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News & Views

Recent advances in diabetes and microbiota

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Diabetes mellitus is a global public health problem that causes great economic and social burdens. Its pathogenesis is complex and unclear. Recently, with considerable attention paid to the interaction between gut microbiota and host, gut microbiota has been found to play an important role in several chronic diseases, including diabetes. In 2012, the first metagenomic study on the role of gut microbiota in diabetes was reported, which revealed that the gut metagenomes in patients with type 2 diabetes (T2D) present moderate gut microbiota dysbiosis, with fewer butyrate-producing bacteria and more opportunistic pathogens [1]. In 2013, it was shown that a model based on microbiota composition and function can identify patients with T2D [2]. In 2017, the involvement of gut microbiota alteration in metformin's antidiabetic effects was explored, and metal homeostasis was suggested to be responsible for this impact [3]. In 2018, a clinical trial proposed that the abundance of specific gut microbiota species, modulated by dietary fiber, alleviates T2D by producing short-chain fatty acids (SCFAs), and the reestablishment of this effective gut microbiome using personalized nutrition may offer a possible approach for T2D management [4]. Furthermore, gut microbiota may be responsible for the varied responses of individuals to exercise interventions on glucose metabolism [5]. In this context, we aim to discuss the recent mechanistic discoveries regarding the contribution of gut microbiota to diabetes and the innovative therapeutic values of gut microbiota for diabetes.

The gut microbiota with compositional and functional shifts in T2D include butyrate-producing species (e.g., *Lactobacillus* species). Although a single species of gut bacteria may not have a prominent effect on changing the risk of T2D, several studies have shown that the increase of the level of *Akkermansia muciniphila* reduces inflammation in adipose tissue and improves insulin signaling. *A. muciniphila* increased insulin sensitivity, improved insulin secretion and decreased total plasma cholesterol, body weight and fat mass [6,7]. The first human trial indicated that both live and pasteurized *A. muciniphila* were well-tolerated, safe, and improved several metabolic parameters [8].

Recently, as metabolomics has gradually become a novel technology for studying biomarkers and precision medicine, gut microbiome-related metabolites have received much attention. These metabolites primarily derived from the fermentation of carbohydrates and proteins were shown to be involved in glucose metabolism (Fig. 1). SCFAs like acetic, propionic, and butyric acids, are the most widely studied gut-derived metabolites. A series of studies have demonstrated that a diet enriched with fermentable dietary fibers can cause weight gain and fat mass development reduction, and insulin sensitivity improvement. The gut microbiota ferment carbohydrates such as resistant starch and arabinoxylans into SCFAs, then produce relevant physiological effects [9]. SCFAs bind to G protein-coupled receptor (GPCR)-41 and GPCR-43 to promote the release of glucagon-like peptide 1 (GLP-1) and peptide YY (PYY), two gastrointestinal hormones with anti-diabetic effects [10].

Besides carbohydrates, the metabolites fermented from protein are more diverse, such as aromatic amino acids (AAA) and branched-chain amino acids (BCAA). Gut microbiota converts tryptophan to indole and its derivatives, some of which act as aryl hydrocarbon receptor (AhR) ligands. Defective activation of the AhR pathway causes the reduced production of GLP-1 and interleukin (IL)-22, which contribute to intestinal permeability and lipopolysaccharide (LPS) translocation, leading to inflammation, insulin resistance, and liver steatosis. Therefore, supplementation of AhR ligands can improve glucose metabolism [10]. And some tryptophan metabolites such as indole-3-ethanol, indole-3-pyruvate, and indole-3-aldehyde can protect the gut epithelial barrier. They affect the integrity of the apical junctional complex including myosin IIA and ezrin [9]. Furthermore, imidazole propionate (ImP), a histidine-derived metabolite, is elevated in patients with prediabetes and T2D. It can activate the mechanistic target of rapamycin complex 1 (mTORC1) to impair insulin signaling at the level of insulin receptor substrate [10]. Gut bacteria can produce or consume BCAAs, including valine, isoleucine, and leucine, modulating BCAA levels. Chronic increase of BCAA causally leads to the development of insulin resistance in humans [10]. A recent study suggested that these adverse metabolic effects of BCAA were mediated by isoleucine and valine [11]. It was tested that BCAAs may suppress insulin signaling in skeletal muscle and adipose tissue through activating mTORC1 [10].

