Göteborg, 2017

On the role of gut microbiota in intestinal physiology and hepatic metabolism

Akademisk avhandling

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

Onsdagen den 22:e mars, klockan 09.00

av Mattias Bergentall

Fakultetsopponent: Professor Eran Elinav

Department of Immunology, Weizmann Institute of Science, Rehovot, Israel

Avhandlingen baseras på följande delarbeten

I. Reinhardt, C., Bergentall, M., Greiner, T.U., Schaffner, F., Östergren-Lundén, G., Petersen L. C., Ruf, W., Bäckhed, F.

Tissue factor and PAR1 promote microbiota-induced vascular remodeling

Nature 2012 Mar 11;483(7391):627-31. Doi: 10.1038/nature10893

II. Bergentall, M., Gustafsson, J.K., Johansson, B.R., Bäckhed, F.

Microbial regulation of tight junction ultrastructure and intestinal permeability mediated through FXR

In Manuscript

III. Bergentall, M., Akrami, R., Tremaroli V., Ståhlman, M., Molinaro, A., Mannerås Holm, L., Dallinga, G. M., Mardinoglu, A., Nieuwdorp, M., Bäckhed, F.

The gut microbiota is required for sucrose-induced steatosis through SREBP-1c

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On the role of gut microbiota in intestinal physiology and hepatic metabolism

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Abstract

The gut microbiota, a complex and dynamic community of microbes in the mammalian gut, has coevolved with us for ample time providing mutual benefits. However, mechanistic knowledge of these has been limited, but are now becoming increasingly clear. We used germ-free mice to study three aspects of host physiology; the effects of the microbiota on small intestinal postnatal vascularization (I), small intestinal permeability (II), as well as the interplay between the gut microbiota and a steatogenic diet and the subsequent effects on hepatic metabolism (III).

In **Paper I** we found a new mechanism underlying microbiota-induced vascular remodeling in small intestinal villi. This mechanism involves activation of protease activated receptor-1 (PAR1) induced by microbial regulation of tissue factor activity. As a consequence of PAR1 signaling we observe increased angiopoietin expression in the intestinal epithelium and subsequent expansion of blood vasculature.

In **Paper II** we applied Ussing chambers technique to measure small intestinal permeability and observed increased permeability in conventionally raised (CONV-R) mice, compared with germ-free (GF) mice. This was accompanied by reduced mRNA expression of tight junction proteins and ultrastructure analyses revealed wider tight junctions and reduced numbers of desmosomes. The alterations between GF and CONV-R mice were abolished in the absence of farnesoid X receptor.

In **Paper III** we investigated if the gut microbiota interacted with dietary sucrose to induce hepatic steatosis. GF and CONV-R mice were fed a zero-fat, high-sucrose diet (ZFD) or control diet and we observed a synergistic effect of diet and microbiota on hepatic steatosis by induction of *de* novo lipogenesis. Furthermore, we could establish a central role for the transcription factor sterol regulatory element-binding protein-1c (SREBP-1c) in this process.

In conclusion, these studies show that the microbiota induces expansion of intestinal vasculature and increased permeability, which may both contribute to metabolic effects. Further, the microbiota is required for a zero-fat, high sucrose diet to be steatogenic. This could give rise to novel treatment options for non-alcoholic fatty liver disease.

Keywords: Gut microbiota, Intestinal permeability, Non-alcoholic fatty liver disease

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