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INTESTINAL MICROBIOTA INFLUENCES TYPE1 DIABETES

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ABSTRACT
Increasing diabetes incidence in the last decades drew the attention of researchers that there are other reasons besides genetic susceptibility. There are several factors that influence the occurrence of type 1 diabetes (T1D) encomposing genetic and environmental components. This review will throw light on the important aspects of T1D development in context with the intestinal microbiota. Gut microbiota provides an immunological barrier to the gut from the invasion of pathogenic microorganisms. Gut microbiota dysbiosis mediates T1D through stimulation of inflammatory cells that induce β-cell destruction. Research in this field is important to find out new protective substances in ameliorating TID.

INTRODUCTION
The gut microbiota is an essential part of the human gut including a wide variety of bacterial constituents to promote important pathological and physiological functions. Investigations conducted on gut microbiota established an important role in the maintenance of some gastrointestinal diseases which diabetes was recently a central interest among them. A primary concern of gut microbiota that influences diabetes incidence and development. Later studies confirmed that the intestinal microbiota has a direct effect on intestinal health and immunity.[1] Increase incidence of T1D in the last decades have strongly addressed with a genetic predisposition, in combination with the environmental factors including hygiene[2], antibiotic use[3], and diet.[4] Sexual dimorphism showed a female bias[5], yet the mechanisms of sex-mediated immune regulation are poorly understood.

Studies of rodent show the importance of the microbiome in T1D pathogenesis. Animals were raised under specific pathogen-free conditions and treated with antibiotics or probiotics to examine the effect of intestinal microbiota.[6,7] The importance of intestinal microbiota was clearly understood after animals raised under germ-free showed higher diabetes incidence while conventionally raised animals did not. Pathogen-free animals lack innate signaling molecule myeloid differentiation primary response 88 (MyD88), protected from diabetes.[8] Starting from this point, innate immune interaction with gut microbiota in the occurrence of the disease was established.

Different influences of gut microbiota on male and female NOD mice leading to variation in diabetes incidence were proposed.[9] In recent studies, intestinal microbes' influences TID attract the interest of researchers, which lead to a strong contribution.

Intestinal microbiota
Diabetes-related studies entered a new promising era where an understanding of host-microbe interactions became center-light. High-quality metagenomics studies provide a wider understanding of the complex and diversified microbiota interactions in the human immune system. Human gut reserves the biggest population of these microbes[10], which accounts for about ten times of total human body cells.[11] The human intestinal microbiota is considered as a key modulator of host health, principally in metabolic diseases with a mutual pathogenic state such as obesity[12], NAFLD[13], and diabetes.[14]

The most extensively studied animal model in T1D is the NOD mouse. Shared phenotypes between human and NOD mice are represented in terms of pathogenesis, autoantigens, and genetic susceptible loci.[15] Similar to human T1D, T1D in NOD mice is polygenic, and more than 20 insulin-dependent diabetes-related loci have been recognized in diabetic NOD mice.[16]

Accumulated evidence built in the T1D and microbiome relationships via very interesting studies. These studies on rodents verified intestinal microbiota and innate immunity interactions in the occurrence of T1D. The most widely studied susceptibility gene to T1D is the MHC gene.[17] Both in human and NOD mice, the MHC class II genes particularly DR/DQ and I-A in human and mice respectively, are adding for TID genetic risk factors, but are not sufficiently explain the causes of disease susceptibility.[18]

Higher T1D incidence in NOD mice is found to be highly associated with environmental triggers. Studies in NOD mice reported that T1D incidence was mostly affected by the hygiene of colony standing[20,21], and exposure to microbes antigens and microbial-derived products over time lead to suppressing T1D development. These studies prompted the use of microbial populations to rescue TID patients by utilizing a NOD mouse model.[19] MyD88 is a major adaptor protein for multiple Toll-like receptors (TLRs) or IL-1R superfamily making it an important fragment for innate immune recognition, and significantly essential in immune–microbial interaction.[20] NOD mice deficient in TLRs adaptor protein MyD88 developed protection from T1D when they raised these mice in conventional pathogen-free conditions, but after the mice were raised in germ-free conditions resulted in lower T1D protection. Lacking MyD88 provided a suitable condition to increase the abundance of bacterial phylum *Bactroidets* that in-turn provided production of immunomodulatory microbial peptides.[8,21] These previously mentioned data established the first conclusive association between innate recognition of the microbiota, the final alterations of the microbial population, and T1D progression in the NOD mouse.[8] Higher incidence of T1D in female NOD than that in male NOD mice under SPF conditions and the similar incidence between male and female NOD when they rose in GF conditions suggest, that gender influence depends on microbiome variation.[21]

