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PORTAL HYPERTENSION (J GONZALEZ-ABRALDES AND E TSOCHATZIS, SECTION EDITORS)

Novel Targets and Drug Development in Portal Hypertension

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Abstract

Purpose of the Review This review aims to introduce animal models of portal hypertension in which targets and drugs can be tested and presents current advances in the field of preclinical and early clinical settings.

Recent Findings The interest in this field has risen in recent years and many promising targets and potential drugs have been tested in preclinical and early clinical studies. Most of these targets are intrahepatic and aim to decrease hepatic stellate cell activity, as this cell type mediates both fibrosis and portal hypertension.

Summary Liver cirrhosis with portal hypertension is a global health burden due to their complications. Besides that, there are only a few therapies available, those are ineffective in a large part of the patients. Therefore, novel targets and treatment options are vastly needed.

Keywords Cirrhosis · Portal hypertension · Animal models · Statins · Renin-angiotensin system · Kinase inhibitors · FXR

Introduction

Liver cirrhosis is a global health care burden with more than 1.2 million death per year [1]. The main etiologies of cirrhosis are viral, alcoholic and non-alcoholic hepatitis. Even though the etiologies are diverse, the resulting hepatic pathophysiology is the same. Due to liver injury, damaged hepatocytes induce inflammation leading to activation of hepatic stellate cells (HSC). As a repair mechanism, activated HSC produce collagen to replace the damaged cells. In chronic liver injury, processes are uncontrolled and excessive amount of extracellular matrix is deposited in the liver. Activated HSCs proliferate and increase contractility [2, 3•]. Together with dysfunction of the liver sinusoidal endothelial cells (LSEC), pronounced HSC activity is responsible for increased liver stiffness resulting in augmentation of intrahepatic resistance. A hallmark in cirrhosis progression is then the onset of portal hypertension. The hepatic blood flow due to increased resistance leading to portal venous congestion and consequent increased portal pressure. Portal hypertension induces splanchnic angiogenesis impairing microcirculation and intestinal barrier permeability further aggravating the syndrome [4•]. This is associated with severe complications of cirrhosis, namely variceal bleeding, ascites, and infections [5], which increases the risk for decompensation of cirrhosis and progression towards acute-on-chronic liver failure (ACLF) [6•]. Especially ACLF shows high short-term mortality [7]. Therefore, not only understanding the mechanisms of portal hypertension but discovering targets and development and testing of drugs is important in this field [8].

Currently, mainly nonselective beta-blockers (NSBB) are used to reduce portal pressure. However, many patients do not respond to NSBBs. Therefore, novel targets and drugs have been investigated and some show promising results preclinical and early clinical studies. To guide this process, the portal hypertension special interest group of the AASLD recently proposed a framework to design preclinical studies and clinical trials to prioritize novel targets and pharmacological therapies [9•].

This review focuses on a few selected current concepts and novel targets or potential drugs to treat portal hypertension. Since the approaches are too diverse to include them all in one review, we have chosen to present the most promising

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approaches according to our experience. Additionally, this review introduces the key models for preclinical studies on portal hypertension.

Animal Models to Test Targets and Potential Drugs in Portal Hypertension

Most potential targets and drugs have not yet made their way into the clinic and others could not be translated into the human situation. Therefore, reliable models to reflect either cirrhotic or non-cirrhotic portal hypertension are of importance to discover and test targets and drugs. Even though targets and potential drugs can be tested in cell culture in initial experiments, animal models are relatively fast to test the complex interactions between different cells, organs, and side effects in the system and a large enough sample size can be easily generated to deliver reliable results.

Bile duct ligation is a well-established fast obstructive jaundice model of cholestatic cirrhosis and can be performed in mice and rats. Following the invasive ligation of the bile duct, mice and rats develop advanced fibrosis and portal hypertension after 14 days or 4 to 6 weeks, respectively [10•]. The model can be used to investigate advanced stages of chronic liver disease with hepatic inflammation, fibrosis, and portal hypertension. Thereby, the model is fast and highly reproducible.

