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Forum Review

Liver Fibrogenesis: A New Role for the Renin–Angiotensin System

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ABSTRACT

Liver fibrosis is the consequence of chronic liver injury of any etiology. When advanced, fibrosis causes portal hypertension and liver insufficiency, and is a risk factor for developing hepatocellular carcinoma. In the last decade, there have been major advances in the knowledge of the pathogenesis of hepatic fibrosis. Hepatic stellate cells (HSCs) are recognized as the main collagen-producing cells in the injured liver, and key fibrogenic factors have been identified. Among these factors, the renin–angiotensin system (RAS) appears to play a major role. Angiotensin II (Ang II) mediates key biological actions involved in hepatic tissue repair, including myofibroblast proliferation, infiltration of inflammatory cells, and collagen synthesis. Activated HSCs secrete Ang II, which induces fibrogenic actions through the activation of NADPH oxidase. Importantly, the blockade of the RAS attenuates fibrosis development in different experimental models of chronic liver injury. Based on these studies, it has been proposed that the blockade of the RAS could be effective in preventing fibrosis progression in chronic liver diseases. Although no prospective studies have evaluated the antifibrotic effect of RAS inhibitors in patients with chronic liver diseases, controlled clinical trials are under way. *Antioxid. Redox Signal.* 7, 1346–1355.

INTRODUCTION

LIVER FIBROSIS is the excessive accumulation of extracellular matrix (ECM) proteins that occurs in liver diseases of any origin (9, 26). When advanced, fibrosis disrupts the normal liver architecture, causing increased resistance to blood flow and impaired liver function. Liver fibrosis is associated with an increased risk of developing hepatocellular carcinoma (14). To date, the most effective therapy for treating hepatic fibrosis is to remove the causative agent [*i.e.,* hepatitis C virus (HCV) infection, alcohol consumption, bile obstruction] (3). When the agent causing liver injury cannot be eliminated, patients are usually examined, but no antifibrotic treatment is administered. In the last decade, there have been major advances in the knowledge of the pathogenesis of hepatic fibrosis. Hepatic stellate cells (HSCs) and portal myofibroblasts are recognized as the main ECM-producing cell type in the damaged liver, and molecules involved in the fibrogenic response to chronic injury have been identified (59). Among fibrogenic factors, the renin–angiotensin system (RAS) appears to play a major role. Epidemiological and experimental studies strongly indicate that angiotensin II (Ang II), the main effector peptide of this system, mediates key steps involved in the hepatic tissue-repairing process, including myofibroblast proliferation, infiltration of inflammatory cells, and ECM synthesis (4, 8, 10, 82, 84). Importantly, the blockade of the RAS attenuates fibrosis development in experimental models of chronic liver injury (20, 30, 35–37, 49, 51, 57, 58, 71, 74–76, 79–81, 83). Based on these studies, it has been proposed that the blockade of the RAS could be effective in preventing fibrosis progression in patients with chronic liver diseases. At present, RAS inhibitors are widely used in patients with predisposing conditions to prevent the development of cardiac and renal fibrosis (66). Although no

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prospective studies have evaluated the antifibrotic effect of RAS inhibitors in patients with chronic liver diseases, clinical trials are under way. In this review, the current knowledge on the role of the RAS in liver fibrogenesis, as well as the potential use of RAS inhibitors in patients with chronic liver disease, will be discussed.

PATHOGENESIS OF LIVER FIBROSIS

Liver fibrogenesis was traditionally considered a "passive" and irreversible process, due to the collapse of the hepatic parenchyma and its substitution by a collagen-rich tissue (39, 40). However, a number of clinical and experimental observations indicate that it is a dynamic process of tissue repair that develops following repeated liver injury (9, 26). Several cell types are actively involved in this process. After an acute liver injury (*i.e.,* acute viral hepatitis), parenchymal cells regenerate and rapidly substitute the necrotic tissue, reestablishing the normal hepatic architecture. This reparative process is usually associated with an inflammatory response, as well as a limited deposition of ECM, mainly nonfibrillar collagen, which is coordinated with the regenerated hepatocytes to restore the normal hepatic histology. If the hepatic injury persists, this reparative process perpetuates. Eventually, the capability of the liver to regenerate is impaired and hepatocytes are progressively substituted by abundant ECM proteins, including fibrillar collagen, fibronectin, and glycosaminoglycans. The distribution of this fibrous material depends on the origin of the liver injury. In chronic viral hepatitis, the fibrotic tissue is initially located around portal tracts, whereas in alcohol-induced liver, it locates in pericentral and perisinusoidal areas (19, 63). In advanced liver diseases, collagen bands are evident and bridging fibrosis develops. This condition precedes the development of regeneration of nodules and liver cirrhosis. While the mechanisms of collagen deposition are well characterized, little is known on the mechanisms of fibrosis resolution. Several clinical reports indicate that liver fibrosis is potentially reversible (2, 21, 24). If the fibrogenic insult is removed (*i.e.,* effective antiviral therapy in chronic hepatitis C), mechanisms are activated to limit the fibrogenic signals and to remove collagen fibers. These mechanisms include apoptosis of activated HSCs and increased activity of metalloproteinases (11).

