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Treg-associated monogenic autoimmune disorders and gut microbial dysbiosis

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Abstract

Primary immunodeficiency diseases (PIDs) caused by a single-gene defect generally are referred as monogenic autoimmune disorders. For example, mutations in the transcription factor autoimmune regulator (AIRE) result in a condition called autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED); mutations in forkhead box P3 (Foxp3) lead to Treg-deficiency-induced multiorgan inflammation, which in humans is called “immune dysregulation, polyendocrinopathy, enteropathy with X-linked inheritance” (or IPEX syndrome). Previous studies concluded that monogenic diseases are insensitive to commensal microbial regulation because they develop even in germ-free (GF) animals, a conclusion which has limited the number of studies determining the role of microbiota in monogenic PIDs. However, emerging evidence shows that although the onset of the disease is independent of the microbiota, several monogenic PIDs vary in severity in association with the microbiome. In this review, we focus on monogenic PIDs associated with Treg-deficiency/dysfunction, summarizing the gut microbial dysbiosis that has been shown to be linked to these diseases. From limited studies, we have gleaned several mechanistic insights that may prove to be of therapeutic importance in the early stages of life.

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Impact:

This review paper serves to refute the concept that monogenic primary immunodeficiency diseases (PIDs) are not linked to the microbiome. The *onset* of monogenic PIDs is independent of microbiota; single-gene mutations such as AIRE or Foxp3 that affect central or peripheral immune tolerance produce monogenic diseases even in a germ-free environment. However, the severity and ultimate outcome of PIDs are markedly impacted by the microbial composition. We suggest that future research for these conditions may focus on targeting the microbiome.

Introduction

Autoimmune diseases (ADs) are a heterogeneous group of disorders in which the immune system responds to self-antigens, leading to damage or dysfunction of tissues (1). Relatively prevalent autoimmune diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), type I diabetes (T1D), and inflammatory bowel disease (IBD) are polygenic autoimmune disorders, which means that the pathogenesis of the diseases may relate simultaneously to the changes of several genes. As an example, in a genome-wide association study (GWAS) including European and Asian subjects − 29,880 patients with RA and 73,758 control subjects −377 candidate genes were identified in 100 non-MHC RA risk loci. Among them, 98 genes were highly related to RA risk (2). GWAS has identified more than 50 robust loci associated with SLE susceptibility (3), and more than 200 robust loci have been associated with IBD (4).

The primary immunodeficiency diseases (PIDs) are genetic in origin and result in autoimmunity that affects different components of the innate and adaptive immune systems. Although PIDs can affect both adults and children, they are more common during childhood, inasmuch as newborns with PIDs generally do not survive into adolescence. The pathophysiological processes of both PIDs and ADs are associated with abnormal T-cell development, immune tolerance, signaling, and inflammation, and they share some common mechanisms (5). However, there are many monogenic PIDs in which a *single* highly penetrant genetic alteration results in an autoimmune disorder. The role of a single mutated gene in the development of autoimmunity helps to elucidate the underlying mechanisms associated with autoimmunity. Understanding the mechanisms will benefit the development of effective treatments for these diseases. Currently, only bone marrow transplantation (BMT) is commonly used to treat these diseases, but this procedure is limited by the procurement of a matched donor, expensive, associated with graft-versus-host disease, and often lethal (6).

The microbiome comprises the live microorganisms and genomes (bacteria, viruses, phage, fungi, and protozoa) that exist in a symbiosis within mammalian tissues. The microbiome has the ability to influence different physiological functions, such as immune defense, energy metabolism, and social behavior (7). The intestinal microbiota drives host immune homeostasis by regulating the differentiation and expansion of immune cells such as regulatory T cells (Tregs) (8–11). Intestinal microbial *dysbiosis* (or imbalance) can develop as a consequence of an abnormal diet, severe or chronic infection, body habitus (lean or obese) or altered gut immunity (12–15). Many studies have provided evidence demonstrating the association between gut dysbiosis with polygenic autoimmune diseases such as RA (16, 17), IBD (4), type I diabetes (18, 19), SLE (20), and multiple sclerosis (MS) (21–23). As a result, the scientific community is developing optimized probiotics and fecal microbial transplantation (FMT) to modify gut microbiota and disease activity for many of these conditions. Additionally, microbiota-associated biological metabolites, called *postbiotics*, may facilitate the treatment of autoimmune diseases (24, 25).

However, there is limited information about monogenic PIDs caused by single gene mutations and how they interact with the microbiome. Thus, this review will highlight

our knowledge of the association of microbiome to monogenic PIDs, focusing on diseases related to Treg deficiency/dysregulation.

Monogenic PIDs related to Treg deficiency or dysfunction

Monogenic PIDs are rare, but more than 350 unique PIDs have been identified so far. The children typically present with autoimmune phenomena and increased susceptibility to infection, eventually developing multi-organ inflammation (26). The main monogenic PIDs related to Treg-deficiency/dysfunction are due to a single gene defect, and the mechanisms that are implicated are listed in Table 1. The representative clinical phenotypes of some diseases listed in Table 1 are cutaneous or onchopathic (fingernail/toenail) manifestations (Figure 1). Treg cells maintain immune homeostasis and play a pivotal role in immune tolerance. Foxp3 is a major transcription factor associated with Treg cell development and function (27). Mutations or deletions of the Foxp3 gene result in IPEX syndrome in humans. IPEX syndrome is characteristically associated with eczema (Figure 1A and 1B), severe enteropathy, type I diabetes, thyroiditis, hemolytic anemia, and thrombocytopenia (28–30). Several other genetic defects that affect the function of Tregs can give rise to IPEX-like syndromes. IPEX-like syndromes include loss of function (LOF)-mutations in the α-chain of the IL-2 receptor (CD25), itchy E3 ubiquitin protein ligase (ITCH), signal transducer and activator of transcription 5B (STAT5B)/BTB domain and CNC homolog 2 (BACH2). Recently there are mutations reported in other genes, including LPS responsive beige-like anchor protein (LRBA), cytotoxic T-lymphocyte associated protein 4 (CTLA4), dedicator of cytokinesis 8 (DOCK8), and mucosa-associated lymphoid tissue lymphoma translocation 1 (MALT1) (31).

Other monogenic PIDs are not classified as IPEX-like syndromes, but they are immunologically associated with Treg deficiency and/or dysfunction and linked to gastrointestinal inflammation. These include APECED syndrome (Figure 1C–1F), Omenn syndrome (OS) (Figure 1G), DiGeorge syndrome (DGS), chronic granulomatous disease (CGD), Wiskott-Aldrich syndrome (WAS) (Figure 1H–1I), and human phosphatidylinositol 3-kinase-gamma (PI3Kγ) deficiency (Table 1, Figure 1) (31–37).

Traditional concept of the innate-adaptive connection and microbial sensitivity at onset of monogenic autoimmunity

Mechanistically, common autoimmune diseases require the innate-adaptive connection for their onset, during which process microbes contribute to the initiation of autoimmunity. Microbes and microbial peptides activate antigen-presenting cells (APCs) through the interaction with innate receptor signaling on APCs. Subsequently, APCs induce effector and memory T cell and B cells by antigen presentation and co-stimulation, and ultimately tissue target cells are destroyed by self-reactive T cells, antibodies, and/or cytokines (38, 39). These autoimmune diseases have been designated as Group I diseases. They follow the rule of innate–adaptive immunity activation and require a microbial environment (Figure 2) (40).

Because alterations in microbial composition often correlate with the loss of immune tolerance, the human microbiome has been proposed to be a major player in autoimmunity. IBDs such as CD and UC represent an example of how the alteration of gut microbiome can induce disease. Many studies have shown that both CD and UC are associated with a reduced complexity of the commensal microbiota and are consistent shifts to a dysbiotic state, characterized by the outgrowth of "pathobionts," such as the phyla proteobacteria, in particular the *Enterobacteriaceae* and *Fusobacteriaceae* families (41, 42). Adherent-invasive *E. coli*, *Yersinia* and *Clostridium difficile* are also much more common in patients with CD than in healthy individuals. These bacteria are also key contributors to IBD in animal models (43–46).

