REVIEW ARTICLE

Autoimmune Diseases and Gut Symbionts: The Unpopular Liaison

S Zulkafli Nor Effa[1], Shou Jin Phang[1, 2], Hajar Fauzan Ahmad[3]

[1] Regenerative Medicine Cluster, Advanced Medical And Dental Institute, Universiti Sains Malaysia, Bertam, 13200, Kepala Batas, Penang.
[2] Inflammation, Immunology And Immunotherapy Division, Institute Of Cellular Medicine, Newcastle University, Newcastle Upon Tyne, Ne2 4hh.
[3] Faculty of Industrial Sciences And Technology, Universiti Malaysia Pahang, Lebuhraya Tun Razak, 26300 Gambang Kuantan Pahang Darul Makmur

ABSTRACT

In the past few years, compelling data have shown the potential crosstalk between dysbiosis of gut microbiota (GM) and impairment of systemic immune system. Since then, ideas on how GM partake in autoimmune conditions was put forward. Although genetic variability have been proven to contribute towards the pathogenesis of autoimmune conditions, epigenetics control have gained interest among researchers. Current review highlights the crosstalk between autoimmune conditions and GM and its potential regulatory mechanisms. Convincing data from existing literature help in paving ways for more well-defined species in the future studies. The studies should focus on identifying the distinct species involve in different types of autoimmune diseases and their definitive role in autoimmunity. Ultimately, these data can be used for the advancement of therapeutic approach in personalized medicine.

Keywords: Autoimmune disease, Immunity, Gut microbiota, Probiotics, Microbiome.

Corresponding Author:
Nor Effa S. Zulkafli, PhD
Email: effa@usm.my
Tel: +604-5622041

INTRODUCTION

The immune system of vertebrae provides systematic approach to combat insults from the inside and outside the body. When immune system go awry, deregulated immune response may result in autoimmunity, a condition where the immune cells destruct body own cells. The pathogenesis of autoimmune condition is multifactorial where genetic predisposition and epigenetics regulation herald changes into uncontrolled immune responses, giving rise to the formation of autoantibodies damaging one's own cell. The presence of pathogenic autoantibodies are highly specific in organ-specific autoimmune diseases such as thyroiditis, type 1 diabetes and primary biliary cirrhosis. Whereas in systemic autoimmune diseases like systemic lupus, the production of autoantibodies is less specific and directed against multiple organs (1).

Interestingly in recent years, it has becoming a common notion that host immunity has co-evolved with the GM due to their long co-existence mutualistic relationship; and this justified the homeostasis between these components are fundamental to both the gut integrity and healthy immune system. The first step towards understanding the symbiotic relationships of the GM with their hosts is to characterize these community at baseline healthy and disease states (2). Mounting evidences suggested that dysbiosis - an imbalance or maladaptation of gut microbiome communities would affect the host bodily functions. Perturbations in gut microbiome have now been linked with disease states such as cardiovascular disease (3, 4) obesity (5, 6) several type of cancers (7, 8) and inflammatory bowel disease (9).

ESSENTIAL MICROBES IN HUMAN HEALTH MAINTENANCE

Overall temporal stability of the core microbial community within healthy individuals conferred health benefits relating to pathogen protection, host metabolism, immune modulation, and food digestion and nutrient absorption (2, 10) However, a number of factors including decline in the physiology of the gastrointestinal tract due to ageing, antibiotic exposure, diet, and environmental factors can cause changes in composition as well as function (11, 12). Furthermore, dysbiosis observed in autoimmune diseases is associated with inflammation during infection, reduced bacteria function and diversity, bacterial translocation, impaired epithelial barrier, and declined regulatory T cells in the gut mucosa (13). Hence, gut microbiota and their

metabolites could regulate immune cells and cytokine release via epigenetic modifications, suggesting their possible role in autoimmune disease development (14). Understanding how the GM affect health and disease requires a shift in focus from individual pathogens, towards an ecological approach considering the community as a whole. Mounting studies showed that manipulating GM via probiotics and prebiotics interventions could be useful to improve immunity in humans and animal models. To this end, is therefore logical that modulating the gut microbiome should be considered as a therapeutic strategy to treat the diseases via supplementation with probiotics (14, 15, 16, 17), the diet or the use of prebiotics (18). Remarkebly, polyphenol-enriched diet modulates mucosal immune responses (19) and dietary cinnamaldehyde enhances acquisition of specific antibodies in animal studies (20). Moreover, reconstitution of bacterial populations by fecal transplantation or by employing antimicrobials to eliminate pathogens or manipulate the GM in a way that will benefit host health (21).

