Targeting bile salt-FGF19 signaling

Appendix II

Impact

Relevance

Social and economic relevance

Enterohepatic circulation (EHC) of bile salt plays an important role in gut-liver function [1]. However, surgical patients, especially patients with hepatobiliary malignancies, often suffer from a disrupted EHC, which has detrimental effects on gut-liver health [2]. For instance, patients with perihilar cholangiocarcinoma (pCCA) have an obstructed EHC, due to malignant obstruction of the bile duct. These patients can develop obstructive jaundice and cholestatic liver injury [3]. Furthermore, for patients undergoing partial hepatectomy, especially when accompanied by concomitant removal of the gallbladder during extended resection procedures, the EHC can be temporarily disrupted due to removal of the 'source' of bile salts. Major liver resection can lead to post-hepatectomy liver failure (PHLF) and death, especially in patients with pCCA [4]. [55, 6744]Likewise, patients with insufficient future liver remnant (FLR) volume suffer unfavorable high risk of PHLF and mortality after partial liver resection [5]. To solve this problem, the nuclear bile salt receptor farnesoid X receptor (FXR) agonist obeticholic acid (OCA) has been shown to accelerate hypertrophy of FLR in experimental portal vein embolization (PVE) model [6]. Pharmacological treatment with OCA has promise to induce augmented FLR hypertrophy in patients scheduled for extended partial liver resection, contributing to decreased incidence of PHLF. From economic perspective, it can avoid more medical costs through decreasing postoperative morbidity.

In addition, intestinal failure (IF) is another common health issue in digestive surgery. IF patients with a temporary double enterostomy (TDE) in the jejunum have a disrupted EHC due to outflow of succus entericus in the stoma bag [7]. These patients require parenteral nutrition (PN) for weeks or even months [8]. However, PN is associated with various complications, such as infectious, mechanical and metabolic complications[9]. An important consequence of IF can be the development of intestinal failure-associated liver disease (IFALD) that is characterized by cholestasis, hepatic steatosis and fibrosis. These complications can result in hospital readmissions and increased healthcare-related costs [7]. Additionally, the patients' quality of life is seriously affected by IF. Chyme (intestinal or fistula secretions) reinfusion (CR), an extracorporeal enteral nutrition technique, contributed to improved nutritional status, better intestinal absorptive function, recovery from IFALD, reduced intestinal secretions and shorter period to weaning of PN.

Scientific relevance

In this thesis, we conducted several studies to investigate the role of enterohepatic bile salt signaling in compensatory liver growth and intestinal failure. Firstly, we systematically assessed the effect and route of preoperative biliary drainage (BD) in patients with resectable pCCA. Due to high risk of bias in the current available evidences, we propose future randomized prospective studies to evaluate the value of preoperative BD in resectable pCCA. Furthermore, we explored the suitability of human precision-cut liver slices (hPCLS) as an *in vitro* model to study liver regeneration. Further optimization of the procedure and/or culture conditions, and consideration of patient factors are required before (un)suitability of hPCLS as a model system can be judged. In addition, we revealed that OCA improves bile salt homeostasis after PVE in rabbits, likely through inhibiting hepatic synthesis and promoting export of bile salts. This underlies in part the accelerated hypertrophy of the non-embolized liver lobe. It is promising to further evaluate the effect of OCA in surgical patients with small FLR scheduled for (extended) hepatectomy. A large body of safety data with OCA is available from phase III and ongoing phase IV trials in patients with chronic cholestatic and metabolic liver diseases[10-12]. Finally, through analyzing bile salt-FGF19 signaling in IF patients treated with chyme reinfusion, we revealed that chyme reinfusion restored EHC of bile salt and bile salt-FGF19 signaling, which partly contributed to improved gut-liver function in this patient population.

Target groups

The studies performed in this thesis provide novel knowledge and perspectives for the scientific community. We demonstrated that OCA improved bile salt homeostasis, and this in part contributes to accelerated hypertrophy of the non-embolized liver lobe after PVE in rabbits. These observations can inspire scientists and clinicians to explore the use of pharmacological activation of FXR to accelerate PVE-induced liver growth in human studies.

Meanwhile, insights form the studies described here can also benefit clinical doctors. Given the importance of the EHC of bile salts in daily practice, nutritionists can consider chyme reinfusion as first-line treatment in IF patients with a TDE. This can also improve/prevent some PN-related complications. In addition, because internal biliary

drainage can restore EHC of bile salt, physicians can consider this potential benefit when choosing a drainage method in patients with biliary obstruction.

The ultimate aim of medical research is to improve the health of humans. Our findings may contribute to improve outcomes of surgical patients, including patients planned for (extended) liver partial resection, and IF patients with TDE.

Innovation and Implementation

In this thesis, we investigated the link between enterohepatic bile salt signaling and liver regeneration and intestinal failure. For the first time, a systematic review of systematic reviews was conducted to assess the effect and route of preoperative BD in patients with resectable pCCA and indicated a high risk of bias in current available systematic reviews. Additionally, although our previous study [6] showed that OCA promoted liver regeneration following PVE in a rabbit model, the mechanism was not clarified. Our study indicated that improved bile salt homeostasis contributed to accelerated liver growth induced by PVE in OCA-treated animals. Furthermore, for IF patients with TDE, the RESCUE study revealed that restored enterohepatic bile salt-FGF19 signaling underlies in part the beneficial effects of chyme reinfusion on gut-liver function, thus reversing IFALD.

The effect of preoperative BD in resectable pCCA is under debate. Further studies with large sample sizes should focus on the indications for BD, subsequently determine what kind of patients with pCCA can benefit from preoperative BD. Additionally, the effectiveness of OCA for promoting liver growth has been investigated in the rabbit model of PVE. Future research to study effect of OCA on tumor growth in embolized lobes in pre-clinical setting are recommended. Moreover, in the nutritional units, chyme reinfusion (Fig. 1) should be considered as preferred treatment for IF patients with TDE to avoid potential PN-associated morbidity and improve intestinal rehabilitation. A portable roller pump would allow patients to be ambulant during the pre-operative setting [13].

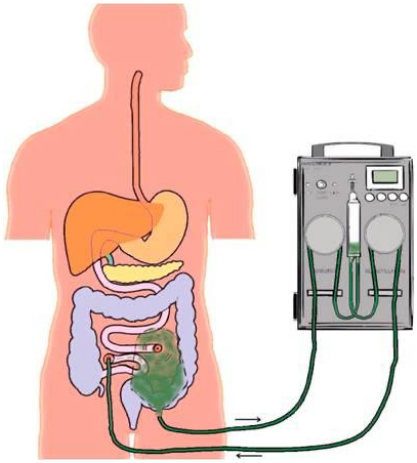

Figure 1. Chyme reinfusion technique with the automated roller pumps. Continuous chyme reinfusion was performed in a closed system of extra-corporal circulation of chyme using the Enteromate II® system (Labodial, Clayes-sous-Bois, France). The left pump works permanently and aspirates the jejunal effluent from the stoma bag toward a plastic container. When the minimal volume of about 10 ml in the container is exceeded, the second pump starts and the contents are infused into the downstream small intestine. This illustration is a modification from a picture of Picot *et al.* (2017) [7].

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