HHS Public Access

Author manuscript

Pharmacol Res. Author manuscript; available in PMC 2016 August 01.

Published in final edited form as:

Pharmacol Res. 2015 August ; 98: 9–15. doi:10.1016/j.phrs.2015.02.006.

Type 1 diabetes and gut microbiota: friend or foe?

Changyun Hu[1], **F. Susan Wong**[2], and **Li Wen**[1]

[1]Section of Endocrinology, Department of Internal Medicine, Yale School of Medicine, New Haven, USA

[2]Institute of Molecular and Experimental Medicine, Cardiff University School of Medicine, Cardiff, UK

Abstract

Type 1 diabetes is a T cell-mediated autoimmune disease. Environmental factors play an important role in the initiation of the disease in genetically predisposed individuals. With the improved control of infectious disease, the incidence of autoimmune diseases, particularly type 1 diabetes, has dramatically increased in developed countries. Increasing evidence suggests that gut microbiota are involved in the pathogenesis of type 1 diabetes. Here we focus on recent advances in this field and provide a rationale for novel therapeutic strategies targeting gut microbiota for the prevention of type 1 diabetes.

Type 1 diabetes (T1D) is an autoimmune disease characterized by the immune cell-mediated destruction of insulin-secreting pancreatic beta cells in genetically predisposed individuals upon environmental stimulation. The interaction between pancreatic β-cells and immune cells leads to the development of T1D (1). Strategies targeting cells or signaling pathways of immune system have been proven effective in preventing and reversal of T1D (2–7). Nevertheless, over the past few decades, there has been a steady 3~4% increase in the incidence of T1D, particularly in young children, in developed countries (8). Although genetic factors, especially genes in the HLA region, can predispose an individual to T1D, twin and family studies show that only a fraction of those genetically predisposed individuals will develop the disease (9–11). The cumulative incidence among monozygotic co-twins of persons with T1D is less than 50 % (11). Comparison of the frequency of HLA class II haplotypes in patients diagnosed more than 50 years ago with age and sex-matched patients between 1985 and 2002 suggests that the impact of environment on children with lower-risk HLA class II genes accounts for the rising incidence and decreasing age at diagnosis of T1D (12, 13). Thus, it is strongly believed that environmental factors are important for the development of T1D (14). Furthermore, environmental factors participate in the initiation, as well as various stages of the natural history of the T1D (15, 16).

Correspondence: li.wen@yale.edu.

Conflict of Interest: the authors declare no conflict of interest

There have been a variety of environmental factors, including viral infection and diet, suggested to promote T1D. A recent study provides evidence for the presence of enterovirus in pancreatic islets of newly diagnosed patients with type 1 diabetes (17), suggesting that a low-grade enteroviral infection in the pancreatic islets contributes to disease progression in humans. Consistent with the detection of virus in islets, virus-responsive interferon responsive factor 7 (IRF7) network genes and their regulatory locus are implicated in the pathogenesis of T1D by integrated genome-wide approaches (18). Coxsackie B virus (CVB) infected engrafted human islets in mice contain viral RNA, express viral protein, and show reduced insulin production compared to the grafts from uninfected mice (19). These observations imply that viral infection may trigger islet autoimmunity. In addition to virus, it has also been shown that various foods or food components such as cow's milk and gluten affect the development of T1D (20–23). The insulin from cow's milk may activate insulin-specific autoimmunity before the establishment of oral tolerance (22, 23). Other components from cow's milk, such as casein, can alter gut permeability and potentially promote the incidence of T1D (22, 23). Food-derived gluten has also been shown to modify gut permeability and again potentially affect the development of T1D (20, 21). Interestingly, mice treated with a gluten-free diet showed modifications in gut microbiota and protection from T1D (20, 21). Consistently, accumulating studies showed in recent years the involvement of environment factors, particularly an association with gut microbiota, in the pathogenesis of T1D.

In this review, we will focus on the possible roles of gut microbiota in the development of T1D and provide the notion of using prebiotics, probiotics or even antibiotics as a potential strategy for the prevention of T1D.

Understanding the Gut microbiota

Gut microbiota and host have a symbiotic relationship due to their co-existence and co-evolution. On one hand, gut microbiota depend on the host for their growth and survival. On the other hand, most of the gut microbiota are non-pathogenic and can benefit the host in many ways: 1) extraction of nutrients and energy from diet intake (24–26), 2) protection from enteropathogen invasion (27), 3) contribution to the development of a normal immune system or function (28–30). In contrast, the imbalance between the gut microbiota and the host has been associated with many diseases including malnutrition (26), obesity (31–34), autoimmune disorders (35–40) and neurological diseases (41, 42). Thus, an understanding of how the gut flora may affect health and disease will provide an insight into how to promote health by the modification of gut microbiota.

The inability to culture the majority of the gut microbiota in the past had hindered our understanding of the microbial communities. With the advent of high-throughput sequencing technology, it has dramatically speeded up the dissection of the symbiotic relationship between gut microbes and their host. Several large-scale projects such as the US Human Microbiome Project and the European Metagenomics of the Human Intestinal Tract have substantially contributed to the understanding of healthy composition and functional states of gut microbiota (43–47). The analysis of 16S rRNA gene sequences of bacteria from human stool samples has identified that the majority of gut microbial populations comprise

bacteria from four main phyla: *Bacteriodetes*, *Firmicutes*, *Actinobacteria* and *Proteobacteria* (48). The results from metagenomics analysis also provided information about the functional properties of gut bacteria, particularly the important function of low-abundance gut microbes, involved in an array of physiological processes (47, 49). Furthermore, the metabolomics analysis revealed the effect of metabolites derived from microbiome on their host (50). Equipped with knowledge at different levels, we are gaining better recognition about the importance of gut microbiota in our health.

Gut microbiota and type 1 diabetes

During the last decade, there has been considerable research activity and a sharp increase in the amount of experimental data on the role of gut microbiota in health and disease. Of note, gut microbiota play an important role in the regulation of autoimmunity and tolerance (36, 39, 40, 51). However, the contribution of gut microbiota to the development of T1D remains limited, although involvement of the microbiota has been suggested in the development of T1D as early as 1987 (52). Following on from this, experiments using NOD mice that were transferred from specific pathogen-free (SPF) conditions to germ free (GF)-conditions showed a marked change in insulitis and the incidence confirmed the role of gut microbiota as a regulator of islet-specific autoimmunity (53, 54).

The first gut microbiota study in humans for T1D compared the microbiome between 4 Finnish children with T1D and 4 age- and HLA-DQ-matched healthy children (55, 56). By employing the16S rRNA pyrosequencing method, lower diversity and stability of the fecal microbiome was identified in the children in their first year of life who later went on to develop T1D when compared with the healthy control subjects (55). Recent data from the Human Microbiome Project also imply that higher diversity and stability of the gut microbiome is associated with health (46). Furthermore, in the follow-up study, those Finnish children who developed T1D had a decreased ratio of *Firmicutes* vs *Bacteroidetes*, supporting a cross-sectional study showing that *Bacteroidetes* were more abundant in islet-specific autoantibody-positive children than in autoantibody-negative children (57, 58). All the evidence from both animal and human studies thus far further supports the involvement of gut microbiota in the development of T1D. There are several mechanisms by which gut microbiota could affect the development of T1D as discussed below.

