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Gut microbiota and immunopathogenesis of diabetes mellitus type 1 and 2

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1. ABSTRACT

Diabetes mellitus (DM) is a major increasing global health burden in the aging population. Understanding the etiology of DM is beneficial for its prevention as well as treatment. In light of the metagenome hypothesis, defined as the overall bacterial genome, gut microbes have attracted increasing attention in the pathogenesis of DM. Many studies have found that gut microbes are involved in the immunopathogenesis of DM. Probiotics strengthen the host's intestinal barrier and modulate the immune system, and have therefore been investigated in DM management. Recent epigenetic findings in context of genes associated with inflammation suggest a possible way in which gut microbiota participate in the immunopathogenesis of DM. In this review, we discuss the role of gut microbiota in the immunopathogenesis of DM.

2. INTRODUCTION

Diabetes mellitus (DM) comprises a group of metabolic diseases characterized by high blood sugar levels over a prolonged period (1). In 2013, 382 million people worldwide were suffering from DM (2); 90% with type 2 diabetes (T2D) and 10% with type 1 diabetes (T1D) (3). DM caused 1.5 million deaths worldwide in 2012, making it the eighth leading cause of death (4). DM causes a series of acute complications, including diabetic ketoacidosis and nonketotic hyperosmolar coma, or long-term complications such as stroke, kidney failure, foot ulcers, and ocular damage (5,6). DM doubles the risk of cardiovascular disease (7) and about 75% of deaths in DM patients are due to coronary artery disease (8). Over the past decade, diabetes has been the cause of lethal cardiovascular events that have seen a 62% increase (9, 10). Therefore, there is an urgency to identify the risk factors and etiology of DM, along with new therapeutic targets.

Recently, based on the advancements of high-throughput sequencing technology, the metagenome hypothesis has been proposed, and is defined as the overall bacterial genome. Gut bacterial fragments might diffuse throughout the mucosa and bind to receptors at the surface of intestinal epithelial cells. This is beneficial for maturation of the intestinal epithelial layer, innate mucosal immune system, enteric nervous system, as well as the intestinal vascular system (11, 12). In T2D patients, gut microbiota has been found to differ from those in non-diabetic patients (13). In a mouse model of DM induced by high-fat diet, gut microbiota relieved the disease symptoms through the regulation of endotoxemia, thus suggesting a role of gut microbiota in inflammation and pathogenesis of diabetes (14). In this review, we discuss the role of gut microbiota in the immunopathogenesis of T1D and T2D, and the new insights into the probiotic treatment.

3. GUT MICROBIOTA IN IMMUNOPATHOGENESIS OF DIABETES

3.1. T1D

T1D is caused by the autoimmune destruction of the insulin-producing β-cells in the pancreas. It is estimated that ~80,000 children develop T1D each year

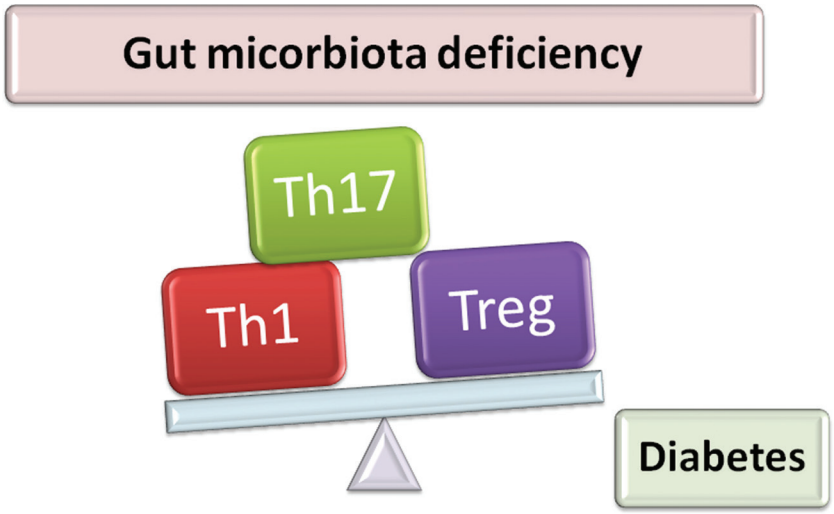

Figure 1. Gut microbiota regulates T cells in diabetes. Gut microbiota deficiency promotesan imbalance between Th1, Th17 and Treg celldifferentiation in the intestine of a mouse model of diabetes.

worldwide (15). In a rat model, gut microbiota was found to promote virus-induced T1D (16). In children with T1D, fecal microbiota was found to be imbalanced and patients had higher levels of the genus *Bacteroides*, whereas controls had higher levels of *Prevotella* (17). Soyucen and colleagues (18) found a decrease in beneficial anaerobic bacteria levels and a concomitant increase in *Enterobacteriaceae* in T1D children, thus proposing that this disturbance in the ecological balance of intestinal flora may be a trigger for T1D.

