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Review

Origins and functions of liver myofibroblasts ☆

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ABSTRACT

Myofibroblasts combine the matrix-producing functions of fibroblasts and the contractile properties of smooth muscle cells. They are the main effectors of fibrosis in all tissues and make a major contribution to other aspects of the wound healing response, including regeneration and angiogenesis. They display the *de novo* expression of α-smooth muscle actin. Myofibroblasts, which are absent from the normal liver, are derived from two major sources: hepatic stellate cells (HSCs) and portal mesenchymal cells in the injured liver. Reliable markers for distinguishing between the two subpopulations at the myofibroblast stage are currently lacking, but there is evidence to suggest that both myofibroblast cell types, each exposed to a particular microenvironment (*e.g.* hypoxia for HSC-MFs, ductular reaction for portal mesenchymal cell-derived myofibroblasts (PMFs)), expand and exert specialist functions, in scarring and inflammation for PMFs, and in vasoregulation and hepatocellular healing for HSC-MFs. Angiogenesis is a major mechanism by which myofibroblasts contribute to the progression of fibrosis in liver disease. It has been clearly demonstrated that liver fibrosis can regress, and this process involves a deactivation of myofibroblasts, although probably not to a fully quiescent phenotype. This article is part of a Special Issue entitled: Fibrosis: Translation of basic research to human disease.

1. Introduction

Myofibroblasts are the main effectors of fibrosis in all tissues. They also make a major contribution to other aspects of the wound healing response, including regeneration, inflammation, angiogenesis, normal tissue repair after acute injury and to the stromal reaction in tumors. They combine phenotypic features of fibroblasts, such as the production of extracellular matrix, with the contractile functions of the smooth muscle cells involved in tissue architecture distortion. Myofibroblasts may be defined as cells that develop contractile force and stress fibers, *de novo*, and *in vivo* [1]. The most widely used and accessible marker of these cells is the *de novo* expression of α-smooth muscle actin (α-SMA), although this is not an absolute requirement for the identification of a cell as a myofibroblast. Other markers of myofibroblasts (endosialin, P311, integrin α11β1, osteopontin, periostin) have been proposed, but all were identified in specific conditions, and it remains unclear whether they could serve as general markers [1]. The precursors of myofibroblasts have also yet to be identified. In most tissues, myofibroblasts are thought to originate from resident fibroblasts, but they may also be derived from other cell types, mostly of mesenchymal origin, such as vascular smooth muscle cells, pericytes and adipocytes. There is also evidence to suggest that myofibroblasts may be derived from circulating fibrocytes or resident epithelial cells, through epithelial-to-mesenchymal transition, although recent studies argue against a significant contribution of these mechanisms to fibrosis. In addition, resident fibroblasts are themselves heterogeneous and may even include antifibrotic subpopulations, such as lung Thy-1-expressing fibroblasts [2].

2. Origins of myofibroblasts in liver fibrosis

Myofibroblasts are absent from the normal liver, but they accumulate at sites of injury, in patients with chronic liver diseases. They are the major source of extracellular matrix constituents in the injured liver, as clearly demonstrated by clinical and experimental studies. However, although myofibroblasts appear to be necessary for the development of fibrosis, they may not be sufficient. For example, in scleroderma [1] and focal nodular hyperplasia (unpublished personal observation), the liver may contain large numbers of myofibroblastic cells without significant fibrosis. In the liver, as in

Abbreviations: α-SMA, α-smooth muscle actin; HSC, hepatic stellate cell; PMF, portal myofibroblast

