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The Influence of the Microbiome on Type 1 Diabetes

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Type 1 diabetes (T1D) is characterized by the autoimmune destruction of pancreatic β cells. The rapid rise in T1D incidence during the past 50 y suggests environmental factors contribute to the disease. The trillion symbiotic microorganisms inhabiting the mammalian gastrointestinal tract (i.e., the microbiota) influence numerous aspects of host physiology. In this study we review the evidence linking perturbations of the gut microbiome to pancreatic autoimmunity. We discuss data from rodent models demonstrating the essential role of the gut microbiota on the development and function of the host's mucosal and systemic immune systems. Furthermore, we review findings from human longitudinal cohort studies examining the influence of environmental and lifestyle factors on microbiota composition and pancreatic autoimmunity. Taken together, these data underscore the requirement for mechanistic studies to identify bacterial components and metabolites interacting with the innate and adaptive immune system, which would set the basis for preventative or therapeutic strategies in T1D. *The Journal of Immunology*, 2017, 198: 590–595.

The recent recognition that an individual's intestinal microbial community may modify risk for type 1 diabetes (T1D) has emerged from a rich history of investigation into the multifactorial causes of the disease. The acute clinical consequences of diabetes mellitus have been documented in the medical literature for centuries. Following the discovery of insulin at the University of Toronto in the early 1920s, treatment of T1D patients with the purified hormone dramatically improved the primary disease symptoms. However, it would take another half-century of work to firmly establish that a disease characterized by profound metabolic dysfunction resulted from an autoimmune destruction of insulin-producing cells. A new, and at inception unorthodox, focus on associations with HLA polymorphisms was crucial to building the paradigm that T1D results from a T cell mediated autoimmune attack on pancreatic β cells (1, 2).

The most widely used animal model for the study of T1D is the NOD mouse model. The NOD model displays significant

similarities with the human disease both in terms of pathogenesis, the autoantigens being recognized, and genetic susceptibility loci (reviewed in Ref. 3). Genetic and DNA sequence analysis in humans and the NOD mouse model demonstrated that the most potent inherited determinant of susceptibility to T1D were variants in the MHC class II genes encoding DQ β -chain and I-A β -chain (4, 5). Functional studies in mouse models then provided direct evidence that the T1D-associated class II variants impact the presentation of islet-derived peptides to T cells. Although MHC haplotypes are key contributors to T1D risk, they clearly act in concert with multiple non-MHC genetic factors. Genome-wide association studies have identified over 50 human T1D susceptibility regions that control disease risk (6, 7). Similar studies in the NOD mouse model uncovered multiple non-MHC susceptibility genes, several of which were also associated with diabetes risk in humans (e.g., *CTLA-4*, *PTPN22*, *IL2RA*) (8), supporting the relevance of the NOD mouse model for investigation of dysregulated immune pathways in the disease.

What the identification of human genetic risk variants does not explain is the sharp rise in T1D incidence and change in age at onset over the past 50 y. Evidence of increasing prevalence of childhood T1D emerged from European data beginning after the Second World War (9–11). Studies confirm an annual increase averaging 3% in both low and high incidence countries between 1960 and 1996 (12). Equally striking is the increased frequency of T1D diagnosed in very early childhood (10). Recent reports from international prospective birth cohort studies demonstrate the appearance of anti-islet Abs in children carrying high risk *HLA* haplotypes during the first year of life (13, 14). Rapid change in disease incidence among genetically stable populations points to recent, dynamic environmental factors acting in concert with heritable T1D risk. Given the autoimmune basis of the disease, these factors ultimately tune immune responses, particularly in early post-natal life, increasing the probability of responses to islet Ags. These environmental factors are not yet defined. In this study, we discuss the burgeoning evidence in rodent models and in prospective studies of at-risk children that the composition of the intestinal microbial community has likely been impacted by improved public health, and the use of antibiotics in agriculture

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Abbreviations used in this article: ABX, antibiotic; CR, cathelicidin-related; GF, germ free; SCFA, short chain fatty acid; SPF, specific pathogen free; T1D, type 1 diabetes; TEDDY, The Environmental Determinants of Diabetes in the Young.

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and for treatment of childhood illnesses over the past seven decades. Elegant studies in rodent models demonstrate that the gut microbiota have essential effects on the development and function of the host's mucosal and systemic immune systems (reviewed in Ref. 15). The understanding of this fundamental interaction between commensal microbes and human immunity, coupled with the rapid advancement in approaches to characterize the genomic composition and begin to predict the function of these organisms, provide the framework necessary to address the role of the gut microbiome in T1D development.

