Portal hypertension is a serious complication of chronic liver disease resulting in decompensated cirrhosis and associated with high morbidity and mortality. It is primarily caused by increased intrahepatic vascular resistance (IHVR) to portal blood flow resulting from profound changes in all sinusoidal cells and intrahepatic vasoconstriction. Increased IHVR is further associated with expansion of contractile elements and extracellular matrix produced by activated hepatic stellate cells (HSCs), which compress sinusoids. In addition, liver sinusoidal endothelial cells and resident hepatic macrophages (Kupffer cells) contribute to the pathogenesis of portal hypertension by secretion of highly effective vasoconstrictors and by reducing their sensitivity towards vasodilators.

Important preclinical and clinical studies have shown that the activation of the Wnt/β-catenin pathway significantly contributes to the pathogenesis of different forms of liver injury. In the context of HSC, Wnt antagonism inhibits HSC activation and liver fibrosis, identifying Wnt as a common downstream mediator of fibrogenic effects in the liver (Cheng et al., 2008).

In a recent study published in this issue, Wnt/β-catenin signalling correlated with and promoted HSC contraction in portal hypertension (Zhang et al., 2020). Mechanistically, the authors found that Wnt/β-catenin signalling induces TCF4-dependent trans-repression of Sufu, leading to Gli1 activation and RhoA-mediated HSC contraction via LARG activation. The Gli1 protein is a member of a family of Kruppel-like factors acting as transcriptional effectors of the hedgehog signalling pathway. Their dynamic bidirectional transport between the cytoplasm and the nuclear compartment is critical for the regulation of many transcription factors. There is already considerable knowledge of understanding the contribution of the RhoA/Rho-kinase pathway in regulating smooth muscle contraction (Nunes & Webb, 2020). However, the study from Zhang and colleagues adds some important new aspects. These authors showed that from all Wnt ligands tested, the Wnt3a mRNA levels were most significantly increased in human cirrhotic livers. Immunohistochemistry revealed that β-catenin was significantly overexpressed in the peri-sinusoidal space and fibrous septa of cirrhotic livers and co-localized with α-smooth muscle actin (a reliable marker of HSCs). Moreover, recombinant Wnt3a increased cell proliferation and contractility and markedly increased phosphorylation of the myosin light chain 2 (MLC2) in the immortalized human HSC cell line LX2, effects that were blunted in the presence of XAV-939 or IWR-1-endo specifically inhibiting β-catenin and by siRNA targeting β-catenin. Importantly, Wnt3a-induced HSC contractility was also inhibited by application of the selective Gli1 inhibitor GANT-58 and siRNA-mediated knockdown of Gli1. Under these conditions, the activation of RhoA was markedly inhibited by blocking Wnt3a-induced LARG induction.

Altogether, Zhang and colleagues present a regulatory network of factors that orchestrate HSC contractility. These cells represent 5%–8% of all liver cells and are located in the peri-sinusoidal space of Disse beneath the endothelial barrier. Physiologically, these mesenchymal cells are believed to be the major storage site for vitamin A. During hepatic insult, these retinoid-storing cells are activated and
undergo a phenotypic switch leading to an extracellular matrix-producing phenotype, called myofibroblasts (MFBs). During the last decades, it has become clear that HSCs/MFBs are involved in the regulation of hepatic microcirculation and portal hypertension. Therefore, these pro-fibrogenic cells are regarded not only as an attractive target for anti-fibrotic interventions but also for drugs interfering with cellular contractility and portal blood flow. Apart from drugs that help to restore the normal hepatic sinusoidal diameter (e.g., somatostatin), selective blockade of endothelin ET<sub>A</sub> receptors, relaxing agents such as nitric oxide (NO), and specific drugs blocking angiotensin AT<sub>1</sub> receptors (e.g., losartan) were proposed in many studies as pharmacological treatment options.

However, none of these drugs interfering with HSC contractility are presently in clinical use. At present, endoscopic therapy, dietary changes, and non-selective β-adrenoceptor antagonists (β-blockers) such as nadolol or propranolol, are (non-optimal) therapeutic options to reduce pressure in the veins (EASL, 2018). Most often, invasive surgical procedures such as transjugular intrahepatic portosystemic shunt (TIPS) that decompresses the portal system by shunting an intrahepatic portal branch into a hepatic vein are necessary to reduce portal hypertension and its main complications, such as oesophageal varices, ascites and hepatorenal syndrome (EASL, 2018). Unfortunately, this surgical procedure can lead to additional complications such as bacterial infections, damage of surrounding vessels, internal bleeding, and ammonia-induced hepatic encephalopathy. Therefore, new and more targeted pharmacological interventions would be extremely helpful for the management of portal hypertension. In this regard, pharmacological blockade of the Wnt/β-catenin pathway with specific inhibitors might be an elegant therapeutic option to reduce portal hypertension by restriction of HSC contractility.

Zhang and colleagues have already shown that a curative treatment (i.e., treatment of established disease) of cirrhotic mice with the β-catenin inhibitors XAV-939 or IWR-1-endo for 1 week or 4 weeks markedly reduced portal pressure, accompanied by reduced contractility of primary HSCs, isolated from treated animals, compared with untreated, control cirrhotic mice (Zhang et al., 2020). The inhibitors were effective in restoring Sufu expression, reducing nuclear abundance of Gli1 and lowering expression of hepatic α-smooth muscle and F-actin. As a consequence, the inhibitors improved liver histology, reduced collagen deposition and hepatic inflammation, and mitigated sinusoidal capillarization.

Because current available therapeutic options are limited or carry substantial risks, these findings are highly encouraging. In most preclinical studies, only preventive effects of hepatoprotective agents have been tested and information about curative effects is scarce. In the present study, the curative treatment of animals showed that the Wnt/β-catenin inhibitors XAV-939 and IWR-1-endo were effective in reducing fully developed portal hypertension. XAV939 stimulates β-catenin degradation by stabilizing tankyrase 1 and tankyrase 2, enzymes required for β-catenin degradation, while IWR-1-endo stabilized Axin, a protein that is a key component of the β-catenin destruction complex. Both compounds decreased Wnt signalling and were effective in reducing portal hypertension. The authors provide additional evidence that Sufu, a protein regulating Gli1 expression that is a key negative regulator of hedgehog signalling, further offers a new potential druggable target to modulate portal hypertension.

A recent position paper prioritized targets and proposed a novel framework for the design of clinical trials in patients with cirrhosis and portal hypertension (Abraldes et al., 2019). The list of selected candidate drugs with a proven effect in reducing portal hypertension in preclinical studies is rather long and includes ET<sub>A</sub> receptor antagonists, AT<sub>1</sub> receptor blockers, statins, PDE5 inhibitors, caspase inhibitors, FXR agonists and many other compounds. In the light of the present publication, drugs targeting the Wnt/β-catenin pathway might be another source of good candidates, that should be added to this list. The finding that Wnt/β-catenin inhibitors interfere with HSC/MFB contractility might offer new therapeutic avenues. It will now be of fundamental interest to test these drugs in other experimental models of portal hypertension.

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in the IUPHAR/BPS Guide to PHARMACOLOGY (http://www.guidetopharmacology.org) and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20 (Alexander, Christopoulos et al., 2019; Alexander, Cidlowski et al., 2019; Alexander, Fabbro et al., 2019).

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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