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other tissues, the origin of myofibroblasts is a matter of debate. During liver development, the septum transversum-derived mesothelium, which signals to induce hepatogenesis from the foregut endoderm, gives rise to sinusoidal pericytes, called hepatic stellate cells (HSCs), and perivascular mesenchymal cells, including portal fibroblasts, smooth muscle cells and fibroblasts around the central veins [3]. All these cells therefore have a common mesodermal origin, different from that of sinusoidal endothelial cells, Kupffer cells and hepatoblasts. It is now more than 35 years since the initial demonstration by Hans Popper and coworkers that transitional cells with the morphologic characteristics of vitamin A-containing cells (*i.e.* HSCs) and fibroblasts, overproduce fibrillar collagen in rats with carbon tetrachloride-induced liver injury [4]. The paradigm of hepatic stellate cell (HSC) activation giving rise to myofibroblasts has since dominated the focus of research on liver fibrosis [5]. HSC was the first major cell type in the liver to be identified as a prominent source of collagen production in the injured liver [6], and to be shown to acquire a myofibroblastic phenotype in culture, with the ability to overproduce extracellular matrix, to contract and to undergo chemoattraction [7–10]. The factors and mechanisms triggering the myofibroblastic differentiation of hepatic stellate cells have been reviewed extensively elsewhere [5]. They include biological (*e.g.* lipopolysaccharide) [11], physicochemical (*e.g.* hypoxia) [12] and mechanical (*e.g.* substrate stiffness) [13] stimuli. There is now both *in vitro* and *in vivo* evidence for the existence of more than one origin of liver myofibroblasts. In preparations of cells isolated from the liver, HSCs are recognized by the fluorescence of their retinoid droplets under UV excitation at a wavelength of 328 nm. Culture studies have clearly demonstrated that other liver cell types, without fluorescent retinoid droplets, can give rise to myofibroblasts [14,15]. *In situ* ultrastructural studies have shown that fibroblasts reside in the portal mesenchyme and accumulate, with fibrosis, around bile ducts in bile duct-ligated rats [16], precisely in the zones in which α-SMA can be detected [15]. Moreover, immunohistochemical studies have shown that, in fibrotic human or rat liver, portal and septal myofibroblasts have expression profiles different from those of interface myofibroblasts or sinusoidally located HSCs, suggesting that at least two subpopulations of myofibroblasts — HSC-derived myofibroblasts (HSC-MFs) and portal mesenchymal cell-derived myofibroblasts (PMFs) — populate the injured liver [17]. The possible contribution of epithelial-to-mesenchymal transition to renal fibrosis *in vivo* has been challenged by studies based on genetic cell lineage tracing in mice [18]. Likewise, studies based on genetic cell fate tracking have strongly challenged the concept that either hepatocytes or cholangiocytes acquire a mesenchymal phenotype *in vivo* through epithelial-to-mesenchymal transition to produce the extracellular matrix in liver fibrosis [19–21]. A number of studies have also suggested that circulating cells from the bone marrow can function as stem cells, contributing to the liver myofibroblast population [22]. However, a recent study based on a system for the exclusive detection of bone marrow-derived collagen-producing cells, showed that bone marrow-derived cells played a limited role in collagen production during liver fibrosis [23].