Alteration of intestinal permeability

Heightened gut permeability has been demonstrated to be one of the phenomena that precede the clinical onset of T1D in both animal models of autoimmune diabetes, as well as in patients with T1D and prediabetic individuals (59–63). Evidence from animal studies has been largely derived from two rodent models: NOD mice and the BioBreeding diabetes-prone (BBDP) rat. It has been suggested that the imbalance of bacteria, such as *Bacteroidetes*, which ferment short-chain fatty acid (SCFA), can affect the gut permeability. Indeed, in parallel to the changed gut permeability, BBDP rats, before clinic onset, have a different gut bacterial composition from that of diabetes-resistant (BBDR) rats, with relatively higher abundance of *Bacterioides* sp in diabetic rat (64, 65). At disease onset, the gut bacterial profile was also different between BBDP and BBDR rats (66). Specifically, the BBDP rats had a lower proportion of the probiotic-like bacteria, such as *Bifidobacterium*

and *Lactobacillus*, but had higher numbers of *Bacteroides*, *Ruminococcus* and *Eubacterium* (66). At the cellular level, there were also structural changes in the intestinal morphology, such as greater percentage of goblet cells and mucosal crypt depth, accompanying the increased permeability in BBDP rats (59, 62, 67). At the molecular level, the expression of multiple tight junction proteins was down- or up-regulated, in both BBDP rats and T1D patients, thus affecting the gut permeability, including occludin, members of claudin family and zonulin (61, 67, 68).

However, there is not much evidence, thus far, suggesting that the gut microbiota are actually responsible for the cellular and molecular changes in gut. Nevertheless, a study has shown that the metabolites of gut microbiota, such as butyrate, an anti-inflammatory factor, can affect gut permeability by enhancing the gut barrier function via tight junctions (69). In the children with beta cell autoimmunity, there was a low abundance of butyrate-producing bacteria including *Clostridium* clusters XIVa and IV (55–57). Butyrate can be metabolized from lactate. Children with T1D also have low numbers of lactate-producing bacteria, such as *Bifidobacterium adolescentis* (57). Those studies provided supporting evidence that gut microbiota could affect gut permeability through their metabolites. Nevertheless, gut permeability is only an index for the later possible beta cell autoimmunity. Although both BBDP and BBDR rats showed transient increases in gut permeability during early life, only BBDP rats that exhibited morphological changes and inflammation in intestine developed the disease (59), which implies that the enteropathy is fundamentally linked to the disease development. Thus, we have to be cautious in interpreting the gut permeability data in this setting.

Modification of intestinal immunity

Gut microbiota are essential for healthy development of the mammalian immune system (70). Direct evidence comes from germ-free mice, in which multiple defects in the gut immune system have been noted, including impaired development of gut-associated lymphoid tissue (GALT) (71), generation of colonic regulatory T cells (72) and production of IgA (73). Importantly, the profound effects that commensal microbiota have on immunity is not limited to the gut immune system, but extends to the systemic immune response (74). Germ-free mice have an elevated IgE level and overall are skewed toward Th2 immune responses, which can be normalized by exposure to a diverse microbiota during early life (75). Interestingly, administration of *Bacteroides fragilis*-derived polysaccharide A (PSA) to GF mice can correct the Th1/Th2 imbalance in the spleen (74).

Although the various mechanisms by which gut microbiota regulate host immunity are, as yet poorly elucidated, a couple of mechanisms have been proposed: 1) directly activating the innate immune response through Toll-like receptors (TLR) by molecular patterns from gut bacteria (76–79); 2) modulating immune responses via G-protein-coupled receptor (GPCR) by bacterially-derived metabolites (80, 81). The activation of innate immune responses by gut microbiota-derived molecular patterns that are mostly bacteria cell wall components such as flagellin (78, 82) and PSA (79), as well as commensal genomic DNA (77). For example, mice that are deficient in the flagellin receptor, TLR5, develop metabolic syndrome in a gut microbiota-dependent manner (82). The transfer of gut bacteria from

TLR5-deficient mice into germ-free mice leads to development of many features of the metabolic syndrome in the recipients (82). This suggests that malfunction of the innate immune system may promote the development of metabolic syndrome through modification of the gut bacterial profile. On the other hand, *Bacteroides fragilis*-derived PSA, a TLR2 ligand, can induce IL-10-producing CD4 T cells and reciprocally suppress Th17 responses, thus protecting against experimental colitis (79). Similarly, TLR9-deficient mice display an elevated frequency of $Foxp3^+$ Treg at intestinal effector sites and suppressed constitutive IL-17- and IFN-γ-producing effector T cells (77). Further mechanistic studies indicate that DNA from gut flora plays a major role in intestinal homeostasis through TLR9 engagement (77). In the NOD mouse model of T1D, we also demonstrated that a deficiency of the master adaptor protein MyD88 led to resistance to the development of T1D through the modification of gut bacteria (54). All the observations imply that different innate immune-activating components of gut bacterial origin have a different role in the regulation of gut immune homeostasis and our results provide the first evidence of the “missing” link between gut microbiota and innate immunity with T1D development.

Similar to the diet-independent components, diet-dependent gut bacteria-derived metabolites, such as short-chain fatty acid (SCFA) and vitamins, have far-reaching effects on the immune responses (70, 83). SCFAs are produced through fermentation of dietary fiber by gut microbiota, which bind the G-protein-coupled receptor 43 (Gpr43), also called free fatty acid receptor 2 (FFA2/FFAR2). Studies have demonstrated the anti-inflammatory role of SCFAs on immune cells (80, 84, 85). Several SCFAs, including acetate (27, 80, 84), butyrate(84), and propionate (84), have been well characterized as playing a role in gut immune homeostasis. Mice that take in acetate through drinking water display suppressed dextran sulfate sodium (DSS)-induced colitis, inflammatory arthritis and asthma in a Gpr43-dependent manner (80). The oral administration of acetate, butyrate or propionate not only augments population size but also enhances the suppressive function of colonic Treg in SPF mice (84). Among these three SCFAs, butyrate is the most potent inducer of the differentiation of naïve T cells into Treg, while acetate and propionate are important for the migration of Treg to intestine (86, 87). On the other hand, certain *Bifidobacteria* produce B-group vitamins that can activate mucosa-associated invariant T cells and the Jurkat T cell line (88, 89). Although it has been shown that vitamin D plays a role in the development of T1D (90), studies identifying how SCFAs directly affect islet-specific autoimmunity are still lacking.