When neonatal infants are treated with vancomycin, a glycopeptide antibiotic specifically directed against Gram-positive bacteria, many major genera of Gram-positive and Gram-negative microbes in the gut are depleted, whereas only *Akkermansia muciniphila* becomes dominant. This suggests that the early postnatal period is crucial for T1D microbial protection, and *A. muciniphila* plays a protective role (19). Moreover, $CD4^+$ T cells are increased and produce proinflammatory cytokines in neonatally treated mice (19). Collectively, these findings suggest that the number and function of $CD4^+$ T cells may be influenced by gut microbiota in T1D. Alam and colleagues (20) have demonstrated that in the mouse model, gut microbial deficiency promotes an imbalance between T helper (Th)1, Th17 and T regulatory (Treg) cell differentiation in the intestine (Figure 1). Moreover, the Treg cells in the islets may help control diabetogenic T cells (20). Another study reported that there is a substantial population of Th17 cells in the small-intestinal lamina propria of T1D mice with segmented filamentous bacteria, suggesting that these bacteria are associated with the gut immune system, especially Th17 cells (21). Recently, Wang and colleagues (22) reported that interleukin (IL)-22 from innate lymphoid cells and $CD4^+$ T cells alleviate metabolic disorders and restore mucosal immunity, especially in the colon during infection with *Citrobacter rodentium* (22), further elucidating the immune interaction between microbiota and $CD4^+$ T cells.

Gut microbiota can also be influenced by a casein hydrolysate diet in rats with autoimmune diabetes (23). The cereal diet is associated with impaired gut immune homeostasis (24). Recently, Hansen and colleagues (25) found that the incidence of diabetes was reduced by a gluten-free diet during fetal and early postnatal life via changes in the gut microbiota and shifting the response to a less proinflammatory immunological milieu in the gut and pancreas. This finding suggests the regulatory function of a gluten-free diet on gut microbiota in diabetes. Another study in a mouse model further confirmed the significant role of exposure time in early life to the gut bacterial composition, which in turn affects the mucosal immune system and can delay the development of autoimmune diabetes (26).

3.2. T2D

As in T1D, gut microbiota has also been found to participate in the immunopathogenesis of T2D. In a mouse model of obesity and diabetes induced by high-fat diet, gut microbiota was altered, leading to limitation of metabolic endotoxemia and inflammation, and increasing the intestinal permeability (27). T2D in humans is also associated with compositional changes in intestinal microbiota (28). In the fecal microbiota of T2D patients, *Bacteroides vulgates* and *Bifidobacterium* were decreased, suggesting that the changes in gut microbiota were associated with occurrence and development of diabetes (29). Sato and colleagues (30) found that in the fecal samples from T2D patients, the counts of the *Clostridium coccoides* group, *Atopobium* cluster,

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and *Prevotella* (obligate anaerobes) were decreased, whereas the counts of *Lactobacillus* (facultative anaerobes) were increased as compared to the controls. Even in the circulation, gut bacteria, mostly Gram-positive, were detected at a higher rate in T2D patients than in controls (30).

4. PROBIOTICS IN DIABETES

The gut microbiota is involved in the pathogenesis of DM via its effect on immune dysregulation; therefore, regulation of gut microbiota may be used as one of the strategies in DM treatment. In a mouse model, modulation of intestinal microbiota could prevent T1D development (31). As previously described, in addition to a gluten-free diet, probiotic supplements may also serve as a more direct way to change gut microbiota. Probiotics can be defined as monocultures or mixed cultures of live microorganisms, which, when administered in adequate amounts, confer a health benefit to the host (32). Probiotics have the ability to secrete antimicrobial substances, competing with other pathogens, strengthening the intestinal barrier, and modulating the immune system (33). In breeding diabetes-prone rats, *Lactobacillus*, one of the most common types of microbe used as probiotic (34), stimulates the innate immune response (35). Thus, probiotics may influence the immunopathogenesis of DM.

4.1. T1D

Certain enteral microbes and patterns of gut microbiome are associated with a low risk of T1D (36). Therefore, it is possible to develop preventive interventions for T1D based on use of protective microbes as probiotics. In a previous study, *Lactobacillus* strains with cinnamoyl esterase activity, *Lactobacillus johnsonii* N6.2. and *Lactobacillus reuteri*, were negatively correlated with T1D development (37). In a rat model of T1D, *L. johnsonii* N6.2. mitigated the development of T1D (38), which may have been associated with regulating the innate immune response via Toll-like receptor (TLR)9, as shown *in vitro* in Caco-2 cells (35). However, the effect of probiotics on T1D needs to be further investigated in large clinical trials.

4.2. T2D

In patients with diabetes complicated with gastrointestinal cancer, microbiota and enteral nutrition can reduce insulin resistance and improve immune status (39). The number of $CD4^+$cells, CD4/CD8 ratio, and natural killer cells are all increased after microbiota-enteral nutrition treatment (30), suggesting immune enhancement by microbiota supplementation. A clinical trial comprising of 34 T2D patients, however, showed that probiotics do not significantly reduce the level of triglyceride, malondialdehyde, and IL-6, as well as insulin resistance (40). On the contrary, in a randomized, double-blind, placebo-controlled trial of 120 T2D patients, probiotics induced beneficial changes in gut microbiota, and reduced the systemic inflammatory response (41). Although the effect of probiotics in T2D patients is still contradictory, the latter study provides more convincing evidence. A recent study confirmed the effect of probiotics in T2D management via positive intestinal microbiota modulation (42). However, the precise effect of probiotics in T2D patients still needs further investigation, with a more rigorous study design and larger sample size.

