Prometheus’ little helper, a novel role for fibroblast growth factor 15 in compensatory liver growth

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Abstract: Objective: Cholestasis is associated with increased liver injury and morbidity after partial hepatectomy (PH), yet bile acids (BAs) are emerging as important mediators of liver regeneration. Fibroblast growth factor 15 (Fgf15, human FGF19) is a BA-induced ileum-derived enterokine that governs BA metabolism. We evaluated the relevance of Fgf15 in the preservation of BA homeostasis after PH and its potential role in the regenerative process. Design: Liver regeneration after PH was studied in Fgf15+/− and Fgf15+/− mice. The effects of the BA sequestrant cholestyramine and adeno-avirally delivered Fgf15 were examined in this model. The role of Fgf15 in BA-induced liver growth was tested in Fgf15−/− mice upon cholic acid (CA) feeding. The direct mitogenic effect of Fgf15 was evaluated in cultured mouse hepatocytes and cholangiocytes. Results: Fgf15+/− mice showed marked liver injury and mortality after PH accompanied by persistently elevated intrahepatic BA levels. Cholestyramine feeding and adeno-avirally delivered Fgf15 reduced BA levels and significantly prevented this lethal outcome. Fgf15 also reduced mortality after extensive hepatectomy in Fgf15+/− animals. Liver growth elicited by CA feeding was significantly diminished in Fgf15−/− mice. Proliferation of hepatocytes and cholangiocytes was also noticeably reduced in CA-fed Fgf15−/− mice. Fgf15 induced intracellular signaling and proliferation of cultured hepatocytes and cholangiocytes.

Conclusions: Fgf15 is necessary to maintain BA homeostasis and prevent liver injury during liver regeneration. Moreover, Fgf15 is an essential mediator of the liver growth-promoting effects of BA. Preoperative administration of this enterokine to patients undergoing liver resection might be useful to reduce damage and foster regeneration.

Keywords: Bile salts; Enterohepatic circulation; FGF signaling; Liver failure; Liver regeneration.

Post-resection liver failure (PLF) is a feared and potentially lethal complication occurring in up to 9% of patients undergoing partial hepatic resection [1]. Insufficient quantity or quality of the remnant liver resulting in inadequate liver regeneration (LR) plays a major role in its pathogenesis. An elaborate study by Uriarte and colleagues in Gut demonstrates that tight control of hepatic bile salt homeostasis is crucial to prevent bile salt toxicity and allow successful LR, and provides a rationale for prevention of PLF.

Already recognized by the ancient Greeks (“The myth of Prometheus”), the liver has unparalleled capacity for regrowth following injury or loss of tissue mass [2]. The regenerative potential of the liver is exploited in surgical treatment of hepatic and biliary tract tumors, as well as in living-donor and split liver transplantation. The rodent partial hepatectomy (PH) model is frequently used to study LR, and consists of resection of the median and left lateral lobes. The resultant loss of two-thirds of hepatic mass triggers a proliferative response in the remnant liver that restores liver mass in approximately one week. While LR after PH involves activation and expansion of existing parenchymal cells, activation of hepatic progenitor cells is required for compensatory regrowth after extensive hepatocytic damage, e.g., acute toxic insult or chronic liver injury [3].

A multitude of interconnected signaling pathways responding to cytokines, growth and metabolic factors, is involved in the initiation, progression, and termination of the regenerative response after PH [2]. LR is impaired in partially hepatectomized animals with external biliary diversion and/or bile duct ligation, and in patients undergoing resection for obstructive hepatobiliary malignancies [4]. This underscores the importance of an intact enterohepatic circulation for LR and alludes to involvement of intestine- and/or liver-derived signaling molecules. Earlier studies in mice established that bile salt feeding induces a hyperplastic response in the liver in the absence of a regenerative stimulus, and accelerates liver regrowth after PH [5]. This relies on the presence of the bile salt-activated transcription factor Fxr...
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(Farnesoid X Receptor), with a recent study revealing that intestinal and liver Fxr are both required for efficient LR after PH [6]. Given the involvement of FXR in a multitude of processes, the mechanisms underlying delayed LR in Fxr−/− mice are expected to be complex but include perturbed bile salt homeostasis and failure to induce Foxm1b, a key regulator of cell cycle progression [5,7].