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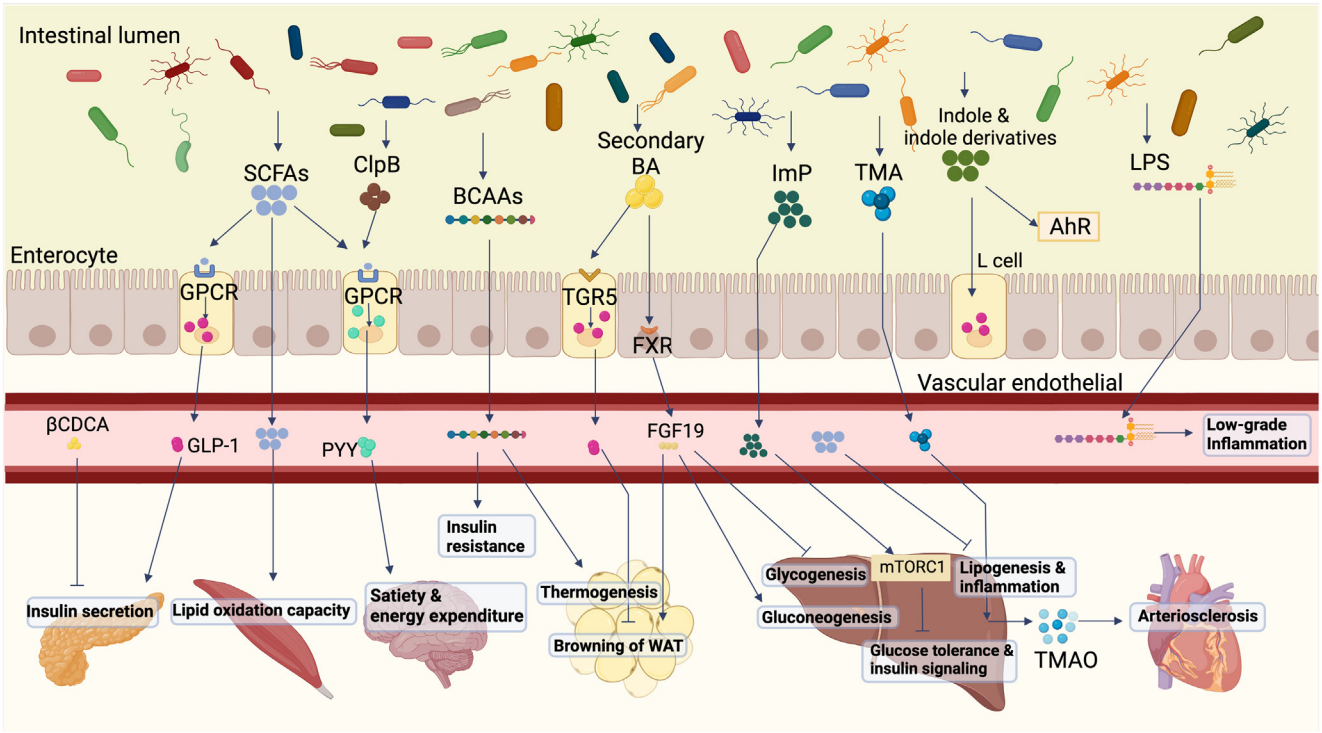