In humans, more males develop diabetes than females develop T1D after puberty. However, in NOD mice, females develop diabetes earlier and in a greater proportion than the male mice. In NOD mice, the gut microbiota were shown to be involved in the gender bias of T1D and there is sex hormones play a role in altering commensal gut microbiota which influence the development of diabetes through the IFN-γ signaling pathway (35).

It is clear that gut bacteria affect systemic immunity. Mounting evidence also suggests that gut microbiota have profound effects on autoimmunity. Several studies in animal models implied that alterations in the gut microbiota are associated with the development of T1D (54, 59, 91, 92). During early life, BBDP rats have impaired intestinal barrier function that may be the underlying cause for the altered response to luminal antigens, but the intestinal

inflammation might be a trigger that leads ultimately to diabetes development (59, 62). Studies have confirmed the role of gut microbiota as a regulator/facilitator of inflammation in the pancreatic islets. Antibiotic treatment partially protects against T1D in BBDP rats (64, 65). Germ-free NOD mice display an imbalance between Th1, Th17 and Treg differentiation in the intestine (53). This imbalance is associated with accelerated insulitis, which can be interpreted by the shared immune cell homing receptors, such as α4β7-integrin, in the gut and inflamed pancreas (93). Compared with BBDP rats, BBDR rats carry more probiotic-like bacteria in stool, such as *Lactobacillus johnsonii* (66). *Lactobacillus johnsonii* can induce Th17 responses in mesenteric lymph nodes and spleen, thus, affecting the development of T1D (76, 94, 95), although the role of Th17 immunity in T1D has been controversial (96–102). The transfer of gut bacteria from diabetes-resistant MyD88 deficient NOD mice can reduce insulitis and significantly delay the onset of diabetes through the upregulation of IgA and TGF-β production in the intestine (92).

Modifying gut flora to prevent T1D

Existing evidence has suggested the role of dysbiosis in T1D development, including reduced bacterial and functional diversity, which are accompanied by impaired gut barrier function and elevated inflammation due to decreased induction of Treg (55–58). With the improvement in our understanding of the role of gut microbiota in autoimmunity, we can develop therapies targeting intestinal immunity by modification of gut microbiota to prevent T1D development. It has been shown that experimental manipulation of gut microbiota in young NOD mice can significantly protect them from T1D development, which provides proof of concept that therapy targeting gut microbiota is effective in genetically predisposed individuals (38, 92). During infancy, the intestinal environment undergoes major developmental changes and the gut microbiome is extensively remodeled; it later becomes relatively resistant to variation after puberty, due to the regulation by intestinal immunity (25, 103). Therefore, minor modifications at the early stages in life would have profound effects on normal intestinal immune homeostasis in adulthood (104). Previous studies also suggested that neonatal gut immunity plays an important role in controlling the development of diabetes (105, 106). Thus, early life treatment with the antimicrobial drug vancomycin can expand *Akkermansia muciniphila* and reduce diabetes incidence in the NOD mouse (107). Our recent study also demonstrated that the offspring from NOD mothers treated with antibiotics that target gram-negative bacteria had reduced and delayed T1D development (Hu, et al., unpublished data). Neonatal oral administration of DiaPep2, an analogue of HSP60 peptide p277, in combination with hydrolyzed casein diet can protect against T1D in BBDP rats (105). These treatments during early life have a crucial effect on the intestinal barrier function, cytokine production and the development of diabetes (106). Long term administration of “friendly” gut bacteria or the probiotic compound VSL#3 to NOD mice starting from 4 weeks of age could also prevent the NOD mice from T1D development in regulatory cytokine IL-10 or TGF-β dependent mechanism (92, 108). Furthermore, administration of genetically modified gut bacteria can even reverse diabetes. Oral delivery of genetically-modified *Lactococcus lactis* alone or in combination with low dose of systemic anti-CD3 can reverse new-onset T1D in NOD mice (109, 110).

Although administration of gut microbiota can successfully prevent and reverse T1D in animal models, the application of this therapeutic strategy in humans has not yet been tested. One of the obstacles is the lack of reproducible development and manufacture of microbial mixtures with well-defined genetic content and metabolic output such as the one used for *Clostridium difficile* infection treatment (111, 112). Nevertheless, there are studies manipulating microbiota-induced immunoregulation by non-bacterial strategies including diet and/or bacterial metabolites. A gluten-free diet could affect gut microbiota and thus reduce the incidence of diabetes (20, 21). It has been shown that gut microbiota-derived metabolites, such as acetate, butyrate, propionate, can modulate intestinal immunity through induction or recruitment of Treg (80, 84–87). Regulatory T cells are essential for the controlling of islet autoimmunity. Thus, testing the effect of those SCFAs on the development of T1D would be important in future preclinical studies.

Conclusion

A better understanding of how gut bacteria-induced immunoregulation contributes to the pathogenesis of T1D is necessary. The existing evidence is exciting and encouraging in that modulation of gut microbiota can affect the progress of diabetes in preclinical studies. It is likely that the beneficial effects of gut microbes come from both the live bacteria and their metabolites (Figure 1). As an ecosystem, the gut microbiome is a community in which the components affect each other and a balance is important for the health of host. Although “omics” analyses can significant improve our understanding of the profile of gut flora and their metabolites, we have to be cautious in thinking that a single bacterial strain or molecule may be useful as therapeutics. Nevertheless, the advantages of microbial therapies are obvious: less expensive, less invasive and potentially long-lasting beneficial effects. Once we gain a better knowledge of specific host and gut microbial functional pathways involved in the development of T1D, direct or indirect microbiota-based therapies can be developed to prevent or cure T1D.

Acknowledgments

This work was supported by NIH DK-088181, DK092882, JDRF and IACOCCA family foundation.

References

1. Lehuen A, Diana J, Zaccone P, Cooke A. Immune cell crosstalk in type 1 diabetes. Nat Rev Immunol. 2010; 10:501–513. [PubMed: 20577267]
2. Ansari MJ, Fiorina P, Dada S, Guleria I, Ueno T, Yuan X, Trikudanathan S, Smith RN, Freeman G, Sayegh MH. Role of ICOS pathway in autoimmune and alloimmune responses in NOD mice. Clin Immunol. 2008; 126:140–147. [PubMed: 17889619]
3. Guleria I, Gubbels Bupp M, Dada S, Fife B, Tang Q, Ansari MJ, Trikudanathan S, Vadivel N, Fiorina P, Yagita H, et al. Mechanisms of PDL1-mediated regulation of autoimmune diabetes. Clin Immunol. 2007; 125:16–25. [PubMed: 17627890]
4. Ben Nasr M, D’Addio F, Usuelli V, Tezza S, Abdi R, Fiorina P. The rise, fall, and resurgence of immunotherapy in type 1 diabetes. Pharmacol Res. 2014
5. Herold KC, Bluestone JA, Montag AG, Parihar A, Wiegner A, Gress RE, Hirsch R. Prevention of autoimmune diabetes with nonactivating anti-CD3 monoclonal antibody. Diabetes. 1992; 41:385–391. [PubMed: 1532369]

