CURRENT TREND

Rationale and targets for antifibrotic therapies

Rationnel et cibles des traitements antifibrosants

D. Schuppan*, Y. Popov

Division of Gastroenterology and Hepatology, Beth Israel Deaconess Medical Center, Harvard Medical School, Dana 501, 330, Brookline avenue, MA 02215 Boston, MA, USA

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Summary We have made striking progress in our understanding of the biochemistry and cell biology that underlies liver fibrosis and cirrhosis, including the development of strategies and agents to prevent and reverse fibrosis and incipient cirrhosis. However, translation of this knowledge into clinical practice has been hampered by the limitation of many in vitro and in vivo models to confirm mechanisms and to test antifibrotic agents, as well as the lack of sensitive methodologies to quantify the degree of liver fibrosis and the dynamics of fibrosis progression or reversal. Furthermore, while cirrhosis and subsequent decompensation are accepted hard clinical end-points, fibrosis and fibrosis progression alone are merely plausible surrogates for future clinical deterioration. This review focuses on basic mechanisms that underlay liver fibrosis progression and reversal and optimized strategies for preclinical antifibrotic drug development and validation. Therapies include several drugs that are of proven safety for other indications, agents that interfere with major fibrogenic or fibrolytic mechanisms, targeted drug delivery to the fibrogenic liver cells, and their potential combinations with hepatocyte or stem cell replenishment.

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Résumé De nombreux progrès ont été effectués dans la compréhension de la biochimie et de la biologie cellulaire impliquées dans la physiopathologie de la fibrose et de la cirrhose, incluant le développement de stratégies et de molécules pour prévenir et faire régresser la fibrose et la cirrhose. Cependant, le transfert de ces connaissances à la pratique clinique a été limité par l’incapacité de nombreux modèles in vitro et in vivo à confirmer les mécanismes et étudier les agents antifibrosants, aussi bien que le manque de sensibilité des méthodes permettant de quantifier le degré de fibrose et la dynamique de progression ou de régression de la fibrose. De plus, tandis que la cirrhose et sa décompensation sont des points cliniques clés, la fibrose et la progression de la fibrose seuls ne sont que des étapes potentielles vers une aggravation clinique à venir. Cette mise au point se focalise sur les mécanismes fondamentaux qui conduisent à la progression ou à la régression de la fibrose et sur les stratégies optimisées pour le développement et la validation préclinique des molécules antifibrosantes. Les traitements incluent plusieurs molécules qui ont montré leur bonne tolérance dans d’autres indications,

* Corresponding author.

E-mail address: dschuppa@bidmc.harvard.edu (D. Schuppan).

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Mechanisms of hepatic fibrogenesis

Chronic liver diseases often lead to hepatic fibrosis which can progress to excessive scarring and architectural distortion (cirrhosis). Cirrhosis causes complications of portal hypertension and progressive loss of liver function, often despite the use of agents that address the underlying liver disease, such as immunosuppressants, antiviral or anti-inflammatory drugs.

Fibrosis results from excessive accumulation of extracellular matrix (ECM). The excess accumulation of collagens is a central molecular target for antifibrotic therapies, since collagens:

- represent the major matrix proteins;
- form important scaffolds and barriers during progressive architectural distortion;
- their proteolysis by specific proteases appears to be ratelimiting for ECM removal.

The fibrillar forming interstitial collagens type I and III, and the sheet-forming basement membrane collagen type IV, are the most abundant ECM components in liver, and are increased up to tenfold in cirrhosis [1]. A variety of adverse stimuli such as toxins, viruses, cholestasis, or hypoxia, usually coupled with inflammation, can trigger fibrogenesis, i.e., the excess synthesis and deposition of ECM by (mainly mesenchymal) cells, either indirectly by induction of profibrogenic cytokines/growth factors and other mediators in neighbouring cells, or by exposing the mesenchymal cells to an altered ECM environment causing enhanced mechanical stress [1—5] (Fig. 1).

