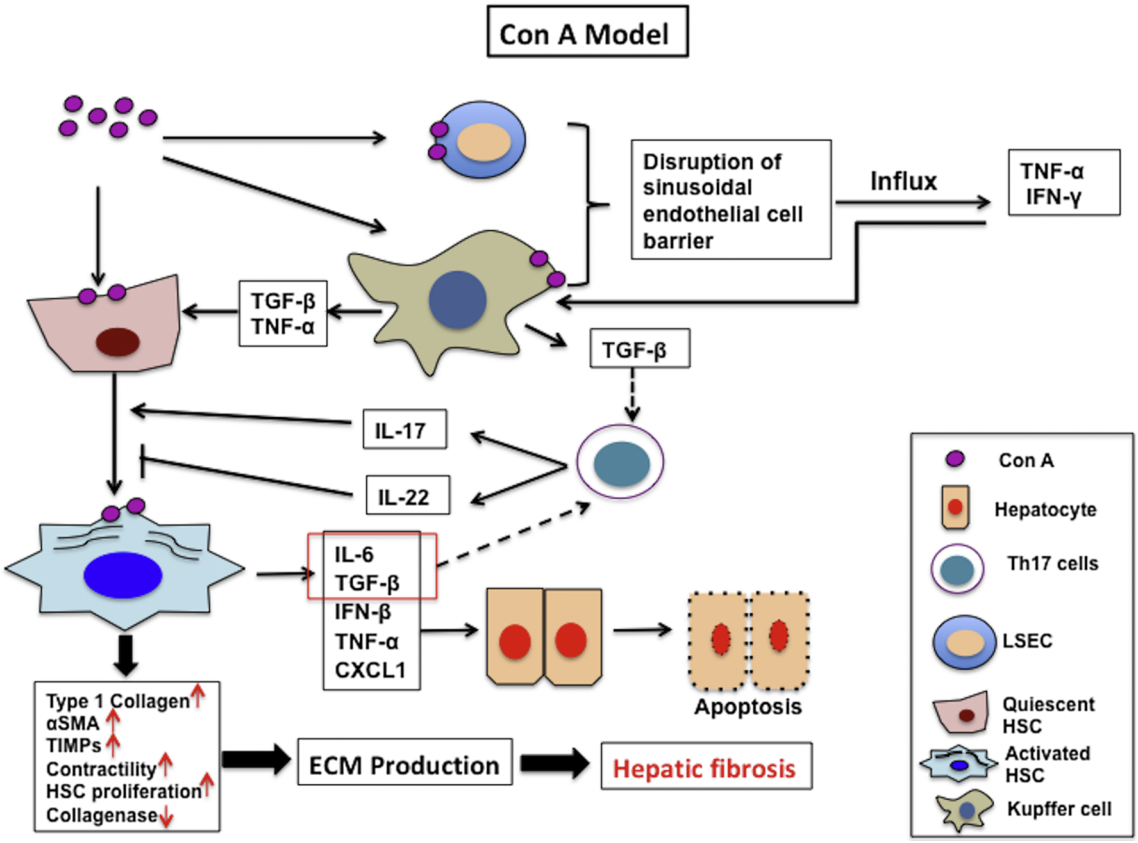

Fig. 1. Role of HSCs in fibrosis during Con A induced hepatitis. Con A binds to multiple cell types in the liver including liver sinusoidal endothelial cells (LSECs), HSCs and Kupffer cells. Binding of Con A to LSECs and Kupffer cells causes disruption of sinusoidal endothelial cell barrier resulting in influx of inflammatory cytokines like TNF-α and IFN-γ, that are released by the T cells in the periphery in response to Con A. HSCs are activated directly by Con A and indirectly by activated Kupffer cells- derived TGF-β and TNF-α, leading to the release of a wide array of cytokines and chemokines including IL-6, TGF-β, IFN-β, TNF-α and CXCL1. These cytokines act on hepatocytes resulting in their apoptosis. HSCs-derived IL-6 and TGF-β are also capable of promoting Th17 cells differentiation and activation leading to the production IL-17 and IL-22, cytokines that have been shown to inhibit (IL-22) or promote (IL-17) the activation of HSCs. Activated HSCs release Type 1 collagen, αSMA, and TIMP leading to increased ECM production, fibrin deposition and hepatic fibrosis.

ligands and promote liver fibrogenesis [99,100]. However, NKT cells can kill activated HSCs to promote anti-fibrotic mechanism [95,101].