Fig. 1. The role of the gut microbiota in diabetes. Gut microbiota affects host metabolism in several different ways. SCFAs production is reduced, and stimulation of the release of GLP-1 and PYY through GPCRs is attenuated, thus affecting satiety and energy expenditure in the brain and reducing the browning of WAT. SCFAs also can improve skeletal muscle lipid oxidative capacity and suppress lipogenesis and inflammation in the liver. ClpB protein can activate the anorexigenic pathway in the brain probably via PYY. Increased systemic levels of BCAAs increase adipose tissue thermogenesis and insulin resistance. Alteration of the gut microbiota leads to a decrease in secondary bile acid production, and the effect of increasing GLP-1 by activating TGR5 is inhibited. It also reduces FXR expression and FGF19 production, then reduces the browning of white adipose tissue and gluconeogenesis, and increases glycogenesis. Increased βCDCA results in decreased insulin secretion. Impaired glucose metabolism results from ImP through activation of the p38/mTORC1 signaling pathway. The production of indole, which could act as ligands for AhR, is reduced, leading to reduced production of GLP-1 increasing intestinal permeability and LPS translocation, which leads to low-grade inflammation. TMA is oxidized to TMAO in the liver. TMAO accelerates arteriosclerosis. Arrow indicates stimulation, and arrow with bar indicates inhibition. SCFAs: Short-chain fatty acids; GLP-1: glucagon-like peptide1; PYY: YY peptide; ClpB: Caseinolytic protease B; GPCRs: G protein-coupled receptors; WAT: white adipose tissue; BCAAs: branched-chain amino acids; TGR5: Takeda G-protein-coupled receptor 5; FXR: Farnesoid X receptor; FGF19: fibroblast growth factor 19; BA: bile acid; βCDCA: 3β-chenodeoxycholic acid; ImP: imidazole propionate; mTORC1, mechanistic target of rapamycin complex 1; AhR: aryl hydrocarbon receptor; LPS: lipopolysaccharide; TMA: L-carnitine-derived trimethylamine; TMAO: trimethylamine-*N*-oxide. (Created with BioRender.com)

Gut microbiota can convert primary bile acids (BAs) into secondary BAs. Generally, primary BAs display pro-inflammatory effects on intestinal epithelial cells, whereas most secondary BAs act as anti-inflammatory agents. Impaired signaling can lead to hyperglycemia and T2D [12]. Furthermore, disruption of the gut microbiota limits BA absorption in the ileum, which typically occurs through the apical sodium bile acid transporter, leading to the reduction of farnesoid X receptor (FXR) and fibroblast growth factor (FGF) 19 and an imbalance of BAs. GLP-1 and insulin productions are enhanced in transgenic mice overexpressing Takeda-G protein receptor (TGR)-5, resulting in improved glucose tolerance [10]. Providing evidence for a related role for bile acids, recent studies have shown that metformin partly acts by reducing bile salt hydrolase (BSH)-producing *Bacteroides fragilis* in the gut which increases the glycine-ursodeoxycholic acid (GUDCA), an FXR antagonist [12]. Additionally, hyocholic acid species were found to improve glucose homeostasis through a distinct TGR-5 and FXR signaling mechanism [13].

Other gut microbial molecules also affect glucose metabolism. Earlier mechanistic studies have indicated that the translocation of bacteria-derived components like LPS or peptidoglycan from the gut to the systemic circulation could lead to low-grade inflammation, thereby aggravating insulin resistance, and eventually leading to the development of diabetes. Pathogen-associated molecular patterns exert their effects by activating specific pattern recognition receptors (PRRs). The toll-like receptor 4, a PRR, recognizes LPS and promotes myeloid differentiation antigen 88-mediated signaling [9]. Recently, P9, a protein secreted by *A. muciniphila* was reported to bind to intercellular adhesion molecule 2, increasing GLP-1 secretion and improving glucose homeostasis [9]. Choline and L-carnitine-derived trimethylamine (TMA) are elevated in patients with diabetes. TMA is oxidized to trimethylamine-*N*-oxide (TMAO) in the liver, but there is also a direct intestinal source of TMAO. Earlier investigations have linked a high plasma TMAO level to T2D and gestational diabetes mellitus [10]. The mechanisms are still unclear. Moreover, some intestinal bacteria contain the *N*-acyl amide synthase gene. Mice administered with engineered bacteria that produce *N*-acyl serinol had improved glucose tolerance. Caseinolytic protease B (ClpB) protein, secreted by *Escherichia coli*, can activate the anorexigenic pathway probably via PYY. Furthermore, gut bacteria synthesize some neurotransmitters, including catecholamines, histamine, etc., which affect host metabolism [12].

Due to increasing evidence of gut microbiota's role in diabetes, researchers are inspired to explore microbiota-targeted therapies for diabetes. There are different studies related to diet intervention, microbiota transplantation, and medicine (Table S1 online). Accumulating evidence has shown the benefits of regulating blood glucose of conventional microbiota-based interventions including prebiotics, probiotics, and fecal microbiota transplantation (FMT). A recent study combined oral encapsulated FMT with adjunctive fiber supplementation [14], and its major breakthrough is that it

showed that single-dose oral FMT could be engrafted in patients with the help of low-fermentable fibers, which also increased its beneficial effect on insulin resistance, providing a safer and more practicable FMT protocol than invasive duodenal or rectal infusion; however, the trial lasted only 6 weeks, therefore the long-term effect remains to be evaluated.

