Hepatocyte Regeneration and Inhibition of Proliferation: Two Sides of a Coin

ABSTRACT 1

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Constitutive Androstane Receptor (CAR)-Driven Regeneration Protects Liver From Failure Following Tissue Loss

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Background & aims: Liver can recover following resection. If tissue loss is too excessive, however, liver failure will develop as is known from the small-for-size-syndrome (SFSS). The molecular processes underlying liver failure are ill understood. Here, we explored the role and the clinical potential of Nr1h3 (constitutive androstane receptor, CAR) in liver failure following hepatectomy.

Methods: Activators of CAR, various hepatectomies, CAR^{-/-} mice, humanized CAR mice, human tissue, and ex vivo liver slice cultures were used to study CAR in the SFSS. Pathways downstream of CAR were investigated by in vivo siRNA knockdown.

Results: Excessive tissue loss causing liver failure is associated with deficient induction of CAR. Reactivation of CAR by an agonist normalizes all features associated with experimental SFSS. The beneficial effects of CAR activation are relayed through Foxm1, an essential promoter of the hepatocyte cell cycle. Deficiency in the CAR-FOXM1 axis likewise is evident in human SFSS. Activation of human CAR mitigates SFSS in humanized CAR mice and improves the culture of human liver slices.

Conclusions: Impaired hepatic CAR-Foxm1 signaling provides the first molecular characterization of liver that fails to recover after tissue loss. Our findings place deficient regeneration as a principal cause behind the SFSS and suggest that CAR agonists may bear clinical potential against liver failure.

ABSTRACT 2

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Ursodeoxycholic Acid in Advanced Polycystic Liver Disease: An International Multicenter Randomized Controlled Phase 2 Trial

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Background & aims: Ursodeoxycholic acid (UDCA) inhibits proliferation of polycystic human cholangiocytes in vitro and hepatic cystogenesis in a rat model of polycystic liver disease (PLD) in vivo. Our aim was to test whether UDCA may beneficially affect liver volume in patients with advanced PLD.

Methods: We conducted an international, multicenter, randomized, controlled trial in symptomatic PLD patients from three tertiary referral centers. Patients with PLD and total liver volume (TLV) ≥ 2500 mL were randomly assigned to UDCA treatment (15–20 mg/kg/day) for 24 weeks, or to no treatment. Primary endpoint was proportional change in TLV. Secondary endpoints were change in symptoms and health-related quality of life. We performed a post hoc analysis of the effect of UDCA on liver cyst volume (LCV).

Results: We included 34 patients and were able to assess primary endpoint in 32 patients, 16 with autosomal dominant polycystic kidney disease (ADPKD) and 16 with autosomal dominant polycystic liver disease (ADPLD). Proportional TLV increased by $4.6 \pm 7.7\%$ (mean TLV increased from 6697 mL to 6954 mL) after 24 weeks of UDCA treatment compared to $3.1 \pm 3.8\%$ (mean TLV increased from 5512 mL to 5724 mL) in the control group

($P = 0.493$). LCV was not different after 24 weeks between controls and UDCA-treated patients ($P = 0.848$). However, UDCA inhibited LCV growth in ADPKD patients compared to ADPKD controls ($P = 0.049$).

Conclusions: UDCA administration for 24 weeks did not reduce TLV in advanced PLD, but UDCA reduced LCV growth in ADPKD patients. Future studies might explore whether ADPKD and ADPLD patients respond differently to UDCA treatment.

COMMENTARY

The regenerative capability of the liver has been described in the Greek mythology. In ancient times, Zeus punished Prometheus by chaining him to Mount Caucasus where he was tormented by an eagle. Prometheus' liver renewed every day after being eaten by an eagle. In a classical experiment involving a rodent model, two-thirds of the liver was removed and the remaining liver enlarged within 1 week after resection.¹ Similarly, in humans post resection and after transplantation of partial livers, within 4 weeks there is restitution of the liver mass. These facts highlight the extraordinary regenerative capacity of the liver. Once the injury is removed, the liver grows back to its normal size and regains its functions, unless the injury persists and leads to the development of complications or other secondary diseases, which may prevent liver regeneration.² Liver volume plays an important role in regeneration, both after resection and liver transplantation. In the absence of adequate liver volume, there remains a risk of liver failure, which is clinically defined as small-for-size syndrome (SFSS).³ The cause of this entity and the residual liver volume below which it occurs are poorly understood.

Tschuor et al.⁴ explored the mechanisms involved in liver regeneration, especially the role of Nr1h3 (constitutive androstane receptor, CAR) in mice models. CAR plays a role in detoxification of endo- and xenobiotics. In a step-wise manner, authors documented the role of CAR. In the first step, they showed that CAR deficiency is responsible for experimental SFSS. For this, they compared CAR^{-/-} mice and wild-type mice post standard hepatectomy (70%) and extended hepatectomy (86%). The survival after standard hepatectomy in CAR^{-/-} mice was reduced to approximately 80% (similar to extended hepatectomy), as compared to expected 100% survival in wild-type mice. In the second step, the authors documented that CAR agonists prevent the development of SFSS and improved survival. TCP (1,4-bis(2-(3,5-dichloropyridyloxy))benzene), which is a potent CAR ligand, resulted in 40% survival in mice even after 91% hepatectomy. In the next step, the authors studied the role of Foxm1 in mediation of the CAR effects. Foxm1 knockdown resulted in reduced liver weight, reduced synthetic functions, and steatosis.

Knockdown of Foxm1 before extended hepatectomy resulted in the loss of the effect of TCP. Thus, the authors concluded that Foxm1 mediates CAR effects in experimental SFSS.

The CAR of mice is distinct from the CAR of humans. To extend the results beyond mice into humans, authors developed transgenic mice with humanized CAR and performed similar hepatectomies. They demonstrated that human CAR had a similar role in liver regeneration. CITCO (CAR agonist) had a beneficial effect on liver regeneration, although it was less pronounced when compared with the effect of TCP in mice. Multiple additional factors may be involved, which are presently not known, or CITCO may not be a strong agonist.

The results of the study, if replicated and shown to be safe in humans, would have important consequences. The clinical benefits in humans include its role in liver regeneration after surgical resections, liver transplantations, and possibly a role in acute liver failure (early regeneration will lead to survival benefit). These results are exciting as they open up new pathways and targets for liver regeneration. However, it is also important to understand that excessive unchecked proliferation will lead to cancers—for instance, after liver resection for hepatocellular carcinomas, use of proliferation agonists may lead to the development of new tumors. Further, more data is required regarding safety before this therapy becomes a reality in humans.

In another interesting study, D'Agnolo et al.⁵ explored the role of ursodeoxycholic acid in reducing the cyst size in advanced polycystic liver disease. The background for the current hypothesis of reduction in the size of cysts in polycystic liver disease stems from their initial study in the polycystic kidney (PCK) rats, in which they showed decreased hepatic cystogenesis after 5 months of UDCA therapy.⁶ The results of the current multicenter trial involving 34 humans showed that there was no significant effect of UDCA on the total liver volume. Post hoc analysis revealed a significant reduction in liver cell volume in autosomal dominant polycystic kidney disease, as compared with the autosomal dominant polycystic liver disease. There are multiple reasons for these findings: dose of UDCA used and mouse model may not be a true representation of the human disease, along with small sample size. The results of the current study highlight an important fact that extrapolation of animal data to humans may not work, which is a well-known fact. Any new finding in animal model studies needs to be confirmed in humans, before its true clinical application can be understood.

CONFLICTS OF INTEREST

The authors have none to declare.

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