Brain Behavior and Immunity Integrative 5 (2024) 100046

Contents lists available at ScienceDirect

Brain Behavior and Immunity Integrative

journal homepage: www.editorialmanager.com/bbii

Influence of gut microbiota on autoimmunity: A narrative review

Abhay Sai [a], Geetha B. Shetty [b], Prashanth Shetty [c], Nanjeshgowda H L [d,*]

[a] Department of Dietetics and Nutrition, S.D.M. College of Naturopathy and Yogic Sciences, Ujire (D.K), Karnataka, India
[b] Dean division, Department of Dietetics and Nutrition, S.D.M. College of Naturopathy and Yogic Sciences, Ujire (D.K.), Karnataka, India
[c] Department of Dietetics and Nutrition, S.D.M. College of Naturopathy and Yogic Sciences, Ujire (D.K.), Karnataka, India
[d] Department of Natural Therapeutics, S.D.M. College of Naturopathy and Yogic Sciences, Ujire (D.K.), Karnataka, India

ARTICLE INFO

Keywords:
Gut microbiome
Gut dysbiosis
Immune dysregulation
Autoimmune diseases

ABSTRACT

Gut microbiota consists a majority of bacteriodetes, firmicutes, actinobacteria, proteobacteria, fusobacteria, verrucomicrobiota which has evolved a long way alongside humans where it helps in digestion and even other complex functions which include development of gut lymphoid tissue, vitamin synthesis, polarization of specific immune responses, prevention of colonization by pathobionts. Innate and adaptive immunity has been set in the body in contrast to gut microbiota involving helper T cells and cytotoxic cells along with immunoglobulins. Hence immunomodulatory action of gut microbiota is already been studied and explained along with mast cell degranulation. A few factors like age, diet, antibiotics, and others shape normal gut flora into dysbiosis possibly through translocation of microbes, molecular mimicry, and altered metabolite production bringing unfavoured immunological actions like imbalance in helper T cells and improper gut permeability in the body causing, autoimmunity. Changes in microbes from phylum like bacteriodetes, firmicutes, actinobacteria, and proteobacteria bring the changes that lead to various autoimmune diseases like multiple sclerosis, type 1 diabetes mellitus, rheumatoid arthritis etc. This review explains the possible mechanisms along with causes leading to autoimmunity.

1. Introduction

A failure in immunologic tolerance that triggers an immune response to self-molecules is the cause of autoimmune diseases (Davidson and Diamond, 2001). The majority of the time, it is unknown what triggers the immune system's reaction to self-molecules, however, several studies have shown links to hereditary, environmental, specific infection types, and gut microbiota (Alzabin and Venables, 2012). The gut microbiota, a diverse and dynamic collection of microorganisms found in the human gastrointestinal (GI) tract (Sekirov et al., 2010). But it's still unclear how the gut microbiota affects or causes systemic immunity in autoimmune disorders. Aryl hydrocarbon receptor is a ligand-activated transcription factor that influences host metabolism and immune system formation, making it a master regulator of host-microbiota interactions (Xu et al., 2019). Microbe phyla like *Bacteroidetes, Firmicutes, Actinobacteria, Proteobacteria, Fusobacteria and Verrucomicrobia* constitute more than 90% of the gut microbes (Arumugam et al., 2011; Rinninella et al., 2019) More than 200 distinct genera, including *Lactobacillus, Bacillus, Clostridium, Enterococcus,* and *Ruminicoccus,* make up the *Firmicutes* phylum which are gram-positive in nature. To keep the gut healthy, there must be a complicated interplay between the microbiota and the host immune system.

Functions of these gut microbiota include development of gut associated lymphoid tissue, vitamin synthesis, digestion and fermentation of carbohydrates, polarization of specific immune responses, prevention of colonization by pathobionts (Allin et al., 2015; de Oliveira et al., 2017; Littman and Pamer, 2011; Renz et al., 2012). The annual increases in the incidence and prevalence of autoimmune illnesses globally are estimated to be 19.1% and 12.5%, respectively (Lerner et al., 2015). The gut microbiota, however, may be the cause of or contribute to the development of infectious illnesses and autoimmune disorders when this mutualistic connection is harmed by changes in bacterial activity and diversity, a condition known as dysbiosis (de Oliveira et al., 2017; Honda and Littman, 2012). Numerous variables, including infections, nutrition, exercise, sleep habits, antibiotic exposure, and a number of co-morbidities, might contribute to the instability of the gut microbiota. A general term for the imbalance of the gut microbiota linked to unfavorable outcomes is gut dysbiosis (Hooks and O'Malley, 2017; Martinez et al., 2021).