6. Herold KC, Hagopian W, Auger JA, Poumian-Ruiz E, Taylor L, Donaldson D, Gitelman SE, Harlan DM, Xu D, Zivin RA, et al. Anti-CD3 monoclonal antibody in new-onset type 1 diabetes mellitus. N Engl J Med. 2002; 346:1692–1698. [PubMed: 12037148]
7. Hu CY, Rodriguez-Pinto D, Du W, Ahuja A, Henegariu O, Wong FS, Shlomchik MJ, Wen L. Treatment with CD20-specific antibody prevents and reverses autoimmune diabetes in mice. J Clin Invest. 2007; 117:3857–3867. [PubMed: 18060033]
8. Tuomilehto J. The emerging global epidemic of type 1 diabetes. Curr Diab Rep. 2013; 13:795–804. [PubMed: 24072479]
9. Todd JA, Walker NM, Cooper JD, Smyth DJ, Downes K, Plagnol V, Bailey R, Nejentsev S, Field SF, Payne F, et al. Robust associations of four new chromosome regions from genome-wide analyses of type 1 diabetes. Nat Genet. 2007; 39:857–864. [PubMed: 17554260]
10. Barrett JC, Clayton DG, Concannon P, Akolkar B, Cooper JD, Erlich HA, Julier C, Morahan G, Nerup J, Nierras C, et al. Genome-wide association study and meta-analysis find that over 40 loci affect risk of type 1 diabetes. Nat Genet. 2009; 41:703–707. [PubMed: 19430480]
11. Redondo MJ, Yu L, Hawa M, Mackenzie T, Pyke DA, Eisenbarth GS, Leslie RD. Heterogeneity of type I diabetes: analysis of monozygotic twins in Great Britain and the United States. Diabetologia. 2001; 44:354–362. [PubMed: 11317668]
12. Gillespie KM, Bain SC, Barnett AH, Bingley PJ, Christie MR, Gill GV, Gale EA. The rising incidence of childhood type 1 diabetes and reduced contribution of high-risk HLA haplotypes. Lancet. 2004; 364:1699–1700. [PubMed: 15530631]
13. Fourlanos S, Varney MD, Tait BD, Morahan G, Honeyman MC, Colman PG, Harrison LC. The rising incidence of type 1 diabetes is accounted for by cases with lower-risk human leukocyte antigen genotypes. Diabetes Care. 2008; 31:1546–1549. [PubMed: 18487476]
14. Bach JF. The effect of infections on susceptibility to autoimmune and allergic diseases. N Engl J Med. 2002; 347:911–920. [PubMed: 12239261]
15. Trucco M. Gene-environment interaction in type 1 diabetes mellitus. Endocrinol Nutr. 2009; 56(Suppl 4):56–59. [PubMed: 20629235]
16. Todd JA. Etiology of type 1 diabetes. Immunity. 2010; 32:457–467. [PubMed: 20412756]
17. Krogvold L, Edwin B, Buanes T, Frisk G, Skog O, Anagandula M, Korsgren O, Undlien D, Eike M, Richardson SJ, et al. Detection of a low-grade enteroviral infection in the islets of Langerhans of living patients newly diagnosed with type 1 diabetes. Diabetes. 2014
18. Heinig M, Petretto E, Wallace C, Bottolo L, Rotival M, Lu H, Li Y, Sarwar R, Langley SR, Bauerfeind A, et al. A trans-acting locus regulates an anti-viral expression network and type 1 diabetes risk. Nature. 2010; 467:460–464. [PubMed: 20827270]
19. Gallagher GR, Brehm MA, Finberg RW, Barton BA, Shultz LD, Greiner DL, Bortell R, Wang JP. Viral infection of engrafted human islets leads to diabetes. Diabetes. 2014
20. Marietta EV, Gomez AM, Yeoman C, Tilahun AY, Clark CR, Luckey DH, Murray JA, White BA, Kudva YC, Rajagopalan G. Low incidence of spontaneous type 1 diabetes in non-obese diabetic mice raised on gluten-free diets is associated with changes in the intestinal microbiome. PLoS One. 2013; 8:e78687. [PubMed: 24236037]
21. Hansen CH, Krych L, Buschard K, Metzdorff SB, Nellemann C, Hansen LH, Nielsen DS, Frokiaer H, Skov S, Hansen AK. A maternal gluten-free diet reduces inflammation and diabetes incidence in the offspring of NOD mice. Diabetes. 2014; 63:2821–2832. [PubMed: 24696449]
22. Vaarala O. Is type 1 diabetes a disease of the gut immune system triggered by cow's milk insulin? Adv Exp Med Biol. 2005; 569:151–156. [PubMed: 16137120]
23. Kolb H, Pozzilli P. Cow's milk and type I diabetes: the gut immune system deserves attention. Immunol Today. 1999; 20:108–110. [PubMed: 10203699]
24. Sonnenburg JL, Xu J, Leip DD, Chen CH, Westover BP, Weatherford J, Buhler JD, Gordon JI. Glycan foraging in vivo by an intestine-adapted bacterial symbiont. Science. 2005; 307:1955–1959. [PubMed: 15790854]
25. Yatsunenko T, Rey FE, Manary MJ, Trehan I, Dominguez-Bello MG, Contreras M, Magris M, Hidalgo G, Baldassano RN, Anokhin AP, et al. Human gut microbiome viewed across age and geography. Nature. 2012; 486:222–227. [PubMed: 22699611]