The influence of the microbiome in animal models of T1D

Rodent models, particularly the NOD mouse, have provided a wealth of data regarding the complex genetic etiology and breakdown of immunological tolerance in T1D. NOD is an inbred mouse strain with a high incidence of spontaneous autoimmune diabetes. Diabetes in the NOD mouse shares many features with multiple aspects of human T1D, including genetic susceptibility, immunopathogenesis, and responsiveness to environmental influences.

Like human T1D, T1D in NOD mice is polygenic; over 20 insulin-dependent diabetes loci have been identified in the NOD mouse model of T1D (16). Several of these loci, and the pathways in which they act, are shared with human T1D risk variants. In both NOD mice and humans, the MHC haplotype, particularly the class II genes I-A in the mouse and DR/DQ in humans, contribute the greatest component of genetic risk for T1D, but are not sufficient to confer the disease (5, 17).

The immunopathology seen in NOD T1D mirrors key aspects of T1D in humans: prior to T1D onset, APC and lymphocyte infiltration of the islets, termed insulinitis (18), can be observed. Furthermore, islet auto-Ab production (19), an important preclinical phenotype in T1D pathogenesis in humans, is also present in NOD mice, with multiple shared specificities.

Interestingly, T1D incidence in the NOD mouse is highly dependent on environmental exposure. Early in the study of the NOD model, researchers noted that T1D incidence in NOD mice was strongly affected by the colony hygiene status (20, 21), and exposure to a wide range of microbes and microbially derived products could suppress T1D. In light of inconclusive associations between hygiene and T1D incidence in the human population, these observations prompted studies into the effects of microbial exposure and colonization on T1D in the NOD model.

TLRs detect exposure to pathogen-associated molecular patterns and regulate host immune responses. MyD88 is a common adaptor protein for multiple TLRs, as well as IL-1R, making it a crucial molecule for innate immune sensing, and likely important in immune-microbial cross-talk. To investigate the role of microbial exposure and innate immune sensing in T1D, NOD mice genetically deficient in MyD88 (NOD.*MyD88*^{-/-}) were generated and raised under specific pathogen free (SPF) or germ-free (GF) conditions (22). NOD.*MyD88*^{-/-} mice were protected from T1D under SPF but, surprisingly, not under GF conditions. These results suggested that MyD88-dependent signaling was important for T1D development, and that the protective effect of MyD88 deficiency was dependent on the presence of microbiota. Furthermore, high-throughput sequencing of gut bacterial 16S

ribosomal rDNA showed that MyD88 deficiency resulted in altered gut microbiota compared with NOD animals, and colonization of GF NOD mice by cohousing with SPF NOD. *MyD88*^{-/-} animals resulted in reduced insulinitis, suggesting colonization by NOD.*MyD88*^{-/-}-associated microbiota was T1D protective.

These data provided the first clear links between innate sensing of the microbiota, the resulting alterations in microbiota composition, and T1D development in the NOD mouse (22). Analysis of several TLR signaling-knockout NOD animals under GF conditions helped to refine the possible roles of TLRs in immune-microbial cross-talk and T1D. TLR4 and TLR2 microbiota-dependent signaling were found to mediate T1D protection and increased susceptibility, respectively (23). It is still unclear if TLR signaling is directly T1D protective, or if it results in microbiota modulation, which has downstream or feedback effects on the host. Subsequent studies further explored potential mechanisms of microbiota modulation of host physiology, and downstream effects on T1D immunopathology.