In the early phase of liver diseases, fibrogenesis is counterbalanced by fibrolysis, i.e., the removal of excess ECM by proteolytic enzymes, the most important of which are the matrix metalloproteinases (MMPs). MMP-1, -2, -3, -8, -9, -12, -13 and -14 are the major MMPs expressed in human liver [6]. With repeated injury of sufficient severity, fibrogenesis prevails over fibrolysis, resulting in excess ECM deposition, i.e. progressive fibrosis. Fibrogenesis is characterized by upregulation of ECM synthesis, downregulation of MMP secretion and activity, and by an increase of the physiological inhibitors of the MMPs, i.e., the tissue inhibitors of MMPs (TIMPs). Among the four known TIMPs, the universal MMP-inhibitor TIMP-1 is prominent and represents another important target molecule for antifibrotic approaches [7]. However, activation of MMPs at the wrong place and time can lead to removal of the regular, differentiation-inducing ECM, such as basement membranes, with subsequent unfavourable tissue remodeling, architectural distortion and a fibrogenic response. An example is MMP-2 which degrades basement membrane collagen and denatured collagens, and which is upregulated during fibrogenesis and in advanced fibrosis. Most collagens and other ECM components, but also TIMP-1 and TIMP-2 are produced by activated myofibroblasts which either derive from activated hepatic stellate cells or from activated (portal and perivascular) fibroblasts (collectively termed hepatic stellate cells in this review) [8].

More recently, it has become evident that cells resembling activated hepatic stellate cells may originate from even more sources than originally thought. These include bone marrow-derived circulating fibrocytes [9,10], recruited from the bloodstream during chronic liver injury, and liver epithelia, via the process of epithelial-to-mesenchymal transition [11,12]. However, even in the most aggressive, toxin-induced rodent models of liver fibrosis, these pathways contribute no more than 5—10% to the myofibroblast population.

Activated Kupffer cells/macrophages, proliferating bile ductal epithelia, but also endothelia, other mononuclear cells and myofibroblasts themselves are sources of fibrogenic cytokines and growth factors that can stimulate hepatic stellate cells and perivascular fibroblasts to become myofibroblasts, or can recruit inflammatory cells themselves (Fig. 1).

A prominent role of activated cholangiocytes, i.e., epithelial cells of small bile ductules and aberrant ductular proliferations in fibrogenesis has only recently become evident. These cells, which are related to or identical with hepatic progenitor (oval) cells, are a universal finding in liver fibrosis and their proliferation correlates with liver fibrosis progression [13,14]. Activated cholangiocytes produce fibrogenic growth factors such as TGFβ1, TGFβ2, CTGF and PDGF-BB which drive the activation of hepatic stellate cells [15—18]. In addition, they produce basement membrane proteins [19] and elicit early programs of ductal plate formation by releasing hedgehog ligands that stimulate hepatic stellate cells activation [20,21]. The activated hepatic stellate cells, in turn, produce growth and survival factors for the adjacent cholangiocytes, resulting in a crosstalk between hepatic stellate cells and cholangiocytes that represents a powerful driving force of hepatic fibrogenesis (Fig. 2).

The most prominent profibrogenic cytokine, and thus another prime molecular target, is transforming growth factor β (TGFβ2 from activated cholangiocytes/progenitor cells and TGFβ1 from the other cells), which is released from almost any cell during inflammation, tissue regeneration and fibrogenesis. Apart from immunosuppressive and, in most cell types, antiproliferative effects, TGFβ1 or TGFβ2 strongly upregulate production and deposition of the major ECM molecules [22,23]. Therefore, collagen synthesis, TIMP-1, TGFβ activated hepatic stellate cells, activated cholangiocytes/progenitor cells, and perhaps Kupffer cells (see below) are prime targets for antifibrotic therapies.
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Figure 1  Cellular mechanisms of hepatic fibrogenesis.
Activated hepatic stellate cells/myofibroblasts are a heterogeneous cell population arising from transdifferentiation of quiescent hepatic stellate cells and portal/perivenular fibroblasts. Apart from upregulating the synthesis and deposition of various extracellular matrix components, fibrolysis is further compromised via an increased synthesis of TIMP-1 and a decreased production of fibrolytic matrix metalloproteinases (MMP). Other cell types and various stimuli trigger or maintain active fibrogenesis.

Reversibility of hepatic fibrosis

Animal experimental studies clearly showed that liver fibrosis, and even incipient cirrhosis, are reversible once the fibrogenic stimulus is removed. This can occur when biliary obstruction is relieved by biliary drainage via a Roux-en-Y anastomosis or when a hepatotoxin is discontinued [24,25]. In humans, reversibility of liver fibrosis has been observed in patients with reconstitution of intestinal continuity after jejunoileal bypass for morbid obesity [26], relief of biliary obstruction [27], treatment of autoimmune hepatitis with immunosuppressants [28], or effective therapy of hepatitis B or C with antivirals [29—31]. Thus, the possibility to induce regression or even reversal of advanced fibrosis or even cirrhosis is a promising option for antifibrotic treatments [32].