26. Kau AL, Ahern PP, Griffin NW, Goodman AL, Gordon JI. Human nutrition, the gut microbiome and the immune system. Nature. 2011; 474:327–336. [PubMed: 21677749]
27. Fukuda S, Toh H, Hase K, Oshima K, Nakanishi Y, Yoshimura K, Tobe T, Clarke JM, Topping DL, Suzuki T, et al. Bifidobacteria can protect from enteropathogenic infection through production of acetate. Nature. 2011; 469:543–547. [PubMed: 21270894]
28. Olszak T, An D, Zeissig S, Vera MP, Richter J, Franke A, Glickman JN, Siebert R, Baron RM, Kasper DL, et al. Microbial exposure during early life has persistent effects on natural killer T cell function. Science. 2012; 336:489–493. [PubMed: 22442383]
29. Ahern PP, Faith JJ, Gordon JI. Mining the human gut microbiota for effector strains that shape the immune system. Immunity. 2014; 40:815–823. [PubMed: 24950201]
30. Turnbaugh PJ, Ley RE, Hamady M, Fraser-Liggett CM, Knight R, Gordon JI. The human microbiome project. Nature. 2007; 449:804–810. [PubMed: 17943116]
31. Turnbaugh PJ, Backhed F, Fulton L, Gordon JI. Diet-induced obesity is linked to marked but reversible alterations in the mouse distal gut microbiome. Cell Host Microbe. 2008; 3:213–223. [PubMed: 18407065]
32. Moran CP, Shanahan F. Gut microbiota and obesity: role in aetiology and potential therapeutic target. Best Pract Res Clin Gastroenterol. 2014; 28:585–597. [PubMed: 25194177]
33. Ley RE, Turnbaugh PJ, Klein S, Gordon JI. Microbial ecology: human gut microbes associated with obesity. Nature. 2006; 444:1022–1023. [PubMed: 17183309]
34. Bekkering P, Jafri I, van Overveld FJ, Rijkers GT. The intricate association between gut microbiota and development of type 1, type 2 and type 3 diabetes. Expert Rev Clin Immunol. 2013; 9:1031–1041. [PubMed: 24138599]
35. Yurkovetskiy L, Burrows M, Khan AA, Graham L, Volchkov P, Becker L, Antonopoulos D, Umesaki Y, Chervonsky AV. Gender bias in autoimmunity is influenced by microbiota. Immunity. 2013; 39:400–412. [PubMed: 23973225]
36. Wu HJ, Wu E. The role of gut microbiota in immune homeostasis and autoimmunity. Gut Microbes. 2012; 3:4–14. [PubMed: 22356853]
37. Sorini C, Falcone M. Shaping the (auto)immune response in the gut: the role of intestinal immune regulation in the prevention of type 1 diabetes. Am J Clin Exp Immunol. 2013; 2:156–171. [PubMed: 23885333]
38. Markle JG, Frank DN, Mortin-Toth S, Robertson CE, Feazel LM, Rolle-Kampczyk U, von Bergen M, McCoy KD, Macpherson AJ, Danska JS. Sex differences in the gut microbiome drive hormone-dependent regulation of autoimmunity. Science. 2013; 339:1084–1088. [PubMed: 23328391]
39. Longman RS, Yang Y, Diehl GE, Kim SV, Littman DR. Microbiota: host interactions in mucosal homeostasis and systemic autoimmunity. Cold Spring Harb Symp Quant Biol. 2013; 78:193–201. [PubMed: 24913313]
40. Chervonsky AV. Microbiota and autoimmunity. Cold Spring Harb Perspect Biol. 2013; 5:a007294. [PubMed: 23457255]
41. Sherman MP, Zaghouani H, Niklas V. Gut microbiota, the immune system, and diet influence the neonatal gut-brain axis. Pediatr Res. 2014
42. Gonzalez A, Stombaugh J, Lozupone C, Turnbaugh PJ, Gordon JI, Knight R. The mind-body-microbial continuum. Dialogues Clin Neurosci. 2011; 13:55–62. [PubMed: 21485746]
43. Backhed F, Fraser CM, Ringel Y, Sanders ME, Sartor RB, Sherman PM, Versalovic J, Young V, Finlay BB. Defining a healthy human gut microbiome: current concepts, future directions, and clinical applications. Cell Host Microbe. 2012; 12:611–622. [PubMed: 23159051]
44. Cantarel BL, Lombard V, Henrissat B. Complex carbohydrate utilization by the healthy human microbiome. PLoS One. 2012; 7:e28742. [PubMed: 22719820]
45. Gevers D, Knight R, Petrosino JF, Huang K, McGuire AL, Birren BW, Nelson KE, White O, Methe BA, Huttenhower C. The Human Microbiome Project: a community resource for the healthy human microbiome. PLoS Biol. 2012; 10:e1001377. [PubMed: 22904687]
46. Human Microbiome Project C. Structure, function and diversity of the healthy human microbiome. Nature. 2012; 486:207–214. [PubMed: 22699609]

47. Qin J, Li R, Raes J, Arumugam M, Burgdorf KS, Manichanh C, Nielsen T, Pons N, Levenez F, Yamada T, et al. A human gut microbial gene catalogue established by metagenomic sequencing. Nature. 2010; 464:59–65. [PubMed: 20203603]

48. Eckburg PB, Bik EM, Bernstein CN, Purdom E, Dethlefsen L, Sargent M, Gill SR, Nelson KE, Relman DA. Diversity of the human intestinal microbial flora. Science. 2005; 308:1635–1638. [PubMed: 15831718]

49. Wu GD, Lewis JD, Hoffmann C, Chen YY, Knight R, Bittinger K, Hwang J, Chen J, Berkowsky R, Nessel L, et al. Sampling and pyrosequencing methods for characterizing bacterial communities in the human gut using 16S sequence tags. BMC Microbiol. 2010; 10:206. [PubMed: 20673359]

50. Wikoff WR, Anfora AT, Liu J, Schultz PG, Lesley SA, Peters EC, Siuzdak G. Metabolomics analysis reveals large effects of gut microflora on mammalian blood metabolites. Proc Natl Acad Sci U S A. 2009; 106:3698–3703. [PubMed: 19234110]

51. Atarashi K, Honda K. Microbiota in autoimmunity and tolerance. Curr Opin Immunol. 2011; 23:761–768. [PubMed: 22115876]

52. Suzuki, T.; YT; Takao, T.; Fujimura, T.; Kawamura, E.; Shimizu, ZM.; Tamashita, R.; Nomoto, K. Diabetogenic effects of lymphocyte transfusion on the NOD or NOD nude mice. In: Rygaard, MBJ.; Graem, N.; Sprang-Thomsen, M., editors. Immune-deficient animals in biomedical research. Basel: Karger; 1987. p. 112-116.

53. Alam C, Bittoun E, Bhagwat D, Valkonen S, Saari A, Jaakkola U, Eerola E, Huovinen P, Hanninen A. Effects of a germ-free environment on gut immune regulation and diabetes progression in non-obese diabetic (NOD) mice. Diabetologia. 2011; 54:1398–1406. [PubMed: 21380595]

54. Wen L, Ley RE, Volchkov PY, Stranges PB, Avanesyan L, Stonebraker AC, Hu C, Wong FS, Szot GL, Bluestone JA, et al. Innate immunity and intestinal microbiota in the development of Type 1 diabetes. Nature. 2008; 455:1109–1113. [PubMed: 18806780]

55. Giongo A, Gano KA, Crabb DB, Mukherjee N, Novelo LL, Casella G, Drew JC, Ilonen J, Knip M, Hyoty H, et al. Toward defining the autoimmune microbiome for type 1 diabetes. ISME J. 2011; 5:82–91. [PubMed: 20613793]

56. Brown CT, Davis-Richardson AG, Giongo A, Gano KA, Crabb DB, Mukherjee N, Casella G, Drew JC, Ilonen J, Knip M, et al. Gut microbiome metagenomics analysis suggests a functional model for the development of autoimmunity for type 1 diabetes. PLoS One. 2011; 6:e25792. [PubMed: 22043294]