3. Portal myofibroblasts

In almost all types of chronic liver disease, including biliary (*i.e.* primary biliary cirrhosis, biliary atresia), viral, alcoholic and non-alcoholic fatty liver diseases, fibrosis develops predominantly in the portal area and appears to progress from this area, even if the primary targets of injury are intralobular hepatocytes [24–28]. This observation suggests that the contribution of PMFs to liver fibrosis may be more important than generally assumed. Furthermore, in chronic liver diseases of various origins, including viral hepatitis and non-alcoholic fatty liver disease, fibrogenesis is associated with the occurrence of a ductular reaction, in which duct-like cells with progenitor features proliferate, expanding outwards from the portal area. The correlation between the extents of the ductular reaction and of replicative senescence in hepatocytes suggests that ductular/progenitor cells may be recruited in situations in which the regeneration of mature hepatocytes is impaired. One possible explanation for this is that ductular/oval cells are less sensitive to TGF-β-induced growth inhibition than hepatocytes [29]. Several potential mechanisms by which cholangiocytes or hepatic progenitor cells may promote fibrogenesis (Fig. 1) have been reviewed elsewhere [30] and new mechanisms have recently been put forward. Ductular/progenitor cells may act on matrix accumulation directly, through the release of tissue inhibitor metalloprotease 1 (TIMP1), for example [31]. They may act on myofibroblasts by releasing promitogenic, profibrogenic, chemotactic or anti-apoptotic factors. Hepatic progenitor cells have been shown to increase hepatic fibrogenesis, in an experimental model in which rat liver fibrosis is induced by chronic treatment with a combination of carbon tetrachloride and acetylaminofluorene, promoting activation of the hepatic progenitor cell compartment [32]. Chronic treatment with carbon tetrachloride alone caused liver fibrosis, which began around the central veins, eventually extending to form incomplete centro-central septa with sparse fibrogenic cells expressing α-smooth muscle actin. In acetylaminofluorene/carbon tetrachloride-treated animals, the fibrogenic response was strongly amplified and an expansion of the subpopulation of hepatic progenitor cells expressing transforming growth factor-β (TGF-β) was observed. In this model, hepatic progenitor cells, through their production of TGF-β, contributed to the accumulation of α-SMA-positive myofibroblasts in the ductular reaction, enhancing fibrosis but also leading to disease progression and a pattern of fibrosis similar to that observed in humans. Furthermore, ductular cells produce much more αvβ6 integrin than normal cholangiocytes. This molecule is closely linked to periductal fibrogenesis, through the activation of TGF-β [33]. Ductular cells secrete growth arrest-specific protein 6 (Gas6), which protects myofibroblasts against apoptosis [34]. A role for the hedgehog pathway in the interaction between ductular cells and portal myofibroblasts was also recently highlighted. Both cell types produce hedgehog ligands, thereby enhancing each other's viability and proliferation, and the activation of this pathway in mice amplifies both the ductular and fibrogenic responses triggered by bile duct ligation [35]. Notch signaling is essential to the development of tubular epithelial cells in the kidney, and activation of this pathway in tubular cells has been implicated in renal fibrosis [36]. Notch signaling is also essential in biliary differentiation and has recently been shown to be activated in rat experimental liver fibrosis. In this context, high levels of Notch3, Jagged1 (a Notch ligand) and Hes1 (a downstream target gene) were observed and the blocking of Notch signaling activation by a γ-secretase inhibitor significantly attenuated portal fibrosis [37]. In Alagille syndrome, a disease caused by genetic defects of Notch signaling and characterized by severe ductopenia, reactive ductular cells and hepatic progenitor cells are very rare and liver fibrosis is much less severe than in biliary atresia, a disease in which an intense ductular reaction is associated with rapid progression to biliary cirrhosis [38]. The importance of the Notch pathway in liver fibrosis has also been demonstrated in double-heterozygous mice haploinsufficient for both Jagged1 and another gene (Lunatic) altering ligand–receptor affinity. In this model, intense ductular proliferation contrasted with low levels of fibrosis [39]. Finally, hepatic progenitor cells have been shown to produce adipokines. In pediatric non-alcoholic fatty liver disease, the degree of fibrosis is related to the production of resistin [28], an adipokine with proinflammatory effects on HSCs [40] and hepatic progenitor cells.

No reliable markers have yet been identified for distinguishing between HSCs and portal mesenchymal cells at the myofibroblast stage. We have established a culture model for PMFs obtained by outgrowth from rat bile duct preparations [15]. These cells have several features in common with rat liver myofibroblasts [14,41]