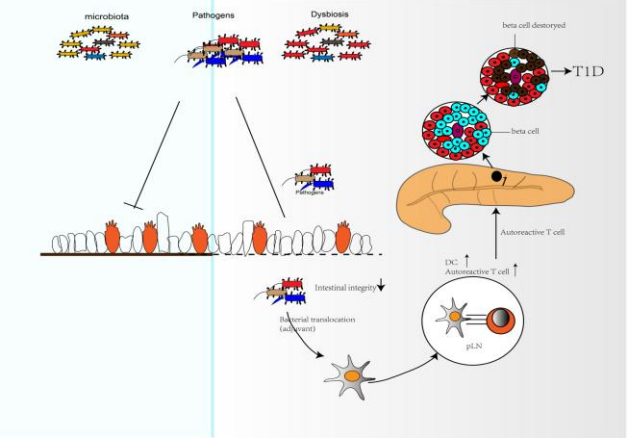

Figure 1. Intestinal integrity.

Gut microbiota alters the intestinal integrity through the production of metabolite. Dysbiosis resulted in the impaired intestine and allow translocation of pathogenic bacteria. Bacterial antigens captured with antigen presenting cells (APCs) to prime Autoreactive T cells in the pancreatic lymph nodes. Consequently activated T cells mediate β cells destruction and cause type 1 diabetes.

Candidate Gender: Interestingly many of human autoimmune diseases are more frequent in the female, whereas identified T1D does not.[22,23] The factors that mediate gender-dependent differences in autoimmunity are not fully understood. Moreover, gut microbiota composition is similar to young in male and female mice but start to differ after puberty. Fecal microbiota transplantation (FMT) from an adult male to adult female (M-F) but not from adult female to adult female (F-F) resulted in constant alterations in the gut microbiota constituents of female NOD. Interestingly, (M-F) group showed higher protection value against T1D. Serum testosterone and also other serum metabolite levels were increased in M-F NOD mice. Furthermore, T cell adoptive transfers into 5 weeks old female NOD-SCID mice showed delayed T1D onset, suggestive of alterations in the microbiota may affect T cell pathogenicity. Significantly, male microbiome transfer related effects were testosterone dependent, after the mice treated with an androgen receptor antagonist. Significantly, the disease outcomes detected after male microbiota transfer were testosterone dependent, which showed higher protection against islet destruction. These data suggested that microbiota constituents are mainly modulated during early life depending on sex hormones, and that may directly affect the concentration of downstream metabolites resulting in significant alteration of immune cells and T1D onset.

Later, another study conducted on adult female NOD and adult castrated NOD male mice to avoid sex-based bias, established that differences in microbiota signature occur prior to puberty. Furthermore, particular bacterial taxa that are abundant in SPF males, but not in females such as *Enterobacteriacae* and *Segmented Filamentous*

bacteria were colonized in GF raised NOD mice when compared to testosterone-induced females. These data suggested that microbiome development depends on hormone window, and also microbial colonization is important in maintaining host hormone levels.[24]

Antibiotic usage

In the past 50 years, antibiotic use was increased dramatically for the treatment of some frequent diseases.[25] A study performed in NOD mice born from mothers used wide spectrum ABX or vancomycin alone during pregnancy displayed higher TID proportion in adulthood. Sequencing of 16s rDNA gene for ABX induced mice displayed abundant bacterial genera *Escherichia, Lactobacillus* and *Sutterella* and lesser of *Clostridiales, Lachnospiraceae, Prevotellaceae, and Rikenellaceae* genera.[26]

Microbiota divergence associated with the lower IL-17 production in the intestinal lamina propria of ABX induced mice, suggesting a direct effect of microbiota in the mucosal immunity. Short-period antibiotics intake in young male NOD mice resulted in alteration of gut microbiota composition, immune cells phenotypes, and T1D incidence.[3]

On the other hand, a cohort study of Danish singleton children born during 1995–2003 were studied. The incidence of type 1 diabetes investigated between different antibiotic use groups. The different classes of antibiotics used were designed which found no association between antibiotics use and T1D incidence, depending on a number of courses, the use of specific antibiotics, and the age of onset, and use of antibiotics.[27] Also German et al. found no association between antibiotics use in pregnant women and childhood with T1D.[28]

The evidence for the effects of antibiotic use and its subsequent alterations were confirmed in the context of modulation of the gut microbiota and immune system.[29] Blom et al. concluded that the latest use of antibiotics was more frequent in cases than in controls, while the effect of antibiotics in early life showed similarities between cases and controls.[30]

Diabetes in the human context

Modulation of the gut microbiota during entire life is very complex. The gut microbiome starts to shape from birth until 3 years of age.[31] Then several environmental factors that affect the microbiota composition starting from the mode of delivery[32]+ breastfeeding[33], the introduction of solid food[31], and antibiotics use.[34] Microbiota composition/ mucosal and systemic immunity continuously interact during host life and direct the development of host immune and endocrine systems. Detection of the particular causative factor that mediates the continuous gut microbiota changes and immune system development is difficult. HLA molecules susceptibility to T1D was evidenced in some prospective cohort studies.[35-37] Association of MHC class II genes such as DR/DQ and I-A in human mice, to disease, was established for human and mice.[18]