In addition to microbiome-based interventions, some of the conventional therapeutic effects of diabetes treatment may be mediated or modified by microbial communities (Table S2 online). Lifestyle interventions, drugs, and bariatric surgery may modify gut microbiota; however, it is unclear whether the alterations are causative or a response to improved overall metabolism. In recent years, studies have gone further to decipher the role of gut microbiota in treatment. One study addressed the association between bariatric surgery, gut microbiota, and diabetes improvement. Mechanically, after sleeve gastrectomy, cholic acid-7-sulfate production increases through microorganisms, which then stimulates GLP-1 secretion [15]. Metformin, the first-line T2D medication, has long been recognized to lower glucose concentration by a gut-mediated mechanism. Recently, a well-designed randomized trial showed that metformin has a long-term effect on the microbiome and SCFAs, independent of weight loss, suggesting the gut-mediated effect of metformin may be partly linked to compositional and functional alterations in the microbiota [16]. As mentioned above, the gut microbiota mediated the effect of exercise on prediabetes [5]. Our team has initiated a clinical trial to study the effect of exercise on patients with T2D, focusing on the gut-brain axis, in an attempt to assess the effects of exercise on alteration of the gut microbiome, appetite, and cognition (ChiCTR2100046148; https://www.chictr.org.cn/index.aspx). In East Asia, traditional Chinese medicine is essential in clinical practice. Studies suggest that Chinese medicine may improve glucose metabolism partially by altering the gut microbiome. On-going studies, such as the "Study on the characteristics of intestinal damp-heat syndrome and the intervention mechanism of Gegen Qinlian decoction in type 2 diabetes from the 'bacteria-toxic-inflammation-sugar' pathogenic pathways" (ChiCTR-IOR-15006626; https://www.chictr.org.cn/index.aspx) and "Gut microbiota-based clinical curative effects and mechanism research of preventive treatment of prediabetes and borderline hyperlipidemia by adjusting phlegm-dampness constitution with Hua Tan Qu Shi decoction" (ChiCTR1900020674; https://www.chictr.org.cn/index.aspx) are expected to offer more insights on the roles of gut microbiota-mediated treatment of diabetes in Chinese medicine.

The advances in gut microbiota and diabetes achieved in the last few years are encouraging, and they provide valuable mechanistic or therapeutic insights into the contributions of microbes to diabetes. The composition of gut microbiota is extremely complicated, and studies at both the translational and fundamental levels are still in their infancy. Future research shall focus on the following aspects. First, the dynamic changes in the gut microbiome and metabolites during multiple stages of diabetes remain unclear since most studies have focused only on the changes at a certain time point. Second, it is necessary to design more gut microbiota-centric interventional studies to shift from association studies toward causation. Third, the development of novel technologies in preclinical animal models and microbiology is expected to accelerate the study of the roles of particular metabolites, receptors, and microbes in diabetes. Notably, the issues of individuation and colonization efficiency are urgent problems to be solved. There are large inter-individual variations in the gut microbiota composition, even though individual microbes have been suggested as beneficial or detrimental in the development and progression of diabetes. Additionally, it is challenging to ensure the colonization and persistence of exogenous bacteria in the gut, along with the production of adequate amounts of therapeutic metabolites to exert antidiabetic effects. Fourth, compared to gut microbes, metabolites have several advantages while being used as therapeutic tools. There are a handful of clinical studies on the application of gut microbial metabolites in disease treatment. Fifth, not only treatment but also more in-depth studies on predicting diabetes based on the gut microbiome are needed. A recent prospective study [17] in a Finnish population laid the foundation for the use of the gut microbiome for diabetes prediction. Last but not least, the safety of the translation of gut microbiota and their derivatives to humans should be strengthened. More microbiota-associated studies are needed, whether in the depth of mechanisms, the setting of clinical trials, or the study of specific species, in order to bring us closer to the new therapeutics of diabetes gradually.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgments

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Appendix A. Supplementary materials

Supplementary materials to this news & views can be found online at https://doi.org/10.1016/j.scib.2022.07.027.

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