57. de Goffau MC, Luopajarvi K, Knip M, Ilonen J, Ruohtula T, Harkonen T, Orivuori L, Hakala S, Welling GW, Harmsen HJ, et al. Fecal microbiota composition differs between children with beta-cell autoimmunity and those without. Diabetes. 2013; 62:1238–1244. [PubMed: 23274889]

58. de Goffau MC, Fuentes S, van den Bogert B, Honkanen H, de Vos WM, Welling GW, Hyoty H, Harmsen HJ. Aberrant gut microbiota composition at the onset of type 1 diabetes in young children. Diabetologia. 2014; 57:1569–1577. [PubMed: 24930037]

59. Neu J, Reverte CM, Mackey AD, Liboni K, Tuhacek-Tenace LM, Hatch M, Li N, Caicedo RA, Schatz DA, Atkinson M. Changes in intestinal morphology and permeability in the biobreeding rat before the onset of type 1 diabetes. J Pediatr Gastroenterol Nutr. 2005; 40:589–595. [PubMed: 15861021]

60. Bosi E, Molteni L, Radaelli MG, Folini L, Fermo I, Bazzigaluppi E, Piemonti L, Pastore MR, Paroni R. Increased intestinal permeability precedes clinical onset of type 1 diabetes. Diabetologia. 2006; 49:2824–2827. [PubMed: 17028899]

61. Sapone A, de Magistris L, Pietzak M, Clemente MG, Tripathi A, Cucca F, Lampis R, Kryszak D, Carteni M, Generoso M, et al. Zonulin upregulation is associated with increased gut permeability in subjects with type 1 diabetes and their relatives. Diabetes. 2006; 55:1443–1449. [PubMed: 16644703]

62. Graham S, Courtois P, Malaisse WJ, Rozing J, Scott FW, Mowat AM. Enteropathy precedes type 1 diabetes in the BB rat. Gut. 2004; 53:1437–1444. [PubMed: 15361491]

63. Vaarala O. Leaking gut in type 1 diabetes. Curr Opin Gastroenterol. 2008; 24:701–706. [PubMed: 19122519]

64. Schwartz RF, Neu J, Schatz D, Atkinson MA, Wasserfall C. Comment on: Brugman S et al. (2006) Antibiotic treatment partially protects against type 1 diabetes in the Bio-Breeding diabetes-prone

rat. Is the gut flora involved in the development of type 1 diabetes? Diabetologia. 2007; 49:2105–2108.Diabetologia. 50:220–221.

65. Brugman S, Klatter FA, Visser JT, Wildeboer-Veloo AC, Harmsen HJ, Rozing J, Bos NA. Antibiotic treatment partially protects against type 1 diabetes in the Bio-Breeding diabetes-prone rat. Is the gut flora involved in the development of type 1 diabetes? Diabetologia. 2006; 49:2105–2108. [PubMed: 16816951]
66. Roesch LF, Lorca GL, Casella G, Giongo A, Naranjo A, Pionzio AM, Li N, Mai V, Wasserfall CH, Schatz D, et al. Culture-independent identification of gut bacteria correlated with the onset of diabetes in a rat model. ISME J. 2009; 3:536–548. [PubMed: 19225551]
67. Watts T, Berti I, Sapone A, Gerarduzzi T, Not T, Zielke R, Fasano A. Role of the intestinal tight junction modulator zonulin in the pathogenesis of type I diabetes in BB diabetic-prone rats. Proc Natl Acad Sci U S A. 2005; 102:2916–2921. [PubMed: 15710870]
68. Vaarala O, Atkinson MA, Neu J. The “perfect storm” for type 1 diabetes: the complex interplay between intestinal microbiota, gut permeability, and mucosal immunity. Diabetes. 2008; 57:2555–2562. [PubMed: 18820210]
69. Hague A, Butt AJ, Paraskeva C. The role of butyrate in human colonic epithelial cells: an energy source or inducer of differentiation and apoptosis? Proc Nutr Soc. 1996; 55:937–943. [PubMed: 9004335]
70. Brestoff JR, Artis D. Commensal bacteria at the interface of host metabolism and the immune system. Nat Immunol. 2013; 14:676–684. [PubMed: 23778795]
71. Bouskra D, Brezillon C, Berard M, Werts C, Varona R, Boneca IG, Eberl G. Lymphoid tissue genesis induced by commensals through NOD1 regulates intestinal homeostasis. Nature. 2008; 456:507–510. [PubMed: 18987631]
72. Atarashi K, Tanoue T, Shima T, Imaoka A, Kuwahara T, Momose Y, Cheng G, Yamasaki S, Saito T, Ohba Y, et al. Induction of colonic regulatory T cells by indigenous Clostridium species. Science. 2011; 331:337–341. [PubMed: 21205640]
73. Moreau MC, Ducluzeau R, Guy-Grand D, Muller MC. Increase in the population of duodenal immunoglobulin A plasmocytes in axenic mice associated with different living or dead bacterial strains of intestinal origin. Infect Immun. 1978; 21:532–539. [PubMed: 357289]
74. Mazmanian SK, Liu CH, Tzianabos AO, Kasper DL. An immunomodulatory molecule of symbiotic bacteria directs maturation of the host immune system. Cell. 2005; 122:107–118. [PubMed: 16009137]
75. Cahenzli J, Koller Y, Wyss M, Geuking MB, McCoy KD. Intestinal microbial diversity during early-life colonization shapes long-term IgE levels. Cell Host Microbe. 2013; 14:559–570. [PubMed: 24237701]
76. Kingma SD, Li N, Sun F, Valladares RB, Neu J, Lorca GL. Lactobacillus johnsonii N6.2 stimulates the innate immune response through Toll-like receptor 9 in Caco-2 cells and increases intestinal crypt Paneth cell number in biobreeding diabetes-prone rats. J Nutr. 2011; 141:1023–1028. [PubMed: 21490291]
77. Hall JA, Bouladoux N, Sun CM, Wohlfert EA, Blank RB, Zhu Q, Grigg ME, Berzofsky JA, Belkaid Y. Commensal DNA limits regulatory T cell conversion and is a natural adjuvant of intestinal immune responses. Immunity. 2008; 29:637–649. [PubMed: 18835196]
78. Oh JZ, Ravindran R, Chassaing B, Carvalho FA, Maddur MS, Bower M, Hakimpour P, Gill KP, Nakaya HI, Yarovinsky F, et al. TLR5-mediated sensing of gut microbiota is necessary for antibody responses to seasonal influenza vaccination. Immunity. 2014; 41:478–492. [PubMed: 25220212]
79. Round JL, Lee SM, Li J, Tran G, Jabri B, Chatila TA, Mazmanian SK. The Toll-like receptor 2 pathway establishes colonization by a commensal of the human microbiota. Science. 2011; 332:974–977. [PubMed: 21512004]
80. Maslowski KM, Vieira AT, Ng A, Kranich J, Sierro F, Yu D, Schilter HC, Rolph MS, Mackay F, Artis D, et al. Regulation of inflammatory responses by gut microbiota and chemoattractant receptor GPR43. Nature. 2009; 461:1282–1286. [PubMed: 19865172]
81. Thangaraju M, Cresci GA, Liu K, Ananth S, Gnanaprakasam JP, Browning DD, Mellinger JD, Smith SB, Digby GJ, Lambert NA, et al. GPR109A is a G-protein-coupled receptor for the

bacterial fermentation product butyrate and functions as a tumor suppressor in colon. Cancer Res. 2009; 69:2826–2832. [PubMed: 19276343]