The separation of monogenic from polygenic autoimmune disorders is based on evidence in germ-free (GF) mice that the innate-adaptive connection is not critical for onset of monogenic disorders. For example, re-deriving AIRE$^{-/-}$ mice, a mouse model of human APECED, into a GF condition does not alter the disease phenotype. The implication of these studies was that the loss of central tolerance in the thymus alone can lead to autoimmunity that overrides peripheral tolerance mechanisms (47). Additionally, Foxp3 mutant scurfy (SF) mice, as mentioned a mouse model of human IPEX syndrome, exhibit an autoimmune phenotype in the GF condition, due to loss of control of inflammatory effector T cells by Tregs (48). These observations were interpreted to prove that monogenic diseases related to Treg deficiency e.g. APECED and IPEX are independent of commensal microbial regulation. Authors suggested that autoimmune T cells are activated in the absence of the innate-adaptive connection (38), leading to the designation of Group II diseases, said to result from genetic alterations in lymphocyte development and not from microbial factors (Figure 2) (40).

Microbial dysbiosis and Treg-associated monogenic autoimmunity

Chinen et al. proposed that monogenic autoimmunity is not associated with the gut microbiome, because innate-adaptive connection is not critical for disease onset (48). However, in a Treg-depleted model (Foxp3-DTR), inflammation in the small intestine of SPF mice was more severe than in GF mice, as shown by significantly increased gut lymphocyte infiltration, decreased body weight, and increased percentage of IFN-γ-producing T helper cells. That study suggested that Treg-deficiency-induced inflammation is indeed modified by gut microbiota (48).

Other experiments provided evidence that the severity of single gene mutation-associated autoimmune diseases is modified by the gut microbiota. We observed that development of autoimmunity was accompanied by gut microbial dysbiosis during the first 22 days of life in SF mice (49), at which time these mice had reduced bacterial diversity and composition. Altered gut microbiota has also been found in immunodeficient mice lacking B cells (Ighm$^{-/-}$); T cells (Cd3e$^{-/-}$); or both B and T cells (Rag1$^{-/-}$). Furthermore, the administration of Foxp3^{+}Treg cells to T-cell-deficient mice restored bacterial diversity (50). A study of APECED patients also concluded that the composition of their intestinal flora was abnormal (51), and consequently the patients developed early and sustained immunological responses to gut microbial antigens (Ags). Additionally, abnormal immune

recognition of gut commensals is linked to gut-associated Tregs, indicating that AIRE is an important regulator of intestinal homeostasis (52). A detailed study comparing $Rag1^{+/+}$ and $Rag1^{-/-}$ mice of the same genetic background (with the appropriate elimination of cage effect) demonstrated that Rag1 status was a source of variation in gut microbiota community structure (53).

A related study examining a mouse model of Omenn syndrome with hypomorphic mutations in Rag genes found that impaired Treg function played a role in development of intestinal inflammation, while mucosal B cell deficiency caused enhanced bacterial translocation and altered microbiota composition. Reducing bacterial load by broad-spectrum antibiotics ameliorated intestinal and systemic autoimmunity by diminishing the frequency of mucosal and circulating gut-tropic $CCR9^{+}$Th1 and Th17 cells and normalizing very the high levels of serum IgE, a hallmark of the disease. These observations indicate that intestinal microbes play a critical role in the distinctive immune aberrations seen in OS (54).

Furthermore, studies of children with Wiskott-Aldrich syndrome found aberrant microbial community richness and structure in WAS children. WAS children had reduced microbial community richness and diversity. The relative abundance of *Bacteroidetes* and *Verrucomicrobia* in WAS children was significantly reduced, whereas *Proteobacteria* were at markedly higher levels (55). WASp-KO mice modeling human WAS harbored a significantly decreased relative abundance of *Firmicutes* (55). In humans, up to 50% of WAS patients develop IBD, often early-onset and severe in phenotype (56). Fecal microbial dysbiosis caused by WASp deficiency was quite similar to that observed for polygenic IBD (41, 55, 57), indicating that WASp may play crucial function in microbial homoeostasis and/or that microbial dysbiosis may contribute to WAS-related IBD.

Interestingly, a recent study by using PIK3CG-deficient mice, tried to mimic a monogenic condition in humans, PI3Kγ deficiency. This investigation found a lack of spontaneous inflammation in lung and gut of PIK3CG-deficient mice when the mice were housed in specific pathogen-free environments. However, “dirty” PIK3CG-deficient mice that were co-housed with “pet-store mice” shared many of the features of disease witnessed in patients with human PI3Kγ deficiency. Specifically, they exhibited elevated IL12 release from macrophages, defective immunoglobulin production, increased inflammatory T cell infiltration in the intestine, and a reduced frequency of circulating Tregs (37). This natural pathogen-dependent mouse model of immunodeficiency and immunopathology indicates a crucial role of microbes to contribute to the clinical features of human monogenic PI3Kγ deficiency.

In addition to gut microbial dysbiosis in gastrointestinal disorders, children with severe atopic dermatitis were found to harbor altered fungal skin microbiomes. Notably, in monogenic PIDs such as STAT3, WAS, and DOCK8 deficiency, skin mycobiome has been found to differ from that of healthy controls (58). PID skin also displayed altered microbial population structures not observed in controls, including colonization with *Clostridium* species, and *Serratia marcescens*, as well as elevated fungal diversity and increased representation of opportunistic fungi such as *Candida* and *Aspergillus*. Clinical parameters, including markers of disease severity, correlated positively with prevalence of

Staphylococcus and *Corynebacterium*. Further investigation is needed to determine if an altered landscape of the human skin microbiome contributes to disease in patients with these Treg-related monogenic PIDs.

Increasingly children with IBD are monogenic gene deficiencies (Table 1) that can lead to very early onset IBD (VEO-IBD), as defined by disease development before the age of 6 years. VEO-IBDs are phenotypically and genetically distinct from older-onset IBD (59), even though their discovery indicated a polygenic component (60). It is important to remember that the gut microbiota colonizes and develops primarily between birth and 3 years of life (61), at a time that coincides with the age of onset of VEO-IBD. Advances in next-generation sequencing (NGS) methods improves identification of known molecular defects in VEO-IBD caused by single gene mutations (62). As mentioned, it is noteworthy that CGD caused by the CYBB mutation results in deficiency of NADPH oxidase 2 (Nox2) that impairs the production of reactive oxygen species (ROS) in colon. Once patients with CGD are infected with encapsulated bacteria, these patients often develop VEO-IBD, with a distal colitis and Treg-deficiency (36, 63). Recently rare variants in Nox1 have been found in patients with VEO-IBD, showing elevated level of ROS in patient-derived colonic organoid cultures, and constitutively generating a high level of ROS in the crypt lumen within colonic crypts (64).

A recent report compared fecal microbiota composition of patients with VEO-IBD and 3 types of PIDs: CGD (11 samples), X-linked inhibitor of apoptosis (XIAP) deficiency (7 samples), and partial tetratricopeptide repeat domain 7A (TTC7A) deficiency (7 samples), comparing their 16S sequences with those patients with non–VEO-IBD (18 samples) and healthy subjects (23 samples) (65). Abnormal stool microbiota composition and diversity in these PIDs was characterized by disease-specific changes, with a dramatic increase in *Proteobacteria* from the *Enterobacteriaceae* family in the TTC7A group; an increased proportion of bacteria from the *Bacteroidetes* phylum in CGD; and increased *Clostridiaceae* family in XIAP. Patients with CGD also exhibited an increased abundance of *Ruminococcus gnavus*, an organism that has also been associated with ileal Crohn's disease in children (65). The dysbiosis induced by the host genetic defect might play a role in the PID phenotype, such as perpetuating inflammation and intestinal involvement, but it seems unlikely that dysbiosis is the cause of IBD. In support of this concept, treatment of the primary immunodeficiency may "cure the dysbiosis." SCID-X1 gene therapy for children with severe combined immune deficiency (SCID-X1) caused by mutation of the IL2RG gene has been shown to reconstitute T cell repertoire and modulate antibiotic resistance gene levels. Interestingly, SCID-X1 gene therapy enabled not only the expression of therapeutic *IL2RG* gene but also cleared microbial pathogens (viruses) and normalized the gut microbiome (66).

