Göteborg, 2018

Microbial modulation of metabolic diseases

Akademisk avhandling

Som för avläggande av medicin doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Medicinaregatan 3, Göteborg fredagen den 19 Oktober, klockan 9.00

av Antonio Molinaro

Fakultetsopponent:

Professor: Anna Mae Diehl

Duke Clinical Research Institute, Durham, NC, USA

Avhandlingen baseras på följande delarbeten

I. *Molinaro A, Caesar R, Holm LM, Tremaroli V, Cani PD, Bäckhed F.* **Host–microbiota interaction induces bi-phasic inflammation and glucose intolerance in mice.**

Molecular Metabolism 2017 Nov;6(11):1371-1380. doi: 10.1016/j.

II. *Koh A, Molinaro A, Ståhlman M, Khan MT, Schmidt C, Mannerås-Holm L, Wu H, Carreras A, Jeong H, Olofsson L, Bergh PO, Gerdes V, Hartstra A, de Brauw M, Perkins R, Nieuwdorp M, Bergström G, Bäckhed F.* **Microbially produced imidazole propionate impairs insulin signaling through mTORC1.**

Manuscirpt

III. *Molinaro A, Wu H, Schoenauer US, Datz C, Bergström G, Marschall HU, Tilg H, Tremaroli V, Bäckhed F.* **Steatosis is associated with altered microbiome in humans.**

Manuscript.

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Microbial modulation of metabolic diseases

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ABSTRACT

The gut microbiota, the ensemble of microorganisms living in the gastrointestinal tract, and the host have a mutualist relationship. Alterations of this delicate equilibrium can lead to changes in microbiota composition and/or function leading to the onset of metabolic diseases (e.g., type 2 diabetes and non-alcoholic fatty liver diseases). The current knowledge of host-microbiota interaction, in health and disease, is limited. Here, by using a translational science approach, we were able to identify some of the mechanisms underlying the influence of the microbiota on impaired glucose and lipid metabolism. Specifically:

In **Paper I**, I explored the microbiota-host interaction and its effect on glucose metabolism. Particularly, by performing colonization of germ-free mice, I studied the effect on glucose metabolism over time. I investigated the different molecular mechanisms underlying the impaired metabolic profile induced by the colonization over time. These findings provide fundamental information on how to conduct studies on microbiota and metabolic diseases.

In **Paper II**, I identified a novel microbially-produced molecule, imidazole propionate, which is increased in the portal vein of subjects with type 2 diabetes. I demonstrated causality of this molecule in impaired glucose metabolism by administering it in both *in-vivo* and *in-vitro* models. Moreover, I identified molecular targets of imidazole propionate in the insulin signaling cascade, specifically on the insulin receptor substrate proteins, and showed that this effect is mediated by activation of the mTOR complex.

In **Paper III**, I investigated whether the gut microbiota composition and function is altered in subjects with non-alcoholic fatty liver disease. In presence of steatosis, I observed a shift in microbiota composition characterized by increased abundance of bacteria from the oral cavity, ethanol-producing bacteria, and a reduction in butyrate producing bacteria. On a functional level, I observed an enrichment in functions related to metabolic functions and production of lipopolysaccharides in subjects with steatosis.

In conclusion, these findings show that the microbiota is an environmental factor that modulates metabolic diseases. Understanding the mechanisms underlying microbial impacts on host metabolism will aid in discovery of novel targets for the treatment of metabolic diseases in humans.

Keywords: gut microbiota, glucose metabolism, type 2 diabetes, imidazole propionate, non-alcoholic fatty liver disease

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