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Review

Impact of gut microbiota on diabetes mellitus

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Abstract

Various functions of the gut are regulated by sophisticated interactions among its functional elements, including the gut microbiota. These microorganisms play a crucial role in gastrointestinal mucosa permeability. They control the fermentation and absorption of dietary polysaccharides to produce short-chain fatty acids, which may explain their importance in the regulation of fat accumulation and the subsequent development of obesity-related diseases, suggesting that they are a crucial mediator of obesity and its consequences. In addition, gut bacteria play a crucial role in the host immune system, modulation of inflammatory processes, extraction of energy from the host diet and alterations of human gene expression. Dietary modulation of the human colonic microbiota has been shown to confer a number of health benefits to the host. Simple therapeutic strategies targeted at attenuating the progression of chronic low-grade inflammation and insulin resistance are urgently required to prevent or slow the development of diabetes in susceptible individuals. The main objective of this review is to address the pathogenic association between gut microbiota and diabetes, and to explore any novel related therapeutic targets. New insights into the role of the gut microbiota in diabetes could lead to the development of integrated strategies using probiotics to prevent and treat these metabolic disorders.

Keywords: Diabetes mellitus; Diabetic complications; Gut microbiota; Inflammation

1. Introduction

"Father of Medicine" Hippocrates' famous statement that "all disease begins in the gut" recognized the essential role played by the gut and diet in many of the vital homoeostatic functions of the human body. Indeed, the role of the human gut microbiota is crucial, as it is populated by a number of different microbial groups [1]. Every one of us has our own exclusive microbiota and gut microbiome (the microorganisms' genes). The number of genes of the microbiota outnumbers human genes by a hundredfold [2]. Studies examining the influence of nutrients (such as dietary fibres and fats) and dietary habits (whether omnivores, vegetarians or vegans) in different populations have allowed stratification of the human population based on three principal bacteria and their microbiome's genetic abundance [3]. Gut microbiota from different individuals have been classified into enterotypes, depending on their function, metabolism of dietary components, and ability to tolerate and metabolise drugs [4]. A healthy gut microbiome is characterized by the presence of microbes that enhance metabolism, and are resilient to infection and inflammation and resistant to autoimmunity and cancer [5].

Increasing evidence indicates that gut microbiota are strongly associated with diabetes development [6,7]. In addition, the autoimmune mechanisms involved in the pathogenesis of type 1 diabetes (T1D) might also implicate peptidergic enteric neurons, which regulate immune-cell function and influence pro- and anti-inflammatory cytokine production, resulting in neurodegeneration [8]. Lymphokines produced in the pathogenic cascade involved in the development of autoimmune islet-cell damage could also lead to myenteric neuropathy [9]. Notably, the gut microbiota affect the intestinal mucosa via interactions with epithelial cells and the enteric nervous system, leading to changes in gut motility, sensory functions and pain perception (microbiota–brain–gut axis) [10]. The present review aims to provide some mechanistic insights by highlighting the role of the gut microbiota in diabetes to prompt the development of innovative therapeutic targets for the prevention, treatment and slowing of diabetes and other metabolic-associated disorders.

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2. Gut microbiota

Several studies from the Human Microbiome Project and the European Commission's Metagenomics of the Human Intestinal Tract (MetaHIT) consortium have contributed to our better knowledge and understanding of the healthy composition and functional properties of the gut microbiota [1]. These studies indicate that host health is associated with the diversity and stability of the gut microbiome [11]. Gut microbiota constitute a dynamic entity that is modified by diet, lifestyle, antibiotics and genetic background [12]. Microbiota gut colonization probably starts at birth, as no large variations appear during healthy life. Interestingly, the type of microorganisms that colonize the gut of newborns depends on the delivery procedure. Infants born vaginally display a microbiota composed of *Lactobacillus*, *Prevotella* and *Sneathia* spp coming from the maternal vaginal tract. In contrast, newborns delivered by caesarean section display predominantly *Staphylococcus*, *Corynebacterium* and *Propionibacterium* spp [13]. During early childhood, Actinobacteria, and particularly of the genus *Bifidobacterium*, dominate the gut microbiota of breastfed infants. Also at this time, the microbiota acquires a variety of new strains influenced by changes in diet, such as the introduction of solid foods, and by disease, such that gradually over time, it begins to resemble the adult composition [14]. Moreover, physical exercise is able to modulate gut microbiota, and increasing physical activity can increase the abundance of beneficial microbial species [15].