8. HSC and liver inflammation

Liver serves as a primary lymphoid organ that is tasked with surveillance of the large and diverse antigens that the host encounter such as bacterial components and food antigens. During liver inflammation, hepatic sinusoids function as the gateway to inflammation. Hepatic sinusoids contain immune cells and endothelial cells which first encounter inflammatory signals, such as bacterial products or toxins that enter the liver through the portal circulation. Kupffer cells and leukocytes, which together constitute the hepatic immune cells, release copious amounts of inflammatory cytokines and chemokine that disrupt the endothelial cells and HSCs. Sinusoidal inflammation inflicts injury to the hepatocytes either through cytokines or by allowing entry of leukocytes into the liver parenchyma [102]. The immune regulatory role of HSCs have been demonstrated in different models of liver inflammation:

8.1. Concanavalin A (Con A)-induced hepatitis

Intravenous administration of Con A, a carbohydrate binding plant-derived lectin, activates intrahepatic and systemic immune cells resulting in massive liver damage [103,104]. Mechanistically, Con A targets Kupffer cells and sinusoidal endothelial cells by binding to their surface glycoproteins and disrupting sinusoidal endothelial cell barrier, thereby allowing inflammatory cytokines and sinusoidal cells to come in contact with HSCs and Kupffer cells [105,106]. The deleterious inflammatory cytokines like TNF-α and IFN-γ are released in the sinusoids in two waves. In the first wave, they are produced by Kupffer cells and T cells while in the second wave they are released by HSCs in a paracrine manner [102]. Moreover, Con A-treated HSCs showed increased expression of IFN-β, TNF-α, and CXCL1, which induce oxidative stress in hepatocytes resulting in their apoptosis [107]. Cytokine gene deletion and neutralization studies confirmed that TNF-α, IFN-γ and IFN-β contribute to liver damage in Con A induced hepatitis [107–110]. That HSCs play a key role in aggravating Con A-induced liver inflammation was confirmed by studies which showed suppression of Con A-induced inflammation in HSC-depleted mice along with reduced infiltration of neutrophils, $CD4^+$ T cells and NK T cells [107]. Likewise, other studies have also shown that stimulation of DP1, a receptor for prostaglandin D2, by selective agonist, BW245C, prevented HSC activation leading to suppression of Con A-induced hepatitis as evident by low amounts of inflammatory cytokines like TNF-α and IFN-γ. Furthermore, microarray gene expression studies of the liver identified numerous TNF-α-and/or IFN-γ–inducible proinflammatory genes including *iNOS*, *Tf*, *Edn1*, *Vcam1* and *Sele* that were inhibited following DP stimulation of HSCs [111].

HSCs have also been shown to control trafficking of $CD4^+$ T cells to the liver parenchyma. In Con A-treated mice, $CD4^+$ T cells were distributed in the liver parenchyma but upon HSC inactivation, these cells failed to enter the liver parenchyma [102,111]. In particular, Th17 cytokines, IL-22 and IL-17, have antagonistic effect on the outcome of

Con A-induced hepatitis by differentially regulating HSCs activities. IL-22, produced by $CD4^+$ Th17 cells [112] or innate lymphoid cells (ILCs) [113], plays a suppressive role in Con A-induced hepatitis by inducing senescence in HSCs and thereby restricting fibrosis. Indeed, HSCs have been shown to express IL-22R1 and IL-22 treatment of HSCs leads to phosphorylation of STAT3, a key signaling molecule that leads to induction of several proinflammatory genes. This also led to increase in senescence-associated beta-galactosidase-positive HSCs along with reduced expression of α-SMA in fibrotic livers [114]. On the other hand, IL-17A, produced by $CD4^+$ Th17 and neutrophils, activates HSC as evident by elevated mRNA expression of IL-6, α-SMA, collagen, and TGF-β, pointing towards a IL-17A–driven fibrotic process [115]. In line with this, IL-17A released during Con A-induced hepatitis, activates of HSCs resulting in increased collagen production [116] (See Fig. 1).

8.2. LPS/GalN induced hepatitis

LPS, a TLR4 agonist, injected simultaneously with D-galactosamine (GalN), a hepatotoxic agent, impedes protein biosynthesis and mediates killing of hepatocytes. This model of hepatitis is also called fulminant hepatitis, and several cytokines are known to be critical in the disease pathogenesis. Inflammatory cytokines such as IL-1, IL-6, IFN-γ TNF-α and IL-17 [111,117–119] are induced following LPS/GalN treatment and contribute to apoptosis and destruction of liver tissues. Studies with cytokine deficient and cytokine receptor deficient mice confirmed the role of TNF-α IFN-γ, IL-1 and IL-17 in promoting liver damage following LPS/GalN treatment [118–121]. Enhanced levels of TNF-α induced HMGB1 and the interaction of HMGB1-TLR4-IL-23 pathways leads to the generation of IL-17-producing T cells, which mediated hepatocyte apoptosis [119,122]. Furthermore, STAT1, a key signaling molecule for IFN-γ, was increased during inflammation and mice deficient in STAT1 were able to resist liver inflammation and apoptosis [123].