Although T1D is a T cell-mediated disease, the production of autoantibodies was detected during the progression of T1D in candidates.[38] T1D susceptibility is determined with several variables including family history, genetic predisposition, and production of islet antigen autoantibodies. Once individuals at risk identified, following cohort studies to find out environmental factor/s to T1D become possible.[19]

Two studies from Finland using dietary intervention were done to test if the bovine insulin in cow milk has a role in diabetes onset or not.[38] Another study from the FINDIA (Finnish Dietary Intervention Trial for the Prevention of Type 1 Diabetes) resulted that the application of a bovine insulin-free formula during first 6 months of age, decrease the release of β-cell autoantibodies until 3 years old.[39]

Gut microbiota composition in feces of seroconverted compared with nonconverters detected differently. Increase abundance of *Bacteroides*, associated with decreased *Bifidobacterium* species were observed in nonconverters while lactate and butyrate-producing bacteria were characteristic features of seroconverted individuals.[40]

Susceptible HLA molecules to T1D and celiac disease individuals are shared.[41] The German BABYDIET cohort study was examined whether delayed exposure to dietary gluten had a beneficial protective effect on the development of β-cell autoantibodies. No detectable differences in the microbiota composition were found between cases and controls. They concluded that other factors such as geographical site or ethnic background may influence the role of the gut bacteria in both protection or sensitivity to diseases.[42]

An international cohort study of the Environmental Determinants of Diabetes in the Young (TEDDY) tested 8000 children from Finland, Sweden, Germany, and the U.S. was conducted to test the impact of the gut microbiota on pancreatic autoimmunity. The study resulted in the influences of the geographic factor in the shaping of the microbiota constitution. Children from Colorado and Finland have had considerably less varied microbiota than children from Germany, Sweden, and Washington state. Bacterial genera *Bifidobacterium* was abundant in 10 months age of infants from Sweden and Washington, whereas *Clostridium*, *Bifidobacterium*, and *Veillonella* were most clearly abundant in infants from Germany and from states of Florida and Georgia.[43] These data suggest that microbiota based treatment should take the geographic location influences in the microbiota composition under consideration.

Another cohort study examined 76 subjects of T1D child in Turku (Finland), their results found a greater abundance of *Bacteroides dorei* in islet autoantibodies positive subjects.[44] In the DIABIMMUNE cohort study of Finnish and Estonian individuals, from 11 seroconverted children, four of whom developed diabetes during the study period, plus 22 nonseroconverted children were subjected to 16S rRNA sequencing. Decreased microbiota variety and bacterial gene content were detected in serological-positive children during T1D development. Exclusively, decrease the number of *Veillonellaceae* and *Lachnospiraceae* with increased *Streptococcus*, *Blautia*, and *Ruminococcus* genera were observed in diabetic children. Analysis of metabolites from bacterial gene content displayed that multiple genes are required for glucose metabolism while fewer genes required for the biosynthesis of an amino acid.[45]

Another cohort study examined children from Finish, Estonian, and Russian, found that there is no association between gut microbiota composition and TID. The authors were focused on the source of LPS biosynthesis. They concluded that *Bacteroides* are the main source of LPS in Finnish and Estonian children, whereas in Russian children *Escherichia coli* was a responsible source of LPS. Moreover, LPS derived from *E. coli* have more immunostimulatory and induced endotoxin tolerance than *Bacteroides* LPS. They suggest that experience to LPS during early life may add a beneficial protection value leading to a decreased immune response to autoantigens.[2]

The interaction between innate immunity and the gut microbiome is taken through recognition of pathogen-associated molecules patterns (PAMPs) such as LPS by pattern recognition receptors such as Toll-like receptors. Previous studies established that the failure of innate immunity to sense microbial peptides may enhance T1D development.[8,20]

Recent studies confirmed that the gut microbiota has an important contribution in order to ameliorate immune-mediated diseases. Cohort studies in humans revealed that impaired microbiota diversity or dysbiosis is accompanied by an increased incidence of autoimmune diseases. Human cohort studies conducted in T1D individuals observed a decrease in microbiota diversity and dysbiotic flora contents. Moreover, any external influence leads to change at the level of gut microbiota composition mediate autoimmune destruction was not well clear.[46] More studies are required to examine how changes in the gut mediated by microbial signals, play a role in the development of anti-islet immunity. More specifically, studies focus on different susceptible mechanisms of microbial peptides and metabolites to control the immune responses via inflammatory or regulatory conditions are needed.

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