Göteborg, 2020

UNDERSTANDING THE MOLECULAR MECHANISMS OF BILE ACID RECEPTOR ACTIVATION FOR THE TREATMENT OF HUMAN LIVER DISEASE

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs Universitet kommer att offentligen försvaras i Arvid Carlsson, Academicum, Medicinaregatan 3, den 11 – 06 – 2020, klockan 9:00

av Samer Al-Dury

Fakultetsopponent:
Andreas Geier, Professor
University of Würzburg, Germany

Avhandlingen baseras på följande delarbeten

I. **Al-Dury S**, Wahlström A, Wahlin S, Langedijk J, Elferink R O, Ståhlman M, & Marschall HU. **Pilot study with IBAT inhibitor A4250 for the treatment of cholestatic pruritus in primary biliary cholangitis.** *Scientific Reports* 2018; *8*(1):6658.

II. **Al-Dury S**, Wahlström A, Panzitt K, Thorell A, Ståhlman M, Trauner M, Fickert P, Bäckhed F, Fändriks L, Wagner M & Marschall HU. **Obeticholic acid may increase the risk of gallstone formation in susceptible patients.** *Journal of Hepatology* 2019;71: 986–991.

III. Jungwirth E, Panzitt K, **Al-Dury S**, Wahlström A, Thorell A, Ståhlman M, Fickert P, Fändriks L, Wagner M & Marschall HU. **Human FXR-DNA binding is associated to the obese phenotype.** *Manuscript.*

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Abstract

Farnesoid X receptor (FXR) is a nuclear transcription factor that is activated by bile acids in the liver and intestine and regulates bile acid homeostasis, glucose and lipid metabolism. Direct FXR activation by a ligand has been identified as a therapeutic modality for a range of liver and metabolic diseases. FXR activation studies have exclusively been conducted in mouse models, which are of limited human relevance due to species differences between mice and humans in bile acid composition, metabolism and FXR activation patterns. The ileal bile acid transporter (IBAT) is pivotal for the reabsorption of conjugated bile acids from the ileum back to the liver and an important FXR target gene. FXR activation leads to reduction in hepatic bile acid synthesis via secreted FGF19. IBAT inhibition indirectly represses intestinal FXR by interruption of the enterohepatic circulation of bile acids, and this concept has been tested in the treatment of cholestatic itch, fatty liver disease and dyslipidemia.

In paper I, we explored whether pharmacological inhibition of IBAT might ameliorate cholestatic pruritus in patients with primary biliary cholangitis. Despite some subjective improvement, the study needed to be prematurely stopped due to abdominal side effects.

In paper II, we examined how FXR activation by obeticholic acid (OCA) impacts on gallbladder physiology in patients awaiting gallstone surgery. We found that OCA increased the risk for gallstone formation, by decreasing biliary bile acids, with concomitant increases in cholesterol saturation and bile acid hydrophobicity indices, and increasing biliary fibroblast growth factor 19 (FGF19).

In paper III, we investigated OCA effects on FXR-DNA binding sites in patients awaiting bariatric or gallstone surgery. We found by performing ChIP-Seq that the expression of FXR-DNA binding sites was not related to OCA-treatment; rather, it seems to be predetermined by the phenotype (obese vs non-obese). In contrast, RNA-Seq indicated induction of FXR target genes by OCA as compared to placebo.

Keywords: bile acids, farnesoid X receptor, FGF19, ASBT, pruritus, obesity, gallstones, chip-seq, multi-omics.

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