Microbial modification as a potentially therapeutic strategy

Microbial dysbiosis associated with Treg-related monogenic autoimmunity may be altered by targeting the enteric microbiota with the aim of modifying the course of these monogenic disorders. The early assembly of a healthy microbiome is heavily influenced by the mode of delivery (vaginal or C-section) and feeding type (breast milk or formula) (61). Recently

Aagard et al. reported that the placenta contains a unique microbiota, which can affect the formation of a child's microbiome (67). Mothers are key determinants in establishing the microbiota in early stages of life. Maternal influences in early life, including gestation, birth history, breastfeeding, and toddler exposures, are extremely important in microbiota formation, making this period a promising target for bio-therapeutics that may prevent diseases later in life (68). Factors such as diet, antibiotic use, and enteric diseases will also impact the composition of the microbiota, but the community generally will subsequently recover (69).

Current strategies for gut microbiota modulation include prebiotics, probiotics, postbiotics, and FMT (68). Prebiotics are foods (containing high dietary fiber and other substrates such as polysaccharides and casein-derived amino acids) used by probiotics or commensal bacteria for growth. Recent studies showed that a lack of dietary fiber induces a substantial loss of microbial community diversity and influences the ability of gut bacteria to be transferred from parents to their offspring (70).

Probiotics have been defined as live, natural microorganisms that are given orally to confer health benefits to the host (71). *Bifidobacterium* and *Lactobacillus* strains are the most widely available commercialized probiotics, although there are numerous other species with proposed or demonstrated health benefits. The beneficial effects of probiotics in treating diseases are strain-specific, which means that different probiotic strains are not equally potent. Probiotics interact with the host within a very complex microbiota ecosystem. Therefore, it has been challenging to define the crosstalk between individual bacterial strains and the host. However, studies suggest that probiotics modulate immune responses, ensure homeostasis of the healthy mucosal microbiota, and may ameliorate immune-mediated diseases. Their mechanisms of action include enhanced production of antimicrobial peptides; maintenance of the gastrointestinal epithelial barrier; and facilitation of adequate interactions between the gut microbes, intestinal epithelial cells and mucosal immune cells. Finally, probiotics or their associated microbiota produce biologically functional metabolites that modulate the immune system and may act as neurotransmitters to modulate brain functions (72).

Probiotics have been studied for autoimmune diseases in humans and animal models, mostly in polygenic autoimmune disorders including T1D, MS, RA, SLE, and IBD (73). Stirsciuglio et al found that a commercial probiotic (Tribif), composed of 3 strains of *Bifidobacterium* (*B. longum*, *B. breve*, and *B. infantis*) improved antigen sampling and processing by dendritic cells, ameliorated the impairment of intestinal innate immunity and reduced uncontrolled microbial expansion in the intestine of children with CD, but not in those with UC (74). The study evaluated how probiotics may be used as potential preventive therapy for chronic pediatric inflammatory diseases (CIDs) including celiac disease and IBD through altering the balance of Tregs and inflammatory T effector cells in the diseases (75). However, high-quality studies of the effect of probiotics in pediatric IBD are limited (75, 76).

For monogenic PIDs, as exemplified by the IPEX syndrome, we have demonstrated that the gut microbial dysbiosis due to Foxp3^{+} Treg deficiency in SF mice, a mouse model of

IPEX syndrome, could be reprogramed by probiotic *Lactobacillus reuteri* DSM 17938 (*L. reuteri*), a human-derived probiotic, which has been used to treat infantile colic and acute infectious diarrhea (77–79). In several studies, we found that *L. reuteri* prolongs the survival and reduces hepatic and lung autoimmunity in SF mice. The *L. reuteri* mechanism of action involved modulating gut microbiota to produce functional metabolites. One key metabolite, adenosine-derived inosine we found exerted anti-inflammatory effects that were mediated via the adenosine 2A (A_{2A}) receptors. The A_{2A} receptors expressed on T cells once bound with A_{2A} agonists result in inhibition of inflammatory Th1 and Th2 differentiation and reducing Th1- and Th2- associated cytokines (Figure 3). It is now well-established that one of the ways by which Tregs control inflammatory T effector cells (Teffs) (Th1/Th2/Th17) is by producing adenosine, generated from ATP/AMP by CD39/CD73 signaling expressed on Treg cells (Figure 3A) (80, 81). However, this adenosine-mediated control Treg/Teff balance was broken in the setting of Treg-deficiency (Figure 3B).

In our studies, the probiotic *L. reuteri* increased production adenosine (73, 82) and its metabolite inosine (49), which directly interacted with A_{2A} expressed on Teffs (in the absence of Tregs) to control inflammation/autoimmunity (Figure 3C) (49, 83). We proved the importance of this adenosine-A_{2A} receptor mechanism by (a) blocking A_{2A} receptors by a pharmacological blocker (Figure 3C) and (b) genetic knockout of A_{2A} receptors in SF mice (Figure 3D). Either manipulation prevented any beneficial effect of *L. reuteri* in ameliorating clinical symptoms (49, 84). The exact mechanism of how *L. reuteri* produces adenosine and inosine, either individually and/or by *L. reuteri*-modulated commensal bacteria requires further characterization. *L. reuteri* may additionally have a therapeutic effect in other monogenic autoimmune disorders that involve reduced numbers and/or dysfunction of Tregs, for example in IPEX-like syndromes as listed in Table 1. Currently, there are no reports on FMT as a treatment for monogenic PID.

In summary, the metabolic byproducts from probiotics with beneficial biological activity in the host, for example adenosine/inosine, short-chain fatty acids (SCFAs acetate, butyrate and propionate), and tryptophan have been termed *postbiotics* (68). The engineering of genetically modified probiotics that produce this type of postbiotic, or the choice and dose of postbiotic, to benefit host health is a formidable challenge for scientists dedicated to improving the outlook of people with autoimmune diseases.

Conclusion

The onset of monogenic PIDs related to Treg deficiency/dysfunction is not linked to the composition of the intestinal microbiome. However, current evidence shows that Treg-associated monogenic autoimmune disorders are clearly associated gut microbial dysbiosis. The therapeutic effect of probiotics and the probiotic-derived inosine in a mouse model of human IPEX syndrome provides a good example of how modulating gut microbiota can be of therapeutic value in treating monogenic PID. The translatability of microbiome-directed therapies for the diseases listed in Table 1 will undoubtedly be hindered by the fact that these conditions are rare, and clinical trials will initially lack statistical power. To aid in discovery, mouse models with a humanized immune system such as mice with humanized Foxp3-gene edited mutations (85, 86) and/or with a humanized microbiome may become very useful

tools. Thus, translational research will help to assess the impact of prebiotics, probiotics, synbiotics, postbiotics, and FMT for children with these disorders.