Sex-microbiome interaction in T1D

Many human autoimmune diseases display a strong female bias, whereas isolated T1D does not. The mechanisms that control these sex-dependent differences in auto-immunity are poorly understood. Although a sex bias is not observed in most human T1D, NOD mice exhibit a sex bias (greater in females than males) (20) in T1D incidence. Under GF conditions, male NOD mice have similar T1D incidence to females, suggesting that the sex bias is microbiome dependent (24). In NOD mice, microbiota composition is similar between males and females until divergence around puberty. Surprisingly, the transfer of adult male (M→F) but not adult female (F→F) intestinal microbiota into weanling-age female NOD mice by oral gavage resulted in durable changes in recipient gut microbiota composition and, significantly, protected them against T1D. M→F NOD mice also showed increased serum testosterone levels and alterations in other serum metabolites. Furthermore, T cell adoptive transfers into NOD.SCID mice showed T cells from M→F NOD mice were delayed in their ability to induce T1D, suggesting changes in the microbiota could alter T cell pathogenicity. Interestingly, all the effects of male microbiome transfer were testosterone dependent, as treatment of recipients with an androgen receptor antagonist abrogated changes in metabolites and protection against anti-islet autoimmunity. These data suggested that there is a window in early life for durable modification of the gut microbial community, and induced changes in the gut microbiota composition can result in changes in host hormones, leading to downstream metabolite modulation, altered immune cell function, and T1D protection.

A subsequent study confirmed that microbiota composition diverges near puberty, and that the sex differences were absent when comparing castrated adult NOD males to females (25). Moreover, colonization of GF NOD mice by specific bacterial taxa (*Enterobacteriaceae* and *Segmented Filamentous Bacteria*) that were enriched in SPF males versus females induced an elevation in testosterone levels. These data further confirmed a hormone-dependent window of microbiome development, and the importance of microbial colonization in modulating host hormone levels.

These studies demonstrate that transfer of microbiota in young prepubescent mice can result in durable changes in microbiota composition and T1D protection, suggesting an early life window for the microbiome modulation of the immune system and T1D susceptibility. As we will discuss in the context of human cohort studies, microbiome is heavily influenced in early life by a number of environmental factors, including mode of delivery, maternal and offspring diet, and antibiotic treatment.

Antibiotic perturbation of the microbiota in T1D

Antibiotic (ABX) use in agriculture and medicine has increased substantially over the past 50 y and is implicated in the concurrent rise in diseases, including obesity and susceptibility to enteric pathogens such as *Clostridium difficile* (26, 27). NOD pups born to mothers treated from conception with a broad-spectrum ABX (streptomycin, colistin, and ampicillin) or vancomycin alone displayed an increase in T1D incidence in adulthood (28). 16S rDNA sequencing found major ABX-induced alterations of gut microbiota composition, with the expansion of the genera *Escherichia*, *Lactobacillus* and *Sutterella* and loss of *Clostridiales*, *Lachnospiraceae*, *Prevotellaceae* and *Rikenellaceae*. These changes in the microbial community were correlated with loss of IL-17 producing T cells in the gut lamina propria in ABX-treated mice, suggesting alterations in the microbiome resulted in corresponding changes in the mucosal immune system.

Interestingly, ABX treatment need not be long term to produce similar effects on T1D incidence, microbiota composition, and immune cell phenotypes. Pulsed ABX treatment with the macrolide tylosin in early life resulted in increased insulinitis and T1D incidence in male NOD mice (29). Furthermore, pulsed ABX treatment altered the gene expression associated with sterol metabolism in male mice, as well as innate immunity and T cell differentiation, corroborating the previous studies that suggested microbiome modulation of host hormone production, and innate and adaptive immunity.

Clearly, robust evidence supports microbiome modulation of the mucosal immune system, and the connection between microbiome and T1D immunopathology. However, the signals — molecular, cellular or otherwise — that mediate the connection between the microbiome and extraintestinal sites are still poorly understood. Antimicrobial peptides, expressed primarily in the gut, control commensal microbes and have immunomodulatory effects in the mucosa. Recently, antimicrobial peptides have been implicated in modulating pancreatic autoimmunity in the NOD model. Levels of cathelicidin-related (CR) antimicrobial peptide produced by pancreatic β cells were found to be greater in C56BL/6 compared with NOD mice (30). Exogenous systemic administration of CR antimicrobial peptide suppressed T1D incidence in NOD mice and was associated with augmented frequencies of islet-associated regulatory macrophages and T cells. CR antimicrobial peptide production by β -cells was correlated with short chain fatty acid (SCFA) concentration in the blood and feces of the mice, and administration of supra-physiological levels of SCFA resulted in increased CR antimicrobial peptide production and decreased T1D incidence. Furthermore, perturbations of the microbiome by antibiotic treatment or M \rightarrow F gut microbiota transfer were associated with alterations in islet CR antimicrobial peptide concentration and regulatory cell phenotypes. The authors suggested that microbial metabolites regulate β -cell function

and immune cells in the pancreatic compartment, resulting in control of the immunopathology of T1D. It will be of interest to determine whether physiological levels of SCFA in systemic circulation act through CR antimicrobial peptides, and other antimicrobial peptides, to regulate the function of regulatory T cell and macrophages in pancreatic autoimmunity.