Carbon tetrachloride (CCl_4) intoxication mimics the toxic genesis of chronic liver disease and is especially used as a model for alcoholic liver disease. CCl_4 is metabolized by hepatocytes deploy its hepatotoxic properties by the resulting toxic radicals, which initiate membrane degradation and induce inflammation leading to fibrogenesis in chronic experiments [11]. Effects of CCl_4 intoxication can be potentiated by additional oral administration of barbiturates. Intoxication can be performed either by injection in a solution with oil or by inhalation and duration until advanced fibrosis and portal hypertension develops average 10 to 16 weeks depending on the method of administration [10•, 12]. Due to frequent subcutaneous or intraperitoneal injections during the initialization of liver fibrosis and portal hypertension, intoxication by injections entails higher risks of tissue necrosis and mortality than intoxication by inhalation, which is therefore preferred with respect to animal welfare. Intoxication by inhalation, however, needs to be performed in a protected setting due to the risks for the operator (effects on the central nervous system and carcinogenic properties) and nature (ozone-depleting).

Intoxication with thioacetamide (TAA) is another model of toxic liver disease. Hepatotoxic effects of TAA are caused by production of reactive oxygen species [13]. Similar to CCl_4, TAA can be administered using different techniques, either by intraperitoneal injections or orally in the drinking water with weight adopted doses. Advanced fibrosis and portal hypertension develop in a comparable timeframe to CCl_4 after 6 to 18 weeks. In later stages, however, the risk to develop cholangiocarcinoma increases. The main advantage of this model is the restriction of toxicity to the liver [12]. Similar to CCl_4, it has to be handled carefully due to its carcinogenic properties.

Idiopathic portal hypertension is a non-cirrhotic vascular cause of portal hypertension affecting mainly young adults and histologically characterized by micro-thrombotic lesions in small portal venules [12, 14]. This syndrome can be imitated in rats by repetitive injection of microspheres in the ileocecal vein. The procedure needs to be performed weekly for 3 weeks and requires a laparotomy each time, which represents also one of its biggest disadvantages since only very skilled persons can perform this procedure. The microspheres cause micro-thrombotic insults in the liver, which lead to portal hypertension with hyperdynamic circulation [15].

The partial portal vein ligation (PPVL) is a model for non-cirrhotic portal hypertension and is usually performed in rats. A ligature is placed around the portal vein and a blunt needle. Thereby, the degree of portal hypertension can be adjusted by the used diameter of the needle. Removal of the needle leads to a calibrated stenosis of the portal vein. Distinct portal hypertension develops almost immediately after the procedure. In the following days, portal pressure slightly decreases due to the formation of portosystemic collaterals. Experiments using this model are usually performed 2 weeks after PPVL. This model can be used to study angiogenesis and hemodynamics independent of cirrhosis. Detailed step-by-step instruction has been published by us and others [10•, 12].

The gradual occlusion of the inferior vena cava (IVC) is a model for post-hepatic portal hypertension and leads to features that are comparable with Budd-Chiari syndrome. The occlusion is achieved by a hygroscopic ring that is placed around the IVC. The ring successively constricts by body fluid uptake leading to almost full constriction of the IVC after 4 weeks. The blockade of hepatic outflow leads to ascites formation and hepatomegaly [12, 16].

In all of these animals, hemodynamics can be assessed to identify the degree of portal hypertension and test the effects of treatment. While portal pressure can be measured directly and serves as the primary output, additional hemodynamic parameters can be assessed using the microsphere technique. Thereby, colored microspheres should be favored over radioactive ones, since they are less harmful. Using this technique, the blood flow in and the resistance of different organs can be calculated [10•].

Current Concepts in the Clinics

Inflammation not only contributes to the development of liver fibrosis and cirrhosis but also manipulates intra- and

extrahepatic vascular function and thereby aggravates portal hypertension [17]. Strong correlations of inflammatory markers with hepatic venous pressure gradient (HVPG) have been demonstrated [18] besides an association of systemic inflammation with increased portal hypertension in cirrhosis [19]. Inhibition of caspase-mediated inflammation by emricasan improved MELD score by more than 2 points in half of the patients of a total of 74 patients as demonstrated recently in an open-label placebo-controlled trial [20•]. Furthermore, in 23 patients in an open-label uncontrolled trial, it was also well tolerated and decreased portal pressure in 12 of the patients with severe portal hypertension. The decrease was rather moderate (4 of 8 patients with more than 20%) [21•]. Overall, the effect of emricasan is modest and more data are necessary.