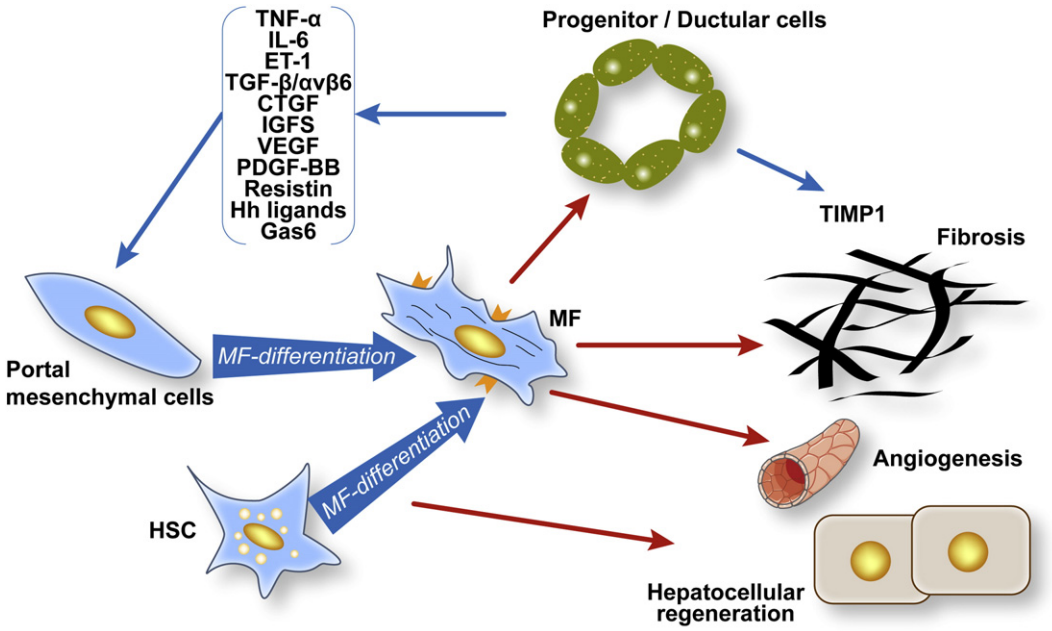

Fig. 1. Interaction of ductular/hepatic progenitor cells with liver myofibroblasts in wound healing. Ductular/hepatic progenitor cells bidirectionally interact with myofibroblasts, through multiple pathways, to proliferate and trigger profibrogenic, proangiogenic and/or proregenerative actions, depending on their origin and microenvironment.

and with portal fibroblasts in culture [41] obtained by other isolation procedures, and can be distinguished from HSC-MFs on the basis of morphological criteria and growth behavior. Their myofibroblastic differentiation requires TGF-β and mechanical tension [41], and can be triggered by PDGF-BB [41] or bile acids [42]. Following isolation from normal rat liver and culture in the same conditions, HSC-MFs are round, with an enlarged cytoplasm and poor survival after three or four passages, whereas PMFs tend to be more elongated, with more stress fibers, and proliferate more strongly during multiple passages [43]. Desmin production is differentially regulated, being upregulated during activation in HSCs and shut down in portal fibroblasts. Staining for desmin might therefore be useful for distinguishing between the two cell populations at the myofibroblast stage [15,16,41,44]. In two models of cholestatic liver injury induced by bile duct ligation and hepatic arterial deprivation, fibrosis involves myofibroblasts that are predominantly desmin-negative and, thus, presumably, of portal origin [45]. In these models, HSCs undergo massive early phenotypic changes, marked by increases in proliferation and desmin overproduction [44,45], but only a minority of these cells are converted into matrix-producing myofibroblasts, which, after prolonged injury, appear to circumscribe wounded hepatocytes to form micronodules [45].