Second hits and genetic predisposition for hepatic fibrosis

Apart from a primary chronic liver disease, other conditions that affect the liver can contribute to rapid fibrosis progression. These are either superinfections, such as schistosomiasis in chronic hepatitis C, other environmental (toxic) exposures, metabolic alterations, or genetic predispositions, i.e. ''second hits'' [35], as exemplified for hepatitis C in Fig. 4.

The variable susceptibility to liver fibrosis and cirrhosis in individuals with similar risk factors such as hepatic C virus infection, obesity or alcohol abuse had long been enigmatic. In the last years, a growing number of functional genetic polymorphisms that apparently increase the risk of fibrosis progression have been described. These genes code for cytokines or chemokines and their receptors [36,37], molecules involved in fibrogenesis or fibrolysis [38], blood coagulation [39], antigen presentation [40], iron uptake [41], oxidative enzymes [42], detoxification [43] and polygenetic traits linked to the metabolic syndrome and non
Reversal of hepatic fibrogenesis and fibrosis.

Once the profibrogenic triggers subside, and/or with the help of antifibrotic agents, fibrosis can be resolved via proteolytic removal of excess extracellular matrix, often by the same cells that play a central role in fibrogenesis, such as hepatic stellate cells and macrophages/Kupffer cells. A future scenario is the combination with hepatocyte transplantation or stem cell renewal that could lead to reversal of decompensated liver disease.

Alcoholic steatohepatitis [44]. A gene association study in 574 patients with chronic hepatitis C revealed a 7-gene signature that predicted advanced fibrosis progression, among them DDX5, a gene with a particularly strong link to fibrosis [45]. Together with established extrinsic risk factors like excess alcohol consumption, obesity or advanced age, these SNPs may allow determination of individual risk profiles for patients.

Aims of antifibrotic therapies

Antifibrotic treatment should be offered to patients with no reasonable option for causative therapy or with advanced fibrosis and a high risk of progression due to comorbidities. In addition, it would be indicated for cirrhotic patients with the hope of speeding up reversion to a noncirrhotic state.

While a reduction in fibrotic tissue by an effective antifibrotic agent has long been considered the prime goal, a decrease of fibrosis should lead to reconstitution of a favourable angioarchitecture [46]. Favourable modulation of angiogenesis should lead to a decrease of blood shunted from portal vessels to central veins, an improvement of sinusoidal perfusion and a decrease of ECM and endothelial abnormalities in the space of Disse (i.e., a decrease of the features of sinusoidal capillarization). Both, a reduction in fibrous tissue and reconstitution of a normal angioarchitecture should result in an improvement of portal hypertension and liver function, and finally in lower morbidity and mortality due to cirrhosis. These hard endpoints will be difficult to reach in most clinical studies, but improvement of biologically plausible surrogates are increasingly being accepted by regulatory authorities.

Antifibrotic drug development

A major obstacle to antifibrotic drug development is the slow evolution of significant fibrosis, which takes years or even decades in most patients. In addition, short-term (<2 years) studies using sequential biopsies and low numbers of patients (<200) do not have the power to detect antifibotic drug effects. This is mainly due to the limited reliability of liver biopsy, which by representing only 1/20,000—1/50,000 of the liver is subject to sampling error [47—49]. Consequently, prospective studies in patients have to be large and long, which precludes the testing of the wide spectrum of potential antifibrotic agents and poses a big risk and obstacle even for big pharmaceutical companies. However, surrogate markers and techniques to quantitate fibrosis stage, and more importantly fibrosis progression, are being developed, and may speed up clinical testing of antifibrotic agents [4]. These are discussed in the previous chapter.