Inherent to the amphiphatic nature of bile salts, tight regulation of their intracellular levels is warranted to prevent hepatotoxicity that may impede LR. The FXR-induced enterokine FGF19 (Fibroblast Growth Factor 19, termed Fgf15 in rodents) plays an important role in the negative feedback loop that controls hepatic bile salt synthesis. Consequently, disturbances in the enterohepatic circulation perturb this control mechanism. Unlike in humans where FGF19 is also expressed in the cholestatic liver, in adult mice Fgf15 is solely expressed in the small intestine [8]. Using mice with global deficiency of Fgf15 and (re)gain-of-function studies, Uriarte et al. now demonstrate that Fgf15 is responsible for – at least part of – the effects of bile salts on liver (re)growth and acts as a direct mitogen for hepatocytes and cholangiocytes in vitro [9].

Two-thirds PH resulted in marked liver injury and mortality (ca. 70%) in Fgf15−/− mice in the first 48 hr post-resection, with mortality notably higher than previously reported for Fxr−/− mice (30% mortality within 7 days) [5,9]. Liver regrowth in surviving Fgf15−/− mice was slower in the early phase of LR, with normal liver mass restoration after 5–7 days. While a transient accumulation of bile salts in the liver accompanied PH in control mice, hepatic bile salt levels were higher prior to PH and immediately rose and remained elevated throughout the early phase of LR in Fgf15−/− animals. This strongly suggests that Fgf15-mediated reduction of bile salt synthesis is needed to prevent bile salt toxicity in the remnant liver. The toxic build-up of bile salts likely accounted for the lethal outcome of PH in Fgf15−/− mice. In agreement with this, lowering of hepatic bile salt levels by feeding of a sequestrant prior to PH resulted in drastic improvement in 3-day survival (30–80%). Suggestive of a role beyond bile salt homeostasis, Fgf19 had a direct mitogenic action on primary hepatocytes and cultured cholangiocytes. The aggregated data demonstrate that intestine-derived Fgf15 is crucial for efficient LR after PH, and emphasize the importance of tight control of bile salt homeostasis in recovery from liver injury (Fig. 1).

It remains to be determined if these effects of Fgf15 are exerted through its alleged receptor Fgfr4, which appears dispensable for liver regrowth after PH [10]. Immunoglobulin-like domain IIIc-spliced FGFRs can act as alternative receptors for FGF19 but these are predominantly expressed by stromal cells rather than epithelial cells. Other intriguing questions to be explored include the role of FGF15 in progenitor cell-mediated LR, and the interplay between miRNAs and FGF19 signaling in the context of LR. Of particular interest is miR-34a, which is induced in the termination phase of LR and interferes with FGF19 signaling by targeting the expression of an essential co-receptor [11,12]. In addition, upregulation of this miRNA in steatotic liver and impairment of FGF19 signaling may contribute to defective regeneration in the fatty liver [12].

The findings of Uriarte et al. provide a rationale for prevention and treatment of PLF by targeting the FXR/FGF19 gut-liver axis. Factors conferring risk for PLF and impairing LR include small remnant liver volume, advanced age, steatosis, cholestasis, and cirrhosis [1]. FXR agonism largely overcomes the age-related LR defects after PH in mice [7]. Moreover, FXR activation or FGF19 administration has beneficial effects on hepatic lipid and bile salt homeostasis [13,14]. Therapeutic strategies resulting in persistent elevation of circulating FGF19 levels, however, require comprehensive study of undesirable proliferative actions of FGF19. Pre-neoplastic changes in the liver (after 4 months) and development of hepatocellular carcinoma at 10–12 months of age, are apparent in mice with chronic overexpression of FGF19 [15]. The role of FGF19 in human hepatocarcinogenesis is currently unclear. The short-term application of FXR agonists or FGF19 in reducing PLF-related mortality should be considered. As a proof of principle, Uriarte et al. demonstrate that (adenoviral) Fgf15 delivery improves 3-day survival (0–46%) in the 85% hepatectomy model of acute liver failure [9].

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

References