We investigated the relative contributions of PMFs and HSC-MFs to various aspects of the liver wound-healing response, by comparing these two cell populations at similar stages of myofibroblastic differentiation (*i.e.* with similar levels of α-SMA) in culture, by comparative 2-DE MS/MS proteomic analysis [43]. We identified proteins displaying differentially expression, all with myofibroblast-related functions, in PMFs. Phospho-cofilin, a small actin-binding protein that accumulates during myofibroblast differentiation and promotes stress fiber formation and collagen contraction, was the protein for which the difference in levels was the greatest. Most of the proteins overproduced in HSC-MFs were involved in stress responses, relating to hypoxic stress in particular, in keeping with the interplay known to occur between interlobular hypoxia, angiogenesis and fibrogenesis in the liver [46]. The protein displaying the highest level of overproduction in these cells was cytoglobin, which is also known as stellate cell activation-associated protein (STAP), a hypoxia-inducible hexacoordinated globin with reactive oxygen species (ROS)-scavenging properties. In HSCs, cytoglobin is upregulated during myofibroblastic differentiation [43,47] and protects against oxidative stress and fibrosis [48]. In this analysis, we identified new potential markers in addition to those previously identified as distinguishing between the two myofibroblastic cell populations (*e.g.* fibulin 2 and Thy-1 cell surface antigen in PMFs; reelin, cytoglobin, α2-macroglobin, mannan-binding lectin serine peptidase 1 (MASP-1), glial fibrillary acidic protein (GFAP) and retinol-binding protein (RBP) in HSC-MFs (Table 1)). Overall these and other ongoing studies suggest that both myofibroblastic cell types, each exposed to a particular microenvironment (hypoxia for HSC-MFs, ductular reaction for PMFs), expand and carry out specialist functions, in scarring and inflammation for PMFs, and in vasoregulation and hepatocellular healing for HSC-MFs.

4. Myofibroblasts in liver angiogenesis

Liver injury causes vascular disorganization and local tissue hypoxia, which begins early in the course of disease [46]. Soon after the induction of injury and long before the onset of cirrhosis hypoxia-induced VEGF expression occurs, triggering angiogenesis, in various experimental models [12,49,50]. An oxygen gradient is established by unidirectional blood flow from the portal vein and hepatic artery to the central vein. Consequently, the periportal area is less likely to undergo extreme oxygen deprivation than intralobular areas. Interestingly, in a proteomic comparison of the two cell types, we found that genes encoding proteins involved in the response to hypoxia, such as cytoglobin, were more strongly expressed in HSC-MFs than in PMFs. It has been suggested that HSC-MFs contribute to angiogenesis at the leading edge of fibrotic septa [51].

Angiogenesis leads to the formation of new blood vessels from pre-existing vessels. In chronic liver diseases, angiogenesis has several major consequences: it contributes to portal hypertension [52,53], aggravates fibrosis [52,54–56] and promotes tumorigenesis (review in [46]). The role of liver myofibroblasts in angiogenesis has been documented in the contexts of both cancer and fibrosis. Research on the angiogenic functions of myofibroblasts has, to date, focused on HSCs, but our personal unpublished data indicate that portal mesenchymal cells also develop these functions. HSCs act as liver pericytes for sinusoidal endothelial cells [5,57]. The two cell types are found in close proximity and interactions between them

may be crucial for their development and function. The use of a transgenic zebrafish model, in which HSCs were identified by the presence of a basic helix–loop–helix transcription factor, revealed that sinusoidal cells were required for the correct localization of HSCs during development [58]. As mature liver pericytes, HSCs have direct, physical interactions with endothelial cells and regulate vascular development, stabilization, maturation and remodeling. HSCs have been shown to develop focal adhesions (involving Ena/VASP proteins), which promote angiogenesis [59]. HSCs also establish paracrine interactions with endothelial cells. Once their differentiation into myofibroblasts has been activated during fibrogenesis, they secrete proangiogenic cytokines: VEGF [12,49,51,60–62] and angiopoietin-1 [56,63] (Fig. 2). They also produce PDGF, a profibrogenic factor that also induces a proangiogenic phenotype in HSCs [64]. PDGF induces angiopoietin production in HSCs [63]. Leptin, a circulating peptide hormone produced by the adipose tissue, has also been shown to induce the production of VEGF and angiopoietin-1 in HSCs *in vitro* [60]. Intercellular communication may also occur through the release of microparticles, which are transported in the bloodstream to act on distant cells. HSCs can secrete microparticles containing Hedgehog ligands able to modulate gene expression in endothelial cells [65]. Another important way in which myofibroblasts promote angiogenesis is the generation of hypoxia, through the production and deposition of extracellular matrix. Hypoxia induces the HIF-dependent expression of VEGF in hepatocytes and of VEGF, angiopoietin-1 and their respective receptors in HSCs [51].