To date, around 100 large groups of bacteria, known as "phyla", have been identified, each with a different repertoire of biochemical capabilities. In the adult gut microbiota, the majority of the microbial populations belong to the phyla Actinobacteria and Proteobacteria, and approximately 90% to the Bacteroidetes and Firmicutes phyla [16]. These phyla are differentially distributed throughout the gut and determine different microbial ecosystems [17]. In the Firmicutes phylum, the *Clostridium coccoides* group is the dominant population in the gut microbiota, with a large number of cultured and enculturated spp. A recent study showed that changes in the diversity of the *C. coccoides* group population in the gut microbiota correlates with age, and it was hypothesized that these changes could affect the health of the host [18]. Gut microbiota fulfil structural and histological functions, and play important metabolic roles for health maintenance, including amino-acid synthesis and the absorption of dietary fats and fat-soluble vitamins, and affect the protective actions that prevent pathogenic colonization and the composition of converted bile acids (Fig. 1) [19]. Bile acids bind to cellular receptors, which are internalised, and which activate distinct pathways involved in glucose homoeostasis and lipid energy metabolism [20–22]. Furthermore, the gut microbiota help the host to eliminate calories from indigestible complex carbohydrates and plant polysaccharides via enzymes that are not encoded within the human genome [23]. Non-digestible carbohydrates are fermented by colonic microbes, leading to the production of short-chain fatty acids (SCFAs) such as butyrate, which has trophic effects on intestinal epithelium [24].

On the basis of the clustering patterns seen in the world's population with variations in the levels of dominant microbiota genera, three enterotypes have been proposed: *Bacteroides*; *Prevotella*; and *Ruminococcus* [25]. Differences among these enterotypes are dependent on different combinations of microbial trophic chains. *Bacteroides* (enterotype 1) develops energy principally from fermentation of carbohydrates, as this genus has a very broad saccharolytic potential. *Prevotella* (enterotype 2) degrades mucin glycoproteins of the gut mucosal layer, while *Ruminococcus* (enterotype 3) binds mucins, and transports and degrades the constituent sugars. In addition, *Bacteroides* and *Prevotella* are enriched by the biosynthesis of different vitamins [25]. These enterotypes have been associated with long-term dietary patterns. *Bacteroides* spp have been correlated with diets dominated by high levels of animal protein and saturated fats, as found in the typical Western diet, whereas *Prevotella* is predominant in people with higher consumption of carbohydrates and simple sugars, as observed in agrarian and vegetarian societies [4].

In addition, microorganisms in the microbiota can regulate intestinal architecture by altering gut permeability. Intestinal epithelium is not only responsible for the assimilation of ingested food and nutrients, but also for the prevalence of crosstalk with the external surface of the body as well as between gut microbes. Epithelial cells constitute a physical barrier, impeding the translocation of the luminal contents of the inner tissues. The two main types of interconnecting junctions are the adherens junctions (AJs) and tight junctions (TJs). AJs are predominantly formed by cadherins linked to the actin cytoskeleton through a family of catenins, while TJs are the result of interactions of occludin, claudins and junctional adhesion molecule (JAM)-A, linked to the actin cytoskeleton via zonula occludens proteins (ZO-1, ZO-2) and α-catenin [26]. Myosin phosphorylation and contraction of the actin–myosin complex regulate the permeability of the epithelial barrier [27]. Damage to intestinal permeability allows the passage of endoluminal molecules into deeper layers which, in turn, weakens the intercellular connections and triggers activation of the inflammatory response [28]. Thus, enterohaemorrhagic *Escherichia coli* (EIIEC) and enteropathogenic *E. coli* (EPEC) have the ability to adhere to intestinal epithelial cells (IECs) and disrupt the integrity of the barrier through TJ alterations [29]. Subsequent activation of the inflammatory response leads to increased concentrations of proinflammatory mediators, such as interferon (IFN)-γ and tumour necrosis factor (TNF)-α, which can both modulate the expression of several TJ proteins, such as ZO-1, JAM-A, occludin, claudin-1 and claudin-4 [30].

Thus, the intestinal epithelium and intestinal innate immune system are symbiotic, and cooperate in interactions between gut microbiota and the host. This synergy arises through a mechanism that can destroy pathogens while equally tolerating the presence of commensals, using strategies that generate ecological niches for beneficial gut microbiota [31]. Recognition of pathogen-associated molecular patterns (PAMPs) by epithelial cells via pathogen recognition receptors (PRRs) is important for this equilibrium. To date, the system linking gut microbial and host signals, and the onset or progression of metabolic alterations

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