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References

1. Anaya JM, Shoenfeld Y, Rojas-Villarrage A, Cervera R. Autoimmunity. From bench to bedside. Bogota: Rosario University Press (2013).
2. Okada Y et al. Genetics of rheumatoid arthritis contributes to biology and drug discovery. Nature 506, 376–381 (2014). [PubMed: 24390342]
3. Deng Y, Tsao BP Advances in lupus genetics and epigenetics. Curr. Opin. Rheumatol 26, 482–492 (2014). [PubMed: 25010439]
4. Momozawa Y et al. IBD risk loci are enriched in multigenic regulatory modules encompassing putative causative genes. Nat. Commun 9, 2427 (2018). [PubMed: 29930244]
5. Amaya-Uribe L, Rojas M, Azizi G, Anaya JM, Gershwin ME Primary immunodeficiency and autoimmunity: A comprehensive review. J Autoimmun. 99, 52–72 (2019). [PubMed: 30795880]
6. Castagnoli R, Delmonte OM, Calzoni E, Notarangelo LD Hematopoietic Stem Cell Transplantation in Primary Immunodeficiency Diseases: Current Status and Future Perspectives. Front Pediatr. 7, 295 (2019). [PubMed: 31440487]
7. Sonnenburg ED, Sonnenburg JL The ancestral and industrialized gut microbiota and implications for human health. Nat. Rev. Microbiol 17, 383–390 (2019). [PubMed: 31089293]
8. Arpaia N et al. Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. Nature 504, 451–455 (2013). [PubMed: 24226773]
9. Furusawa Y et al. Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. Nature 504, 446–450 (2013). [PubMed: 24226770]
10. Round JL, Mazmanian SK Inducible Foxp3+ regulatory T-cell development by a commensal bacterium of the intestinal microbiota. Proc. Natl. Acad. Sci. U. S. A 107, 12204–12209 (2010). [PubMed: 20566854]
11. Ruohtula T et al. Maturation of Gut Microbiota and Circulating Regulatory T Cells and Development of IgE Sensitization in Early Life. Front Immunol. 10, 2494 (2019). [PubMed: 31749800]
12. David LA et al. Diet rapidly and reproducibly alters the human gut microbiome. Nature 505, 559–563 (2014). [PubMed: 24336217]
13. Goodrich JK et al. Human genetics shape the gut microbiome. Cell 159, 789–799 (2014). [PubMed: 25417156]
14. Lukens JR et al. Dietary modulation of the microbiome affects autoinflammatory disease. Nature 516, 246–249 (2014). [PubMed: 25274309]
15. Lupp C et al. Host-mediated inflammation disrupts the intestinal microbiota and promotes the overgrowth of Enterobacteriaceae. Cell Host. Microbe 2, 119–129 (2007). [PubMed: 18005726]
16. Kishikawa T et al. Metagenome-wide association study of gut microbiome revealed novel aetiology of rheumatoid arthritis in the Japanese population. Ann. Rheum. Dis 79, 103–111 (2020). [PubMed: 31699813]
17. Maeda Y, Takeda K Host-microbiota interactions in rheumatoid arthritis. Exp. Mol. Med. 51, 1–6 (2019).
18. Durazzo M, Ferro A, Gruden G Gastrointestinal Microbiota and Type 1 Diabetes Mellitus: The State of Art. J Clin. Med 8, 2019).

19. Thomas RM, Jobin C Microbiota in pancreatic health and disease: the next frontier in microbiome research. Nat. Rev. Gastroenterol. Hepatol 17, 53–64 (2020). [PubMed: 31811279]
20. Kim JW, Kwok SK, Choe JY, Park SH Recent Advances in Our Understanding of the Link between the Intestinal Microbiota and Systemic Lupus Erythematosus. Int. J Mol. Sci 20, 2019).
21. Brown J, Quattrochi B, Everett C, Hong BY, Cervantes J Gut commensals, dysbiosis, and immune response imbalance in the pathogenesis of multiple sclerosis. Mult. Scler1352458520928301 (2020).
22. He B et al. Lactobacillus reuteri Reduces the Severity of Experimental Autoimmune Encephalomyelitis in Mice by Modulating Gut Microbiota. Front Immunol. 10, 385 (2019). [PubMed: 30899262]
23. Kadowaki A, Quintana FJ The Gut-CNS Axis in Multiple Sclerosis. Trends Neurosci.2020).
24. Balakrishnan B, Taneja V Microbial modulation of the gut microbiome for treating autoimmune diseases. Expert. Rev. Gastroenterol. Hepatol 12, 985–996 (2018). [PubMed: 30146910]
25. Vangoitsenhoven R, Cresci GAM Role of Microbiome and Antibiotics in Autoimmune Diseases. Nutr. Clin. Pract 35, 406–416 (2020). [PubMed: 32319703]
26. Schmidt RE, Grimbacher B, Witte T Autoimmunity and primary immunodeficiency: two sides of the same coin? Nat. Rev. Rheumatol 14, 7–18 (2017). [PubMed: 29255211]
27. Ouyang W et al. Foxo proteins cooperatively control the differentiation of Foxp3+ regulatory T cells. Nat. Immunol 11, 618–627 (2010). [PubMed: 20467422]
28. Bennett CL et al. The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of FOXP3. Nat. Genet 27, 20–21 (2001). [PubMed: 11137993]
29. Bennett CL, Ochs HD IPEX is a unique X-linked syndrome characterized by immune dysfunction, polyendocrinopathy, enteropathy, and a variety of autoimmune phenomena. Curr. Opin. Pediatr 13, 533–538 (2001). [PubMed: 11753102]
30. Halabi-Tawil M et al. Cutaneous manifestations of immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome. Br. J Dermatol. 160, 645–651 (2009). [PubMed: 18795917]
31. Azizi G et al. Monogenic polyautoimmunity in primary immunodeficiency diseases. Autoimmun. Rev 17, 1028–1039 (2018). [PubMed: 30107266]
32. Albert MH, Freeman AF Wiskott-Aldrich Syndrome (WAS) and Dedicator of Cytokinesis 8-(DOCK8) Deficiency. Front Pediatr. 7, 451 (2019). [PubMed: 31750279]
33. Candotti F Clinical Manifestations and Pathophysiological Mechanisms of the Wiskott-Aldrich Syndrome. J Clin. Immunol 38, 13–27 (2018). [PubMed: 29086100]
34. El-Darouti MA, Al-Ali FM Alopecia, nail dystrophy, vitiligo, and hypoparathyroidism. Challenging Cases in Dermatology 2, 199–206 (2019).
35. Hsu C, Lee JYY, Chao SC. Omenn syndrome: a case report and review of literature. Dermatologica Sinica 29, 50–54 (2011).
36. Roos D et al. Mutations in the X-linked and autosomal recessive forms of chronic granulomatous disease. Blood 87, 1663–1681 (1996). [PubMed: 8634410]
37. Takeda AJ et al. Human PI3Kgamma deficiency and its microbiota-dependent mouse model reveal immunodeficiency and tissue immunopathology. Nat. Commun 10, 4364 (2019). [PubMed: 31554793]
38. Chervonsky AV Microbiota and autoimmunity. Cold Spring Harb. Perspect. Biol 5, a007294 (2013). [PubMed: 23457255]
39. Mogensen TH Pathogen recognition and inflammatory signaling in innate immune defenses. Clin. Microbiol. Rev 22, 240–73, Table (2009). [PubMed: 19366914]
40. Chervonsky AV Influence of microbial environment on autoimmunity. Nat. Immunol 11, 28–35 (2010). [PubMed: 20016507]
41. Frank DN et al. Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. Proc. Natl. Acad. Sci. U. S. A 104, 13780–13785 (2007). [PubMed: 17699621]
42. Gevers D et al. The treatment-naive microbiome in new-onset Crohn's disease. Cell Host. Microbe 15, 382–392 (2014). [PubMed: 24629344]