In order to find future viable strategies based on the gut microbiota

* Correspondence to: Department of Natural Therapeutics, S.D.M College of Naturopathy and Yogic Sciences, Ujire, Belthangady (D.K.) Karnataka 574240, India.
E-mail address: nanjeshgowadhl@gmail.com (N. H L).

https://doi.org/10.1016/j.bbii.2024.100046
Received 18 September 2023; Received in revised form 2 January 2024; Accepted 11 January 2024
Available online 15 January 2024

for avoiding autoimmune illnesses, we here present probable mechanism connecting dysbiosis of the gut microbiota with autoimmune pathways implicated in disease development.

2. Methods

Data were obtained from articles published in English belonging to journals indexed in PubMed from inception to January 2023. Included search terms were related to Gut microbiome, Gut dysbiosis, immune dysregulation, Autoimmune diseases.

3. Interaction between gut microbiota and immune system

Gut microbiota has been coevolving and coexisting with human beings since their birth. These gut microbiotas coexist with the human body and play a role in immunity. despite of powerful immunity system in the body (Iacob et al., 2018). Important roles in inflammatory signaling are played by gut microbial metabolites, which interact with host immune cells both directly and indirectly (Kau et al., 2011). In a state of optimal function and regularity, the immune system and gut microbiota collaborate to integrate the innate and adaptive arms of immunity in a dialogue that determines, modifies, and ends responses in the most suitable way (Belkaid and Hand, 2014).

3.1. Innate immunity enhanced by microbiota

The intestinal tract is where innate immunity, which recognizes microorganisms at the earliest stage, is most developed. There, a range of immune and epithelial cells encode receptor molecules for ligands of microbial origin, including flagellin, muramic acid, peptidoglycan, capsular polysaccharides (PSA) and lipopolysaccharides (LPS), unmethylated CpG motifs typical of bacterial DNA, and peptidoglycan (Platt and Mowat, 2008). There are several immune cells along which has role on the homeostasis of innate immunity by the influence of gut microbiome as follows.

3.1.1. The intestinal antigen presenting cells (APCs)

has been coevolving with the gut microbiota since the starting and hence few adjustments are made for the gut microbiota like Inflammation anergy, which refers to the noninflammatory profile of intestinal macrophages when they meet microbial stimuli in homeostatic settings, are critical for initiating, maintaining and shaping T-cell mediated immune responses comprises of dendritic cells (DCs) and macrophages. DC are unique in their ability to drive primary T-cell responses (Steinman, 2012), also it is a distinctive phenotype that gut macrophages develop as a result of their intimate contact to the intestinal microbiota (Platt and Mowat, 2008). In healthy individual gut because of thick mucosa immunotolerance is maintained, Similarly when exposed to microbial stimuli like Toll-like receptor (TLR) ligands, a group of molecular patterns linked with microbes, intestinal macrophages do not create pro-inflammatory cytokines (Smythies et al., 2010). While in a steady state, the gut microbiota suppresses inflammation and autoimmune by limiting the amount of bacteria that are transported to the mesenteric lymph nodes (MLN) by mononuclear phagocytes (Diehl et al., 2013).

When compared to splenic dendritic cells (DCs) stimulated under the same circumstances, maintain immune tolerance in the gut by generation of tolerogenic T-cell responses (Chirdo et al., 2005). (DCs) of Peyer's patches (lymphoid nodules implanted in the gut wall) produce higher quantities of interleukin-10 (IL-10)(Iwasaki and Kelsall, 1999). In GF(germ free) animals, there were fewer intestinal but not systemic DCs, and monocolonizing GF animals with Escherichia coli was sufficient to draw DCs into the intestines (Williams et al., 2006). The microbiome plays a critical role in gut development since TLR activation was sufficient to teach extraintestinal DC gut-homing imprinting ability. Internal homeostasis and DC function, Such changes in bacterial populations are probably going to have an impact on gut DC function related to immunity and tolerance (Mann and Li, 2014).