DP1 stimulation results in decreased levels of systemic and intrahepatic TNF-α resulting in suppressed LPS/GalN induced liver hepatitis, suggesting that HSCs contribute to production of inflammatory cytokines in LPS/GalN model of hepatitis [111]. Moreover, HSC depleted mice have low hepatic infiltration of neutrophils along with reduction in TNF-α and IL-6 levels following LPS/GalN administration [124]. HSCs also induced MMP-9 expression upon IL-1 stimulation following LPS/GalN treatment, which causes ECM degradation and collapse of sinusoids [118]. LPS/GalN treatment activates hepatic NLRP3 inflammasome resulting in increased levels of IL-1β. HSCs, which express inflammasome machinery [125], might therefore be involved in hepatic IL-1β production.

Although the liver can be infected by a wide variety of bacteria leading to hepatitis, pyogenic abscesses or granulomatous liver disease, not much is known about the interaction of HSCs with hepatotropic bacterial pathogens that do not possess LPS such as *Listeria*. It is conceivable that other bacteria components such as peptidoglycan, teichoic acids and lipoteichoic acids can regulate HSCs. Additional studies are needed to understand if these bacterial pathogens can possibly regulate HSCs to modulate host immunity.

8.3. Nonalcoholic steatohepatitis (NASH)

NASH is a disease condition that stems from intrahepatic inflammation together with hepatocyte damage with or without fibrosis [126]. It results from multifactorial parameters acting simultaneously, including genetic predisposition, abnormal lipid metabolism, oxidative stress, lipotoxicity, mitochondrial dysfunction, altered production of cytokines and adipokines, gut dysbiosis and endoplasmic reticulum stress [127]. Free fatty acids have also been implicated in the activation of cellular stress and hepatocyte apoptosis during NASH [128]. Apoptosis is induced by activation of TNF-related apoptosis-inducing ligand (TRAIL-R), Fas and tumor necrosis factor receptor (TNFR). A recent report showed that TRAIL-R deficient mice were resistant to NASH and had low steatosis, inflammation and fibrosis that is associated with low apoptosis of hepatocyte, supporting the importance of TRAIL-R-induced apoptosis in NASH [129]. Th1/Th2 imbalance may also contribute to the development of inflammation in NASH [130]. Typically, cytokines like TNF-α [131,132], IL-6 [133], TGF-a [134], IL-33 [130] and IL-1β [135] have been implicated in NASH. Studies have shown that inhibition of TNF-α decreased inflammation, necrosis, and fibrosis in NASH [136]. IL-6 has a paradoxical role in liver damage. Neutralization studies targeting IL-6 receptor showed increased hepatic steatosis, but improved liver damage during NASH [137]. In contrast, another study showed increased levels of IL-6 accompanied by marked decrease in hepatic IL-6/STAT 3 signaling that favors progression of NASH [138].

Given that HSCs produce and respond to these cytokines, they play important roles in NASH pathogenesis. Indeed, it has been shown that HSCs have increased sensitivity to TGF-β due to increased accumulation of free cholesterol in the cells resulting in exaggerated liver fibrosis in NASH [139]. Interestingly, it has been shown that TGF-β expression in HSCs is regulated by IL-β [140], an important proinflammatory cytokine that plays a key role in liver fibrosis. Inflammasomes contribute to IL-1β production in NASH and blockade of NLRP3 inflammasome led to reduction in liver inflammation and fibrosis [135]. Additional studies on HSCs, having functional NLRP3 machinery, might show its contribution to IL-1β-mediated immunopathology during NASH. Another cytokine that plays a key role in NASH is IL-13. Treatment with IL-13-PE38 (a cytotoxin directed against IL-13Rα2), led to a significant reduction in pathological features of NASH in rat liver [141]. IL-33, a Th2 cytokine belonging to IL-1 family, is produced by HSCs and there is increased expression of IL-33 and its receptor, ST2 in NASH [142]. Moreover, treatment with recombinant IL-33 resulted in enhanced activation of HSCs as observed by increased levels of α-SMA and aggravated hepatic fibrosis in NASH [130]. Th17 cells were increased in NASH [143] and *in-vivo* neutralization of IL-17 alleviated liver injury [143]. Similarly, studies with IL-17 KO mice showed that IL-22 was protective in NASH but had no effect in presence of functional IL-17 [144]. Given that HSCs are activated by IL-17A through STAT3 signaling [145], it is conceivable that the regulation of HSCs by IL-17A and IL-22 during NASH might provide additional mechanistic insights into how HSCs regulate liver inflammation (See Fig. 2).

8.4. HSC_S and infectious diseases

8.4.1. Viral hepatitis

Infection with Hepatitis C virus (HCV) causes hepatic damage resulting in fibrosis and cirrhosis [146]. HCV-induced liver fibrosis is primarily accompanied by activation of HSCs. HCV directly or indirectly activates HSC leading to profibrogenic response.[146] Studies have shown that E2 protein of HCV directly engages CD81 present on the surface of HSCs [147]. Additionally, HCV core proteins, NS3-NS5 interact with HSCs resulting in the induction of pro-inflammatory cytokines like RANTES, MCP-1, and IL-8 [148]. dsRNA from HCV has also been shown to induce HSC activation via TLR3 resulting in the production of Type 1 IFNs (IFN-α/β) [149]. Moreover, RIG-I, a cytoplasmic sensor of viral RNA, activated LX-2 cells (HSCs) producing Type 1 IFN (IFN-β) and Type III IFN (IFN-γ) [149].