43. Chassaing B et al. Crohn disease--associated adherent-invasive E. coli bacteria target mouse and human Peyer's patches via long polar fimbriae. J Clin. Invest 121, 966–975 (2011). [PubMed: 21339647]
44. Lamps LW et al. Pathogenic Yersinia DNA is detected in bowel and mesenteric lymph nodes from patients with Crohn's disease. Am J Surg. Pathol 27, 220–227 (2003). [PubMed: 12548169]
45. Leu SB et al. Pathogenic Yersinia DNA in intestinal specimens of pediatric patients with Crohn's disease. Fetal Pediatr. Pathol. 32, 367–370 (2013). [PubMed: 23611062]
46. Navaneethan U, Venkatesh PG, Shen B Clostridium difficile infection and inflammatory bowel disease: understanding the evolving relationship. World J Gastroenterol. 16, 4892–4904 (2010). [PubMed: 20954275]
47. Gray DH, Gavanescu I, Benoist C, Mathis D Danger-free autoimmune disease in Aire-deficient mice. Proc. Natl. Acad. Sci. U. S. A 104, 18193–18198 (2007). [PubMed: 17991771]
48. Chinen T, Volchkov PY, Chervonsky AV, Rudensky AY A critical role for regulatory T cell-mediated control of inflammation in the absence of commensal microbiota. J. Exp. Med 207, 2323–2330 (2010). [PubMed: 20921284]
49. He B et al. Resetting microbiota by Lactobacillus reuteri inhibits T reg deficiency-induced autoimmunity via adenosine A2A receptors. J. Exp. Med 214, 107–123 (2017). [PubMed: 27994068]
50. Kawamoto S et al. Foxp3(+) T cells regulate immunoglobulin a selection and facilitate diversification of bacterial species responsible for immune homeostasis. Immunity. 41, 152–165 (2014). [PubMed: 25017466]
51. Dobes J et al. Gastrointestinal Autoimmunity Associated With Loss of Central Tolerance to Enteric alpha-Defensins. Gastroenterology 149, 139–150 (2015). [PubMed: 25982289]
52. Hetemaki I et al. Anticommensal Responses Are Associated with Regulatory T Cell Defect in Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy Patients. J. Immunol 196, 2955–2964 (2016). [PubMed: 26903483]
53. Zhang H, Sparks JB, Karyala SV, Settlage R, Luo XM Host adaptive immunity alters gut microbiota. ISME. J 9, 770–781 (2015). [PubMed: 25216087]
54. Rigoni R et al. Intestinal microbiota sustains inflammation and autoimmunity induced by hypomorphic RAG defects. J Exp. Med 213, 355–375 (2016). [PubMed: 26926994]
55. Zhang L, Li YY, Tang X, Zhao X Faecal microbial dysbiosis in children with Wiskott-Aldrich syndrome. Scand. J Immunol. 91, e12805 (2020). [PubMed: 31267543]
56. Ohya T et al. Childhood-onset inflammatory bowel diseases associated with mutation of Wiskott-Aldrich syndrome protein gene. World J Gastroenterol. 23, 8544–8552 (2017). [PubMed: 29358862]
57. Packey CD, Sartor RB Commensal bacteria, traditional and opportunistic pathogens, dysbiosis and bacterial killing in inflammatory bowel diseases. Curr. Opin. Infect. Dis 22, 292–301 (2009). [PubMed: 19352175]
58. Oh J et al. The altered landscape of the human skin microbiome in patients with primary immunodeficiencies. Genome Res. 23, 2103–2114 (2013). [PubMed: 24170601]
59. Kelsen JR, Baldassano RN, Artis D, Sonnenberg GF Maintaining intestinal health: the genetics and immunology of very early onset inflammatory bowel disease. Cell Mol. Gastroenterol. Hepatol 1, 462–476 (2015). [PubMed: 26393237]
60. Serra EG et al. Somatic mosaicism and common genetic variation contribute to the risk of very-early-onset inflammatory bowel disease. Nat. Commun 11, 995 (2020). [PubMed: 32081864]
61. Dominguez-Bello MG et al. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. Proc. Natl. Acad. Sci. U. S. A 107, 11971–11975 (2010). [PubMed: 20566857]
62. Charbit-Henrion F et al. Diagnostic Yield of Next-generation Sequencing in Very Early-onset Inflammatory Bowel Diseases: A Multicentre Study. J Crohns. Colitis 12, 1104–1112 (2018). [PubMed: 29788237]
63. Kraaij MD et al. Induction of regulatory T cells by macrophages is dependent on production of reactive oxygen species. Proc. Natl. Acad. Sci. U. S. A 107, 17686–17691 (2010). [PubMed: 20861446]

64. Schwerd T et al. NOX1 loss-of-function genetic variants in patients with inflammatory bowel disease. Mucosal. Immunol 11, 562–574 (2018). [PubMed: 29091079]
65. Sokol H et al. Intestinal dysbiosis in inflammatory bowel disease associated with primary immunodeficiency. J Allergy Clin. Immunol 143, 775–778 (2019). [PubMed: 30312711]
66. Clarke EL et al. T cell dynamics and response of the microbiota after gene therapy to treat X-linked severe combined immunodeficiency. Genome Med. 10, 70 (2018). [PubMed: 30261899]
67. Aagaard K et al. The placenta harbors a unique microbiome. Sci. Transl. Med 6, 237ra65 (2014).
68. Vieira AT, Fukumori C, Ferreira CM New insights into therapeutic strategies for gut microbiota modulation in inflammatory diseases. Clin. Transl. Immunology 5, e87 (2016). [PubMed: 27757227]
69. Lozupone CA, Stombaugh JI, Gordon JI, Jansson JK, Knight R Diversity, stability and resilience of the human gut microbiota. Nature 489, 220–230 (2012). [PubMed: 22972295]
70. Walker AW et al. Dominant and diet-responsive groups of bacteria within the human colonic microbiota. ISME. J 5, 220–230 (2011). [PubMed: 20686513]
71. Hill C et al. Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nat. Rev. Gastroenterol. Hepatol 11, 506–514 (2014). [PubMed: 24912386]
72. Liu Y, Tran DQ, Rhoads JM Probiotics in Disease Prevention and Treatment. J Clin. Pharmacol 58 Suppl 10, S164–S179 (2018). [PubMed: 30248200]
73. Liu Y, Alookaran JJ, Rhoads JM Probiotics in Autoimmune and Inflammatory Disorders. Nutrients. 10, 2018).
74. Strisciuglio C et al. Bifidobacteria Enhance Antigen Sampling and Processing by Dendritic Cells in Pediatric Inflammatory Bowel Disease. Inflamm. Bowel. Dis 21, 1491–1498 (2015). [PubMed: 25895109]
75. Serena G, Fasano A Use of Probiotics to Prevent Celiac Disease and IBD in Pediatrics. Adv. Exp. Med. Biol 1125, 69–81 (2019). [PubMed: 30565165]
76. Miele E et al. Nutrition in Pediatric Inflammatory Bowel Disease: A Position Paper on Behalf of the Porto Inflammatory Bowel Disease Group of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr. Gastroenterol. Nutr 66, 687–708 (2018). [PubMed: 29570147]
77. Savino F et al. Lactobacillus reuteri DSM 17938 in infantile colic: a randomized, double-blind, placebo-controlled trial. Pediatrics 126, e526–e533 (2010). [PubMed: 20713478]
78. Dinleyici EC et al. Lactobacillus reuteri DSM 17938 shortens acute infectious diarrhea in a pediatric outpatient setting. J Pediatr. (Rio J) 91, 392–396 (2015). [PubMed: 25986615]
79. Fatheree NY et al. Lactobacillus reuteri for Infants with Colic: A Double-Blind, Placebo-Controlled, Randomized Clinical Trial. J Pediatr. 191, 170–178 (2017). [PubMed: 28969890]
80. Ohta A, Sitkovsky M Extracellular adenosine-mediated modulation of regulatory T cells. Front Immunol. 5, 304 (2014). [PubMed: 25071765]
81. Romio M et al. Extracellular purine metabolism and signaling of CD73-derived adenosine in murine Treg and Teff cells. Am. J Physiol Cell Physiol 301, C530–C539 (2011). [PubMed: 21593451]
82. Liu Y et al. Lactobacillus reuteri DSM 17938 feeding of healthy newborn mice regulates immune responses while modulating gut microbiota and boosting beneficial metabolites. Am J Physiol Gastrointest Liver Physiol 317, G824–G838 (2019). [PubMed: 31482733]
83. Antonioli L, Pacher P, Vizi ES, Hasko G CD39 and CD73 in immunity and inflammation. Trends Mol. Med. 19, 355–367 (2013). [PubMed: 23601906]
84. He B, Hoang TK, Tran DQ, Rhoads JM, Liu Y Adenosine A2A Receptor Deletion Blocks the Beneficial Effects of Lactobacillus reuteri in Regulatory T-Deficient Scurfy Mice. Front Immunol. 8, 1680 (2017). [PubMed: 29270168]
85. Santoni de Sio FR et al. Role of human forkhead box P3 in early thymic maturation and peripheral T-cell homeostasis. J Allergy Clin. Immunol. 142, 1909–1921 (2018). [PubMed: 29705245]
86. Goodwin M et al. CRISPR-based gene editing enables FOXP3 gene repair in IPEX patient cells. Sci. Adv 6, eaaz0571 (2020). [PubMed: 32494707]