The cellular basis of hepatic fibrogenesis has been recently delineated (Fig. 1). HSCs, formerly known as Ito cells, fat-storing cells, or lipocytes, have been identified as the main ECM producers in the injured liver (59). In the normal liver, HSCs are located in the space of Disse and participate in the storage and metabolism of vitamin A. Following chronic injury, HSCs transdifferentiate into myofibroblast cells, a process named "cell activation." Activated HSCs accumulate at the sites of tissue repair, acquiring contractile, proinflammatory, and fibrogenic properties. Moreover, they regulate other key processes in fibrogenesis, such as angiogenesis and ECM degradation. Besides HSCs, other cell types have fibrogenic potential in the injured liver. Myofibroblasts derived from small portal vessels proliferate around biliary tracts in cholestasis-induced liver fibrosis (32). Abundant collagen is deposited around myofibrobasts, suggesting a role for these cells in the generation of a fibrous scar. Moreover, a recent study shows that, similar to what occurs in other organs, myofibroblasts from bone marrow origin infiltrate livers undergoing tissue remodeling (25). The relative importance of each of these cell types in liver fibrogenesis may depend on the origin of the liver injury. While HSCs are the main fibrogenic cell type in pericentral areas, portal fibroblasts may play a major role when liver injury is located around portal tracts. It is unknown whether other potential fibrogenic cell types (*i.e.,* mesenchymal cells derived from epithelial cells) also play a role in liver fibrosis.

A complex interplay among different hepatic cell types takes place during hepatic fibrogenesis (Fig. 1). Parenchymal cells (hepatocytes), nonparenchymal cells (HSCs, endothelial sinusoidal cells, Kupffer cells, and biliary cells), as well as inflammatory cells, are involved in this process (33). Hepatocytes are targets for a number of hepatoxic agents, including hepatitis viruses, alcohol metabolites, and bile acids. Moreover, apoptosis of damaged hepatocytes releases fibrogenic substances and stimulates the immune response leading to the infiltration by inflammatory cells. Moreover, apoptosis of damaged hepatocytes stimulates the proliferation and fibrogenic actions of liver myofibroblasts (16, 64). Inflammatory cells found in the areas of hepatocellular necrosis, either lymphocytes or polymorphonuclear cells, attract fibrogenic cell types such as HSCs (42). On the other hand, activated HSCs secrete inflammatory chemokines and express cell adhesion molecules that activate leukocytes. Therefore, a vicious circle in which inflammatory and fibrogenic cells stimulate each other is likely to occur. Kupffer cells are resident macrophages that play a major role in liver inflammation by releasing reactive oxygen species (ROS) and cytokines (46, 73). In alcohol-induced liver disease, activation of Kupffer cells results in tumor necrosis factor-α (TNFα) and other cytokines, resulting in the accumulation of polymorphonuclear cells and the sensitization of hepatocytes to undergo apoptosis (78). The role of sinusoidal endothelial cells in liver fibrogenesis is not well known. *In vitro* studies indicate that sinusoidal cells secrete inflammatory and fibrogenic factors such as leptin and stimulate the proliferation of lymphocytes (34). Moreover, endothelial cells regulate angiogenesis, which is a key step in the repairing process (43). Finally, recent interest has been focused on biliary epithelial cells. In chronic cholestatic disorders, these cells stimulate the accumulation of myofibroblasts to initiate collagen deposition around damaged bile ducts (32).