The first proof of antifibrotic potential usually comes from cell culture studies that show inhibition of proliferation, induction of apoptosis and/or downregulation of...
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fibrogenic growth factor or ECM production in the key fibrogenic liver cells, i.e. activated hepatic stellate cells or activated cholangiocytes. This has to be followed by suitable animal models of hepatic fibrosis to show the antifibrotic effect in vivo in the presence of general toxicity. Rat or mouse models are preferable, since significant fibrosis can be produced within 3–12 weeks and, most importantly, total liver collagen, the gold standard for the degree of fibrosis, can be determined easily in representative tissue samples using biochemical methods. However, the in vivo models must include a sizable number of animals per treatment group \((n=10–20)\). The antifibrotic agent can be reliably tested when there only limited hepatic inflammation or necrosis, e.g. not during the application of a toxin such as thioacetamide, dimethylnitrosamine, or carbon tetrachloride, but rather after its discontinuation, i.e. to induce (more rapid) fibrosis reversal. This is important, because drugs with anti-inflammatory, antinecrotic or radical scavenging properties can prevent necrosis and collapse as hepatoprotectants, but are not truly antifibrotic. Suitable models are reversal of toxin-induced fibrosis, biliary cirrhosis due to bile duct occlusion or due to deletion of the \(Mdr2\) gene in mice, and recently developed models of non-alcoholic steatohepatitis using fibrogenic diets \([50–53]\). The literature is replete with reports of antifibrotic drug effects which do not fulfil the above-mentioned criteria. The following examples refer to those studies that provide sufficient in vivo evidence for an antifibrotic drug effect.

**Pharmacological strategies to inhibit hepatic fibrosis**

The following highlights some examples of promising antifibrotic strategies. Table 1 and Fig. 5 show an overview of such therapeutic approaches, although this list is not exhaustive. Several recent reviews provide a broader overview \([2–4,54–56]\).

**Antagonizing profibrogenic TGF-β or blocking its activation**

TGF-β1 is considered the most potent fibrogenic cytokine and thus its inhibition therefore is promising. Soluble TGF-β1 decoy receptors (binding the cytokine but not mediating signal transduction) or adenoviral constructs that block molecules involved in TGF-β1 signaling have been developed that show some antifibrotic efficacy in vitro and in vivo \([57–59]\). It appears that an approach targeting activated hepatic stellate cells and myofibroblasts is necessary, since TGF-β receptors are expressed on most cell types and systemic inhibition that reaches sufficient levels to completely block hepatic fibrogenesis may trigger autoimmune diseases and cellular dedifferentiation.

A more specific antifibrotic therapy is possible by inhibiting activation of TGF-β1 and TGF-β2. Their inactive precursors (latent TGF-β1 and TGF-β2) are highly expressed by activated hepatic stellate cells, Kupffer cells/macrophages and activated cholangiocytes \([2–4,22,23,60]\). On activated cholangiocytes, the integrin receptor \(αvβ6\) is necessary for proteolytic activation of latent TGF-β1, and inactivation of this integrin with an oral non-peptide inhibitor or a blocking antibody inhibits cholangiocyte proliferation and collagen deposition in biliary and nonbiliary fibrosis \([50,61,62]\).

**Stimulating fibrolysis**

Most agents predominantly suppress profibrogenic activity. Therefore, introducing drugs that stimulate fibrolysis should have additive or overadditive effects. Halofuginone is an

