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MICROBIOME

Gut microbial short-chain fatty acids and the risk of diabetes

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A new study used genome-wide association data and Mendelian randomization to investigate associations between the gut microbiome and metabolic traits. The researchers demonstrate that host genetic variants influence levels of the short-chain fatty acids butyrate and propionate in the gut, which in turn modulate host glycaemic metabolism.

Refers to Sanna, S. et al. Causal relationships among the gut microbiome, short-chain fatty acids and metabolic diseases. *Nat. Genet.* https://doi.org/10.1038/s41588-019-0350-x (2019).

Disruptions in the gut microbiome have been implicated in the pathophysiology of numerous illnesses including diabetes, chronic kidney disease (CKD), obesity, inflammatory bowel disease, dyslipidaemia, cardiovascular disease, cancer and allergic disorders[1]. The metabolites produced by the gut microbiota include short-chain fatty acids (SCFAs), which are generated by the fermentation of indigestible carbohydrates (that is, saccharolytic fermentation) and have an important role in host metabolism (FIG. 1a). The main SCFAs produced by the gut microbiota include butyrate, acetate and propionate[1]. In addition to being an essential nutrient for host enterocytes, SCFAs modulate insulin sensitivity, systemic inflammation, and glucose and lipid homeostasis. With respect to energy and glucose metabolism, SCFAs suppress appetite by increasing the release of satiety hormones and stimulating vagal afferent chemoreceptors, increase energy expenditure by upregulating thermogenesis-related proteins in the liver and adipose tissue, and increase glucose-stimulated insulin secretion from pancreatic β-cells[2] (FIG. 1a). Now, Sanna and colleagues provide further evidence of a causal relationship between the gut microbiome and metabolic traits[3].

Accumulating data indicate that an imbalance in SCFAs has a role in the pathogenesis of both type 1 diabetes mellitus (T1DM) and T2DM. In The Environmental Determinants of Diabetes in the Young (TEDDY) study, in which stool microbiomes were analysed monthly from 3 months to up to 5 years of age, the expression of microbial genes involved in the biosynthesis of SCFAs was lower in children who developed T1DM than in those who did not[4]. Similarly, children with β-cell autoantibodies have a low abundance of butyrate-producing gut microbiota[5]. Moreover, Zhao et al. demonstrated that giving a diet rich in complex fibre to individuals with T2DM for 12 weeks not only significantly increased microbial subpopulations that produce acetate and butyrate, but also decreased haemoglobin A_{1c} levels and improved glucose tolerance by ~20%[6].

The new study by Sanna et al. advances the field further by using bidirectional Mendelian randomization to establish a causal effect of host genetics on microbial expression of SCFAs in the gut and its subsequent impact on glycaemic indices[3]. Mendelian randomization is based on the concept that inheritance of genetic variants at conception is analogous to the randomization process used in clinical trials. An inherent limitation of this type of analysis is that it may be difficult to ascertain the direction of causation — in this case, whether host genetic factors induce changes in the gut microbiome or vice versa. Bidirectional Mendelian randomization (also known as reciprocal Mendelian randomization) strives to overcome this uncertainty by performing separate analyses in both directions[7].

The first step of the analysis reported by Sanna and colleagues focused on genome-wide association study (GWAS) data from the Dutch LifeLines-DEEP (LL-DEEP) cohort of normoglycaemic individuals, to identify host genetic predictors of gut microbiome features that correlated with 17 predefined