At the molecular level, oxidative stress seems to play a crucial role in liver fibrogenesis (50). Most types of liver diseases are associated with increased hepatic ROS production and oxidative stress, and ROS induce fibrogenic actions in hepatic fibrogenic cells (28, 41, 47, 48). Importantly, antioxidants protect against experimentally induced liver fibrosis and have beneficial effects in chronic liver diseases (27, 65, 85). The role of oxidative stress in liver fibrosis is particularly important in alcohol-induced liver injury. In this condition, maneuvers aimed at preventing oxidative stress strongly inhibit the progression of liver fibrosis (40). The molecular mechanisms mediating oxidative stress in the injured liver are under investigation. Increased ROS production and decreased antioxidant mechanisms are probably involved. ROS derived

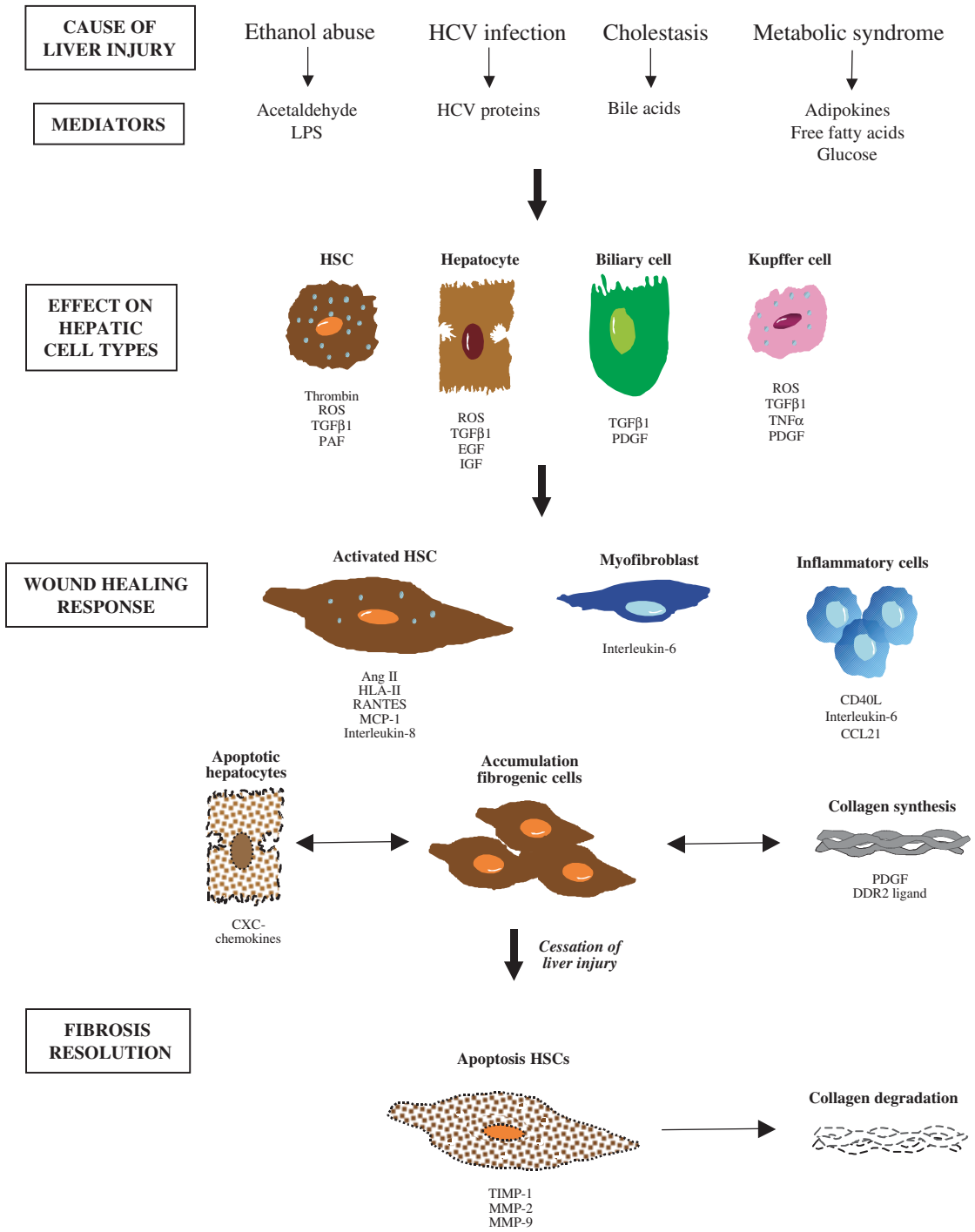


FIG. 1. Cellular basis of hepatic fibrogenesis. Different causes of liver injury activate parenchymal and nonparenchymal hepatic cell types that release a number of cytokines and soluble factors. The resulting wound-healing response to injury leads to the accumulation of fibrogenic cells, including portal myofibroblasts and activated HSCs. Apoptosis of hepatocytes and signals derived from ECM proteins amplify this fibrogenic response. If the cause of liver injury ceases, fibrosis can be reversed by apoptosis of activated HSCs and collagen degradation. CXCR, chemokine type X receptor; DDR, discoidin domain receptors; EGF, epidermal growth factor; IGF, insulin growth factor; LPS, lipopolysaccharide; MCP-1, monocyte-chemotactic factor type 1; MMP, matrix metalloproteinase; PAF, platelet-activating factor; PDGF, platelet-derived growth factor; TIMP, tissue inhibitor of metalloproteinases.

from damaged hepatocytes, activated Kupffer cells, and infiltrating neutrophils are believed to stimulate HSCs in a paracrine manner (18, 52). Exogenous ROS would activate redox-sensitive intracellular pathways in HSCs to increase collagen synthesis (68). However, a recent study provides evidence that HSCs may be also an important source of ROS in liver fibrosis (8). Cytochrome P450 2E1 is the main source of ROS in hepatocytes, whereas NADPH oxidase is the key source in Kupffer cells and HSCs.