HSCs can also be activated indirectly by HCV-infected hepatocytes via TGF-β1 and other profibrogenic factors [150]. HSCs are capable of engulfing apoptotic bodies, released from infected apoptotic hepatocytes, through phagocytosis, which triggers a profibrogenic response [151,152]. Moreover, these activated HSCs also release IL-1α, which in turn stimulates HCV-infected hepatocytes, resulting in the induction of proinflammatory cytokines and chemokines such as IL-6, IL-8, MIP-1α and MIP-1β [153]. Other studies have also shown indirect activation of HSCs by ubiquitin carboxy-terminal hydrolase L1 (UCHL1), a novel secreted protein from HCV-infected hepatocytes that activate JNK signaling resulting in overexpression of α-SMA and subsequent activation of HSCs [154].

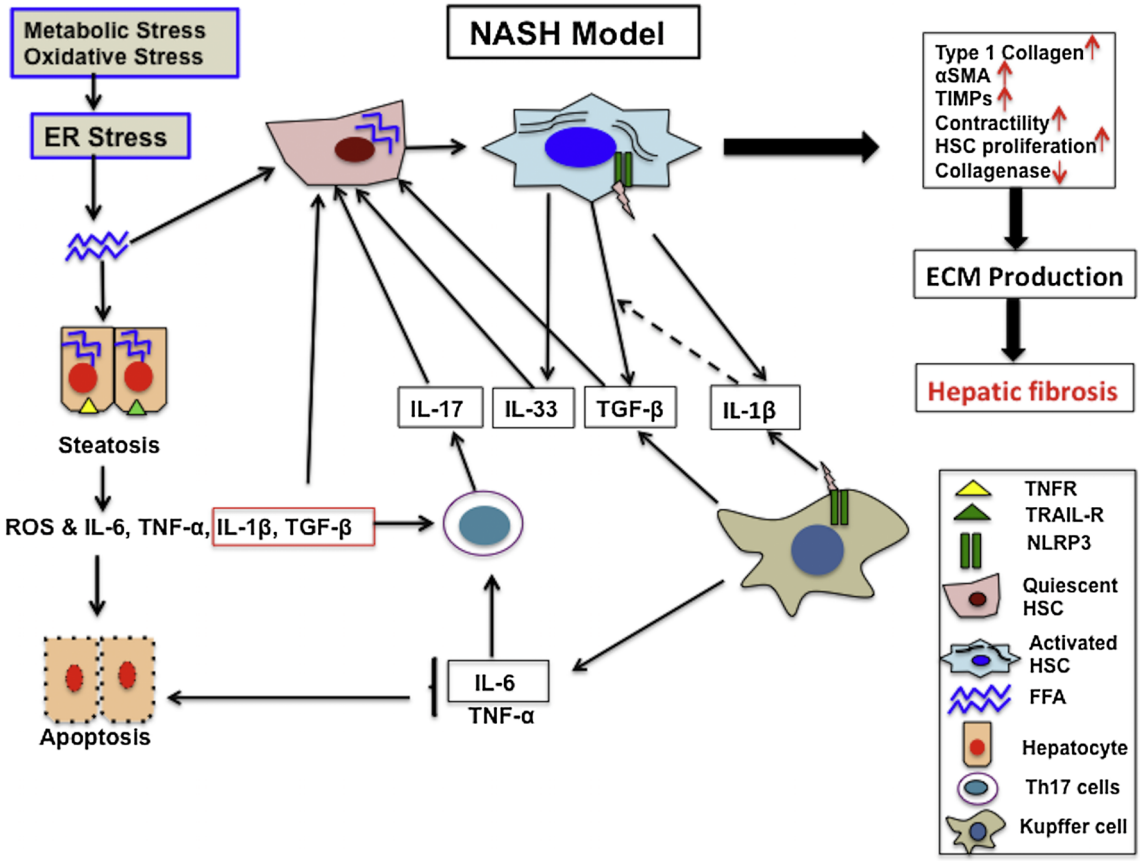

Fig. 2. Role of HSCs in fibrosis during NASH. NASH arises from multifactorial parameters such as genetic predisposition, abnormal lipid metabolism, oxidative stress, lipotoxicity, mitochondrial dysfunction, altered production of cytokines and adipokines, gut dysbiosis and endoplasmic reticulum (ER) stress. These events ultimately result in cellular metabolic and oxidative stresses in the endoplasmic reticulum leading to the release of free fatty acids (FFA). The uptake of FFAs by hepatocytes leads to the production of ROS and a wide variety of cytokines like IL-6, TNF-α, IL-1β & TGF-β, that results in the apoptosis of the hepatocytes. FFAs are also capable of directly activating HSCs. Additionally, HSCs can be activated by hepatocyte- and Kupffer cell- derived IL-1β & TGF-β and Th17 cell-derived IL-17. These activated HSCs produce cytokines like IL-33, IL-1β and TGF-β. Moreover, IL-1β is capable of regulating TGF-β expression in HSCs. These activated HSCs also release Type 1 collagen, αSMA, and TIMP leading to ECM production, which results in hepatic fibrosis.