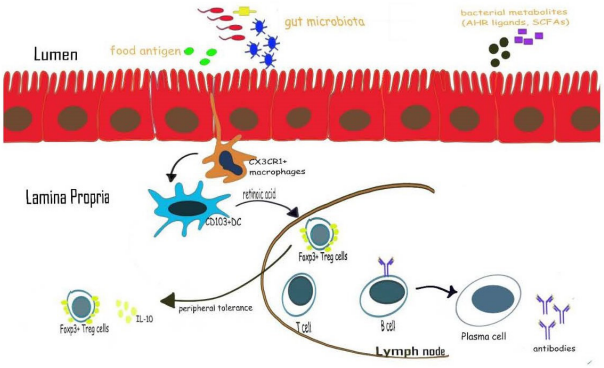

Figure 1: Gut microbiota modulates the intestinal immune homeostasis by their metabolites. CD103⁺ DCs resides in the lamina propria interact with CX3CR1+ macrophages which are capable to reach up for antigens in the lumen and presenting them to the DCs for activation. Activated CD103⁺ DCs will further activate T cells including its subset Foxp3⁺ T-regulatory (Foxp3⁺Treg) cells. Interaction between CD103⁺ DCs and Foxp3+ Treg cells is important to determine the tolerance levels to certain food antigens. Thus, depending on the levels of activation and exposure of particular antigens, the interaction between CD103⁺/Foxp3 Treg cells will eventually lead to peripheral tolerance via IL-10 mechanism.

CROSSTALK OF GM ON IMMUNE SYSTEM

The fact that bacteria in the gut interact with the host immune system is now well accepted and illustrated by *in vitro* and *in vivo* experiments. And this has becoming progressively supported by human intervention trials (22). The symbiotic relationship provides beneficial outcomes to the host by metabolizing ingested nutrients, drugs and substances, maintenance of gut mucosal microenvironments and protection against pathobionts. Also, they produce beneficial outcome to the host by fermentation and digestion carbohydrates into absorbable short-chain fatty acids (SCFAs), vitamin synthesis as well as regulating the gut-associated immune cells (14). GM are essential for the complete development of the immune system, representing a binary network in which the microbiota interact with the host, providing important immune and physiologic function and conversely the bacteria protect themselves from host immune defence (23). Thus, GM play an important role in maintaining normal function of systemic immune system by regulating gut immune system as described in Figure 1.

Bassaganya-Riera and colleagues have demonstrated the manipulation of gut probiotics and their metabolites has potentially alleviates IBD in mouse models (24). In a randomized control trial performed among colicky infants, oral supplement of *Lactobacillus reuteri* for one month have reduced the crying time as opposed to placebo by reducing Th17 cells and promoting Foxp3+ cells thus suppressing inflammatory reactions (25). In fact, previous work has attested that the metabolism of GM modulates serotonin-producing cells which in turn regulates gastrointestinal physiology (26). These metabolites are further appraised as immune regulators shown by induction of tolerance in food-allergy models (27) and improved gut symbionts in children with anti-islet autoantibody (28). Interestingly, supplement of probiotics in addition to breastfeeding has improved the composition of GM in infants treated with antibiotics and caesarean-birth infants by restoring the microbial metabolic capacity of bifidobacteria (29). This significantly contribute to better immune function in compromised caesarean-birth infant as they are prone to develop metabolic diseases and autoimmunity (30,31).

Meanwhile, oral tolerance induced by GM controlled the development of food allergy in mice models fed with high-fibre diet (27). It was shown that the levels of CD103⁺ dendritic cells (DC) is higher in allergy-induced mice fed with high-fibre diet as opposed to zero-fibre diet (27). Modulation of 103⁺ DC is important as they possess the capacity to induce naïve T cells into iTreg cells in MLN to minimize adverse pro-inflammatory responses (32). Moreover, microbial metabolites repertoire has recently been compiled thus intrigued researchers to further investigate their roles on the immune system. One of the compounds that recently came to limelight are tryptophan-derived metabolites which is known to be the ligand for aryl hydrocarbon receptor (AHR). Activation of AHR leads to the activation of anti-inflammatory responses via IL-22 signalling pathway (33, 34). On more detailed understanding as how GM regulate host immune functions, although not many, a few studies have already revealed molecular mechanisms involved in mediating immune responses in animal models. One of the proposed mechanism is via G-protein coupled receptor 43 (GPR43) on epithelial cells and GPR109a on immune cells which serve as receptors for SFCA. Binding of GPR43 receptors to SCFA produced by GM alleviated colitis and allergy in mouse models, suggesting the metabolite of GM as one of mediators in immune regulation (27, 35). A study revealed the capacity of GM to regulate distant organs

such as pancreas from developing autoimmune diabetes by promoting β-defensin 14 expression by pancreatic endocrine cells (36). The distal response is mediated by metabolites of GM and act as AHR ligands and butyrate, which in turn stimulate IL-22 secretion by pancreatic innate lymphoid cells (36).

A retrospective analysis identified the use of antibiotics in early life is associated with subjects diagnosed with inflammatory bowel diseases (IBD) in their childhood and thus promoting the possible role of antibiotics in altering the compositional structure of commensal microbiota (37). In addition, a gut model consisting evolutionarily-conserved mucosal associated invariant T cells known as monomorphic major histocompatibility complex class I-related molecules (MR1) have showed that they require the presence of commensal microbiota for expansion in lamina propria (38). Interestingly, more reports have shown that the established mutual agreement between several strains of *Lactobacillus spp* results in restoration of T-regulatory cells and inactivation of T cell reactivity in lamina propria of animal models (39, 40, 41). DC-derived from this anatomical sites have been shown to be able to reach luminal bacteria through gap junction during low degree of physiological gut leakiness (42, 43), suggesting the potential of pathogenic antigen presentation originally from gut lumen to further drained into nearby mesenteric lymph nodes for clearance. Comprehensive investigations of host cell responses to probiotics display distinct pathogen-associated molecular pattern (PAMP) since then has been put forward. Haller and Jobin (2004) mentioned that the role of *Bifidobacterium animalis* and *E. faecalis* inhibit NF-jB activity and IL-6 gene expression in intestinal epithelial cells (IEC) via pattern recognition receptor stability, chromatin remodelling and modulation of phosphatase activity (44).