82. Vijay-Kumar M, Aitken JD, Carvalho FA, Cullender TC, Mwangi S, Srinivasan S, Sitaraman SV, Knight R, Ley RE, Gewirtz AT. Metabolic syndrome and altered gut microbiota in mice lacking Toll-like receptor 5. Science. 2010; 328:228–231. [PubMed: 20203013]
83. Greer RL, Morgun A, Shulzhenko N. Bridging immunity and lipid metabolism by gut microbiota. J Allergy Clin Immunol. 2013; 132:253–262. quiz 263. [PubMed: 23905915]
84. Smith PM, Howitt MR, Panikov N, Michaud M, Gallini CA, Bohlooly YM, Glickman JN, Garrett WS. The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. Science. 2013; 341:569–573. [PubMed: 23828891]
85. Inan MS, Rasoulpour RJ, Yin L, Hubbard AK, Rosenberg DW, Giardina C. The luminal short-chain fatty acid butyrate modulates NF-kappaB activity in a human colonic epithelial cell line. Gastroenterology. 2000; 118:724–734. [PubMed: 10734024]
86. Arpaia N, Campbell C, Fan X, Dikiy S, van der Veeken J, deRoos P, Liu H, Cross JR, Pfeffer K, Coffer PJ, et al. Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. Nature. 2013; 504:451–455. [PubMed: 24226773]
87. Furusawa Y, Obata Y, Fukuda S, Endo TA, Nakato G, Takahashi D, Nakanishi Y, Uetake C, Kato K, Kato T, et al. Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. Nature. 2013; 504:446–450. [PubMed: 24226770]
88. Rossi M, Amaretti A, Raimondi S. Folate production by probiotic bacteria. Nutrients. 2011; 3:118–134. [PubMed: 22254078]
89. Kjer-Nielsen L, Patel O, Corbett AJ, Le Nours J, Meehan B, Liu L, Bhati M, Chen Z, Kostenko L, Reantragoon R, et al. MR1 presents microbial vitamin B metabolites to MAIT cells. Nature. 2012; 491:717–723. [PubMed: 23051753]
90. Mathieu C, Badenhoop K. Vitamin D and type 1 diabetes mellitus: state of the art. Trends Endocrinol Metab. 2005; 16:261–266. [PubMed: 15996876]
91. Visser JT, Lammers K, Hoogendijk A, Boer MW, Brugman S, Beijer-Liefers S, Zandvoort A, Harmsen H, Welling G, Stellaard F, et al. Restoration of impaired intestinal barrier function by the hydrolysed casein diet contributes to the prevention of type 1 diabetes in the diabetes-prone BioBreeding rat. Diabetologia. 2010; 53:2621–2628. [PubMed: 20853098]
92. Peng J, Narasimhan S, Marchesi JR, Benson A, Wong FS, Wen L. Long term effect of gut microbiota transfer on diabetes development. J Autoimmun. 2014; 53:85–94. [PubMed: 24767831]
93. Hanninen A, Nurmela R, Maksimow M, Heino J, Jalkanen S, Kurts C. Islet beta-cell-specific T cells can use different homing mechanisms to infiltrate and destroy pancreatic islets. Am J Pathol. 2007; 170:240–250. [PubMed: 17200197]
94. Valladares R, Sankar D, Li N, Williams E, Lai KK, Abdelgeliel AS, Gonzalez CF, Wasserfall CH, Larkin J, Schatz D, et al. Lactobacillus johnsonii N6.2 mitigates the development of type 1 diabetes in BB-DP rats. PLoS One. 2010; 5:e10507. [PubMed: 20463897]
95. Lau K, Benitez P, Ardissone A, Wilson TD, Collins EL, Lorca G, Li N, Sankar D, Wasserfall C, Neu J, et al. Inhibition of type 1 diabetes correlated to a Lactobacillus johnsonii N6.2-mediated Th17 bias. J Immunol. 2011; 186:3538–3546. [PubMed: 21317395]
96. Kriegel MA, Sefik E, Hill JA, Wu HJ, Benoist C, Mathis D. Naturally transmitted segmented filamentous bacteria segregate with diabetes protection in nonobese diabetic mice. Proc Natl Acad Sci U S A. 2011; 108:11548–11553. [PubMed: 21709219]
97. Marwaha AK, Crome SQ, Panagiotopoulos C, Berg KB, Qin H, Ouyang Q, Xu L, Priatel JJ, Levings MK, Tan R. Cutting edge: Increased IL-17-secreting T cells in children with new-onset type 1 diabetes. J Immunol. 2010; 185:3814–3818. [PubMed: 20810982]
98. Honkanen J, Nieminen JK, Gao R, Luopajarvi K, Salo HM, Ilonen J, Knip M, Otonkoski T, Vaarala O. IL-17 immunity in human type 1 diabetes. J Immunol. 2010; 185:1959–1967. [PubMed: 20592279]
99. Li S, Joseph C, Becourt C, Klibi J, Luce S, Dubois-Laforgue D, Larger E, Boitard C, Benlagha K. Potential role of IL-17-producing iNKT cells in type 1 diabetes. PLoS One. 2014; 9:e96151. [PubMed: 24788601]

