

The effects of microbial metabolites on host physiology

Akademisk avhandling

Som för avläggande av doktorsexamen vid Sahlgrenska Akademin vid Göteborgs Universitet kommer att offentligens försvaras i lokal M106 K Isaksson, Medicinargatan 16, Göteborg

Måndagen den 14:e September 2015 kl 09.00

av

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Fakultetsopponent: Professor Remy Burcelin

Institutet för metabola och kardiovaskulära sjukdomar, Hôpital Rangueil, Toulouse, Frankrike

Avhandlingen baseras på följande arbeten:

I. Microbiota-induced obesity requires farnesoid X receptor

Ava Parséus*, Nina Sommer*, Robert Caesar, Felix Sommer, Antonio Molinaro, Marcus Ståhlman, Thomas U Greiner, Rosie Perkins and Fredrik Bäckhed.

Manuscript

** Equal contribution*

II. Microbial modulation of energy availability in the colon regulates intestinal transit

Anita Wichmann, Ava Allahyar, Thomas U. Greiner, Hubert Plovier, Gunnel Östergren Lundén, Thomas Larsson, Daniel J. Drucker, Nathalie M. Delzenne, Patrice D. Cani and Fredrik Bäckhed

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ABSTRACT

The effects of microbial metabolites on host physiology

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In recent years it has become increasingly clear that the gut microbial community, the microbiota, has a vast impact on obesity, insulin signaling and glucose homeostasis. More specifically, there are microbiota-derived metabolites that are known to possess important functions, both locally in the gut, but also on a systemic level. However, the impact they have on host physiology in terms of contributors to diet-induced obesity (DIO), effects on insulin signaling and obesity-related dysfunctions has been poorly studied. In this thesis the impact on host physiology of the microbial metabolites short-chain fatty acids (SCFA) and bile acids were studied in more detail. As study models conventionally raised mice (CONV-R), mice colonized at birth with the microorganisms present in their environment, and germ free (GF) mice, mice deprived of any microorganism and hence microbiota, were used.

In paper I, we used as study models wild-type mice and a whole-body knockout of the natural bile acid receptor farnesoid X receptor (FXR) on a CONV-R and GF background. These mice were treated with high-fat diet and the results shows that the gut microbiota promotes DIO via FXR signaling, and more importantly, that the altered bile acid profiles and hence FXR signaling affects DIO. Also, our findings suggest that the genotype is also involved in shaping the microbial composition.

In paper II, we observed a prominent difference between GF and CONV-R mice where the former had significantly higher serum levels of the incretin hormone glucagon-like peptide-1 (GLP-1) and increased colonic proglucagon expression; the gene GLP-1 is transcribed from. We demonstrated that the increased GLP-1 levels in GF mice are regulated via energy supply, namely the SCFAs. More importantly, elevated GLP-1 levels slowed intestinal transit.

From **paper I** we conclude that the microbiotas' impact on shaping the bile acid profile has significant impact on DIO and leads to obesity-related dysfunctions. In **paper II** we conclude that GF mice have slower transit time to allow sufficient energy-and nutrient absorption

Keywords: short-chain fatty acids, bile acids, FXR, GLP-1, germ free and conventionally raised.

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