Intriguingly, the fact that orally ingested probiotics persist and permanently reside in the intestinal lumen is remain elusive. Despite, a number of studies showed that ingested probiotics only transiently persist in the intestine during "dosing" period which is yet to be defined for its relative duration under various circumstances (22, 45, 46, 47). Huttenhower and colleagues (2012) and Gianchecchi and Fierabracci (2019) summarized that the colonization of GM is a dynamic, complex and gradual process with no random events which continuously evolve (48, 49). This is demonstrated by the fact that their composition of humans and other mammals consist of elevated levels of conservation of the same phylum (48).

GM INVOLVEMENT IN AUTOIMMUNE CONDITIONS

A healthy immune system is essential for mounting an effective immune response against foreign antigen in order to eliminate any potential pathogenic infection but still remain tolerant against autoreactive immune cells. However, autoimmune diseases are established when immune tolerance is breached by overexuberant and unwanted immune responses, which may contribute to a lower quality of life and raise health concern. In fact, recent epidemiological data have suggested that the incidence and prevalence of autoimmune diseases is increasing worldwide (50), which provide an insight that environmental factors (e.g. dietary changes and overuse of antibiotics that leads to dysbiosis) might be more important than we initially thought in the pathogenesis of autoimmune disease . In this review, we aimed to highlight the effect of the gut microbiota in autoimmune disease pathogenesis by summarising data from both murine models and human case study.

Probably the most puzzling part is how GM controlling intestinal regulation may affect systemic immune response and organ-specific autoimmune diseases. Indeed, with trillions of GM in adult human, it is possible that any changes in the gut composition or function may alter immune responses in host physiology (24). When SCFA production by gut microbiome are altered as a result of dysbiosis, the intestinal barrier may be disrupted and permeabilise the intestinal epithelium, leading to infiltration of bacteria into the mesenteric lymph node (MLN) (27, 36, 51). As a result, the intestinal dendritic cells at the surface mucosa is activated more frequently (due to more bacteria breaching the intestinal barrier) and more T cells are differentiated, which would result in the over reactivity T cells for the establishment of autoimmune conditions (33, 36). Indeed, the leaky gut hypothesis propose that bacterial translocation could be potentially increased, leading to elevation of cross-antigen presentation between self and nonself-antigen recognition and result in the exacerbation of extra-intestinal autoimmune diseases like T1D, SLE and atopic dermatitis (36, 51, 52, 53, 54, 55) (Figure 2).
The existence of gastrointestinal-related autoantibodies in different types of autoimmune diseases may suggest the crosstalk between GM regulation and onset of autoantibodies formation. The most studied GI-related antibodies include anti-gliadin antibodies (AGA) and anti-tissue transglutaminase (tTG) antibodies. These

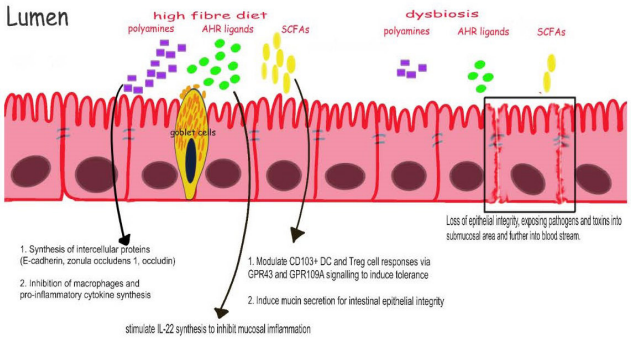

Figure 2: Imbalance in the gut microbiota composition leads to the loss of microbial metabolites that changes the function of intestinal epithelial cells. This affect the physiological and metabolism of normal lining by reducing mucus production, increase pathogenic microbes and toxins into underlying tissues, and stimulate mucosal inflammation by inhibiting IL-22 production and reduce immune tolerance

antibodies have been titred in patients with multiple sclerosis (56, 57, 58) and inflammatory myopathies (59). This in fact is shown clinically by celiac disease as an extra-pancreatic manifestation of type 1 diabetes (51). Similarly, the co-existence of ulcerative colitis in SLE patients is commonly underdiagnosed (60).