In addition to probiotics, prebiotics also have a role in positively modulating the intestinal microbiota (42). Prebiotics are non-digestible food ingredients that selectively stimulate favorable bacterial growth and/or promote activity of a limited number of health-promoting bacteria, hence benefiting the host (43, 44). Prebiotics are not the same as probiotics, but can complement and work together with probiotics by enhancing the survival and action of ingested probiotic bacteria. Prebiotics are helpful to the gut microbiota and improve glucose homeostasis in prediabetic patients via ameliorating impaired insulin signaling and secretion prior to the process becoming irreversible (45). A recent double-blind placebo-controlled randomized crossover clinical trial has confirmed the same effect of prebiotics, and found that prebiotics may protect against pathology related to advanced glycation end products in people at risk of developing T2D (46). Findings on prebiotics in T2D thus suggest that they may benefit people at risk of T2D before the process becomes irreversible.

5. EPIGENETIC REGULATION OF MICROBES IN DIABETES

As already discussed, the gut microbiota can directly affect the immune system in patients with diabetes. The gut microbiota may also interact with the innate immune system in an epigenetic way to modify T1D predisposition (47). In T2D, the composition of gut microbiota can influence the epigenetic regulation, with decreased methylation of free fatty acid receptor genes, which are involve in the binding of short chain fatty acids to the free fatty acid receptors (48). In T2D, both TLR2 and TLR4 decreased methylation, suggesting the epigenetic regulation of inflammatory reactions in T2D immunopathogenesis (49) (Figure 2). The epigenetic changes may last for several generations, even though they do not involve changes in the underlying DNA sequence of the organism (50). These findings suggest an epigenetic view to investigate the mechanism of gut microbes in regulating the immunity in diabetes, which may provide further improve our understanding on the interactions between gut microbiota and diabetes. However, further *in vitro* and *in vivo* studies will be needed to elucidate the mechanism of epigenetic regulation in diabetes.

6. CONCLUSIONS

Gut microbiota is involved in the immunopathogenesis of both T1D and T2D. In particular,

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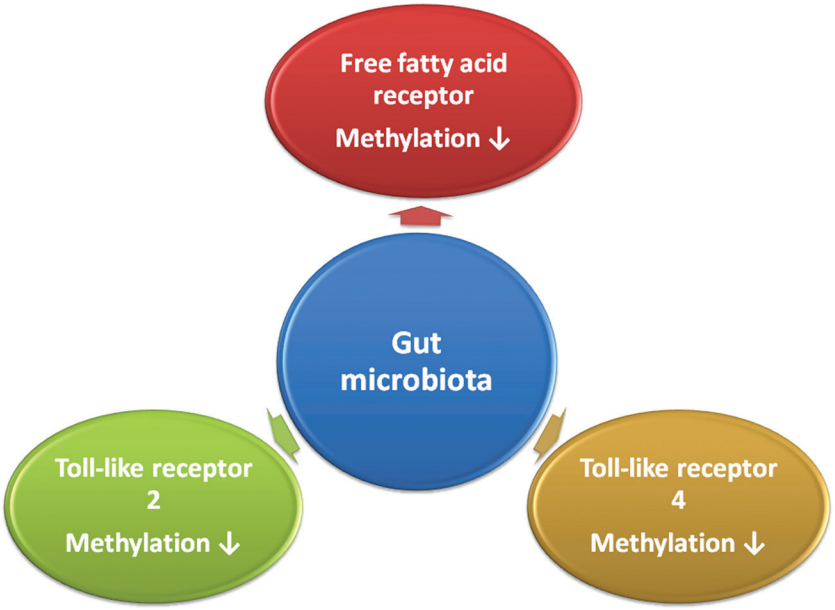

Figure 2. Epigenetic regulation of gut microbiota in T2D. In T2D, composition of gut microbiota can influence epigenetic regulation, with decreased methylation of free fatty acid receptor,TLR2 and TLR4 genes.

gut microbiota regulates immunity of T1D through affecting $CD4^+$ T cell subtype balance. Probiotics can reduce the systemic inflammatory response, although they affect the risk of T2D only at the time before the process becomes irreversible. Moreover, decreased methylation in genes associated with fatty acid and inflammation suggests an epigenetic view to investigate the mechanism of gut microbes in regulating the immunity in diabetes. In future, large clinical studies may provide more information on the effects of probiotics in diabetes. *In vitro* and *in vivo* studies on the mechanism of interaction between gut microbiota and the host may give us further understanding of the immunopathogenesis of diabetes, which may be beneficial for its prevention and management.

7. ACKNOWLEDGEMENTS

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Abbreviations: DM: Diabetes mellitus; T2D: type 2 diabetes; T1D: type 1 diabetes; Treg: T regulatory; (Th)1: T helper 1

Key Words: Diabetes mellitus, Gut microbiota, Treg, Review

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