Therefore, evidence from rodent models of T1D provide a clear framework suggesting microbiota colonization events in early life can be modulated by environmental factors, and that manipulation or disruption of these events can have downstream hormonal and metabolic consequences. Furthermore, these changes in host physiology can lead to alterations in both host innate and adaptive immunity, as well as β -cell biology.

These rodent models also provide a unique opportunity to further interrogate the interaction between genetic and microbe-associated T1D risk factors. The recent availability of gene-editing techniques such as CRISPR-Cas will allow investigation of genetic variants of T1D risk genes in vivo, and the humanization of mouse models by selective editing of orthologous genes. Humanization is also possible on the microbial front, as the isolation and culturing of human-derived microbiota continues. Studies in other animal models of human disease have shown that colonization of GF animals with human-derived microbes can recapitulate disease phenotypes. New strains of genetically and microbially humanized mice will be valuable tools for the future study of the interaction between human genetic variants and commensal organisms, and could be used to test the impact of specific organisms or consortia on T1D susceptibility and pathogenesis.

Human studies link gut microbiota composition to T1D risk

The gut microbiome goes through a period of intense remodeling from birth until 3 y of age when it transitions to an adult-like composition (31). The infant's microbiome depends on delivery mode (32) and is influenced during infancy and early childhood by breastfeeding (33), the introduction of solid foods (31), and administration of antibiotics (34). Given the continuous cross-talk between the microbiome and the mucosal and systemic immunity, investigating the impact of these disruptions on the developing immune and endocrine systems is paramount. Longitudinal cohorts have been established to examine metabolic, immunologic, and microbiome-related parameters from an individual across multiple time points. These studies are designed to address issues such as the microbiota development under the influence of various environmental, dietary, and lifestyle factors and the impact it has on pancreatic autoimmunity.

Although it is difficult to pinpoint individual causal factors, the early childhood period of dynamic changes of the microbiota and immune system coincides with the first measurements of autoantibodies associated with T1D as evidenced by prospective birth cohort studies of children with high risk HLA haplotypes (13, 35–37). T1D is a T cell-mediated disease; however, the development of autoantibodies is a major event in the progression toward T1D in a susceptible individual (38). T1D risk is calculated based on multiple variables, including family history and genetic risk, age, and the presence of autoantibodies against one or more islet Ag groups. Identifying at-risk individuals before disease onset is key for establishing longitudinal study cohorts, which are essential for uncovering the environmental determinants to autoimmunity.

Longitudinal cohort studies of microbiome composition and T1D risk

T1D incidence varies widely across the globe with Scandinavian countries displaying some of the highest incidences in the world (39). The >10-fold difference in diabetes incidence across Europe is only partly explained by the differences in high-risk HLA allele distributions (40). For example, there are striking differences in the rate of T1D in the genetically similar populations of Estonia, Finland and Russian Karelia, which has prompted comparative population studies to investigate the environmental triggers of T1D discussed below.

Two dietary intervention studies were established in Finland to test the hypothesis that bovine insulin present in cow milk protein is a diabetogenic factor (41). In the TRIGR (Trial to Reduce IDDM in the Genetically at Risk) study (42) exposure to foreign dietary proteins was postponed until 6–8 mo of age and the development of autoantibodies was monitored until the age of 6 y. Results from the FINDIA (Finnish Dietary Intervention Trial for the Prevention of Type 1 Diabetes) pilot study indicate the use of a bovine insulin-free formula during the first 6 mo of life decreased the appearance of β -cell autoantibodies at the age of 3 y (43). A cross-sectional study based on these longitudinal cohorts compared the gut microbiomes of 18 children who tested positive for autoantibody and 18 autoantibodies-negative controls (44). An increased abundance of *Bacteroides*, decreased *Bifidobacterium* species and a lower abundance of lactate- and butyrate-producing bacteria characterized the microbiotas of children who seroconverted compared with nonconverters (44).