87. Bacchetta R et al. Defective regulatory and effector T cell functions in patients with FOXP3 mutations. J. Clin. Invest 116, 1713–1722 (2006). [PubMed: 16741580]

88. Bacchetta R, Barzaghi F, Roncarolo MG From IPEX syndrome to FOXP3 mutation: a lesson on immune dysregulation. Ann. N. Y. Acad. Sci 1417, 5–22 (2018). [PubMed: 26918796]

89. Blair PJ et al. CD4+CD8- T cells are the effector cells in disease pathogenesis in the scurfy (sf) mouse. J. Immunol. 153, 3764–3774 (1994). [PubMed: 7930593]

90. Suscovich TJ, Perdue NR, Campbell DJ Type-1 immunity drives early lethality in scurfy mice. Eur. J. Immunol 42, 2305–2310 (2012). [PubMed: 22740092]

91. Caudy AA, Reddy ST, Chatila T, Atkinson JP, Verbsky JW CD25 deficiency causes an immune dysregulation, polyendocrinopathy, enteropathy, X-linked-like syndrome, and defective IL-10 expression from CD4 lymphocytes. J. Allergy Clin. Immunol 119, 482–487 (2007). [PubMed: 17196245]

92. Garg G et al. Type 1 diabetes-associated IL2RA variation lowers IL-2 signaling and contributes to diminished CD4+CD25+ regulatory T cell function. J Immunol. 188, 4644–4653 (2012). [PubMed: 22461703]

93. Goudy K et al. Human IL2RA null mutation mediates immunodeficiency with lymphoproliferation and autoimmunity. Clin. Immunol 146, 248–261 (2013). [PubMed: 23416241]

94. d'Azzo A, Bongiovanni A, Nastasi T E3 ubiquitin ligases as regulators of membrane protein trafficking and degradation. Traffic. 6, 429–441 (2005). [PubMed: 15882441]

95. Liu YC The E3 ubiquitin ligase Itch in T cell activation, differentiation, and tolerance. Semin. Immunol 19, 197–205 (2007). [PubMed: 17433711]

96. Roychoudhuri R et al. BACH2 represses effector programs to stabilize T(reg)-mediated immune homeostasis. Nature 498, 506–510 (2013). [PubMed: 23728300]

97. Buchbinder EI, Desai A CTLA-4 and PD-1 Pathways: Similarities, Differences, and Implications of Their Inhibition. Am J Clin. Oncol 39, 98–106 (2016). [PubMed: 26558876]

98. Charbonnier LM et al. Regulatory T-cell deficiency and immune dysregulation, polyendocrinopathy, enteropathy, X-linked-like disorder caused by loss-of-function mutations in LRBA. J Allergy Clin. Immunol. 135, 217–227 (2015). [PubMed: 25468195]

99. Alroqi FJ et al. DOCK8 Deficiency Presenting as an IPEX-Like Disorder. J Clin. Immunol. 37, 811–819 (2017). [PubMed: 29058101]

100. Biggs CM, Keles S, Chatila TA DOCK8 deficiency: Insights into pathophysiology, clinical features and management. Clin. Immunol 181, 75–82 (2017). [PubMed: 28625885]

101. Charbit-Henrion F et al. Deficiency in Mucosa-associated Lymphoid Tissue Lymphoma Translocation 1: A Novel Cause of IPEX-Like Syndrome. J Pediatr. Gastroenterol. Nutr 64, 378–384 (2017). [PubMed: 27253662]

102. Brustle A et al. MALT1 is an intrinsic regulator of regulatory T cells. Cell Death. Differ. 24, 1214–1223 (2017). [PubMed: 26405015]

103. Liu L et al. Gain-of-function human STAT1 mutations impair IL-17 immunity and underlie chronic mucocutaneous candidiasis. J Exp. Med 208, 1635–1648 (2011). [PubMed: 21727188]

104. Uzel G et al. Dominant gain-of-function STAT1 mutations in FOXP3 wild-type immune dysregulation-polyendocrinopathy-enteropathy-X-linked-like syndrome. J Allergy Clin. Immunol 131, 1611–1623 (2013). [PubMed: 23534974]

105. Weinacht KG et al. Ruxolitinib reverses dysregulated T helper cell responses and controls autoimmunity caused by a novel signal transducer and activator of transcription 1 (STAT1) gain-of-function mutation. J Allergy Clin. Immunol. 139, 1629–1640 (2017). [PubMed: 28139313]

106. Haapaniemi EM et al. Autoimmunity, hypogammaglobulinemia, lymphoproliferation, and mycobacterial disease in patients with activating mutations in STAT3. Blood 125, 639–648 (2015). [PubMed: 25349174]

107. Harris TJ et al. Cutting edge: An in vivo requirement for STAT3 signaling in TH17 development and TH17-dependent autoimmunity. J Immunol. 179, 4313–4317 (2007). [PubMed: 17878325]

108. Milner JD et al. Early-onset lymphoproliferation and autoimmunity caused by germline STAT3 gain-of-function mutations. Blood 125, 591–599 (2015). [PubMed: 25359994]

109. Jenks JA et al. Differentiating the roles of STAT5B and STAT5A in human CD4+ T cells. Clin. Immunol 148, 227–236 (2013). [PubMed: 23773921]
110. Kanai T, Jenks J, Nadeau KC The STAT5b Pathway Defect and Autoimmunity. Front Immunol. 3, 234 (2012). [PubMed: 22912632]
111. Anderson MS et al. Projection of an immunological self shadow within the thymus by the aire protein. Science 298, 1395–1401 (2002). [PubMed: 12376594]
112. Guo CJ, Leung PSC, Zhang W, Ma X, Gershwin ME The immunobiology and clinical features of type 1 autoimmune polyglandular syndrome (APS-1). Autoimmun. Rev 17, 78–85 (2018). [PubMed: 29108822]
113. Laakso SM et al. Regulatory T cell defect in APECED patients is associated with loss of naive FOXP3(+) precursors and impaired activated population. J Autoimmun. 35, 351–357 (2010). [PubMed: 20805020]
114. Cassani B et al. Defect of regulatory T cells in patients with Omenn syndrome. J Allergy Clin. Immunol. 125, 209–216 (2010). [PubMed: 20109747]
115. Lee YN et al. Characterization of T and B cell repertoire diversity in patients with RAG deficiency. Sci. Immunol 1, 2016).
116. de la Chapelle A, Herva R, Koivisto M, Aula P A deletion in chromosome 22 can cause DiGeorge syndrome. Hum. Genet 57, 253–256 (1981). [PubMed: 7250965]
117. McDonald-McGinn DM et al. Phenotype of the 22q11.2 deletion in individuals identified through an affected relative: cast a wide FISHing net! Genet. Med 3, 23–29 (2001). [PubMed: 11339373]
118. Sullivan KE, McDonald-McGinn D, Zackai EH CD4(+) CD25(+) T-cell production in healthy humans and in patients with thymic hypoplasia. Clin. Diagn. Lab Immunol. 9, 1129–1131 (2002). [PubMed: 12204972]
119. Adriani M et al. Impaired in vitro regulatory T cell function associated with Wiskott-Aldrich syndrome. Clin. Immunol 124, 41–48 (2007). [PubMed: 17512803]
120. Marangoni F et al. WASP regulates suppressor activity of human and murine CD4(+)CD25(+)FOXP3(+) natural regulatory T cells. J Exp. Med 204, 369–380 (2007). [PubMed: 17296785]