More reports on established relationship between dysbiosis and autoimmune diseases such as rheumatoid arthritis (61), systemic lupus erythematosus (SLE) (51, 52, 62), type 1 diabetes (T1D) (28) (, primary Sjogren Syndrome (pSS) (63), multiple sclerosis (MS) (64) and also atopic dermatitis (AD) (55) are extensively discussed in recent years. The intertwined relationship between gut symbionts and autoimmune disease can be seen as the microbiome in patients with newly-onset rheumatoid arthritis (RA) is enriched by the pathobiont *Prevotella copri* (65) whereas increasing abundance in *Methanobrevibacter* and *Akkermansia* and a reduction in *Butyricimonas* is observed in human subjects with multiple sclerosis (MS) (64). Following that, several recent cohort studies have demonstrated that the gut microbiota is less diverse in new-borns with AD in conjunction with reduced amounts of *Bifidobacterium* and *Bacteroides* but elevated *Enterobacteriaceae* levels (55, 66, 67). Given the fact that Bifidobacterium exhibit an anti-inflammatory effect and are able to alleviate Th2 immunity, one can imply that the gut microbiome with *Bifidobacterium* deficiency are more susceptible to developing AD (68, 69). Thus, prescription of probiotics regimens containing *Bifidobacteria* and another commonly used species *Lactobacilli* could shed light into the prevention and treatment of AD, although the timing and dose of administration still warrants further investigation (68, 69). However, the hypothesis that each autoimmune disease is resulted from the presence of a single genera may be an over-simplication of the entire picture (70). A study conducted in children with anti-islet cell autoantibodies suggested that the sophisticated networks between each bacterium may also be crucial in the establishment of the anti-islet cell autoimmunity, which may progress into the pre-clinical stage for T1D (70). Ideally, molecular protein possessed by diabetogenic microbes (Mgt protein of *Leptotrichia goodfellowii* found in GM) shares structural similarities with self-antigen in the host (islet-specific glucose-6-phosphatase-related protein (IGRP) found in pancreas) (44), which can lead to the acceleration of T1D pathogenesis via molecular mimicry mechanism, as previously reported (42, 43, 44, 55, 71,72).

Besides, an association between dysbiosis and IBD has also been reported earlier in murine model by Nagalingam and colleagues (73). The interrelationship between RA and celiac disease (CD) suggesting the potential crosstalk between gut-joint pathogenesis (74). GM composition of buccal mucosa from pSS patients are distinctly different with healthy control in such that the microbiome of pSS patients consist of a higher Firmicutes/Proteobacteria ratio when compared to healthy control (54). Similarly, in induced-dysbiosis of pSS mouse models have shown a reduction in the microbiome diversity and accelerate the establishment of autoimmune mucosal inflammation. In specific, the stool samples from antibody-treated mice have shown a reduction in *Clostridium* genus while a pilot study involving pSS patients also shown a significant loss in *Faecalibacterium* among the fecal microbiome (54).

Furthermore, the putative role of gut microbiome in structuring autoimmunity has been demonstrated by Wu and colleagues (2010) on segmented filamentous bacteria (SFB) as a general immunomodulator in which enhance the establishment of autoimmune arthritis (75) and EAE (76), albeit protecting from T1D pathogenesis (77). Notably, a germ-free, IL-1 receptor antagonist deficient (GF IL-1Rn$^{-/-}$) mouse model that represent a spontaneous T-cell mediated arthritis failed to develop autoimmune arthritis but subsequent mono-colonisation of *Lactobacillus bifidus* are able to restore the disease (75, 78). Another reports have shown that three microorganisms, including *Dialister invisus, Gemella sanguinis*, and *Bifidobacterium longum*, are correlated with compromised gut integrity and higher intestinal permeability eventually elevated T1D risk (71,72,79,80). Nonetheless, Tryptophan (Trp) metabolism by GM (e.g. *Clostridium sporogenes*, *Bifidobacteria* infantis and *Lactobacillus reuteri*) can also contribute to the homeostasis of intestinal immune activation and also tolerance (81). Similarly, Lactobacillus reuteri modulate inflammation at different body sites (intestinal and extraintestinal) by regulating the microbiota-adenosine-inosine receptor 2A (A2A) axis and alleviating the pro-inflammatory Th1 and Th2 cell differentiation in Scurfy model to resemble SLE in human (82). Altogether, these studies propose that our gut microbiome is one of the dictators in shaping autoimmune diseases outcome and further investigations are required in order to explore the microbiota/immunity crosstalk thoroughly (83).

CONCLUSION

Compelling data have shown that GM are closely liaised with various types of autoimmune diseases in the form of dysbiosis- alteration of individual species and/or global communities of the GM (dysbiosis) which can give rise to different outcomes of autoimmune conditions. Certainly, gut microbiome could possibly be applied as a biomarker for autoimmune diseases prediction. Furthermore, the knowledge can also be manifested into probiotics enhancement as precision editing of GM may be utilized to reverse autoimmune conditions.

Although encouraging, these reports need to be correspond to the demands for scientific proves on how these microbial colony imbalance lead to dysregulation of immune systems. Further studies are also necessary to justify the role of ingested probiotics as immune

modulators during their "transit" stay in the gut. Furthermore, prescription of lactobacillus probiotics in some circumstances may be unfavourable in infants, leading to the progression of D-lactic acidosis (84). These results have shed like into considerations of administrating the same probiotics regimen into human body as "one probiotic will not fit all". Therefore, further researches are much needed in order to delineate the optimal choice of probiotic composition for each disease entity studies.