Certain high-risk HLA haplotypes are shared between celiac disease and T1D patients (45). The German BABYDIET cohort was initiated to investigate whether delayed exposure to dietary gluten could delay development of β -cell autoantibodies (46). Although no protective effect was found, a longitudinal analysis of the gut microbiota of 22 autoantibody-positive and 22 autoantibody-negative BABYDIET study children revealed altered bacterial interaction networks at the ages of 6 and 24 mo (47). In contrast to the Finnish studies, however, no differences were observed in fecal microbiota diversity or composition between cases and controls. This contrast in outcomes may indicate that similar to the population stratification issue encountered by genome-wide association studies, other variables such as geographical location or ethnicity may preclude the identification of predisposing or protective bacteria across multiple populations.

The Environmental Determinants of Diabetes in the Young (TEDDY) cohort (48) has enrolled over 8000 children with high-risk HLA haplotypes from the U.S., Germany, Sweden, and Finland, and is well positioned to address the question of microbiome heterogeneity and its impact on pancreatic autoimmunity. Indeed, a pilot study of 90 high-risk, prediabetic infants from the TEDDY cohort revealed strong geographical influences on the microbiome composition (49). The early-life microbiomes of children from Finland and Colorado were significantly less diverse than subjects from Sweden, Germany, and Washington state (49). *Bifidobacterium* dominated the microbiota of infants up to 10 mo of age from Sweden and Washington, whereas subjects from the states of Georgia and Florida and from Germany displayed greater abundances of *Clostridium*, *Bifidobacterium*, and *Veillonella* (49). These differences in diversity and composition remained significant after adjustment for early-life and lifestyle variables and suggest

that future microbiome-based therapeutic strategies should be tailored based on geographical location.

A longitudinal gut microbiome analysis from 4 to 26 mo of age in 76 children from the Type 1 Diabetes Prediction and Prevention project from Turku (Finland) found an increased abundance of *Bacteroides dorei* in the children who seroconverted to display autoantibodies compared with nonconverters (50). The abundance of *B. dorei* peaked at 7.6 mo of age in autoantibody-positive children and preceded the appearance of the first anti-islet autoantibodies (50). The same authors later examined the *B. dorei* genome methylation status in stool samples from one case and one control Type 1 Diabetes Prediction and Prevention subject containing high abundances of this bacterium (51). DNA adenosine methylation of the 5'-GATC-3' motif in bacterial genomes regulates gene expression and has been associated with increased bacterial virulence (52). The *B. dorei* genome from the control subject included no DNA methylation sites, whereas in the seroconverted child more than 20,000 methylated sites were found (51). These preliminary findings suggest that in addition to taxonomic composition, microbial gene expression needs to be examined to begin to address microbiome function even when there is no evidence of differential abundance of taxonomic groups.

The DIABIMMUNE cohort study was initiated in 2008 to examine the environmental causes underlying the 6–7-fold higher incidence of autoimmune and allergic diseases in Finland compared with neighboring Russian Karelia (53). This project is designed to test the hygiene hypothesis in T1D in communities with different public health standards. DIABIMMUNE has recruited newborn infants with defined HLA risk haplotypes associated with autoimmunity from Finland, Estonia, and Russian Karelia and collected longitudinal blood and stool samples from 1 mo to 3 y of age along with extensive clinical metadata (53).

An initial analysis of the gut microbiome in the DIABIMMUNE cohort focused on Finnish and Estonian subjects (54). The gut microbiomes of 11 children who developed islet autoantibodies, four of whom became diabetic during the study period, were analyzed together with 22 children who remained autoantibody-free using 16S rRNA sequencing as well as microbial metagenomics. A decrease in microbiome diversity and reduced bacterial gene content were found in autoantibody-positive children during progression to T1D (54). Specifically, a decrease in *Lachnospiraceae* and *Veillonellaceae* was observed in children who became diabetic, accompanied by an increase in *Streptococcus*, *Blautia*, and *Ruminococcus* genera. Functional analysis predicted from bacterial gene content revealed that bacterial metabolism in autoantibody+ subjects was characterized by a greater abundance of genes involved in sugar transport and fewer genes for amino acid biosynthesis (54). Correlation between fecal bacterial abundance and host serum metabolites suggested that the microbiota of children who developed T1D may be linked to an inflammatory environment conducive to autoimmunity (54).