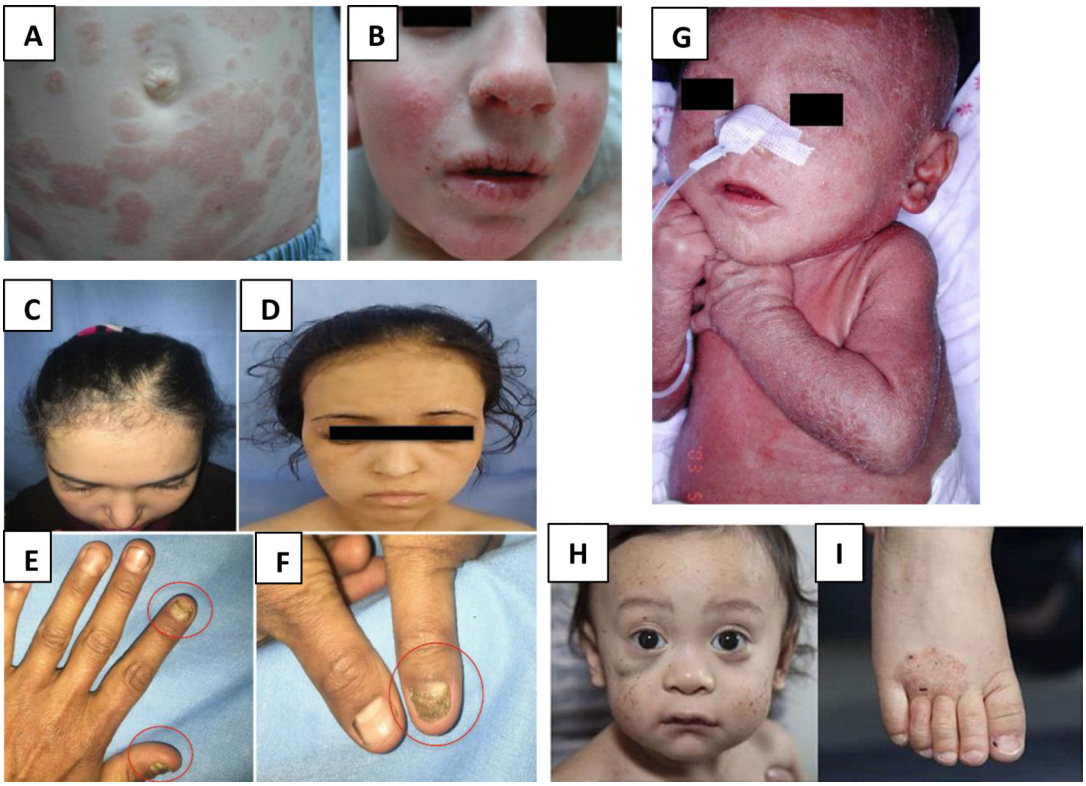

Figure 1.

Clinical autoimmune manifestations of representative monogenic autoimmune diseases. A-B. Immunodysregulation, polyendocrinopathy, and enteropathy syndrome with X-linked inheritance (IPEX syndrome) (30); C-F. Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) (34), G. Omenn syndrome (OS) (35), and H-I. Wiskott-Aldrich syndrome (WAS) (32).

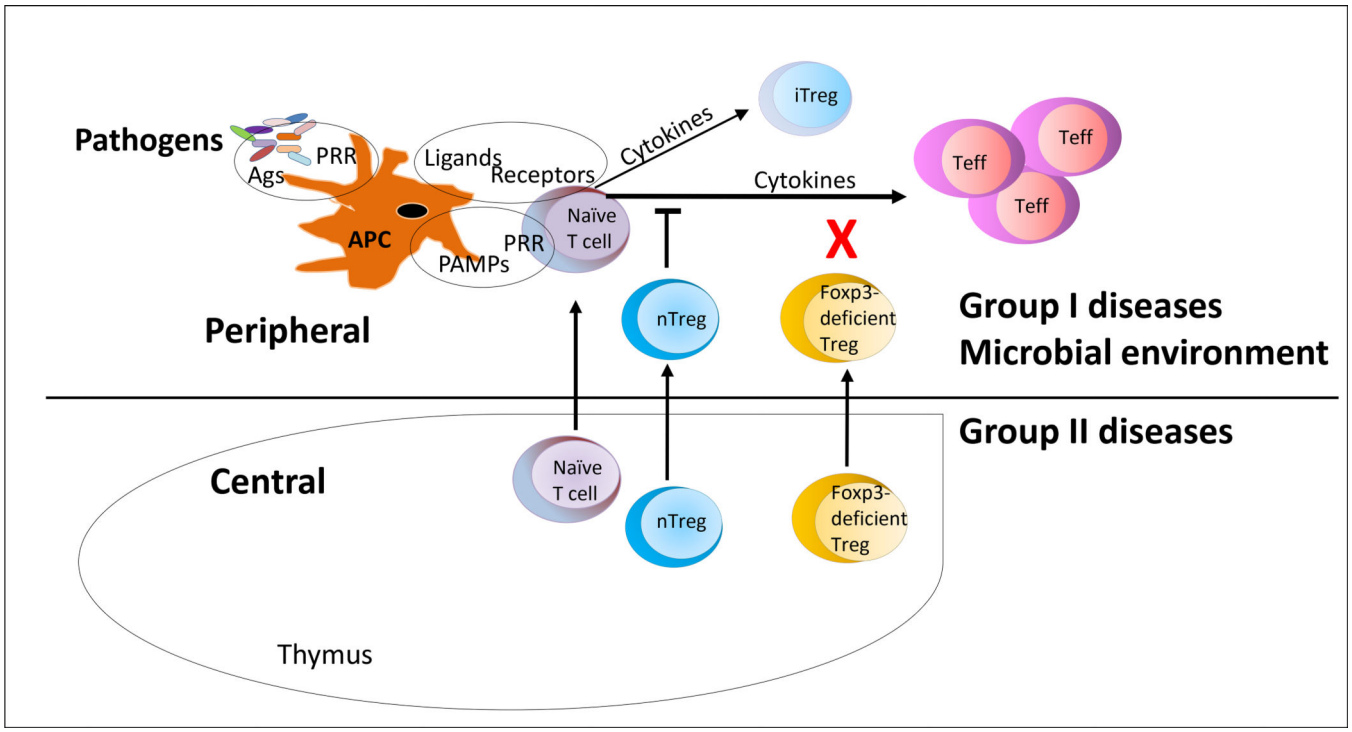

Figure 2. Two main groups of autoimmune diseases as defined by innate-adaptive immunity and microbial environment.

Group I diseases follow the rules of innate-adaptive immunity activation. They can be affected by microbial environment, and/or may result from genetic alterations to PRR sensing and signaling, co-stimulation, or cytokine production. Innate PRR expressed on APC recognizes pathogenic antigens and presents to naïve T cells, activating naïve T cells by several pairs of ligand-receptor interactions to differentiate T cell subsets. This results in more inflammatory Teffs and self-reactive T cells than Tregs, and damage to self-tissues. Group II diseases are caused by genetic alterations in lymphocyte development or regulation. An example shown is a Foxp3 gene mutation in $Foxp3^{+}$Treg cells in thymus, which results in defects in peripheral tolerance due to Treg-deficiency/dysfunction that cannot inhibit inflammatory Teffs, yielding high levels of proinflammatory cytokines. Group II diseases are independent of innate-adaptive immune activation, and their onset is less affected by microbiota.

Ags: antigens; PRR: pattern recognition receptor; PAMPs: pathogen-associated molecular patterns; APC: antigen presenting cell; nTreg: natural regulatory T cell; Teff: effector T cell; Tem: effector/memory T cell.