Newly formed blood vessels can supply tissues with proinflammatory cytokines from the local and systemic circulation. These cytokines maintain chronic inflammation in the liver, leading to fibrosis. This fibrosis leads to angiogenesis, which in turn causes more fibrosis, thereby establishing a vicious circle. Angiogenesis can also lead to an increase in interstitial fluid flow, because newly formed vessels may be leaky before their stabilization. This interstitial fluid flow induces myofibroblast differentiation [66]. Finally, endothelial cells from newly formed vessels may have paracrine effects on myofibroblasts (see Fig. 2). Changes of endothelial cells during angiogenesis may disrupt the subtle balance between endothelial cells and pericytes. For instance, differentiated sinusoidal endothelial cells promote the reversion of HSCs to a quiescent state, whereas capillarized sinusoidal endothelial cells do not [67]. Proangiogenic cytokines also have profibrogenic effects on myofibroblasts. The HSC migration induced by hypoxia is mediated by VEGF [68]. VEGF increases proliferation, extracellular matrix deposition and migration in HSCs [12,51,55,62,69]. The exposure of HSCs to placenta growth factor activates the ERK pathway, and increases migration, proliferation and cytoskeleton remodeling [70]. Neuropilin-1 (VEGF co-receptor) increases HSC migration [71].

Table 1
Previously published proposed markers of hepatic stellate cell-derived myofibroblasts (HSC-MFs) and portal myofibroblasts (PMFs).

	Name (references)
HSC-MFs	Reelin [91]
	Cytoglobin [43]
	α-2-macroglobulin [14]
	Desmin [14]
	Vascular cell adhesion molecule 1 [14]
	Mannan-binding lectin serine peptidase [14]
	Glial fibrillary acidic protein [14,17]
	Pirin (iron-binding nuclear protein) [43]
	Protein disulfide isomerase family A, member 4 [43]
	Neural cell adhesion molecule 1 [14,17]
	Retinol binding protein 1, cellular [92]
PMFs	Fibulin 2 [14]
	Thy-1 cell surface antigen[93]
	Fibronectin 1 [14]
	N CAM[17]
	Gremlin [93,94]
	Heat shock protein 1 [43]
	Latexin [43]
	Cofilin 1, non-muscle [43]

5. Myofibroblasts in liver regeneration

Liver regeneration induced by partial hepatectomy, a model of normal liver tissue repair, is associated with myofibroblastic changes of HSCs, including the loss of vitamin A content and the upregulation of markers such as α-SMA, IL-6 and hepatocyte growth factor [72]. This suggests that HSCs undergoing myofibroblastic differentiation are involved in a regenerative response. Myofibroblastic HSCs can support hepatocellular regeneration through the release of mitogens, such as hepatocyte growth factor, pleiotrophin or epimorphin, and induction of the delta-like 1 homolog [73]. It has also been shown that *Foxf1* (a mesenchyme-specific transcription factor) haploinsufficiency in mice, caused a defect in the myofibroblastic differentiation of HSCs, resulting in abnormal liver regeneration [74]. However, HSCs have also been reported to be negative regulators of hepatocyte regeneration. In one study, this negative regulatory function was attributed to stimulation of the 5-hydroxytryptamine 2B receptor on HSCs by serotonin, which activates the expression of TGF-β1, a powerful suppressor of hepatocyte proliferation [75]. In another study, HSC depletion was achieved in ganciclovir-treated transgenic mice expressing the herpes simplex virus-thymidine kinase gene driven by the mouse GFAP promoter. HSC depletion was associated with a marked attenuation of fibrosis and liver injury, in the carbon tetrachloride and bile duct ligation models, suggesting that activated HSCs amplified liver damage [76]. Hepatocellular stellate cell crosstalk can also drive progression in hepatocellular carcinoma, by generating a permissive inflammatory and proangiogenic microenvironment, in particular [77]. Liver myofibroblasts, probably of portal origin, interact with the ductular/progenitor cells to promote their survival and proliferation *via* the hedgehog pathway [35] and loss of the ectonucleotidase NTPDase2, an antiproliferative factor expressed in normal fibroblasts [78]. Production of the Notch ligand Jagged 1 by myofibroblasts promotes the biliary specification of hepatic progenitor cells, directing their differentiation into cholangiocytes [79]. Myofibroblast-derived PDGF-BB also promotes survival signaling in cholangiocarcinoma cells [80].