In cirrhosis, portal hypertension is linked to systemic inflammation caused by bacterial translocation facilitated from the impaired gut barrier [22]. Therefore, the microbiome is one potential target to reduce portal pressure and manipulation of the microbiome by antibiotic, probiotics, and prebiotics is investigated by several studies. However, so far, results are contradictory with regard to portal hypertension. Cirrhotic patients systemically receive antibiotics to improve overall survival [23, 24] and often NSBBs. NSSBs, besides their primary function to prevent rebleeding, have been shown to improve intestinal permeability in cirrhosis and consequently decreased bacterial translocation [25]. In several unblinded and non-randomized control trials treatment with Rifaximin, a semisynthetic broad-spectrum antibiotic approved for the treatment of hepatic encephalopathy improved HVPG and systemic hemodynamics and lowered the risk of decompensation. These studies included 30, 13, and 23 patients, respectively, and only the last study with 23 patients included non-randomized historical controls [26–28]. Of note, a double-blinded randomized control trial with 54 patients could not confirm these beneficial effects [29••]. Furthermore, Rifaximin seems to have only minor effects on bacterial composition, inflammation, and bacterial translocation [30]. Nevertheless, a combination of Rifaximin and Propanolol seem to be promising, probably due to additive effects of Rifaximin compared with NSBB monotherapy with decreased incidence of side effects due to lower NSBB dose than used normally as shown by an open-label randomized (2:1) trial in 73 patients [31]. Treatment with Norfloxacin, a synthetic broad-spectrum antibiotic active against Gram-positive and Gram-negative bacteria, reversed the hyperdynamic state, but effects on portal pressure were neglectable [32, 33]. However, Norfloxacin seems to improve survival in some cirrhotic patients, especially those with low ascitic fluid protein concentrations, probably due to decreased incidence of bacterial infection [34••].

Another approach could be to support the restoration of the bacterial composition in the intestine by probiotics. Supplementation with VSL#3, a live formulation of lyophilized of eight bacterial species, reduced the severity of liver disease by lowering the rate of hospitalization for hepatic encephalopathy or other complications of cirrhosis [35]. Additionally, one study could demonstrate the improvement of HVPG in 17 patients [36], while another study, again including 17 patients, found no effect [37]. Thereafter, the combination therapy seems more promising, adjunctive VSL#3 improved the response rate of propranolol with respect to HVPG and was safe and well tolerated in cirrhotic patients in a large randomized controlled trial with 94 patients [38].

Fecal transplantation could be a further approach. In a rodent model of non-alcoholic steatohepatitis with portal hypertension, transplantation of stool from healthy animals significantly decreased the portal pressure [39]. Furthermore, this concept has proven successful in a randomized controlled trial with 20 patients [40••].

Cirrhotic patients often develop coagulatory disorders and thrombocytopenia in advanced stages of cirrhosis [41, 42]. Anticoagulation therapy could be beneficial in cirrhosis with portal hypertension and indeed there are some recent hints showing improvement in portal hypertension. A few years ago, a non-blinded randomized controlled trial was performed in 70 outpatients with cirrhosis to investigate the effects of enoxaparin, a low–molecular weight heparin. Treatment for 12 months was safe and was efficient to prevent decompensation and improve survival [43]. Direct oral coagulants (DOAC) require less monitoring with similar bleeding risk as conventional coagulants [44]. A retrospective analysis demonstrated that anticoagulant therapy with DOACs in cirrhosis is safe and effective [45•]. Mechanistically, enoxaparin has been shown to decrease hepatic vascular resistance and portal pressure in experimental cirrhosis, mainly by decreasing HSC activity [46]. Similar results have been achieved using rivaroxaban in two experimental models of cirrhosis with portal hypertension [47]. Furthermore, vasodilatory effects may support these effects by increased eNOS activity [48, 49]. However, a recent study could not support the previous findings and could not show beneficial effects of enoxaparin on liver function, hepatic fibrosis, endothelial dysfunction, and portal hypertension [50]. Therefore, more data and future studies are needed to evaluate the potential of anticoagulant therapy in cirrhosis with portal hypertension.

Another approach targeting portal hypertension are phosphodiesterase type 5 (PDE5) inhibitors, which are in clinical use for erectile dysfunction, and clinical testing in portal and pulmonary hypertension [51]. In cirrhosis, PDE5 is upregulated in hepatic tissue, especially in perisinusoidal cells and the fibrotic septae [52]. Initial studies on PDE5 inhibition in experimental fibrosis showed beneficial effects on fibrosis and portal hypertension via decreased HSC activity [53–55]. Therefore, PDE5 inhibitors have been tested in the clinical setting in a phase-II study in compensated cirrhotic patients.