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REFERENCES

1. Elkon K & Casali P. Nature and functions of autoantibodies. Nat Clin Pract Rheumatol. 2008 Sep;4(9):491-8.
2. Hara AMO & Shanahan F. The gut flora as a forgotten organ. EMBO Reports, 2006; 7(7), 688 –693
3. Kitai T & Tang WHW. Gut microbiota in cardiovascular disease and heart failure. Clinical Science. 2018; 132(1), 85-91.
4. Battson ML, Lee DM, Weir TL & Gentile CL. The gut microbiota as a novel regulator of cardiovascular function and disease. The Journal of Nutritional Biochemistry. 2018; 56, 1–15.
5. Baothman OA, Zamzami MA, Taher I, Abubaker J & Abu-Farha M. The role of Gut Microbiota in the development of obesity and Diabetes. Lipids in Health and Disease. 2012;15(1),108.
6. Wolf KJ & Lorenz RG. Gut Microbiota and Obesity. Current Obesity Reports, 2012;1(1), 1–8.
7. Gopalakrishnan V, Helmink BA, Spencer CN, Reuben A & Wargo JA. The Influence of the Gut Microbiome on Cancer, Immunity, and Cancer Immunotherapy. Cancer Cell. 2018;33(4), 570–580.
8. Tilg H, Adolph TE, Gerner RR & Moschen AR. The Intestinal Microbiota in Colorectal Cancer. Cancer Cell, 2018; 33(6), 954–964.
9. Nishida A, Inoue R, Inatomi O, Bamba S, Naito Y & AndohA. Gut microbiota in the pathogenesis of inflammatory bowel disease. Clinical Journal of Gastroenterology. 2018;11(1), 1–10.
10. Caporaso JG, Lauber CL, Costello EK, Berg-Lyons D, Gonzalez A, Stombaugh J et al. Moving pictures of the human microbiome. Genome Biology. 2011;12(5, p. R50)
11. An R, Wilms E, Masclee AAM, Smidt H, Zoetendal EG & Jonkers D. Age-dependent changes in GI physiology and microbiota: time to reconsider?. Gut, 2018;67(12), 2213–2222.
12. Guinane CM & Cotter PD. Role of the gut microbiota in health and chronic gastrointestinal disease: understanding a hidden metabolic organ. Therapeutic Advances in Gastroenterology, 2013;6(4), 295–308.
13. Manfredo Vieira S, Hiltensperger M, Kumar V, Zegarra-Ruiz D, Dehner C Khan N et al. Translocation of a gut pathobiont drives autoimmunity in mice and humans. Science, 2018;359(6380), 1156–1161.
14. De Oliveira GLV, Leite AZ, Higuchi BS, Gonzaga MI & Mariano VS. Intestinal Dysbiosis And Probiotic Applications In Autoimmune Diseases. Immunology, 2017;152, 1-12.
15. Sбnchez B, Delgado S, Blanco-Mнguez A, Lourenзo A, Gueimonde M & Margolles A. Probiotics, gut microbiota, and their influence on host health and disease. Molecular Nutrition & Food Research, 2016;61(1), 1600240.
16. Corthйsy B, Gaskins HR, & Mercenier A. Cross-Talk Between Probiotic Bacteria And The Host Immune System. J Nutr. 2007;03;137(3 Suppl 2):781s-90s.
17. Kim, J. Y. et al. Effect of probiotic mix (Bifidobacterium bifidum, Bifidobacterium lactis, Lactobacillus acidophilus) in the primary prevention of eczema: a double-blind, randomized, placebo-controlled trial. Pediatr. Allergy Immunol. Off. Publ. Eur. Soc. Pediatr. Allergy Immunol. 2010;21, e386–393.
18. Holscher HD. Dietary fiber and prebiotics and the gastrointestinal microbiota. Gut Microbes, 2017;8(2), 172–184.
19. Andrew RW, Lukasz K, Hajar FBA, Peter N, Kerstin S, Dennis SN & Stig MT. A polyphenol/enriched diet and Ascaris suum infection modulate mucosal immune responses and gut microbiota composition in pigs. PLOS One, 2017;12, 10.
20. Andrew RW, Tina VAH, Lukasz K, Hajar FBA, Dennis SN, Kerstin S & Stig MT. Dietary cinnamaldehyde enhances acquisition of specific antibodies following helminth infection in pigs. Veterinary Immunology and Immunopathology, 2017;189, 43-52.
21. Gupta S, Allen-Vercoe E & Petrof EO. Fecal microbiota transplantation: in perspective. Therapeutic Advances in Gastroenterology, 2015;9(2), 229–239.
22. Klingberg TD & Budde BB. The Survival And Persistence In The Human Gastrointestinal Tract Of Five Potential Probiotic Lactobacilli Consumed As Freeze-Dried Cultures Or As Probiotic Sausage. Int J Food Microbiol. 2006;May 25;109(1-2):157-9.
23. Weis M. Impact Of The Gut Microbiome In Cardiovascular And Autoimmune Diseases. Clin Sci. 2018 Nov 30;132(22):2387-9.
24. Bassaganya-Riera J, Viladomiu M, Pedragosa M, De Simone C, Carbo A, Shaykhutdinov R, Jobin C, Arthur JC, Corl BA & Vogel H. Probiotic Bacteria Produce Conjugated Linoleic Acid Locally In The