3.1.2. Innate lymphoid cells (ILCs)

ILCs are produced from central immune organ bone marrow's common lymphoid progenitors (CLPs) (Montaldo et al., 2015). Researchers have found that the number of ILC1s in the fetal intestinal is extremely low (Bernink et al., 2013, p. 1), suggesting that commensal bacteria are necessary for the formation of ILC1s. In addition, the flexibility of ILC3s to ILC1s transition was hindered in the absence of symbionts (Gury-BenAri et al., 2016). Studies have demonstrated that the microbiota controls the activity of ILC2s in the gut by encouraging the production of IL-25, which strengthens the intestinal barrier that ILC2s mediate (von Moltke et al., 2016).

3.1.3. Neutrophils

are another important part of the innate immunity, are terminally differentiated cells produced in the bone marrow (Y. P. Zhu et al., 2018) and influence of gut microbes on the same has been demonstrated by Ohkubo T et al.l in GF animals where the neutrophils were less in number along with impaired superoxide anion, nitric oxide generation and decreased phagocytic function(Ohkubo et al., 1999). Targeting the hematopoiesis-promoting niche in the bone marrow, the microbiota also controls the generation of neutrophils (D. Zhang and Frenette, 2019). Which senses microbiota-derived signals with their own pattern recognition receptors, including most TLRs (except for TLR3), NODs, and inflammasome (Hayashi et al., 2003). A study found that the cytosolic receptor-nucleotide oligomerization domain 1 (NOD1) recognized peptidoglycan from the gut microbiota and improved the bone marrow neutrophils' capacity to kill (Clarke et al., 2010).

3.1.4. Intestinal mast cells

functions many regulatory mechanisms like blood flow control and coagulation, smooth muscle peristalsis and permeability for electrolyte exchange by intestinal epithelial cells(IEC's) (Bischoff, 2009). It is hypothesized that commensals facilitate mast cell migration into the intestine by inducing CXCR2 ligands from IECs in a TLR-dependent way (Kunii et al., 2011). Also, GF mice were found to have lower intestinal mast cell densities and higher systemic mast cell percentages. Numerous investigations have shown that peptidoglycan and lipopolysaccharide (LPS), which are produced by bacteria, activate macrophage C (MC) through TLR2 and TLR4, respectively (Abraham and St John, 2010). TLR4 triggers the release of cytokines without degranulation, whereas TLR2 mediates the response by first causing degranulation and then cytokine release (Supajatura et al., 2002).

3.1.5. Natural killer cells

were acknowledged that the sole cytotoxic population of ILCs. Their capacity to discriminate between "non-self" and "self" through the signaling pathway system, which is made up of activating and inhibitory receptors, makes them special (Lang et al., 2012). Consequently, Lactobacillus plantarum has the ability to effectively raise the expression of IL22 and members of the natural cytotoxicity receptor (NCR) family in natural killer (NK) cells(Y. Qiu et al., 2017). In vitro, enterotoxigenic Escherichia coli (ETEC)-induced damage to the intestinal epithelium barrier was prevented in NCM460 cells by the transfer of PB NK cells triggered by Lamina propria (Lp). The decrease in transepithelial electrical resistance (TEER) of NCM460 cell monolayers brought on by ETEC may be somewhat countered by PB NK cells induced by Lp. Additionally, the addition of Lp-stimulated NK cells to ETEC-infected NCM460 cells resulted in an increase in the expression of p-Stat3, p-Tyk2, and IL22R1, which are known to be important factors in the function of the intestinal epithelial barrier along with ZO-1, claudin-1, and occluding (Suzuki, 2013).

3.2. Adaptive immunity and microbiota

Adaptive immunity involves specialized immune cells and antibodies that help in maintaining proper health. Two main components of adaptive immunity are B cells (antibody mediated) and T cells (cell mediated).