During chronic hepatitis B virus infection, activated HSCs release IL-6 and IL-1β resulting in Th17 activation. IL-17 produced by the Th17 cells stimulates HSCs via the IL-17R, leading to upregulation of profibrogenic factors like IL-6, TGF-β, α-SMA and collagen [115,155], suggesting that IL-17 has a critical role in the fibrotic process. Similarly, IL-22 also participates in HCV associated fibrotic process by activating HSCs. Moreover, IL-22 also participates in LX-2 cell proliferation, overexpression of α-SMA, and up-regulation of collagen production by LX-2 cells [156]. IL-18, a member of the IL-1 family, promotes proliferation of HSCs during HCV infection by regulating the activation of c-jun levels [157] (See Fig. 3).

8.4.2. Leishmaniasis

Leishmania (*L*) *donovani*, a protozoan parasite and the causative for Visceral leishmaniasis (VL) targets the spleen and liver [158] of infected mammalian hosts. The disease causes pathological and functional changes in the liver, resulting in chronic mononuclear cell infiltrations, degeneration of hepatocytes, and focal fibrosis [159]. Although the exact causes of these changes are unknown, they were speculated to be immunologically driven. Studies have shown that HSCs play a key role in regulating immunity in VL. In an *in vitro* study, *L. donovani* was shown to moderately infect HSC [160]. Furthermore, a recent *in vivo* study showed heavily infected HSCs that displayed enhanced expression of MHC class II and CD86 molecules. These cells produced a plethora of immunoregulatory cytokines like TNF-α, IL-1β, IL-6, IL-4, IL-2, IL-10 and TGF-β. These observations clearly show that *Leishmania* infection is capable of activating HSCs. Moreover, *Leishmania* infected HSCs also induce $CD4^+CD25^-$ T cells to become T regulatory cells via a p110δ-dependent manner. Furthermore, *L. donovani* infected $p110\delta^{D910A}$ mice had fewer numbers of HSCs than their WT counterpart mice, suggesting that signaling via the p110δ isoform of PI3K regulates HSCs expansion. Interestingly, $p110\delta^{D910A}$ HSCs failed to expand and transdifferentiate into myofibroblasts. Furthermore, both naive and *L. donovani*–infected $p110\delta^{D910A}$ HSCs had reduced ability to induce $CD4^+CD25^-$ T cells into $Foxp3^+$ T regulatory cells. The role of HSC in disease pathogenesis and in regulation of expansion and functioning of T regulatory cells was confirmed using targeted HSC depletion using C1-3-gliotoxin that resulted in reduction of hepatic T regulatory cell number and its proliferation, which was associated with a decrease in IL-10 production by hepatic T cells leading to an efficient parasite control [161]. Collectively, these studies showed that *Leishmania* activates HSCs in a p110δ-dependent signaling pathway resulting in the release of immune regulatory cytokines and a concomitant induction and proliferation of hepatic T regulatory cells which promote immunosuppressive milieu that favors parasite survival (See Fig. 4).

8.4.3. Schistosomiasis

Schistosomiasis is a neglected tropical disease that affects millions of people worldwide. The hallmarks of this disease are fibrosis and hepatic granuloma, which causes portal hypertension and variceal bleeding [162]. HSCs play a key role in granulomatous and fibrotic

