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REVIEW

The gut microbiota and Type 1 Diabetes

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Abstract Type 1 Diabetes (T1D) is a multifactorial, immune-mediated disease, which is characterized by the progressive destruction of autologous insulin-producing beta cells in the pancreas. The risk of developing T1D is determined by genetic, epigenetic and environmental factors. In the past few decades there has been a continuous rise in the incidence of T1D, which cannot be explained by genetic factors alone. Changes in our lifestyle that include diet, hygiene, and antibiotic usage have already been suggested to be causal factors for this rising T1D incidence. Only recently have microbiota, which are affected by all these factors, been recognized as key environmental factors affecting T1D development.
In this review we will summarize current knowledge on the impact of gut microbiota on T1D development and give an outlook on the potential to design new microbiota-based therapies in the prevention and treatment of T1D.

Contents

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1. Introduction

Type 1 Diabetes (T1D) is one of the most common metabolic disorders in children and young adults. This autoimmune-mediated disease results in a progressive loss of insulin-producing beta cells in the islets of Langerhans in the pancreas.

Several diabetes-predisposing gene loci have been identified. The strongest association with T1D in humans is with the HLA-DR and -DQ genes, which account for approximately 40–50% of the disease risk [1]. However, despite intensive research, the triggers for T1D are still mostly unknown, whereas the incidence of T1D has sharply risen worldwide in the past few decades. Currently the overall increase in the incidence of T1D in Europe is about 3–4% per year. The fastest increase is observed in children less than 5 years of age [2]. Within this age group the incidence is anticipated to double by 2020 [3,4]. These dramatic changes in the incidence rate cannot be explained merely by genetic changes. The importance of non-genetic, environmental factors contributing to the disease risk becomes obvious when considering that fewer than 10% of individuals who are genetically predisposed to T1D de facto develop the disease [5].

Environmental factors that may affect the risk of developing T1D include birth delivery mode [6,7], diet in early life [8–11], and possibly usage of antibiotics [12,13]. All of these potential environmental risk factors are related to the intestine and its microbiota. The gastrointestinal tract constitutes the largest surface area in the human body and is densely populated by 500–1000 different bacterial species [14]. In recent years, much research effort has been focused on elucidation of the interaction between the host and the gut microbiota in health and disease. The Hygiene Hypothesis, and a more recent refinement, the Old Friends Hypothesis postulate that the increase in the incidence of allergy and autoimmune diseases in Western Countries is associated with reduced or delayed exposure to microbes or parasites in our childhood [15]. The disappearing microbiota hypothesis in contrast focuses more on our ancestral microorganisms rather than cleanliness and postulates the lack of symbiotic microorganisms as being responsible [16]. Numerous studies have documented that coevolution with the microbiota has led to interdependence between the human host and the commensals, which are crucial for maintaining homeostasis. Disturbing the homeostasis, so-called dysbiosis, will have an important impact on immune responses that have been observed in different diseases. Recent studies also suggest that the gut microbiome contributes to the risk of developing T1D in genetically predisposed individuals [Table 1].

As various environmental factors that are known to influence the risk of developing T1D also modulate the composition of the gut microbiome [Fig. 1], it is reasonable to consider microbiota to be a link between those factors and disease promotion, which will be discussed below.

2. Gut microbiota and their effect on T1D

Accumulating evidence from human studies emphasizes the crucial role of the composition of the gut microbiota in diabetes development. Patients with T1D exhibit a less diverse and less stable gut microbiome compared to healthy controls [17,18] and changes of the ratio of Firmicutes to Bacteroidetes have been observed in the patients [17–20]. Prediabetic children harbor more *Bacteriodetes* compared to controls [19]. A decreased abundance of *Faecalibacterium prausnitzii* (butyrate-producing bacterium) in children who had more than two diabetes-related autoantibodies has also been observed [21]. However, these studies are limited at present and there is considerably more evidence in mouse models that had fuelled these studies in humans as discussed below.

The fact that the incidence of T1D in non-obese diabetic (NOD) mice is influenced by the microbial environment in different animal facilities worldwide [22] had suggested that microbiota play a crucial role in diabetes development.

Some early studies showed that NOD mice developed exacerbated diabetes under germ-free (GF) conditions, however, the recent reports did not confirm a disease aggravation in NOD mice housed in GF conditions [23,24]. King, *et al.* demonstrated that an accidental contamination with *Bacillus cereus* in one cohort of otherwise GF NOD mice resulted in delayed diabetes onset and decreased incidence [23]. Hence, it seems more likely that the composition of the gut microbiome and the richness of certain bacteria are the key factors modulating diabetes development. Our recent study provided a strong evidence of another important player—innate immunity. Myeloid differentiation primary response 88 (MyD88) is a 'master' adaptive protein down stream of most innate immune molecules [25]. MyD88-deficient NOD mice were completely protected from diabetes development when housed in specific pathogen free (SPF) conditions; however, GF MyD88-deficient NOD mice developed full-blown diabetes. Colonization with defined gut bacteria restored diabetes protection in those mice although not 100% [26]. Our results reveal a novel influential pathway of innate immunity in T1D development through gut microbiota.

Individual strains of the gut bacteria may have different effects on diabetes. Using the Biobreeding (BB) rat model, Valladares and colleagues reported that *Lactobacillus johnsonii* isolated from diabetes-resistant BB (BB-DR) rats can attenuate diabetes development in diabetes-prone BB (BB-DP) rats whereas *Lactobacillus reuteri,* also from BB-DR rats, failed to affect diabetes development [27]. Contrary results were also obtained in terms of *segmented filamentous bacteria* (SFB) and their effect on diabetes development. Kriegel and coworkers reported an association between SFB colonization and diabetes protection in female SPF NOD mice [28], whereas using GF female NOD mice, Yurkovetskiy and coworkers found SFB did not confer protection in monocolonized gnotobiotic NOD females [29]. The authors showed that the protective effect of SFB could only be seen when other gut bacteria were present [29]. One explanation for this disparity is that SFB act in concert with other bacterial species to modulate the disease. Variations in SFB strains could also be responsible. Interestingly, male GF NOD mice were protected from diabetes development even monocolonized with SFB [29]. This suggests a complex association of sex hormones, gut microbiota and beta cell autoimmunity.

3. Gut permeability and T1D induction

The intestinal epithelial layer constitutes a barrier that separates the luminal antigens from the interior of the body.