Most of the signaling pathways implicated in the hepatic fibrogenic response are redox-sensitive (54). These pathways include the SMAD cascade, mitogen-activated protein kinases (MAPK), AKT/phosphatidylinositol 3-kinase (PI3K) and the activation of transcription factors such as nuclear factor-κB (NFκB) and activated protein-1 (AP-1) and nuclear receptors such as peroxisome proliferator-activated receptors (44). The fibrogenic actions of these factors depend on the cell type. In cultured HSCs, MAPK and AKT/PI3K mediate proliferation, collagen synthesis, proinflammatory actions, and cell migration (7, 58, 60). NFκB mediates proinflammatory actions and is involved in cell resistance to apoptosis. Finally, AP-1 mediates proinflammatory actions and collagen synthesis (52). The pharmacological or genetic ablation of some of these pathways protects rodents from developing liver fibrosis (3). Although some of these inhibitors have potential as antifibrotic drugs, their use in humans is hampered by potential side effects. To avoid this limitation, studies investigating the selective delivery of small inhibitory molecules to activated HSCs are under way.

THE RAS AND LIVER FIBROSIS: EXPERIMENTAL EVIDENCE

In the late 1990s, extensive experimental and clinical work indicated a major role for the remodeling and fibrogenesis (66). Surprisingly, no studies had investigated the role of this system in hepatic fibrosis. However, in the last 4 years, we have witnessed an explosion of information on the potential role of the RAS in the pathogenesis of liver fibrosis (Table 1). Most of the studies have assessed the antifibrotic effect of RAS inhibitors in experimentally induced liver fibrosis (20, 30, 35–37, 49, 51, 57, 58, 71, 74–76, 79–81, 83). Moreover, *in vitro* studies with cultured HSCs have delineated the molecular mechanisms involved in Ang II-induced liver fibrosis (4, 8, 10, 55). These studies have consistently

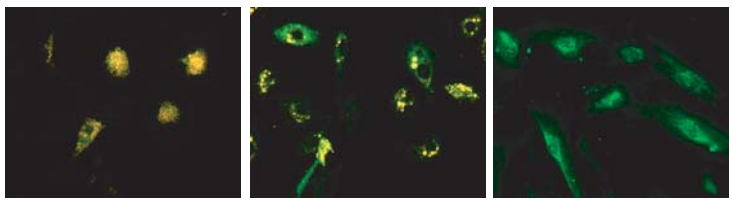
Table 1. Lines of Evidence Implicating the RAS in the Pathogenesis of Liver Fibrosis

Ang II induces fibrogenic actions in cultured HSCs.
Myofibroblastic HSCs express the RAS and synthesize Ang II.
Rat fibrotic livers overexpress key components of the RAS.
RAS inhibition markedly attenuates experimentally induced fibrosis.
Mice lacking AT_{1a} receptors show attenuated liver fibrogenesis.
RAS genetic polymorphisms influence fibrosis progression in humans.
RAS inhibitors slow down fibrosis progression in chronic hepatitis C.
RAS inhibitors have antifibrotic effects in patients with NASH.

NASH, nonalcoholic steatohepatitis.

demonstrated that the RAS is an important system regulating inflammation and repair after repeated liver injury. However, as discussed later, several data suggest that the fibrogenic effect of the RAS on the liver is less marked than in other organs, such as the kidney or the vasculature.