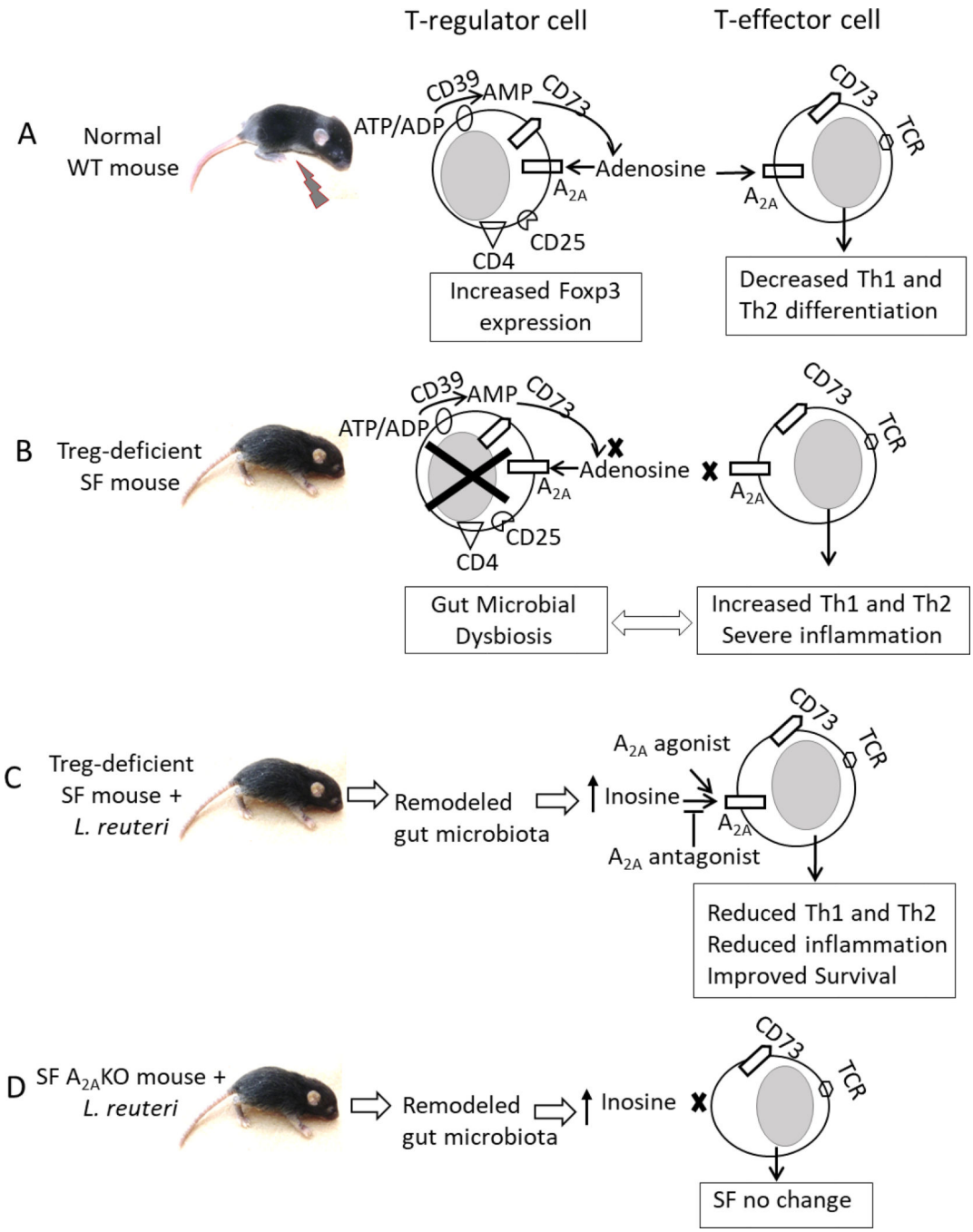

Figure 3.

The mechanism of probiotic *Lactobacillus reuteri* DSM 17938 (*L. reuteri*)-associated protection against Treg-deficiency autoimmunity in SF mice.

A. In WT mice, Tregs generate adenosine from ATP/AMP by CD39/CD73 signaling expressed on Treg cells. Adenosine interacts with A_{2A} expressed on inflammatory Teffs to control Teff s and reduce inflammation. B. In SF mice, inflammatory Teffs lose their control by Tregs through loss of the adenosine mechanism, resulting in severe inflammation and autoimmunity. C. Gavage feeding of *L. reuteri* to SF mice modulates gut microbiota,

generates the adenosine metabolite inosine, an A_{2A} agonist, which interacts with A_{2A} to inhibit Teff cell differentiation and reduce multiorgan inflammation. D. The therapeutic effect of *L. reuteri* and inosine was blocked by genetically knocking out receptor A_{2A} in SF mice, indicating that A_{2A} plays a key role in *L. reuteri* protection.

ATP: adenosine triphosphate; AMP: adenosine monophosphate; A_{2A}: adenosine receptor 2A; TCR: T cell receptor; SF mice: scurfy mice; Th1: T helper cell; Treg: regulatory T cell; Teff: effector T cell.

Table 1.

Main monogenic PIDs related to Treg-deficiency/dysfunction

Monogenic PID	**Genetic defect**	**Mechanisms**
IPEX syndrome	FOXP3	Functional Treg deficiency-defects in peripheral tolerance; increased activation of Th1 and Th2, and high pro-inflammatory cytokine production (28, 30,87–90)
IPEX-like syndromes		Other single gene mutation/deletion-induced IPEX-like syndromes; Treg-deficiency/ dysfunction-defects in peripheral tolerance, increased activation of T helper cells, and high pro-inflammatory cytokine production
CD25 Deficiency	IL2RA	Combined B and T cell deficiency, defective IL10-expressed Tregs (91–93)
ITCH Deficiency or SMAD	ITCH	T cell unresponsiveness to APC, defects in induction of T cell activation, differentiation, and tolerance (94,95)
BACH2 Haploinsufficiency	BACH2	Impaired development of Treg, increased Th1, Th2 and Th17 differentiation, and impaired B cell class-switch recombination (96)
LRBA Deficiency and CTLA4 Deficiency	LRBA CTLA4	Functional dependence of CTLA4 to the LRBA, Treg cell depletion, and impaired Treg-mediated suppression (97,98)
DOCK8 Deficiency	DOCK8	Impaired immune cell migration, function and survival. Also impaired Treg suppression function (via STAT3) (32,99,100)
MALT1 Deficiency	MALT1	Severe combined immune deficiency (SCID) with impaired Treg function (101, 102)
STAT1 (GOF) Or STAT3 (GOF) Or STAT5B (LOF)	STAT1 STAT3 STAT5B	STAT1: Enhanced MHC II expression and activation of Th1 and production high level of IFN-γ, but normal Tregs (103–105). STAT3: Increased Th17, reduced the numbers of Tregs and impaired Treg function (106–108). STAT5B: Reduced Treg numbers and altered Treg function (109,110)
Others		
APECED	AIRE	Defects in negative selection of auto-reactive T cells and generation of Tregs in thymus; defects in central T cell tolerance (47,111–113)
Omenn syndrome (OS)	RAG1 or RAG2	Defects in VDJ recombination; oligoclonal survive of self-reactive B- and T-cells escape from thymus; low levels of Tregs and reduced Treg suppression function (35,114,115)
DiGeorge syndrome (DGS)	BTX1	Disturbances of the central tolerance mechanisms resulting in escape of autoreactive T cells and an altered production of Tregs (116–118)
Chronic granulomatous disease (CGD)	CYBB	Deficiency in NADPH oxidase, which impairs the production of ROS which is considered necessary for macrophages to activate Tregs (36,63)
Wiskott–Aldrich syndrome	WASp	Combined B and T cell dysfunction; reduced antibody production and impaired T cell cytoskeleton rearrangements and immune synapse; reduced Treg suppression function and high pro-inflammatory cytokine production (32, 33,119,120)
PI3Kgamma deficiency	PIK3CG	Facilitation of signaling downstream of G protein-coupled receptors on chemokine receptor responses in myeloid cells, reduced peripheral blood memory B, memory $CD8^+$T, and Tregs, and increased $CXCR3^+$ tissue-homing $CD4^+$ T cells, elevated inflammatory IL12 and IL23 produced by macrophages (37).