A dose of 75-100 mg administered for 1 week decreased portal pressure without systemic side effects in an open-label trial with 30 patients [56].

β3-Adrenoceptor Agonists

β3-adrenoceptors participate in the regulation of vascular tone and are upregulated in hepatic and splanchnic tissue in cirrhotic patients with portal hypertension, as well as in animal models and therefore represent a potential therapeutic target. Stimulation of the β3-adrenoceptors by selective agonists decreased intrahepatic resistance and portal pressure in cirrhotic animals with only minor systemic effects [57, 58].

Statins

Statins are used for prevention and treatment of cardiovascular diseases in patients with high blood lipid levels. The primary mechanism of action is the interruption of cholesterol synthesis by inhibition of HMG-CoA reductase. They feature also additional effects, which make them potential drugs for the treatment of portal hypertension [59].

One of the so-called pleiotropic effects is the inhibition of small GTPase activity. Impaired HMG-CoA activity results in lower isoprenoid levels, pivotal components of cell membrane lipid anchors for small GTPases, such as RhoA and Ras, and thus decreased the activity of small GTPases due to hampered membrane binding [60–62]. Statins inhibit RhoA-dependent HSC activation and activity via Rho-kinase. Furthermore, statins improve hepatic endothelial dysfunction and thereby the communication between HSC and LSEC via Krüppel-like factor 2 (KLF2) and endothelial nitric oxide synthase (eNOS). Taken together, this leads to decreased fibrosis accumulation and intrahepatic resistance resulting in attenuation of portal pressure [63–68]. In cirrhotic rats with a single LPS injection, a vague approximate of ACLF, statins increased survival and prevented complications. Statin treatment reduced hepatic inflammation, improved liver function, and decreased portal pressure in these rats [69].

Recently, NCX 6560, a nitric oxide-releasing atorvastatin, was evaluated and compared with conventional atorvastatin. NCX 6550 decreased the incidence of hepatic and muscular toxicity, while the antifibrotic profile and improvement of portal hypertension were similar to conventional statins [70]. Approaches like this one may be promising to finally establish statins in the clinic for the treatment of portal hypertension in cirrhotic patients.

Additionally, statins improve portal hypertension by antiangiogenic extrahepatic effects. These effects are associated with RhoA and are mediated by the non-canonical hedgehog, which in turn leads to reduced vessel formation and accordingly decreases portal venous inflow [71]. This, however, applies only in the context of cirrhosis, while in non-cirrhotic portal hypertension, statin treatment aggravates the syndrome [71–73].

Due to potential hepatotoxic side effects of statins, evidence of their benefits in portal hypertension was primarily generated in experimental settings. In recent years, however, these concerns fade away since more and more studies prove their safety and overall tolerance in cirrhotic patients with portal hypertension, especially in those with concomitant cardiovascular diseases [74•, 75]. The first prospective study elucidating acute effects of statins in two small cohorts of cirrhotic patients (30 patients in total) was performed more than a decade ago. Although HVPG was not modified in these acute experiments, the authors could describe a decrease in hepatic resistance (around 14%) accompanied by the increased availability of hepatic nitric oxide (NO) products consequently increasing hepatic blood flow. Furthermore, no systemic side effects were identified in these patients [76]. More recently, in a triple-blinded randomized trial with 24 patients, simvastatin decreased portal pressure in patients receiving the drug for 3 months, while placebo did not. Interestingly, the response rate to simvastatin (55% of patients responded) was higher in patients with oesophageal varices and history of variceal bleeding. Again, no adverse events after statin treatment were recorded [77]. A larger double-blinded randomized control trial with patients receiving the standard prophylaxis to prevent variceal bleeding investigated the effects of additional statin administration for 24 months. Here, statins could not be related to decreased risk of rebleeding, but improved survival by decreasing the relative risk by 61%. In this trial, adverse events were reported in some patients [78••]. Two other independent trials investigating the effects of statins additionally administered to beta-blockers could confirm beneficial effects. In both trials combined, the therapy with statins and beta-blockers showed higher response and a stronger decrease in HVPG than single treatment with beta-blockers, especially in patients who did not respond to beta-blockers statins could improve HVPG. Therefore, the authors concluded that a combined therapy of beta-blockers and statins is promising in patients with portal hypertension [79, 80•].