Local expression of the RAS, rather than changes in the systemic RAS, is believed to play a role in tissue repair and fibrogenesis (67, 69). Therefore, the recent finding that an intrahepatic RAS is expressed in livers undergoing tissue remodeling supports its role in liver fibrosis (50). Whereas angiotensinogen is the only component of the RAS expressed in the normal liver, angiotensin-converting enzyme (ACE) and angiotensin type 1 (AT_1) receptors are markedly expressed in fibrotic rat livers. The cellular source of the RAS in the injured liver is not well known. In other tissues (*i.e.,* heart), myofibroblasts accumulated in the areas of tissue express the components of the RAS and generate Ang II, which participates in the tissue repair process. In the human liver, quiescent HSCs neither express the RAS components nor secrete Ang II. In contrast, following cell activation in culture and *in vivo*, myofibroblastic HSCs express key components of the RAS and generate mature Ang II (5) (Fig. 2). Therefore, locally produced Ang II could act as a true cytokine regulating hepatic tissue remodeling in a paracrine manner. Although these data support the existence of a local RAS in the fibrotic liver, there are major points to be addressed. First, it is unknown whether an intrahepatic RAS is differentially expressed in different types of human liver diseases. Second, it is possible that hepatic cell types other than HSCs are capable



Quiescent HSCs *In vivo* activated HSCs Culture-activated HSCs

FIG. 2. Demonstration of immunoreactivity for mature Ang II in human HSCs by immunofluorescence analysis. A positive green staining is observed in both *in vivo* activated and culture-activated HSCs. *In vivo* activated cells were studied freshly isolated from patients with HCV-induced cirrhosis. [From Bataller *et al.* (5) with permission.]

of generating Ang II. Third, alternative pathways known to modulate Ang II synthesis/degradation in the heart (*e.g.,* chymase, ACE-II) should be studied in liver diseases. Finally, it is unknown whether there is a cross-communication between systemic and intrahepatic RAS. For example, angiotensin I is highly generated in the kidney of cirrhotic patients (1). Circulating angiotensin I could reach the hepatic microcirculation, where it would be converted into Ang II by the action of locally overexpressed ACE.

The most convincing evidence supporting a role for the RAS in liver fibrosis is the finding that the blockade of the generation of Ang II and/or its binding to AT_1 receptors attenuates experimental liver fibrosis (20, 30, 35–37, 49, 51, 57, 58, 71, 74–76, 79–81, 83). Remarkably, twelve laboratories using four experimental models of liver fibrosis have yielded similar results (Table 2). While some authors used ACE inhibitors (lisinopril, captopril, and perindopril), others used AT_1 receptor antagonists (losartan, irbesartan, and olmesartan). The hepatic antifibrotic effect of RAS inhibition is well documented, yet the underlying cellular and molecular mechanisms remain obscure. RAS inhibition is associated with decreased transforming growth factor β1 (TGFβ1) expression in the injured liver, a key factor mediating the fibrogenic effect of Ang II in other tissues. Moreover, it causes a decrease in connective tissue growth factor and AT_1 receptor expression. Importantly, RAS inhibition prevents the accumulation of smooth muscle α-actin-positive myofibroblasts. A role for Ang II in liver fibrosis is supported by the finding that mice lacking AT_{1a} receptors are protected from developing liver fibrosis after prolonged bile duct ligation (79). There are important points to be addressed in future studies: Do RAS inhibitors prevent oxidative stress or hepatic inflammation? Which intracellular pathways are blocked by RAS inhibitors? Does RAS inhibition favor the resolution of established fibrosis by increasing collagen degradation and/or promoting HSC apoptosis?