**Table 1** Potential antifibrotic drugs that may be useful in antifibrotic combination therapy.

<table>
<thead>
<tr>
<th>Inhibition of profibrogenic activation of hepatic stellate cells</th>
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<tbody>
<tr>
<td>Cytokines/ cytokine antagonists</td>
</tr>
<tr>
<td>TGFβ- and TGFβ-signaling antagonists (TGFβ antisense oligonucleotides, TGFβ receptor blocking peptidomimetics, soluble TGFβ decoy receptors, TGFβ neutralizing antibody)</td>
</tr>
<tr>
<td>Inhibitors of TGFβ-activation: anti-integrin αvβ6 antagonists (EMD405270) and blocking antibody</td>
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<tr>
<td>MMP-inducers</td>
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<tr>
<td>Halofuginone</td>
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<tr>
<td>Vasoactive modulators</td>
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<tr>
<td>Endothelin A receptor antagonists (LU135252)</td>
</tr>
<tr>
<td>Angiotensin system inhibitors (captopril, enalapril, pirindopril, losartan, irbesartan, telmisartan)</td>
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<tr>
<td>NO-donors (Pyro-NO)</td>
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<tr>
<td>Histone deacetylase inhibitors</td>
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<tr>
<td>Trichostatin A, MS-275</td>
</tr>
<tr>
<td>PPARγ agonists</td>
</tr>
<tr>
<td>Glitazones: pioglitazone, rosiglitazone, troglitazone</td>
</tr>
<tr>
<td>Cannabinoid receptor 1 antagonists</td>
</tr>
<tr>
<td>Rimonabant</td>
</tr>
<tr>
<td>Plant derived, mainly antioxidants</td>
</tr>
<tr>
<td>Apigenin, Compound 861, fuzhenghuayu, glycyrrhizin, inchin-ko-to (TJ-135), quercetin, resveratrol, rooibus, salvia miltiorrhiza, sho-saiko-to (TJ-9), silymarin</td>
</tr>
<tr>
<td>Farnesoid X receptor agonists</td>
</tr>
<tr>
<td>6-ethyl chenodeoxycholic acid</td>
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<tr>
<td>Inhibition of hepatic stellate cells migration/proliferation</td>
</tr>
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<td>HMG-CoA-reductase inhibitors</td>
</tr>
<tr>
<td>Statins</td>
</tr>
<tr>
<td>Diuretics</td>
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<tr>
<td>Aldosterone (spironolactone); Na⁺/H⁺ exchanger (cariporide)</td>
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<tr>
<td>Immunosuppressants</td>
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<tr>
<td>Mycophenolate mofetil, rapamycin</td>
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<tr>
<td>Angiogenesis/kinase inhibitors</td>
</tr>
<tr>
<td>VEGF-receptor 1&amp;2 antagonists (PTK 787)</td>
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<tr>
<td>PDGFβ receptor antagonists (imatinib, SU9518)</td>
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<tr>
<td>Sorafenib</td>
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<tr>
<td>Sunitinib</td>
</tr>
<tr>
<td>Hepatocyte maintenance/protection</td>
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<tr>
<td>Hepatocyte growth factor (HGF)</td>
</tr>
<tr>
<td>Insulin-like growth factor I (IGF I)</td>
</tr>
</tbody>
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Selection of drugs for which antifibrotic activity has been shown in suitable animal models of liver fibrosis or for which an antifibrotic effect can be anticipated.
Antifibrotic approaches targeted at hepatic stellate cells.

AT: angiotensin; CTGF: connective tissue growth factor; ET-1: endothelin-1; ET₆R: endothelin A receptor; IGFIIR: insulin-like growth factor receptor II; MMF: mycophenolate mofetil; NGFR: nerve growth factor receptor; tPA tissue plasminogen activator; PDGF: platelet derived growth factor; PPAR-γ: peroxisome proliferator receptor-γ; TSP-1: thrombospondin-1. Most of the agents have proven safety for other indications and are attractive for combination therapy.

oral semisynthetic alkaloid derived from the antimalarial plant *Dichroa febrifuga* stimulate expression of the putatively fibrolytic MMP-1, -3 and -13 via nuclear factor kappa B and p38 kinase, while suppressing the supposedly profibrogenic MMP-2 in hepatic stellate cells in vitro [52]. In vivo, *Halofuginone* lead to a similar pattern of MMP activation and lowered hepatic collagen content in a fibrosis reversion model after induction of hepatic fibrosis by thioacetamide [52,63]. A more invasive and potentially hazardous approach is adenoviral gene delivery of fibrolytic MMP-1 or MMP-8 (which degrade fibrillar collagens I and III) to the fibrotic liver with consequent amelioration of fibrosis [64,65].

Plant-derived drugs

Plants contain powerful antioxidants such as polyphenols and flavonoids. Intracellular oxidative stress may be a relevant contributor to fibrogenesis, since hydrogen peroxide has been shown to activate transcription of procollagen I (via the transcription factor EBP/c) and of profibrogenic TGF-β1 in hepatic stellate cells [66,67], providing a rationale for the use of hepatotropic antioxidants as (adjunctive) antifibrotic agents. *Silymarin* from the milk thistle contains three prominent flavonoids, with silibinin representing up to 60% of the dried extract. Silibinin stimulates hepatocyte RNA synthesis, acts as a radical-scavenger, and suppresses hepatic stellate cells/myofibroblasts proliferation and collagen synthesis in vitro. In vivo it reduced hepatic collagen accumulation in rat biliary fibrosis secondary to bile duct occlusion, a model which leads to a 10–12-fold increased hepatic collagen accumulation after 6 weeks, by 30–40%, even when treatment was started in an advanced stage of fibrosis [68]. The major alkaloid baikalein from the traditional Chinese/Japanese plant extract *Sho-saiko-to*, which displays a structure similar to silibinin, has radical-scavenging and antifibrotic properties in activated hepatic stellate cells in vitro and in porcine serum-induced fibrosis in vivo [69].