Until now, however, most published studies are either retrospective or trials with small patient cohorts and need to be substantiated by larger randomized controlled studies, with some of those studies already started recruiting patients [81, 82]. For more detailed review of the literature, we recommend to read the publications by Abraldes et al. and Pose et al. [9•, 74].

Renin-Angiotensin System

The renin-angiotensin system (RAS) is a systemic regulatory circuit that regulates blood pressure, splanchnic vasodilation,

and sodium retention. However, local RAS systems can be found in several tissues with functions that are independent of the systemic RAS.

In general, angiotensinogen, mainly produced by the liver, is converted to angiotensin I by renin and further cleaved by the angiotensin-converting enzyme I (ACE I) into angiotensin II. Angiotensin II is the regulatory peptide of the RAS and agonist of the angiotensin II receptor type 1 (AT1R). In chronic liver disease, angiotensin II and the AT1R are highly upregulated and contribute to liver fibrosis and portal hypertension [83, 84]. Therefore, those two components are historically the main targets for anti-hypertensive treatment and are already in clinical use for non-liver related diseases. Inhibitors of angiotensin II formation (ACE inhibitors) and AT1R antagonists ("sartans") are in use for the treatment of arterial hypertension and chronic heart failure and were extensively investigated for their potential in chronic liver diseases. However, the effects on fibrosis are not more than modest with several systemic side effects [85, 86], especially shown in a placebo-controlled randomized double-blinded trial including 36 patients [87]. Even in combination with beta-blockers, the use of RAS inhibitors may still be not safe enough due to the high risk of side effects. This was confirmed in meta-analyses including three studies with 90 patients [88]. Genetic predisposition also seems to play a role in RAS-mediated portal hypertension. Patients with ACE I allele were found to have a higher HVPG and higher risk for variceal bleeding than patients with ACE D allele [89]. Additionally, the role of the angiotensin II receptor type II, another agonist of angiotensin II, to whom opposing effects to the AT1R are attributed has not been investigated so far in liver cirrhosis with portal hypertension. Therefore, manipulation of this classic RAS components has not yet found its way into the clinic.

Nevertheless, there is also an alternative RAS in which Ang1–7 is the key regulatory peptide. Substrates for Ang1–7 can be angiotensin I cleaved by NEP or angiotensin II cleaved by ACE II. Ang1–7 is the agonist of the mas proto-oncogene receptor (MasR) and features vasodilatory properties. In cirrhotic patients, Ang1–7 and the MasR are upregulated in the liver, as well as in splanchnic vessels. In extrahepatic vessels, Ang1–7 antagonizes AT1R signaling potently [90, 91]. Experimental manipulation of the system by MasR inhibition increased the portal pressure. On the other side, MasR stimulation induces eNOS release and thereby counteracts the pro-contractile AT1R [92]. Stimulation of the Ang1–7 agonist by the non-peptidic mimic AVE0991 decreased portal pressure without systemic side effects. Of note, AVE0991 had no effect on hepatic fibrosis [93].

Kinase Inhibitors

Since ACE inhibitors and AT1R blockers seem to be ineffective or cause severe side effects, downstream targets of the RAS may be potential targets to treat portal hypertension. Janus-kinase 2 (JAK2) links the RAS via the AT1R to the pro-fibrotic and pro-contractile RhoA/Rho-kinase pathway [94, 95]. JAK2 is highly upregulated in human cirrhosis, especially in HSC, and correlates with the severity of liver disease [95, 96]. Inhibition of JAK2 by the chemical compound AG490 successfully decreased hepatic vascular resistance and portal pressure in cirrhotic animals [96, 97]. Additionally, JAK2 inhibition decreases hepatic inflammation, angiogenesis, fibrosis, and activation of HSC, mainly via the RhoA/Rho-kinase pathway [95, 97]. This data was independently confirmed [97]. Due to its important role in fibrosis and portal hypertension, JAK2 inhibitors are in development for clinical use, especially since existing inhibitors like AG490 also have a high affinity to block other tyrosine kinases. The multikinase inhibitor ruxolitinib is approved in the USA and Europe for treatment of myelofibrosis and first studies in two experimental fibrosis models showed beneficial effects especially on inflammation and oxidative stress, both drivers of fibrogenesis and development of portal hypertension [98–100]. Due to the poor availability of data, so far, no clinical trials have been published. However, JAK2 inhibition seems promising and more studies need to be performed.