Recent *in vivo* studies have partially addressed some of these questions. Prolonged administration of Ang II to normal rats at subpressor doses induces HSC activation and profound hepatic inflammation and vascular thrombosis, but not parenchymal fibrosis (7). These pathological effects are associated with marked oxidative stress and lipid peroxidation. In contrast, other organs such as the kidney and the heart showed marked fibrosis after Ang II infusion. Based on these data, it is conceivable that the fibrogenic effects of Ang II in the liver are less marked than in other organs such as the kidney. This assumption is supported by recent data showing that mice with different copies of the angiotensinogen gene show different susceptibility to develop renal, but not hepatic, fibrosis (R. Bataller, unpublished observations). Nevertheless, increased systemic levels of Ang II may promote hepatic fibrosis in chronically damaged livers. Emerging data support this hypothesis. Increased systemic Ang II markedly exacerbates fibrosis development in rats undergoing tissue remodeling (10) (Fig. 3). This effect is associated with increased oxidative stress and infiltration by inflammatory cells, as well as increased accumulation of fibrogenic myofibroblasts. Importantly, Ang II perfusion decreases collagen degradation, an important mechanism regulating collagen deposition in chronic liver diseases. The hepatic concentrations of inflammatory cytokines (TNFα and interleukin-1β), as well as the fibrogenic cytokine TGFβ1, are increased in bile duct-ligated rats receiving Ang II compared to saline. Moreover, Ang II

TABLE 2. STUDIES ASSESSING THE EFFECT OF RAS INHIBITORS IN THE PROGRESSION OF LIVER FIBROSIS IN RATS

Reference(s)	*RAS inhibitor*	*Experimental model*	*Proposed mechanism*
58	Captopril	Pig serum	Decreased mast cell accumulation
49	Lisinopril	CCl_4	Decreased stimulation of HSCs Decreased TGFβ expression
30	Captopril	BDL	Decreased TGFβ expression Regulation of MMPs/TIMPs
81	Candesartan Perindopril	Pig serum	Reduced αSMA-positive cells Decreased TGFβ expression
51	Irbesartan	BDL	Decreased TGFβ expression AT_1 down-regulation
74–76	Losartan	CCl_4	Reduced αSMA-positive cells Decreased TGFβ expression
36, 80	Perindopril	Dimethylnitrosamine	Reduced αSMA-positive cells
57	Losartan	BDL	Reduced αSMA-positive cells
20	Losartan	CCl_4	Unknown
83	Perindopril Candesartan	CCl_4 Pig serum	Decreased TIMP-1 expression
35	Olmesartan	BDL	Reduced αSMA-positive cells Decreased TGFβ expression Decreased CTGF expression Effect in HSCs
71	Candesartan Captopril	CCl_4	Reduced αSMA-positive cells

BDL, bile duct ligation; CCl_4, carbon tetrachloride; CTGF, connective tissue growth factor; MMP, matrix metalloproteinase; αSMA, α-smooth muscle actin; TIMP, tissue inhibitor of metalloproteinases.

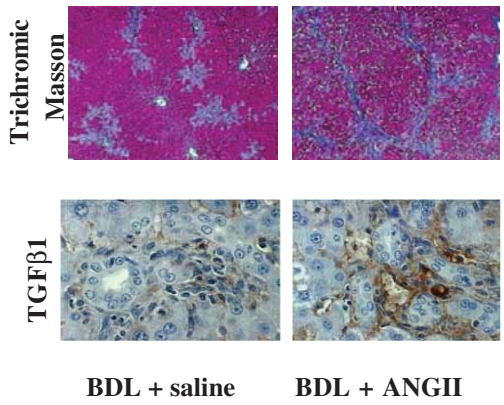


FIG. 3. Effect of Ang II perfusion on hepatic fibrosis in bile duct-ligated rats. Bile duct ligation (BDL) was performed in rats receiving saline or Ang II (50 ng/kg/h) through a subcutaneous pump, and livers were examined after 2 weeks. Ang II perfusion markedly accentuated fibrosis development, as assessed by Trichromic Masson (**top panels**) and TGFβ1 staining (**bottom panels**) (magnification, ×100 and ×40, respectively). [From Bataller *et al.* (10) with permission.]

perfusion increases the proliferative response of cholangiocytes to bile duct obstruction and stimulates intracellular signaling pathways such as MAPK. These data suggest that systemic RAS may contribute to the progression of liver fibrosis. However, systemic RAS is only found activated in patients with advanced fibrosis. Intrahepatic, rather than systemic, RAS may promote the development of fibrosis in patients with earlier stages of liver disease. Further studies are needed to confirm this hypothesis.