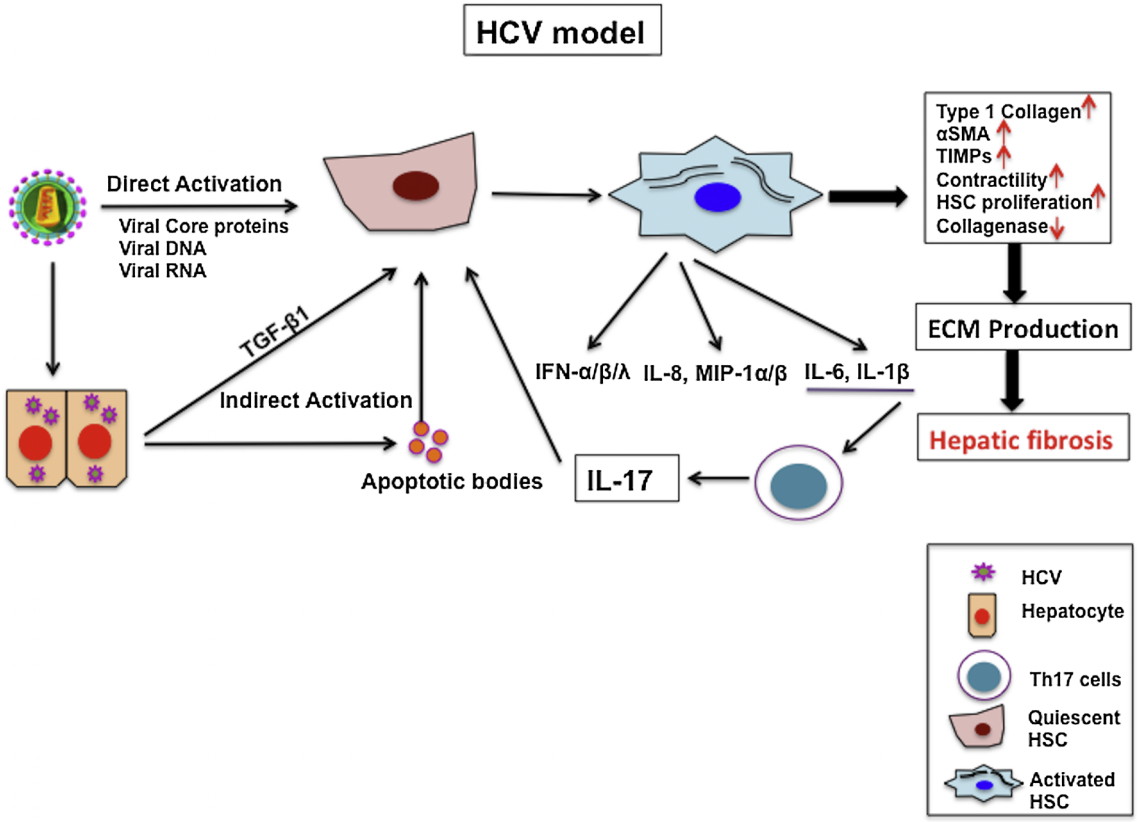

Fig. 3. Role of HSCs in fibrosis during HCV infection. HCV can directly activate HSCs via its core proteins, viral DNA or RNA or indirectly via apoptotic bodies and TGF-β1 that are being released by HCV infected hepatocytes. Activated HSCs release a wide array of cytokines like IFN-α/β/λ, IL-8, MIP-1α/β, IL-6, IL-1β. In particular, IL-6 and IL-1β are capable of activating Th17 cells, which produces IL-17 and that drives the activation of HSCs. Activated HSCs release Type 1 collagen, αSMA, and TIMP leading to increased ECM production, fibrin deposition and hepatic fibrosis.

process during human and experimental murine schistosomiasis [163,164]. *Schistosoma* have been shown to directly regulates the activation of HSCs. In an *in vitro* study with human HSC cell line, LX2, *S. mansoni* eggs were able to downregulate the activation of HSCs and caused regression of the LX-2 cell line into quiescent vitamin A-storing cells characterized by increased expression of PPAR-γ [165]. However, *S. japonicum* eggs induced proinflammatory response in HSCs as evident by the increased expression of MMP-9, CCL2 and IL-6, suggesting *Schistosoma* eggs activate proinflammatory phenotype rather than inducing complete HSC quiescence [166]. Studies have also shown that Schistosomal egg antigen induces IL-1β production via NLRP3-inflammasome in HSCs and thus serves as an early mechanism to turn on the inflammatory response [167].

Typically, HSCs promote both fibrotic and antifibrotic hepatic responses depending on the stage of disease. During the acute phase of *S. japonicum* infection, desmin and α-SMA were detected at the edges of granulomas showing HSC activation [168]. Moreover, the early phase of infection is accompanied by hepatic inflammation. During the early phase of infection, NF-κB was elevated in HSCs, which resulted in increased production of chemokines like CCL2, CCL3 and CCL5 in HSCs [169]. On the other hand, during the chronic and advanced phase of schistosomiasis, there was reduction in the size of the egg granulomas suggesting a reversal of liver fibrosis. Schistosoma promoted this antifibrotic pathway by inducing senescence of activated HSCs. Soluble egg antigens of Schistosoma induced senescence of activated HSCs via STAT3/P53/P21 [170] and/or FoxO3a/SKP2/P27 [171] pathways. Cytokines like, IL-13 and IL-21 also participates in fibrosis during *S. japonicum* infection by activating HSCs. IL-21 activated HSCs might drive more hyaluronic acid production resulting in liver pathology [172]. Likewise, IL-13 mediated induction of HSCs results in the production of profibrogenic factor, cytokine connective tissue growth factor (CTGF) [173]. During schistosomiasis, increased levels of CTGF are associated with fibrosis, which might result from the ability CTGF to increase collagen production [174].