The peroxisome proliferator activated receptor (PPAR—)γ agonists pioglitazone or rosiglitazone reduced collagen accumulation in rat models of toxin-induced and biliary fibrosis [70]. In vitro, the glitazones inhibited fibronectin and procollagen I in hepatic stellate cells/myofibroblasts synthesis induced by TGF-β1. Glitazones, which are suggested as drugs of choice for restoration of insulin sensitivity in non-alcoholic steatohepatitis, are therefore important adjuncts to the arsenal of potential antifibrotics, though their in vivo effect may be mainly based on their anti-inflammatory action [71].

Certain (synthetic) bile acids that are ligands of the nuclear farnesoid X receptor (FXR) inhibited rat biliary fibrosis in biliary fibrosis [72]. Interestingly, FXR signaling intersects with that of PPAR-γ. It remains to be shown to what extent the FXR-ligands also affect lobular fibrosis.

Antagonists of vasoactive mediators

The endothelin A receptor (ET₆R) mediates hepatic stellate cells/myofibroblasts contraction, proliferation and possibly also collagen synthesis, whereas the ET₇R induces myofibroblasts relaxation and inhibition of proliferation. In rat biliary fibrosis, the oral ET₆R antagonist LU135252 reduced hepatic collagen accumulation by up to 60% when given over the 6 weeks of fibrosis induction and still reduced fibrosis by 30% when treatment was begun after Week 3, a time point with an already 4-fold increased liver collagen [73]. Angiotensin 1 receptor antagonists or angiotensin converting enzyme inhibitors can retard liver fibrosis in suitable rat models [74–76]. Importantly, they display a known safety profile for cardiovascular indications. These will be discussed more extensively in the following chapter.
Immunosuppressants and angiogenesis inhibitors

There is an increasing number of other drugs, many of them already in clinical use for other indications, that either block proliferation and migration or induce apoptosis of hepatic stellate cells/myofibroblasts, while other agents have been shown to downregulate matrix production. Examples are the immunosuppressants rapamycin and mycophenolate mofetil [77,78], statins [79], or multikinase/angiogenesis inhibitors [80]. The antifibrotic effect of these drugs has to be confirmed in suitable experimental models of hepatic fibrosis.

Targeted antifibrotic therapies

Specific low molecular weight antagonists can block activation-dependent receptors on hepatic stellate cells. In addition, coupling these antagonists to a drug carrier allows for a highly specific targeting of the activated fibrogenic cells in the liver. This has been shown both in vitro and in vivo with cyclic octapeptides recognizing the receptors for PDGF-B or collagen VI, with mannose-6 phosphate which targets hepatic stellate cells and endothelial cells, and with vitamin A-coupled liposomes [81—86]. After i.v. injection more than 40% of these constructs were found on activated hepatic stellate cells of fibrotic rat livers, and in vitro data demonstrated efficient internalization.

Combination therapy for hepatic fibrosis

It appears that no single agent will effectively halt or reverse liver fibrosis in humans when given in non-toxic concentrations. As in cancer therapy, a combination of several drugs that show different actions by either blocking fibrogenesis, stimulating fibrolysis, by inducing myofibroblast apoptosis, or reversion to a fibrolytic phenotype, is most promising. This will allow the use of lower, non-toxic amounts of single agents for a treatment that will have to be given for years or even lifelong. Combinations of some of these agents are currently being tested in suitable in vivo rat fibrosis models.

Combining antifibrotics with hepatocyte transplantation or stem cell therapy

In order to achieve quick restitution of the functional parenchymal mass in concert with reversal of cirrhosis, the combination of antifibrotic therapy with stimulation of hepatocyte renewal, either with growth factors or by stem cell replacement is attractive [87—92]. Although in its infancy, this strategy may become a reality for desperate patients who are not eligible for liver transplantation, especially in a time of donor organ shortage. However, extensive preclinical testing has to make sure that growth stimulation for hepatocytes in a scenario of matrix removal does not increase the risk of hepatic malignancy.

Conflicts of interest

Nothing to declare.

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