Multikinase Inhibitors

Since most of the JAK2 effects are mediated via the RhoA/Rho-kinase pathway, targeting this pathway directly is another approach to treat portal hypertension. The multikinase inhibitor sorafenib has been investigated in this regard and is approved for the treatment of advanced HCC, which shares several mechanisms with cirrhosis. In experimental models of portal hypertension, sorafenib decreased angiogenesis and vasoconstriction of splanchnic vessels [101–103]. However, in a small cohort of 13 cirrhotic patients, sorafenib (400 mg b.d.) showed only limited effects; only in 4 patients, HVPG decreased [104]. Regorafenib is a more potent multikinase inhibitor than sorafenib and may improve portal hypertension. In experimental models of cirrhotic and non-cirrhotic portal hypertension, acute and long-term treatment with regorafenib was able to blunt angiogenesis and improve portal hypertension. However, in long term–treated fibrotic animals, hepatotoxic side effects were observed [105].

FXR

The farnesoid X receptor (FXR) is also a promising target in chronic liver disease with portal hypertension. It is a transcriptional regulator of bile acid homeostasis and highly expressed in the liver and small intestine [106]. Previous studies have demonstrated its role in inflammation, liver fibrosis, and

vascular homeostasis [107, 108]. Treatment with the selective semisynthetic FXR agonist obeticholic acid (OCA) reduced the hepatic resistance and portal pressure without systemic effects. This was related to increased intrahepatic eNOS activity [109] and mediated by dimethylaminohydrolase-1 which metabolizes the eNOS inhibitor asymmetric-dimethylarginine [110]. Furthermore, OCA has also anti-inflammatory properties as shown by in vitro experiments in Kupffer cells and LSEC, where it inhibits pro-inflammatory pathways via NF-κB. These anti-inflammatory properties downregulated HSC activity in experimental toxic fibrosis [111]. Several agonists and regulators of FXR have been tested in experimental models to demonstrate the impact of this pathway on portal hypertension, either by direct action on HSC or using the communication between HSC and LSEC. Dihydroartemisinin, a regulator of FXR expression, decreased HSC contraction in vivo and improved portal pressure in vitro [112, 113]. In another study, the non-steroidal FXR agonist PX20606 improved portal pressure, by reducing vascular remodeling and sinusoidal dysfunction, while hepatic fibrosis was also decreased [114]. Further, FXR and the bile acid receptor G protein bile acid receptor 1 were targeted in LSEC to improve endothelial dysfunction and as a consequence portal hypertension [115, 116].

So far, the only multicenter double-blinded placebo-controlled randomized clinical trial assessing obeticholic acid was performed in a cohort of 283 non-cirrhotic, non-alcoholic steatohepatitis patients, where it improved liver function and slightly decreased fibrosis after 72 weeks of treatment. Hemodynamics, however, were not assessed in this trial [117].

Targeted Approach

Since the mechanisms of contractility are contrary regulated in the liver and the splanchnic vascular region, more specific effects are desirable. Side effects may lay in the nature of kinase inhibitors since they have several targets and are often expressed in various tissues, where inhibition could cause unwanted effects. Cell-specific kinase inhibition might avoid those side effects. The Rho-kinase inhibitor Y-27632 decreased hepatic resistance in experimental cirrhosis, but showed also massive systemic side effects, since Rho-kinases are widely expressed in other organs too [67, 118]. Bound to a cell-specific carrier targeting activated HSC, Y-27632 was able to have the same beneficial effects, but without systemic side effects. Cell-targeted administration decreased hepatic fibrosis and portal pressure while it increased renal perfusion. These effects were associated with decreased contractility and collagen production by HSC [68, 119, 120].

Conclusions

Promising targets and potential drugs have been discovered in recent years. However, many drugs have failed after encouraging preclinical results due to extrahepatic side effects. Therefore, cell-targeted therapy could avoid unwanted side effects in the treatment of portal hypertension. These promising approaches have to demonstrate their beneficial potential in large randomized controlled clinical trials to find their way into the clinical routine treatment and to improve survival and quality of life of cirrhotic patients with portal hypertension.

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Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest.

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