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Gut microbiota metabolism linked to metabolic health and cardiovascular diseases

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Academicum, Medicinaregatan 3, den 25 september, klockan 9.00

av Matthias Georg Mitteregger

Fakultetsopponent:

PD Dr. Marius Vital

Medizinische Hochschule Hannover, Germany

Avhandlingen baseras på följande delarbeten

I. Mitteregger M*, Chakaroun R*, Olsson L, Pradhan M, Khan MT, Bergh PO, Krämer M, Bergström G, Bäckhed F, Tremaroli V. **Ecological determinants of gut microbiota cholesterol reduction and associations with cardiometabolic diseases.** *Manuscript.* *Contributed equally

II. Mitteregger M, Florén A, Jönsson J, Antonsson S, Krämer M, Bergh PO, Khan MT, Chakaroun R, Bäckhed F, Tremaroli V. **Gut microbiota fermentative and bile acid metabolism during *in vitro* fermentation of oat, rye and wheat bran.** *Manuscript.*

III. Kraft JD, Mitteregger M, Dwibedi C, Makki K, Florén A, Sjöland W, Hempenstall E, Jönsson J, Bäckhed F, Khan MT, Tremaroli V, Caesar R. **Novel species of the Genus *Desulfovibrio* isolated from human faeces.** *Manuscript.*

IV. Wu H, Lv B, Zhi L, Shao Y, Liu X, Mitteregger M, Chakaroun R, Tremaroli V, Hazen SL, Wang R, Bergström G, Bäckhed F. **Microbiome–metabolome dynamics associated with impaired glucose control and responses to lifestyle changes.** *Nat Med (2025). doi: 10.1038/s41591-025-03642-6*

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR MEDICIN

GÖTEBORGS UNIVERSITET

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Abstract

Positioned at the interface of nutrition and host physiology, the gut microbiota produces bioactive metabolites that modulate host lipid and glucose metabolism as well as immune function. Many of these metabolites, although produced in the gut, exert influence on physiological processes in the whole body, with an impact on host cardiometabolic health. Despite increasing associations between individual microbiome features and disease reported, mechanistic insights and ecological understanding remain limited. This thesis aimed to explore the ecology of microbial functions and host interactions relevant to cardiometabolic disease using a combination of metagenomics, metabolomics, *in vitro* fermentation assays, and characterization of isolates.

In **Paper I**, we show that the *ismA* gene, involved in microbial cholesterol reduction to coprostanol, robustly predicts fecal cholesterol conversion and characterizes a microbiome enriched in fermentative and anti-inflammatory features, linked to favorable cardiometabolic profiles in populations at risk. In **Paper II** we demonstrate that microbiota individuality drives short-chain fatty acid and bile acid profiles *in vitro*, with a larger impact than fiber type. These results may have implications for personalized nutrition. In **Paper III**, we characterize three strains initially classified as *Desulfovibrio piger*, revealing major phenotypic and metabolic differences. These results support the designation of a novel species *Desulfovibrio aggregans* sp. nov. and underscore the limitations of current species-level taxonomy. **Paper IV** highlights the predictive power of microbiota-associated circulating metabolites for type 2 diabetes, identifying specific microbe-metabolite-host interactions that are relevant for glucose control and can be modified through lifestyle interventions.

These findings emphasize the importance of acknowledging and understanding the ecological complexity and metabolic impact of the gut microbiota in cardiometabolic disease, and point towards functional, context-dependent microbial signatures as targets for diagnosis, prevention or therapy.

Keywords: gut microbiota, gut microbiome, ecology, cardiometabolic disease, cardiovascular disease, fiber, *Desulfovibrio piger*, type 2 diabetes, atherosclerosis, stroke, metabolomics

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