The cellular mechanisms underlying the fibrogenic effect of Ang II in the liver have been partially elucidated. Studies have focused on HSCs, a potential target for the biological actions of Ang II in liver. Following phenotypic activation, HSCs highly express AT_1 receptors, the activation of which mediates cell contraction, migration, and proliferation (4). Moreover, Ang II stimulates collagen synthesis, TGFβ1 expression, and the expression of proteins that regulate collagen degradation (plasminogen activator inhibitor type 1 and tissue inhibitor of metalloproteinases type 1) (31, 81). Besides the mitogenic and fibrogenic actions, Ang II induces inflammatory effects in these cells, stimulating the secretion of inflammatory cytokines such as interleukin-8 and monocyte chemotactic protein type 1 (8). All these effects are blocked by AT_1 receptor antagonists and are blunted in HSCs from mice lacking AT_{1a} receptors (78). Importantly, activated HSCs are capable of generating Ang II, suggesting that it can act in an autacrine/paracrine manner (6). Recently, the molecular mechanisms mediating the fibrogenic and inflammatory effects of Ang II in HSCs have been delineated (8). Ang II increases intracellular calcium concentration and induces the production of ROS, stimulating key intracellular pathways, such as protein kinase C, PI3K/AKT, and MAPKs. It also increases AP-1 DNA binding, whereas NFκB activity is stimulated in rat, but not human, HSCs. As a consequence, Ang II stimulates the expression of numerous genes involved in hepatic tissue remodeling. Stimulation of intracellular signaling pathways, as well as the biological actions evoked by Ang II, are redox-sensitive. These data confirm previous work in other tissues (*i.e.,* kidney, vasculature) indicating that ROS are key intracellular messengers mediating the actions of Ang II in target cells (13). In HSCs, a nonphagocytic form of NADPH oxidase mediates Ang II-induced ROS formation. This nonphagocytic NADPH oxidase has been documented in vascular cell types (77). Like the phagocytic NADPH oxidase present in white blood cells, nonphagocytic NADPH oxidase reduces oxygen to generate superoxide, which is in turn converted to hydrogen peroxide. However, unlike the phagocytic type, NADPH oxidases present in vascular cell types are constitutively active, producing relatively low levels of ROS under basal conditions and generating higher levels of oxidants in response to cytokines such as Ang II, stimulating redox-sensitive intracellular pathways (71). Importantly, disruption of an active NADPH oxidase protects mice from developing severe fibrosis after bile duct ligation, indicating that NADPH oxidase plays an important role in liver fibrosis (8). It is unknown whether this enzyme is activated by other fibrogenic mediators in chronic liver diseases.

Aldosterone is another peptide related to the RAS with potential fibrogenic effects in the liver. It is secreted by the glomerulosa cells upon stimulation with Ang II and regulates blood volume homeostasis. Besides this hormonal effect, aldosterone can be locally synthesized in tissues undergoing remodeling (22). Antialdosteronic drugs exert antifibrotic effects in patients with chronic heart failure and prolong survival. Little information is available on the fibrogenic effects of aldosterone in the liver. Aldosterone synthesis is elevated in patients with cirrhosis and portal hypertension, and the aldosterone synthase gene CYP11B2 has been identified in the rat fibrotic liver (38). However, it is unknown whether the human fibrotic liver is capable of locally generating aldosterone. In cultured HSCs, aldosterone moderately increases collagen synthesis, and canrenone, an antialdosteronic drug, exerts antifibrotic effects (15, 61). *In vivo* studies assessing the effect of antialdosteronic drugs in experimental liver fibrosis are needed before this approach can be considered in patients with chronic liver diseases.

THE RAS AND LIVER FIBROSIS: CLINICAL EVIDENCE

Although the most convincing evidence implicating the RAS in liver fibrogenesis comes from experimental studies, several lines of evidence suggest that the RAS also participates in the progression of chronic liver diseases in humans. Recent data from our laboratory indicate that human damaged livers express key components of the RAS (J. Colmenero, unpublished observations). Moreover, it has been known for many years that the systemic RAS is markedly activated in patients with cirrhosis (1). Portal hypertension leads to a marked splanchnic vasodilatation that causes a decrease in the effective blood volume. A number of endogenous vasoconstrictor systems (*i.e.,* the RAS and the nervous sympathetic system) become activated in an attempt to restore the normal vascular homeostasis. The increased activity of the systemic RAS con-

tributes to sodium vasoconstriction and renal vasoconstriction, leading to ascites formation (17). Moreover, activation of the systemic RAS is associated with an increase in the intrahepatic resistance to blood flow (45). No studies have investigated whether increased systemic RAS contributes to the progression of advanced liver fibrosis. It is conceivable that locally expressed RAS promotes fibrogenesis in early stages of liver fibrosis, whereas systemic RAS would accelerate the progression of the liver diseases in advanced stages. Further studies should assess this hypothesis.