6. Deactivation of liver myofibroblasts

The deactivation of myofibroblasts is critical for the termination of the reparative response and the restoration of normal tissue structure. It is generally assumed that terminally differentiated myofibroblasts undergo apoptosis when fibrosis regresses. Indeed, some myofibroblasts have been observed to undergo apoptosis [81] or senescence [82] during the regression of liver fibrosis. In myofibroblasts derived from human lung fibroblast cells continuously stimulated with serum, α-SMA levels have been shown to decrease with increasing cell proliferation [83]. These changes, interpreted as dedifferentiation, are associated with the downregulation of MyoD, a basic helix–loop–helix transcription factor with a critical function in myogenic differentiation and in TGF-β1-induced myofibroblast differentiation [83]. It has been shown, with a hydrogel system, that the substrate modulus of valvular myofibroblasts can be decreased, leading to their deactivation and decreases in the levels of α-SMA stress fibers and proliferation, these cells then being redirected to become dormant fibroblasts [84]. Likewise, changes in substrate stiffness have been shown to induce a reversion of the myofibroblastic phenotype in human liver myofibroblasts [85]. Culture studies have suggested that myofibroblastic HSCs may revert to a more quiescent phenotype, characterized by the loss of fibrogenic genes and the expression of adipogenic genes [86]. The cre-loxP-based genetic labeling of myofibroblasts has been used to show that, during recovery from carbon tetrachloride or alcohol-induced liver fibrosis, myofibroblastic stellate cells may revert to an inactive, although not entirely quiescent phenotype, with the capacity