100. Boehm BO, Rosinger S, Sauer G, Manfras BJ, Palesch D, Schiekofer S, Kalbacher H, Burster T. Protease-resistant human GAD-derived altered peptide ligands decrease TNF-alpha and IL-17 production in peripheral blood cells from patients with type 1 diabetes mellitus. Mol Immunol. 2009; 46:2576–2584. [PubMed: 19505724]
101. Silva JA, Ferrucci DL, Peroni LA, Abrahao PG, Salamene AF, Rossa-Junior C, Carvalho HF, Stach-Machado DR. Sequential IL-23 and IL-17 and increased Mmp8 and Mmp14 expression characterize the progression of an experimental model of periodontal disease in type 1 diabetes. J Cell Physiol. 2012; 227:2441–2450. [PubMed: 21826658]
102. Marwaha AK, Tan S, Dutz JP. Targeting the IL-17/IFN-gamma axis as a potential new clinical therapy for type 1 diabetes. Clin Immunol. 2014; 154:84–89. [PubMed: 24947953]
103. Palmer C, Bik EM, DiGiulio DB, Relman DA, Brown PO. Development of the human infant intestinal microbiota. PLoS Biol. 2007; 5:e177. [PubMed: 17594176]
104. Sudo N, Yu XN, Aiba Y, Oyama N, Sonoda J, Koga Y, Kubo C. An oral introduction of intestinal bacteria prevents the development of a long-term Th2-skewed immunological memory induced by neonatal antibiotic treatment in mice. Clin Exp Allergy. 2002; 32:1112–1116. [PubMed: 12100062]
105. Brugman S, Klatter FA, Visser J, Bos NA, Elias D, Rozing J. Neonatal oral administration of DiaPep277, combined with hydrolysed casein diet, protects against Type 1 diabetes in BB-DP rats. An experimental study. Diabetologia. 2004; 47:1331–1333. [PubMed: 15248047]
106. Scott FW, Rowsell P, Wang GS, Burghardt K, Kolb H, Flohe S. Oral exposure to diabetes-promoting food or immunomodulators in neonates alters gut cytokines and diabetes. Diabetes. 2002; 51:73–78. [PubMed: 11756325]
107. Hansen CH, Krych L, Nielsen DS, Vogensen FK, Hansen LH, Sorensen SJ, Buschard K, Hansen AK. Early life treatment with vancomycin propagates Akkermansia muciniphila and reduces diabetes incidence in the NOD mouse. Diabetologia. 2012; 55:2285–2294. [PubMed: 22572803]
108. Calcinaro F, Dionisi S, Marinaro M, Candeloro P, Bonato V, Marzotti S, Corneli RB, Ferretti E, Gulino A, Grasso F, et al. Oral probiotic administration induces interleukin-10 production and prevents spontaneous autoimmune diabetes in the non-obese diabetic mouse. Diabetologia. 2005; 48:1565–1575. [PubMed: 15986236]
109. Robert S, Gysemans C, Takiishi T, Korf H, Spagnuolo I, Sebastiani G, Van Huynegem K, Steidler L, Caluwaerts S, Demetter P, et al. Oral delivery of glutamic acid decarboxylase (GAD)-65 and IL10 by Lactococcus lactis reverses diabetes in recent-onset NOD mice. Diabetes. 2014; 63:2876–2887. [PubMed: 24677716]
110. Takiishi T, Korf H, Van Belle TL, Robert S, Grieco FA, Caluwaerts S, Galleri L, Spagnuolo I, Steidler L, Van Huynegem K, et al. Reversal of autoimmune diabetes by restoration of antigen-specific tolerance using genetically modified Lactococcus lactis in mice. J Clin Invest. 2012; 122:1717–1725. [PubMed: 22484814]
111. Allen-Vercoe E, Reid G, Viner N, Gloor GB, Hota S, Kim P, Lee C, O'Doherty K, Vanner SJ, Weese JS, et al. A Canadian Working Group report on fecal microbial therapy: microbial ecosystems therapeutics. Can J Gastroenterol. 2012; 26:457–462. [PubMed: 22803022]
112. Petrof EO, Claud EC, Gloor GB, Allen-Vercoe E. Microbial ecosystems therapeutics: a new paradigm in medicine? Benef Microbes. 2013; 4:53–65. [PubMed: 23257018]

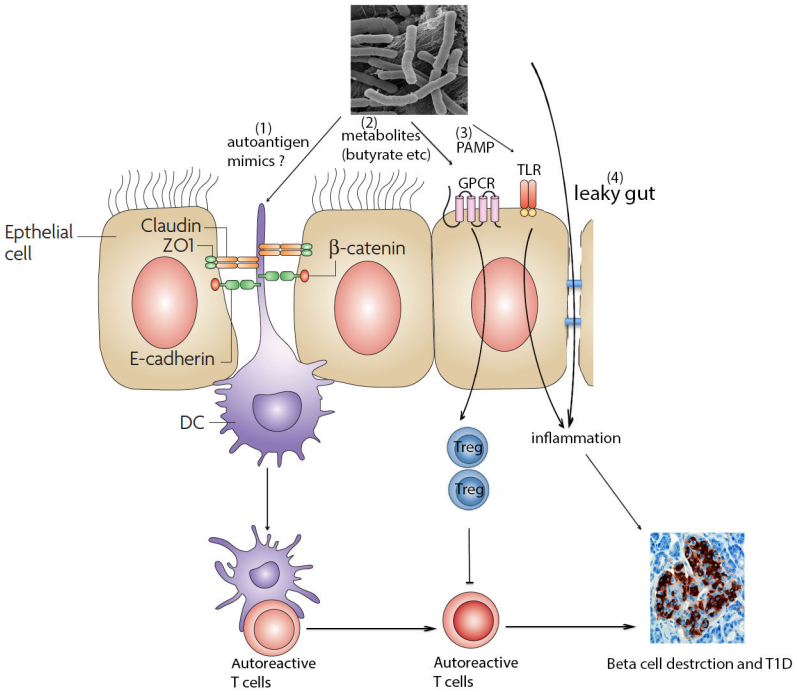

Figure 1.

The role of gut microbiota in the development of T1D. Gut flora can affect islet autoimmunity through mechanisms: 1) expression of autoantigen mimicry to activate autoreactive T cells by antigen-presenting cells to destruct islet beta cells; 2) generating metabolites, such as acetate, butyrate etc, to induce the differentiation or migration of regulatory T cells to control autoreactivity through GPCR signaling pathway (such as Gpr43); 3) gut bacteria-derived pathogen-associated molecular patterns (PAMP) activate TLR signaling pathway to initiate the inflammation, which activates autoreactive T cells and/or directly cause injury to beta cells through inflammatory cytokines; 4) gut bacteria can penetrate the leaky gut and cause inflammation to destruct beta cells.

Table 1

Role of gut microbiota in T1D

Function	Phenotype	References
Alteration of intestinal permeability	Increased ratio of *Bacteroidetes vs Firmicutes*	Ref 64, 65f, 66
	Modified tight junction	Ref 61, 67, 68, 69
Modified mucosal immunity	Impaired GALT development Modified innate immunity:	Ref 71
	1) TLR2	Ref 79
	2) TLR5	Ref 78, 82
	3) TLR9	Ref 77
	Modified adaptive immunity:	
	1) Affecting T cells:	
	i) Treg	Ref 27, 53, 72, 80, 84, 86, 87
	ii) Th1 vs Th2	Ref 53, 74, 75
	iii) Th17	Ref 53, 76, 77, 79, 94, 95
	2) Affecting B cell function	Ref 73, 75, 92
Therapies targeting gut microbiota	Manipulation gut flora at early life prevents T1D;	Ref 38, 92, 104, 106, 107
	Long-term supplement of probiotics prevents T1D;	Ref 92, 108
	Administration of genetically modified bacteria reverses T1D.	Ref 109, 110

GALT: Gut-associated lymphoid tissue