Clinical evidence implicating the RAS in liver fibrogenesis also comes from epidemiological studies (6). Genetic polymorphisms in the angiotensinogen gene, which confer increased activity of the RAS, are associated with a more rapid progression of liver fibrosis in patients with chronic hepatitis C and nonalcoholic steatohepatitis (23, 55). Interestingly, the coexistence of angiotensinogen gene variations with TGFβ1 polymorphism has an additive effect on fibrosis progression. Although these results should be confirmed in a large series of patients, it seems that patients with higher activity of the RAS are more sensitive to develop liver fibrosis.

As detailed in this review, there is overwhelming experimental evidence supporting the use of RAS inhibitors to treat liver fibrosis. Moreover, RAS inhibitors are widely used, as in patients with chronic renal and cardiac diseases, and appear to be safe when administered for prolonged periods of time. Little information is available on the usefulness of RAS inhibitors in human liver fibrosis. A preliminary pilot study suggests that AT_1 receptor blockers attenuate fibrosis progression in patients with chronic hepatitis C (70). Moreover, a retrospective study in transplanted patients with reinfection by HCV has revealed that patients receiving RAS inhibitors as antihypertensive therapy show less fibrosis progression than patients receiving other types of drugs (61). This study is relevant, because fibrosis progression is very aggressive in transplanted patients with reinfection by HCV and is a major cause of graft loss.

Although the use of RAS inhibitors as antifibrotic agents in patients with chronic liver diseases is probably justified, randomized clinical trials should be performed. The antifibrotic profiles of ACE inhibitors and AT_1 receptor blockers are similar, but the use of AT_1 antagonists is usually better tolerated. The target population for clinical trials should be patients with fibrogenic liver diseases in whom the causative agent cannot be removed (*i.e.,* patients with chronic HCV infection not responding to antiviral therapy, obese/diabetic patients with nonalcoholic steatohepatitis). Patients with advanced cirrhosis and activation of the systemic RAS should not be treated with RAS inhibitors, because they can cause arterial renal impairment. Moreover, liver fibrosis is massive in these latter patients, and the beneficial effect of antifibrotic therapies is limited. The duration of antifibrotic therapy to demonstrate changes in liver fibrosis should be considered, depending on the rate of fibrosis progression of the underlying disease. In a recent study, the rates of fibrosis progression in different types of liver diseases were delineated, the most rapid being HIV-HCV coinfection (50% cirrhosis percentile at 52 years of age) and the slowest being primary biliary cirrhosis (50% cirrhosis percentile at 81 years) (56). In transplanted patients with HCV reinfection, the rate of fibrosis progression is very fast, cirrhosis being developed in <5 years in half of the patients (12). Liver-transplanted patients represent potential candidates to evaluate the efficacy of antifibrotic drugs.

Finally, it has been suggested that the RAS could participate in the development and progression of hepatocellular carcinoma by promoting fibrosis and angiogenesis, respectively (80). Experimental studies indicate that RAS inhibition prevents liver carcinogenesis (83). Whether this approach is useful in patients with advanced cirrhosis is unknown and should be evaluated in clinical trials.

CONCLUSIONS

In summary, an increasing body of evidence indicates that the RAS plays a role in liver fibrogenesis. Fibrotic livers overexpress a local RAS, and RAS inhibition markedly attenuates experimental liver fibrogenesis. *In vivo* and *in vitro* studies indicate that Ang II exerts prooxidant, fibrogenic, and proinflammatory actions in the liver. Although the molecular mechanisms underlying the fibrogenic effect of Ang II in the liver are unknown, NADPH oxidase-derived ROS seem to play an important role. Future studies should confirm that a local RAS is expressed in human liver diseases, and better delineate the mechanisms that mediate the fibrogenic actions of Ang II in the liver. Importantly, preliminary clinical data suggest that RAS inhibitors could be useful to prevent fibrosis progression in patients with chronic liver diseases. Controlled clinical trials are anticipated in the coming years.

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ABBREVIATIONS

ACE, angiotensin-converting enzyme; Ang II, angiotensin II; AP-1, activator protein-1; AT_1 receptor, angiotensin receptor type 1; ECM, extracellular matrix; HCV, hepatitis C virus; HSC, hepatic stellate cell; MAPK, mitogen-activated protein kinase; NFκB, nuclear factor-κB; P13K, phosphatidylinositol 3-kinase; RAS, renin–angiotensin system; ROS, reactive oxygen species; TGFβ1, transforming growth factor-β1; TNFα, tumor necrosis factor-α.

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