Gut That Targets Macrophage PPARγ To Suppress Colitis. Plos One, 2012;7, E31238.
25. Savino F, Garro M, Montanari P, Galliano I & Bergallo M. Crying Time And RORγt/Foxp3 Expression In Lactobacillus Reuteri Dsm17938-Treated Infants With Colic: A Randomized Trial. The Journal Of Pediatrics, 2018;192, 171-177. E1.
26. Reigstad CS, Salmonson CE, Rainey III JF, Szurszewski JH, Linden DR, Sonnenburg JL, Farrugia G & Kashyap PC. Gut Microbes Promote Colonic Serotonin Production Through An Effect Of Short-Chain Fatty Acids On Enterochromaffin Cells. The Faseb Journal, 2014;29, 1395-1403.
27. Tan J, Mckenzie C, Vuillermin PJ, Goverse G, Vinuesa CG, Mebius RE, Macia L & Mackay CR. Dietary Fiber And Bacterial SCFA Enhance Oral Tolerance And Protect Against Food Allergy Through Diverse Cellular Pathways. Cell Reports, 2016;15, 2809-2824.
28. Endesfelder D, Engel M, Davis-Richardson AG, Ardissone, AN, Achenbach P, Hummel S, Winkler C, Atkinson M, Schatz D, Triplett E, Ziegler AG & Zu Castell W. Towards A Functional Hypothesis Relating Anti-Islet Cell Autoimmunity To The Dietary Impact On Microbial Communities And Butyrate Production. Microbiome, 2016;4, 17.
29. Korpela K, Salonen A, Vepsäläinen O, Suomalainen M, Kolmeder C, Varjosalo M, Miettinen S, Kukkonen K, Savilahti E, Kuitunen M & De Vos WM. Probiotic Supplementation Restores Normal Microbiota Composition And Function In Antibiotic-Treated And In Caesarean-Born Infants. Microbiome, 2018;6, 182
30. Biasucci G, Rubini M, Riboni, S., Morelli, L., Bessi, E. & Retetangos, C. Mode Of Delivery Affects The Bacterial Community In The Newborn Gut. Early Human Development, 2010;86, 13-15.
31. Bäckhed F, Roswall J, Peng Y, Feng Q, Jia H, Kovatcheva-Datchary P, Li Y, Xia Y, Xie H & Zhong H. Dynamics And Stabilization Of The Human Gut Microbiome During The First Year Of Life. Cell Host & Microbe, 2015;17, 690-703.
32. Scott CL, Aumeunier AM & Mowat AM. Intestinal CD103+ Dendritic Cells: Master Regulators Of Tolerance. Trends Immunol. 2011;Sep;32(9):412-9.
33. Monteleone I, Rizzo A, Sarra M, Sica G, Sileri P, Biancone L et al. Aryl Hydrocarbon Receptor-Induced Signals Up-Regulate Il-22 Production And Inhibit Inflammation In The Gastrointestinal Tract. Gastroenterology. 2011;Jul;141(1):237-48, 248. E1.
34. Zelante T, Iannitti RG, Cunha C, De Luca A, Giovannini G, Pieraccini G et al. Tryptophan Catabolites From Microbiota Engage Aryl Hydrocarbon Receptor And Balance Mucosal Reactivity Via Interleukin-22. Immunity. 2013;Aug 22;39(2):372-85.
35. Maslowski KM, Vieira AT, Ng A, Kranich J, Sierro F, Yu D, Schilter HC, Rolph MS, Mackay F, Artis D, Xavier RJ, Teixeira MM & Mackay CR. Regulation Of Inflammatory Responses By Gut Microbiota And Chemoattractant Receptor GPR43. Nature, 2009;461, 1282-6.
36. Miani M, Le Naour J, Waeckel-Enйe E, Chand Verma S, Straube M, Emond P, Ryffel B, Van Endert P, Sokol H & Diana J. Gut Microbiota-Stimulated Innate Lymphoid Cells Support B-Defensin 14 Expression In Pancreatic Endocrine Cells, Preventing Autoimmune Diabetes. Cell Metabolism, 2018;28,1-16.
37. Shaw SY, Blanchard JF & Bernstein CN. Association Between The Use Of Antibiotics In The First Year Of Life And Pediatric Inflammatory Bowel Disease. Am J Gastroenterol, 2010;105, 2687-92.
38. Treiner E, Duban L, Bahram S, Radosavljevic M, Wanner V, Tilloy F et al. Selection Of Evolutionarily Conserved Mucosal-Associated Invariant T Cells By Mr1. Nature. 2003 Mar 13;422(6928):164-9.
39. Негнаs MY, Hessle C, Telemo E, Midtvedt T, Hanson LA, Wold AE. Immunomodulatory Effects Of Lactobacillus Plantarum Colonizing The Intestine Of Gnotobiotic Rats. Clin Exp Immunol. 1999;116(2):283–290. Doi:10.1046/J.1365-2249.1999.00891.X
40. Kirjavainen PV, El-Nezami HS, Salminen, SJ, Ahokas, JT And Wright, PF. The Effect Of Orally Administered Viable Probiotic And Dairy Lactobacilli On Mouse Lymphocyte Proliferation. FEMS Immunology & Medical Microbiology, 1999;26: 131-135. Doi:10.1111/J.1574-695x.1999.Tb01380.X
41. Mike A, Nagaoka N, Tagami Y et al. Prevention Of B220+ T Cell Expansion And Prolongation Of Lifespan Induced By Lactobacillus Casei In Mrl/Lpr Mice. Clin Exp Immunol. 1999;117(2):368–375. Doi:10.1046/J.1365-2249.1999.00951.X
42. Rescigno M, Rotta G, Valzasina B, Ricciardi-Castagnoli P. Dendritic Cells Shuttle Microbes Across Gut Epithelial Monolayers. Immunobiology. 2001;Dec;204(5):572-81.
43. Niess JH, Brand S, Gu X, Landsman L, Jung S, Mccormick BA et al. CX3CR1-Mediated Dendritic Cell Access To The Intestinal Lumen And Bacterial Clearance. Science. 2005;Jan 14;307(5707):254-8.
44. Haller D & Jobin C. Interaction Between Resident Luminal Bacteria And The Host: Can A Healthy Relationship Turn Sour. J Pediatr Gastroenterol Nutr. 2004 Feb;38(2):123-36.
45. Fuller R. Probiotics In Human Medicine. Gut. 1991 Apr;32(4):439-42.
46. Tannock GW. The Bifidobacterial And Lactobacillus Microflora Of Humans. Clin Rev Allergy Immunol. 2002;Jun;22(3):231-53.
47. Gardiner GE, Casey PG, Casey G, Lynch PB, Lawlor PG, Hill C et al. Relative Ability Of Orally Administered Lactobacillus Murinus To Predominate And Persist In The Porcine

