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What if Prometheus had Steatosis? Potential Use of FGF19 to Promote Regeneration of the Fatty Liver

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Non-alcoholic fatty liver disease (NAFLD), the excess accumulation of triglycerides in the liver, can lead to liver-associated morbidity and mortality,¹ and is associated with extra-hepatic disorders such as diabetes, obesity, and increased cardiovascular risk. NAFLD is becoming extremely prevalent, estimated to affect 30–45% of the population in the US.^{2,3} Given this high prevalence, the impact of NAFLD has become important in other aspects of medical care; one such aspect is liver surgery. Patients with steatosis who undergo major hepatic resection are at an increased risk for perioperative complications and mortality,⁴ and the regeneration of the liver post-resection is slower in the obese and those with NAFLD.^{5,6} Furthermore, in liver transplantation, steatotic grafts show decreased graft survival and function.⁷

Fibroblast growth factor 19 (FGF19) and its mouse ortholog Fgf15 are peptide hormones with myriad metabolic functions. Driven by luminal bile acid content and FXR, FGF15/19 is expressed in, and secreted from, the terminal ileum, and closes the enterohepatic feedback loop by acting on the liver to decrease hepatic bile acid synthesis. In addition, FGF15/19 regulates hepatic lipid and glucose metabolism, and affects energy expenditure and food intake.⁸ An FGF19 analogue is currently in clinical trials for the treatment of NAFLD, as well as other disorders. Uriarte et al⁹ have previously shown a role for Fgf15 in liver regeneration when they elegantly demonstrated that *Fgf15* knockout (*Fgf15*^{−/−}) mice had impaired liver regeneration and increased mortality after partial hepatectomy, and that these effects were mediated by the loss of regulation of bile acid synthesis. Interestingly, in a different model of regeneration, FGF19 was shown to be important in limiting over-growth of the liver in mice populated with human hepatocytes.¹⁰ Thus, the enterohepatic FGF15/19 signal appears to be essential to maintain normal liver size.

Given the role of FGF15/19 in liver regeneration and its ability to decrease liver fat and improve hepatic glucose handling, it is reasonable to explore the potential of exogenous

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FGF19 to enhance the outcomes of liver surgery in steatotic patients. An important step toward this goal is presented in this issue by Alvarez-Sola and colleagues,¹¹ extending the previous work from their group.⁹ Working in *Fgf15*^{-/-} mice, they demonstrate that the absence of *Fgf15* worsens diet-induced steatosis and ER stress and that this phenotype can be reversed with administration or overexpression of FGF19. These findings are in line with previous reports, showing decreased steatosis in FGF19 over-expressing or FGF19-treated mice.^{12,13} The effects of FGF15/19 in the current model seem to be dependent on transcriptional regulation of *Ppary2*, which is upregulated in the *Fgf15*^{-/-} animals and can be downregulated in the same animals with the addition of exogenous FGF19. Interestingly, there was no impact on hepatic expression of lipogenic genes and the Srebp1 pathway, which sets this work apart from other animal and cell-culture studies, and requires further exploration.

As mentioned above, the same group has previously shown increased mortality of *Fgf15*^{-/-} mice after partial hepatectomy and were able to partially ameliorate it by transfection with *Fgf15*,⁹ leading a commentator to label FGF15 as “Prometheus’ little helper.”¹⁴ In their current manuscript, they extend those findings to obese *db/db* mice where FGF19 transfection or treatment improved survival after hepatectomy. However, in both *Fgf15*^{-/-} and *db/db*, the impact of FGF19 on survival was marginal and did not reach the expected survival of control animals. The authors postulated that this less-than-optimal effect was due to the short serum half-life of FGF19. They cleverly tackled this problem by designing a fusion protein, Fibapo, by conjugating FGF19 to human ApoA-I. With its longer half-life, Fibapo normalized or markedly decreased *Ppary2* and downstream targets, decreased liver fat content, reduced ER stress, and also normalized *Cyp7a1* expression and decreased the bile acid pool. Finally, treatment with Fibapo had a remarkably beneficial effect on hepatic regeneration after partial hepatectomy, and treated *db/db* mice had post-surgical survival rates similar to controls. Overall, Alvarez-Sola et al clearly show the crucial role of the FGF15/19 axis in regulating liver fat and regeneration, and provide a potential therapeutic approach to managing steatotic inhibition of liver regeneration.

The results in this study suggest that Fibapo, or a similar FGF19-based therapy, could be used perioperatively to improve the outcome of patients with NAFLD who undergo liver surgery, and potentially improve survival of steatotic liver grafts. However, an important safety concern will need to be addressed first. While other receptors for FGF15/19 may be important for its impact on glucose metabolism, the FGFR4/beta-Klotho receptor complex is responsible for much of FGF15/19’s known signaling with respect to bile acid synthesis.⁸ There is significant evidence supporting a role for FGF19-FGFR4 signaling in the development of hepatocellular carcinoma,^{15,16} cholangiocarcinoma, and hepatoblastoma as well as several non-hepatic cancers. The signaling pathway for Fibapo has not been determined so far, but its effects on *Cyp7a1* do suggest a role for FGFR4. Given that the majority of liver resections are due to cancer, the impact of both short-term Fibapo treatment on existing tumors and long-term treatment on de novo tumor formation will need to be explored. At least one synthetic variant of FGF19 (M70) can downregulate *Cyp7a1* and bile acid synthesis through FGFR4 without promoting tumorigenesis, likely by being a biased ligand;¹⁷ whether Fibapo acts in a same way, and whether its pro-regenerative effects can be separated from the potential to induce malignant proliferation remains to be shown. For now,

Fibapo and other FGF19-based therapies are still unproven, yet promising, candidates for the little helper of the steatotic Prometheus.

Abbreviations:

FGF15	fibroblast growth factor 15
FGF19	fibroblast growth factor 19
NAFLD	non-alcoholic fatty liver disease

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