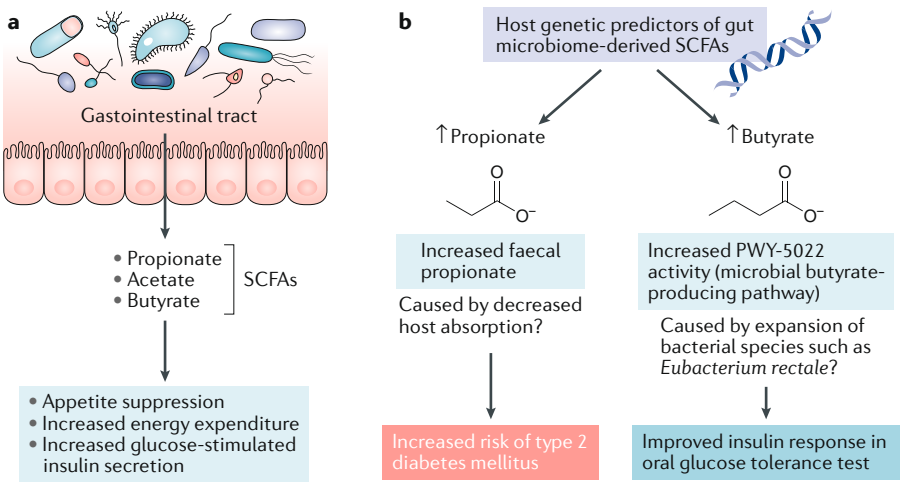

Fig. 1 | **Host genetics, gut microbiota SCFAs and risk of diabetes. a** | Short-chain fatty acids (SCFAs) generated by the gut microbiota include propionate, acetate and butyrate, which are essential nutrients for colonic cells. SCFAs also modulate host energy and glucose metabolism through effects on appetite, energy expenditure and insulin secretion. **b** | Human genetic variants can predict opposing pathways involved in the metabolism of SCFAs by gut microbiota. Increased faecal propionate is associated with an increased risk of type 2 diabetes mellitus (detrimental to the host), whereas increased butyrate production is associated with an improved response of pancreatic β-cells to insulin (beneficial to the host).

> knowledge of host–microbiome interactions would facilitate individualized interventions

anthropometric and glycaemic traits. The analysed traits included body mass index, waist-to-hip ratio, fasting glucose, insulin and proinsulin, 2-hour glucose, homeostasis model assessment of insulin resistance (HOMA-IR) and β-cell function (HOMA-B), glycated haemoglobin A_{1c}, T2DM and seven insulin-response parameters measured during an oral glucose tolerance test. Subsequently, GWAS data from publicly available databases (MAGIC, GIANT and DIAGRAM) were also included in the bidirectional Mendelian randomization analyses that tested the causal relationship between 245 microbiome features of interest identified in the Dutch cohort, and the aforementioned 17 anthropometric and glycaemic traits. Finally, the researchers validated their findings using 500,000 samples from the UK Biobank consortium.

The study identified host genetic predictors in two major areas of microbial metabolism, both of which pertained to SCFAs (FIG. 1b). First, host genetic variants predicted increased activity of the butyrate-producing microbiome pathway PWY-5022, which is linked to 4-aminobutanoate degradation and was associated with improved insulin secretion during an oral glucose tolerance test (but not with the prevalence of T2DM). The presence of butyrate-producing bacteria *Eubacterium rectale* and *Roseburia intestinalis* correlated with the abundance of PWY-5022 activity. Second, host genetic variants predicted higher faecal propionate levels, which were associated with an increased risk of T2DM. The researchers hypothesized that a combination of increased microbial propionate production and impaired host absorption of propionate might lead to increased faecal propionate levels.

A host–microbiome bidirectional relationship has also been described for CKD. Influx of retained waste products, including urea, into the intestinal lumen alters the microbiota composition, resulting in the generation of uraemic toxins such as indole and *p*-cresyl compounds. These toxins enter the bloodstream, induce chronic inflammation and contribute to the progression of kidney disease and adverse cardiovascular outcomes[1]. SCFA metabolism is also impaired in CKD; stool microbiome sequencing in patients with end-stage renal disease demonstrated decreased abundance of Lactobacillaceae and Prevotellaceae, two bacterial families that express butyrate-forming enzymes, compared with healthy controls[8]. Whether host genetic variation influences these alterations in the gut microbiome of patients with CKD has yet to be examined.

The report by Sanna et al. is an important first step towards a better understanding of how host genetic factors influence gut microbiome metabolism and the subsequent risk of glycaemic disorders. Mendelian randomization will continue to gain prominence as a powerful tool for causal inference as the sample size of GWAS databases continues to increase. Further work is needed to elucidate the phenotypes that arise from genetic variants that cause the alterations in SCFA levels. Ultimately, the goal is to enable precision medicine, whereby knowledge of host–microbiome interactions would facilitate individualized interventions to preserve pancreatic β-cell function and minimize the risk of developing diabetes mellitus.

> Mendelian randomization will continue to gain prominence as a powerful tool for causal inference

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Competing interests
The authors declare no competing interests.