Gastrointestinal Tract. Appl Environ Microbiol. 2004;Apr;70(4):1895-906.
48. Huttenhower C, Gevers D, Knight R, Abubucker S, Badger JH, Chinwalla AT et al. Structure, Function And Diversity Of The Healthy Human Microbiome. Nature. 2012;Jun 13;486(7402):207-14.
49. Gianchecchi E & Fierabracci A. Recent Advances On Microbiota Involvement In The Pathogenesis Of Autoimmunity. Int J Mol Sci. 2019;Jan 11;20(2):E283
50. Lerner A, Jeremias P, Matthias T. The world incidence and prevalence of autoimmune diseases is increasing. International Journal of Celiac Disease, 2015;3(4), 151-155.
51. Medeiros DA & Isenberg DA. Systemic Lupus Erythematosus And Ulcerative Colitis. Lupus, 2009;18, 762-3.
52. Hevia A, Milani C, Lypez P, Cuervo A, Arboleya S, Duranti S et al. Intestinal Dysbiosis Associated With Systemic Lupus Erythematosus. Mbio. 2014 Sep 30;5(5):E01548-14.
53. Mu Q, Kirby J, Reilly CM & Luo XM. Leaky Gut As A Danger Signal For Autoimmune Diseases. Frontiers In Immunology, 2017;8, 598.
54. Van Der Meulen TA, Harmsen HJM, Vich Vila A, Kurilshikov A, Liefers SC, Zhernakova A et al. Shared Gut, But Distinct Oral Microbiota Composition In Primary Sjυgren's Syndrome And Systemic Lupus Erythematosus. Journal Of Autoimmunity, 2019;97, 77-87.
55. Seite S, Bieber T. Barrier function and microbiotic dysbiosis in atopic dermatitis. Clin. Cosmet. Investig. Dermatol, 2015;8, 479–483.
56. Tengah CDP, Lock RJ, Unsworth DJ & Wills AJ. Multiple Sclerosis And Occult Gluten Sensitivity. Neurology, 2004;62, 2326-2327.
57. Reichelt KL & Jensen D. IgA Antibodies Against Gliadin And Gluten In Multiple Sclerosis. Acta Neurologica Scandinavica, 2004;110, 239-241.
58. Shor DB, Barzilai O, Ram M, Izhaky D, Porat-Katz BS, Chapman J, Blank M, Anaya JM & Shoenfeld Y. Gluten Sensitivity In Multiple Sclerosis: Experimental Myth Or Clinical Truth? Ann N Y Acad Sci, 2009;1173, 343-9.
59. Orbach H, Amitai N, Barzilai O, Boaz M, Ram M, Zandman-Goddard G & Shoenfeld Y. Autoantibody Screen In Inflammatory Myopathies High Prevalence Of Antibodies To Gliadin. Annals Of The New York Academy Of Sciences, 2009;1173, 174-179.
60. Vitoria JC, Castaco L, Itxaso R, Bilbao JR, Arrieta A & Garcна-Masdevall MD. Association Of Insulin-Dependent Diabetes Mellitus And Celiac Disease: A Study Based On Serologic Markers. Journal Of Pediatric Gastroenterology And Nutrition, 1998;27, 47-52.
61. Dehner C, Fine R, Kriegel MA. The Microbiome In Systemic Autoimmune Disease: Mechanistic Insights From Recent Studies. Current Opinion In Rheumatology, 2019;31(2), 201-207.
62. Wei F, Xu H, Yan C, Rong C, Liu B, Zhou H. Changes Of Intestinal Flora In Patients With Systemic Lupus Erythematosus In Northeast China. Plos One. 2019;14(3):E0213063.
63. De Paiva CS, Jones DD, Stern MM, Bian F, Moore QL, Corbiere S, et al. Altered Mucosal Microbiome Diversity And Disease Severity In Sjυgren Syndrome. Sci Rep. 2016;Apr 18;6:23561.
64. Jangi S, Gandhi R, Cox LM, Li N, Von Glehn F, Yan R et al. Alterations Of The Human Gut Microbiome In Multiple Sclerosis. Nature Communications, 2016;7, 12015.
65. Scher JU, Sczesnak A, Longman RS, SegataN, Ubeda C, Bielski C et al. Expansion Of Intestinal Prevotella Copri Correlates With Enhanced Susceptibility To Arthritis. elife, 2013;2, e01202.
66. Abrahamsson TR, Jakobsson HE, Andersson AF, Biorksten B, Engstrand L, Jenmalm MC. Low diversity of gut microbiota in infants with atopic eczema. J. Allergy Clin. Immunol, 2012;129, 434-440.
67. Reddel S, Del Chierico F, Quagliariello A, Giancristoforo S, Vernocchi P, Russo A et al. Gut microbiota profile in children affected by atopic dermatitis and evaluation of intestinal persistence of a probiotic mixture. Scientific Reports, 2019;9, 4996.
68. Nylund L, Nermes M, Isolauri E, Salminen S, de Vos WM, Satokari R. Severity of atopic disease inversely correlates with intestinal microbiota diversity and butyrate-producing bacteria. Allergy, 2015;70, 241-244.
69. Lee E, Lee SY, Kang MJ, Kim K, Won S, Kim BJ et al. Clostridia in the gut and onset of atopic dermatitis via eosinophilic inflammation. Ann. Allergy Asthma Immunol, 2016;117, 91-92.e91.
70. Endesfelder, D., Zu Castell, W., Ardissone, A., Davis-Richardson, A. G., Achenbach, P., Hagen, M. Compromised gut microbiota networks in children with anti-islet cell autoimmunity. Diabetes, 2014;63(6), 2006-2014.
71. Bibbo, S., Dore, M. P., Pes, G. M., Delitala, G., Delitala, A.P. Is There A Role For Gut Microbiota In Type 1 Diabetes Pathogenesis? Annals Of Medicine, 2017;49(1), 11-22.
72. Brown, C. T., Davis-Richardson, A. G., Giongo, A., Gano, K. A., Crabb, D. B., Mukherjee, N., et al. Gut Microbiome Metagenomics Analysis Suggests A Functional Model For The Development Of Autoimmunity For Type 1 Diabetes. Plos One, 2011;6(10), E25792.
73. Nagalingam NA, Kao JY & Young VB. Microbial Ecology Of The Murine Gut Associated With The Development Of Dextran Sodium Sulfate-Induced Colitis. Inflammatory Bowel Diseases, 2011;17(4), 917–926.
74. Lerner A & Matthias T. Changes In Intestinal Tight Junction Permeability Associated With Industrial