9. HSC mediated therapy and future directions

Because of their pivotal role in inflammation and pathogenesis of liver fibrosis, HSCs are prime targets for therapy against several liver diseases where inflammation and fibrosis play critical roles in the disease process. Therapeutic strategies targeting HSCs to prevent liver fibrosis include inhibition of HSC activation and proliferation, stimulation of HSC apoptosis and infusion of mesenchymal stem cells. Because HSCs are activated in response to oxidative stress, antioxidants such as vitamin E, silymarin, phosphatidylcholine, and S-adenosyl-L-methionine interfere with their activation. This might prevent hepatocytes from undergoing apoptosis thereby resulting in improved outcome during hepatic fibrosis [20]. Alternatively, inhibiting signaling pathways such as PI3K [161], NF-κβ [175], Wnt/β –catenin [176,177], hedgehog [178] and others that activate HSCs, using specific inhibitors such as Pentoxifylline [175], PRI-724 [177], ICG001 [179] and 17-AAG [178] inhibits HSC activation and proliferation and may ameliorate hepatic inflammation and fibrosis.

Cytokine receptor antagonists for TGF-β and PDGF target the proliferative, fibrogenic, or contractile responses of HSCs and have emerged as potential antifibrotic agents [180]. Imatinib mesylate (STI-571), a clinically proven PDGF receptor (PDGFR) tyrosine kinase inhibitor, targets activated HSCs by significantly inhibiting PDGF-induced proliferation and migration, and α-SMA and α2-(I)-procollagen levels [181]. Camostat mesylate prevents excessive generation of active TGF-β, thereby attenuating porcine serum-induced rat hepatic fibrosis [182]. Dual inhibition of PDGF and TGF-β with a combination of

