Göteborg, 2023

The interplay between bile acids and gut microbiota in metabolic and hepatobiliary disease

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Arvid Carlsson, Medicinaregatan 3, den 13 december, klockan 13:00

av Wilhelm Sjöland

Fakultetsopponent:

Docent Emma R. Andersson

Karolinska Institutet, Sverige

Avhandlingen baseras på följande delarbeten

I. Wahlström, A., Brumbaugh, A., Sjöland, W., Olsson, L., Wu, H., Henricsson, M., Lundqvist, A., Makki, K., Hazen, S. L., Bergström, G., Marschall, H.-U., Fischbach, M. A., Bäckhed, F. Production of deoxycholic acid by low-abundant microbial species is associated with impaired glucose metabolism.
In revision.

II. Wahlström, A., Aydin, Ö., Olsson, L., Sjöland, W., Henricsson, M., Lundqvist, A., Marschall, H.-U., Franken, R., van de Laar, A., Gerdes, V., Hofsø, D., Groen, A. K., Hjelmesæth, J., Nieuwdorp, M., Bäckhed, F. Alterations in bile acid kinetics after bariatric surgery in patients with obesity with or without type 2 diabetes.
Submitted manuscript.

III. Sjöland, W., Wahlström, A., Makki, K., Schöler, M., Molinaro, A., Olsson, L., Greiner, T. U., Caesar, R., de Boer, J. F., Kuipers, F., Bäckhed, F., Marschall, H.-U. Absence of gut microbiota reduces neonatal survival and exacerbates liver disease in *Cyp2c70*-deficient mice with a human-like bile acid composition.
Clin. Sci. **137**, 995-1011 (2023).

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR MEDICIN

GÖTEBORGS UNIVERSITET

Göteborg, 2023

The interplay between bile acids and gut microbiota in metabolic and hepatobiliary disease

Wilhelm Sjöland

Department of Molecular and Clinical Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Sweden, 2023

Abstract

The gut microbiota, a metabolic regulator, orchestrates the production of bioactive metabolites such as secondary bile acids. Growing evidence suggests that shifts in the gut microbiota composition are linked to metabolic and hepatobiliary disease. Bile acids are involved in lipid digestion and metabolic signaling and undergo microbial transformation in the gut, producing secondary bile acids. This thesis examines the interplay between bile acids and the gut microbiota. *Clostridium scindens* accounts for a minor fraction of the gut microbiota but is one of the few known species capable of generating secondary bile acids by 7α-dehydroxylation. We showed that even at low abundance, *C. scindens* had a marked impact on metabolism in mice, and we established a link between deoxycholic acid and metabolic dysregulation in type 2 diabetes (T2D). Data suggests that modulation of the bile acid and gut microbiota composition may promote some of the benefits of bariatric surgery, and we examined postprandial bile acid kinetics pre- and post-surgery, revealing an altered post-surgery response. Bariatric surgery increased hyodeoxycholic acid, which was linked to T2D remission. The distinct bile acid profiles of mice and humans are due to CYP2C70, and *Cyp2c70*-deficient mice display manifestations of hepatobiliary disease. We showed that gut microbiota influences neonatal survival and liver disease in *Cyp2c70*$^{-/-}$ mice. Amelioration of the liver phenotype was associated with a more hydrophilic biliary bile acid profile, largely driven by microbially induced ursodeoxycholic acid production. In summary, we provide evidence of the crucial role of the interplay between bile acids and gut microbiota in health and disease.

Keywords: gut microbiota, bile acids, type 2 diabetes, hepatobiliary disease

ISBN: 978-91-8069-521-3 (PRINT) http://hdl.handle.net/2077/78566
ISBN: 978-91-8069-522-0 (PDF)