A subsequent DIABIMMUNE cohort study reported metagenomic characterization of the fecal microbiomes of 222 Finnish, Estonian, and Russian children. The goal was to identify factors associated with the risk of atopy and islet autoimmunity (14). In this study, there were no correlations between islet autoantibodies or T1D status with microbiome composition. The authors reported associations between microbiome taxonomic composition and gene content with geographical location

and considered this a proxy for higher (Finland and Estonia) or lower (Russia) predisposition to immune-mediated diseases. In the early-life microbiome, there were differences between the three locations in abundance of genes associated with the utilization of human milk oligosaccharides from breast milk. Finnish and Estonian infant human milk oligosaccharides were mainly associated with *Bacteroidetes* whereas this function was associated with *Bifidobacteria* in the Russian children (14). This difference in bacterial colonization of the infant gut was associated with microbiome composition later in life, leading the authors to suggest that the higher probability of atopy/autoimmunity in Finnish and Estonian compared with Russian children is associated with an increased abundance of *Bacteroides* species in infancy and early childhood (14). Whether the presence of *Bifidobacteria* conferred protection from immune-mediated diseases in Russian children is still unknown, however, the *Bifidobacterium* species is one of the main components of probiotic preparations available. A recent report from the TEDDY study group revealed that in children with the high-risk *HLA-DR3/4* genotype, administration of probiotics during the first 27 d of life was associated with a 60% reduction in the autoimmunity risk (55).

In terms of predicted microbial function, the DIABIMMUNE study authors focused on the geographical disparities in terms of LPS biosynthesis (14). In Finnish and Estonian children *Bacteroides* were predicted to be the main source of LPS, whereas in Russian subjects LPS may be mainly derived from *Escherichia coli*. Exposure of healthy donor peripheral blood cells to these two sources of LPS revealed that *E. coli*-derived LPS was more immunostimulatory and induced endotoxin tolerance compared with *Bacteroides* LPS. The authors suggested that early exposure to LPS tunes immune responses to subsequent Ag exposures such that signals from stimulatory microbes, like *E. coli*, dampen the immune response to autoantigens and protect from autoimmunity (14). This is an interesting idea that will be pursued as the study cohort continues to mature.

Recognition of LPS and other bacterial components by pathogen recognition receptors is one aspect of the complex cross-talk between the innate immune system and the gut microbiota. Previous studies in NOD mice with defects in various innate immunity-sensing pathways provide mechanistic evidence that abnormal sensing of certain members of the microbiota may promote the development of T1D (22, 23). To elucidate how changes in microbiome composition and function affect diabetes risk in genetically predisposed individuals, future human studies should investigate the cellular players responding to bacterial signals and the mechanisms by which they promote autoimmunity in a distant organ.

A great advantage of prospective longitudinal studies is that they allow the investigation of whether the changes in microbiome composition precede, accompany, or follow the development of T1D. However, establishing a causal relationship between microbiome alterations and autoimmunity in human cohort studies is challenged by the complexity of the microbiota-immune system interaction. Recent findings from heterogeneous populations recruited in multinational studies such as TEDDY (49) observed significant differences in microbiota composition in children at-risk for T1D from the different study sites. Furthermore, the taxonomic composition of the gut microbiota is an important component of these human studies but provides limited mechanistic insight into microbial contributions

to autoimmune disease. Increasingly the focus is shifting to analysis of the microbial genomes, transcripts, metabolites, and their antigenic potential to elucidate how the presence of detrimental microbes or absence of beneficial ones promotes autoimmunity in tissues distant from the intestine.

Taken together, the findings from human cohorts support the existing hypothesis emerging from animal models, i.e., that a continuous dialog exists between the resident gut microbiota and the immune system (56). Beginning with the gestational environment and continuing with infancy and early childhood, the multiple microbial cues promote the development of the immune system, readying it to cope with a more complex microbiota and potential pathogens (57). In the context of this intimate relationship, a microbiome imbalance can lead to autoimmunity in a genetically susceptible host, unable to prevent the development of autoreactive cells.

Conclusions

Recent findings underscore the role of the gut microbiota as a critical factor involved in the development of immune-mediated diseases. Longitudinal studies in humans suggest that individuals progressing to T1D exhibit a decrease in microbiota diversity and intestinal dysbiosis characterized by loss of beneficial organisms. However, the mechanisms by which alterations in the gut microbiota mediate tissue-specific autoimmunity are not yet understood. Future studies are needed to investigate how microbially derived signals are broadcast from the mucosal environment to islet-specific reactivity. These studies should address the interaction of microbial components and metabolites with the adaptive immune system resulting in T cell reactivity to islet Ags.

Disclosures

The authors have no financial conflicts of interest.

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