Food Additives Explain The Rising Incidence Of Autoimmune Disease. Autoimmunity Reviews, 2015;14(6), 479-489.
75. Wu HJ, Ivanov II, Darce J, Hattori K, Shima T, Umesaki Y et al. Gut-Residing Segmented Filamentous Bacteria Drive Autoimmune Arthritis Via T Helper 17 Cells. Immunity, 2010;32(6), 815–827.
76. Lee YK, Menezes JS, Umesaki Y & Mazmanian SK. Proinflammatory T-Cell Responses To Gut Microbiota Promote Experimental Autoimmune Encephalomyelitis. Proceedings Of The National Academy Of Sciences Of The United States Of America, 2011;108(Suppl 1), 4615–4622.
77. Kriegel MA, Sefik E, Hill JA, Wu HJ, Benoist C & Mathis D. Naturally Transmitted Segmented Filamentous Bacteria Segregate With Diabetes Protection In Non-Obese Diabetic Mice. Proceedings Of The National Academy Of Sciences Of The United States Of America, 2011;108(28), 11548–11553.
78. Abdollahi-Roodsaz S, Joosten LA, Koenders MI, Devesa I, Roelofs MF, Radstake TR et al. Stimulation Of Tlr2 And Tlr4 Differentially Skews The Balance Of T Cells In A Mouse Model Of Arthritis. The Journal Of Clinical Investigation, 2008;118(1), 205–216.
79. De Goffau MC, Luopajärvi K, Knip, M, Ilonen J, Ruohtula T, Hɑrkɯnen T et al. Fecal Microbiota Composition Differs Between Children With β-Cell Autoimmunity And Those Without. Diabetes, 2013;62(4), 1238–1244.
80. Maffeis C, Martina A, Corradi M, Quarella S, Nori N, Torriani S, Plebani M, Contreas G & Felis GE. Association Between Intestinal Permeability And Faecal Microbiota Composition In Italian Children With Beta Cell Autoimmunity At Risk For Type 1 Diabetes. Diabetes/Metabolism Research And Reviews, 2016;32(7), 700-709.
81. Liu Y, Alookaran JJ, Rhoads JM. Probiotics In Autoimmune And Inflammatory Disorders. Nutrients, 2018;10(10), E1537.
82. He B, Hoang TK, Wang T, Ferris M, Taylor CM, Tian X, et al. Resetting microbiota by Lactobacillus reuteri inhibits T reg deficiency–induced autoimmunity via adenosine A2A receptors. The Journal of Experimental Medicine. 2016;214(1):107–23.
83. Zheng P, Li Z & Zhou Z. Gut Microbiome In Type 1 Diabetes: A Comprehensive Review. Diabetes/Metabolism Research And Reviews, 2018;34(7), E3043.
84. Bianchetti DGAM, Amelio GS, Lava SAG, Bianchetti MG, Simonetti GD, Agostoni C, et al. D-Lactic Acidosis In Humans: Systematic Literature Review. Pediatric Nephrology, 2018;33(4), 673-681