

Gut microbial regulation of bile acid metabolism and signaling

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska Akademin vid Göteborgs
Universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Medicinaregatan 3,
Göteborg,

Fredagen den 12:e Februari 2016 kl. 13.00

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Avhandlingen baseras på följande delarbeten:

- I. Sayin, SI. Wahlström, A. Felin, J. Jäntti, S. Marschall, HU. Bamberg, K. Angelin B. Hyötyläinen, T. Oresic, M. Bäckhed, F.

Gut microbiota regulates bile acid metabolism by reducing the levels of tauro-beta-muricholic acid, a naturally occurring FXR antagonist

Cell Metabolism 2013; 17: 225-235

- II. Sayin, SI. Sommer, F. Chevalier, J. Rosenstiel, P. Staels, B. Eeckhoute, J. Bäckhed, F.

Differential FXR-mediated regulation by the gut microbiota in the liver and the intestine

In Manuscript



UNIVERSITY OF GOTHENBURG

ABSTRACT

Gut microbial regulation of bile acid metabolism and signaling

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The collection of microbes in our gastrointestinal tract, the gut microbiota, is an environmental factor that has profound impact on host health and disease. Bile acids are endogenous cholesterol-derived molecules that can be modified by the gut microbiota and function as signaling molecules in regulation of host metabolic processes. This thesis investigates the role of the gut microbiota on bile acid metabolism and signaling by comparing mice that lack microbiota with their conventionally-raised counterparts.

We found that the gut microbiota regulates bile acid metabolism at several levels, including proportionalities of individual bile acid species and expression of genes involved in bile acid homeostasis. Specifically, the gut microbiota decreased levels of mouse primary bile acid tauro-beta-muricholic acid (T- β MCA), which we identified as an antagonist of the nuclear receptor farnesoid-x-receptor (FXR). FXR mediates negative feedback regulation of bile acid homeostasis, as well as regulation of several physiological processes. Hence, we identified the molecular mechanism behind microbial regulation of bile acid homeostasis as T- β MCA mediated inhibition of FXR activity. Since humans lack T- β MCA, this thesis plays an important role in explaining the existing discrepancies between mouse and human studies targeting FXR for treating gastrointestinal diseases. Furthermore, in order to better understand the effect of the microbiota on FXR signaling, we re-derived mice that lacked functional FXR as germ-free and mapped microbial regulation of genes through FXR. We found that the microbiota can regulate expression of FXR target genes through direct FXR binding to promoters in the intestine, while protein-protein interactions between FXR and other co-regulators are likely regulated in the liver.

In conclusion, this study establishes the microbiota as a key player in bile acid metabolism and FXR signaling in the liver and the intestine. The findings from this thesis implicate the microbiota as an important factor that needs to be taken into consideration in treating gastrointestinal diseases by targeting bile-acid mediated FXR signaling.

Keywords: gut microbiota, bile acids, tauro-beta-muricholic acid (T- β MCA), farnesoid-x-receptor (FXR)

ISBN: 978-91-628-9702-4

Gothenburg, 2016