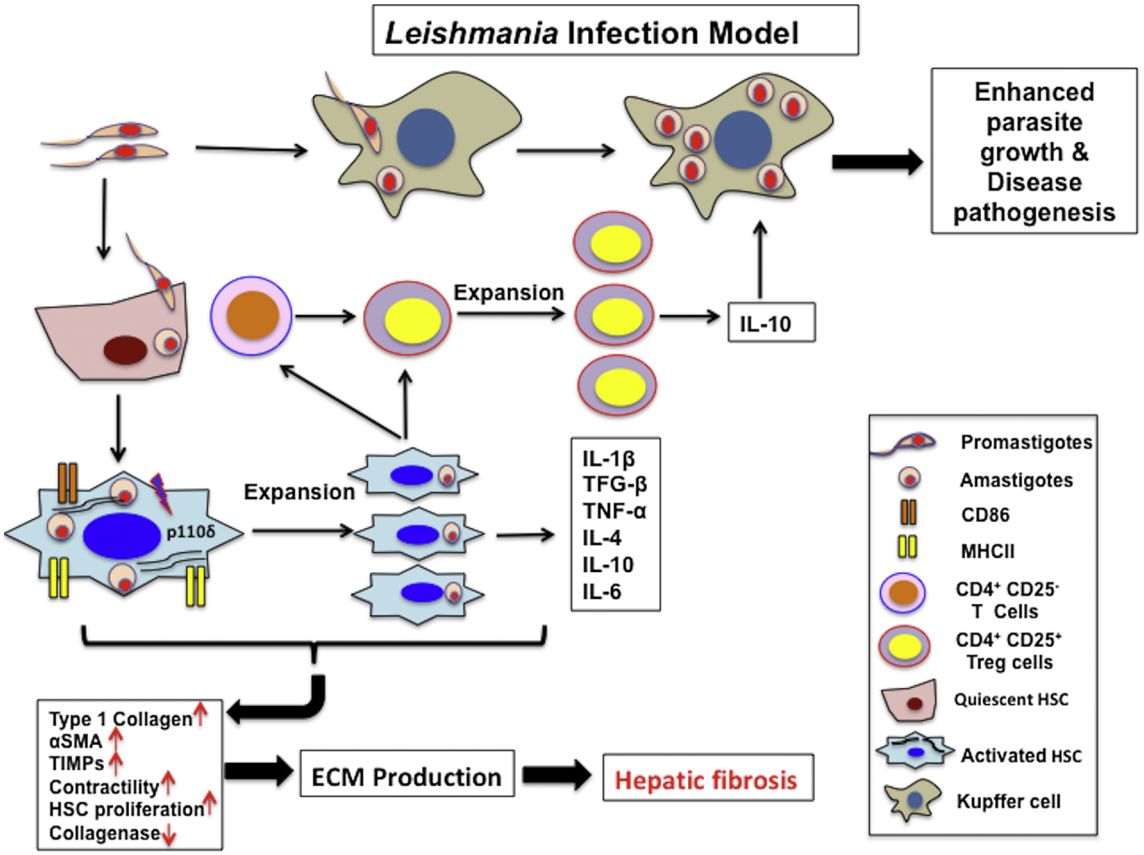

Fig. 4. Role of HSCs in fibrosis during *Leishmania* infection. *Leishmania* donovani primarily infects Kupffer cells in the liver. In addition, Leishmania also infects HSCs resulting in its activation and upregulation of CD86 and MHC Class II molecules via p110δ-dependent signaling pathway. Infected and activated HSCs proliferate and produce a wide array of inflammatory and immunoregulatory cytokines including TNF-α, IL-1β, IL-6, IL-4, IL-2, IL-10 and TGF-β. Activated HSCs also produce increased amounts of Type 1 collagen, αSMA, and leading to increased ECM production and hepatic fibrosis. Moreover, *Leishmania* infected HSCs also induce $CD4^+CD25^-$ T cells to become T regulatory (Treg) cells via a p110δ-dependent manner and also mediates Treg expansion. IL-10 derived from these Tregs inhibits activation and parasiticidal activities of infected Kupffer cells resulting in enhanced parasite growth and disease pathogenesis.

imatinib mesylate and an ACE inhibitor (perindopril) reduced liver fibrosis in rats [183]. Selective induction of apoptosis in HSCs can be another therapeutic route for curing liver fibrosis. Pharmacological agents such as gliotoxin [50], curcumin [184] and bortezomib [185] induce apoptosis in HSCs thereby inhibiting hepatic fibrogenesis. Mesenchymal stem cells (MSCs) regulate the functioning of activated HSCs via paracrine mechanisms, thereby mediating protection in liver inflammation and fibrosis. Blocking IL-10 and TNF-α derived from MSC abolished the MSC induced suppression on HSC proliferation and collagen synthesis [186].

10. Concluding remarks

Due to their strategic location in the sub-endothelial space of Disse, HSCs are in contact and interact with myriads of other cell types during liver injury and/or inflammation. The fact that HSCs are found mainly in the liver but not in other organs or tissues suggests that they may play a unique role in the pathogenesis of liver inflammation. In this context, it raises some key questions such as: (i) Why are HSCs unique to the liver? (ii) How do they uniquely regulate and/or alter liver inflammation distinct from that observed in other organs or tissues that lack HSCs? (iii) Why does the liver rely so much on HSCs for regulating inflammation despite the presence and high abundance of several different immune cells in its tissue?

The liver is an immunologically complex organ that is involved in several physiologic processes such as digestion, cellular metabolism, nutrient storage and detoxification of harmful drugs and metabolites. Moreover, it also functions as an important buffer between gut microbes and systemic circulation [187–190]. The mammalian body must have evolved to adequately preserve and maintain homeostasis in such complex and vital organ as the liver. HSCs are unique in terms of their ability to maintain hepatic homeostasis and regeneration as well as critical functions during the pathogenesis of liver diseases. Other than its involvement in liver fibrogenesis, HSCs also regulate inflammatory as well as immunological processes in injured liver.

The ability of HSCs to act as a control switch or thermostat in the liver endows them with critical regulatory properties to ensure maintenance of liver homeostasis and hence proper liver function. HSCs are capable of sensing various stimulatory signals, including microbial products, metabolites toxins and others, and tailor their responses to these signals by either promoting or suppressing hepatic inflammation [17]. HSCs can directly promote hepatic inflammation by secreting inflammatory cytokines such as IL-6, IL-1β, TNF-α, IFN-γ and others [107,111] or indirectly by activating T cells to secrete inflammatory cytokines such as IL-17, IFN-γ and others [115,155]. On the other hand, HSCs can also suppress hepatic inflammation and mediate tolerance directly by secreting inhibitory cytokines or indirectly by regulating immune cells. IL-10 secreted by HSCs, has potent immunosuppressive activity along with prominent anti-fibrogenic activity [192,193]. HSCs can also activate MSDCs, which can inhibit T cell proliferation via arginase 1, indoleamine 2,3-dioxygenase (IDO), IL-10 and TFG-β [194]. Regulatory T cells that are critical in mediating immunosuppression can also be activated by HSCs in a p110δ dependent pathway [161]. Liver regeneration is also promoted by HSCs by releasing pro-regenerative factors such as IL-6, TNF-α and HGF [189,191]. ECM secreted by HSCs, serves as a platform for the proliferation of hepatocytes and maintains

mechanical stability in damaged regions besides restructuring the architecture of the injured tissue [195,196]. HSCs via its secretion of CCL2 mediate recruitment of inflammatory Ly6C^{hi} macrophages that are pro-fibrotic in nature [89,90,197]. HSCs also regulate the activities of Ly6C^{lo} restorative macrophages that exhibit pro-resolution activities in the liver such as increased expression of fibrinolytic MMP9 and MMP12 [197]. Thus, after inflammation, HSCs mediate a switch of macrophages from pro-inflammatory anti-inflammatory and/or restorative phenotypes. Together with the disappearance of pro-fibrotic macrophages, this HSC-mediated phenotypic change play important roles in liver regeneration and ECM resorption.

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