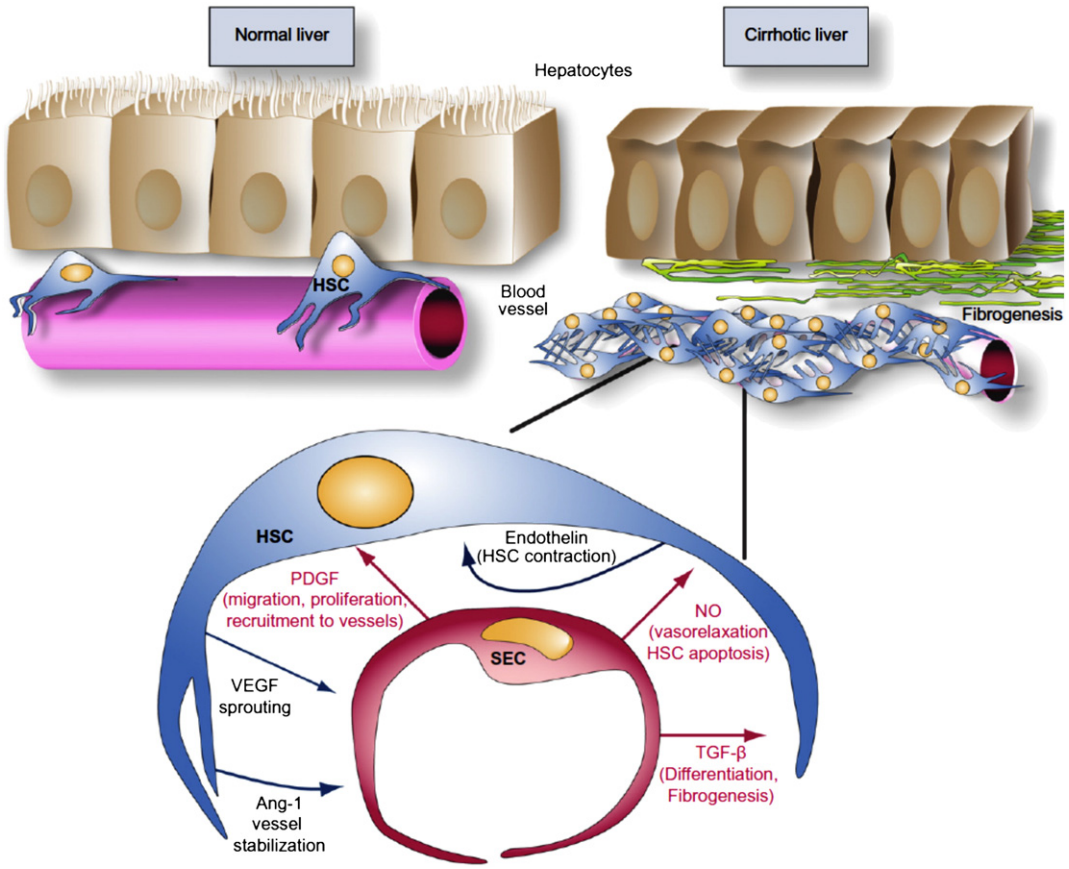

Fig. 2. Myofibroblastic changes of hepatic stellate cells related to sinusoidal remodeling and angiogenesis in the fibrotic liver. In the fibrotic liver, an increasing number of HSCs wrap around sinusoids, thereby contributing to the formation of a high-resistance, constricted sinusoidal vessel. At the cellular level, a number of soluble factors are involved in this process, through autocrine and paracrine signaling between HSC-MFs and sinusoidal endothelial cells.
Reproduced with permission from Thabut & Shah, J Hepatol 2010 [95].

to undergo rapid reactivation to regenerate myofibroblasts [87]. In another study, the authors used single-cell PCR and genetic cell fate tracking to show that about half the HSCs were deactivated, with decreases in α-SMA and collagen I levels, after the cessation of carbon tetrachloride treatment in mice. The deactivated HSCs obtained in this model were also more responsive to profibrogenic stimulation than fully quiescent HSCs [88]. In patients with chronic hepatitis C and a sustained virological response (SVR), the analysis of paired pre- and post-treatment liver biopsies showed that treatment led to the regression of cirrhosis and a decrease in collagen content in most cases. Ductular proliferation also decreased, but sinusoidal capillarization persisted, as assessed by analyses of CD34 and α-SMA, suggesting that the deactivation of HSCs was only partial [89]. However, in this study, α-SMA levels either remained unchanged or increased, despite the regression of fibrosis, suggesting that myofibroblastic differentiation may be irreversible once it has progressed beyond a certain stage. Alternatively, it may depend on the microenvironment, a scenario supported by the fact that activated HSCs revert to quiescence when cocultured with differentiated sinusoidal endothelial cells, but not with capillarized cells [67]. In addition, the fate of portal myofibroblasts needs to be addressed, to clarify the mechanisms underlying fibrosis progression. The triggering of myofibroblast apoptosis by pharmacological [90] or genetic [87] approaches could potentially improve treatment, by causing fibrosis regression. Partial reversion of the myofibroblastic phenotype may also lead to a favorable outcome, but a potential threat remains in cases of subsequent injury. Complete reversion to a quiescent phenotype is clearly the ultimate goal of treatment, but it may be possible to achieve such reversion only in the early stages of disease.

7. Conclusions

At least two populations of liver myofibroblasts, derived from portal mesenchymal cells and hepatic stellate cells, accumulate in the injured liver. We propose a model of liver tissue repair, in which both myofibroblastic populations, each exposed to a different microenvironment, expand and carry out specialist functions, in scarring for PMFs and hepatocellular healing for HSC-MFs. These specific features should be taken into account in the development of antifibrotic drugs, to ensure the targeting of collagen cross-linking or of fully differentiated myofibroblasts, rather than stages of myofibroblastic differentiation, which may be beneficial for the regeneration of liver epithelial cells. Strategies for restoring the normal, quiescent phenotype of myofibroblast precursors should also be considered.

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