3.2.1. T cells

of intestine are broadly classified into helper T cells (CD4 +), cytotoxic T cells (CD8 +) and Regulatory T cells (Treg). Intestinal regulatory T (Treg)/effector T (Teff) cell differentiation is induced by the microbiome. Through different mechanisms, commensal bacteria like Clostridium cluster IV, XIVa and XVIII, Bacteroides fragilis, and altered Schaedler flora (ASF) encourage the differentiation and expansion of Treg cells in the gut. Conversely, intestinal Th17 cells are stimulated by microbially derived ATP and epithelium-adhering bacteria like segmented filamentous bacteria (SFB). Listeria monocytogenes and Toxoplasma gondii are examples of intracellular infections that can stimulate antigen-specific Th1 cell development. Microbiota antigens are obtained by (1) goblet cell-associated antigen passages (GAP), (2) transcytosis via microfold cells (M cell), or (3) transepithelial dendritic cells (DC) dendritic cells. T-cell differentiation is subsequently induced in the mesenteric lymph nodes or de novo in the lamina propria. Both Treg and Teff cells are malleable and can, in some circumstances, differentiate into other T-cell subsets as well as each other (Q. Zhao and Elson, 2018).

3.2.2. CD4 + cells

of intestine are mostly present in the lamina propria of the intestine. Naive CD4 + T cells upon specific stimulation, differentiate into Th1(T helper 1), Th2(T helper 2), Th17(T helper 17), regulatory T cell (Treg), follicular T helper (Tfh) (X. Zhu and Zhu, 2020). After differentiation each of the helper cells have specific functions and some of them are being mediated by some of the bacteria and their metabolites like SCFA. Th1 cells are said to protect against intracellular microbes hyperfunction and B. Fragilis helps in systemic development of Th1 response through polysaccharide A (PSA). Th2 cells function against the intestinal parasites and its over response causes allergy. Th17 cells work on promoting and attenuating inflammation, hence control of infection and segmented filamentous bacteria are potent inducers of these cells. Imbalance between Th1 and Th17 occurs upon altered SCFA production causing autoimmunity. Immunotolerance is achieved through Treg cells by regulation of immune responses and clostridium species is said to induce effect on Treg whose irregulation may lead to autoimmunity as shown in Fig. 1.

3.2.3. CD8 + T

(intestinal) cells are usually present in the intraepithelial compartment of the intestine. There are studies showing decreased number and cytotoxicity of these cells in germ free mice which indicates that the gut microbiota has its upper hand over these cells. CD8 + T cells are conditioned by the gut microbiota to influence other peripheral immune cells such marginal zone B cells, plasmacytoid DCs, and invariant natural killer T cells (Qin et al., 2023; Shimizu et al., 2013). The microbiota-derived short-chain fatty acid (SCFA) butyrate promoted cellular metabolism, enhanced memory potential of activated CD8 + T cells, and SCFAs were required for optimal recall responses upon antigen re-encounter also reveal a role for the microbiota in promoting CD8 + T cell long-term survival as memory cells and suggest that microbial metabolites guide the metabolic rewiring of activated CD8 +T cells to enable this transition (Bachem et al., 2019).

The IgA secreting **B cells** of intestine are usually found in the Peyer's patches in the mucous membrane of the small intestine. Toll-like receptor (TLR) and B cell receptor (BCR) signaling coordinate the mucosal B-cell reaction. B cells can function as antigen-presenting cells (APC) and can generate a significant number of cytokines in addition to generating antibodies. Bregs, or regulatory B cells, which produce IL-10, have the ability to reduce autoimmune inflammation (Mu et al., 2020). B-cell activation and response in the gut shape the gut microbiota through IgA secretion. When naïve B cells reach the mature state, they can activate and differentiate toward plasma cells (PC) through two pathways in the gut. B cells can encounter antigens in extrafollicular areas within the lamina propria, a process that induces their transformation into IgM-secreting PC, Alternatively, B cells can enter the follicular areas located in the Peyer's patches, where they closely interact with previously primed CD4 + T cells (Botía-Sánchez et al., 2021).

3.3. Factors influencing on gut

Numerous studies have demonstrated that the structure and function of the gut microbiota vary greatly across people and are influenced by

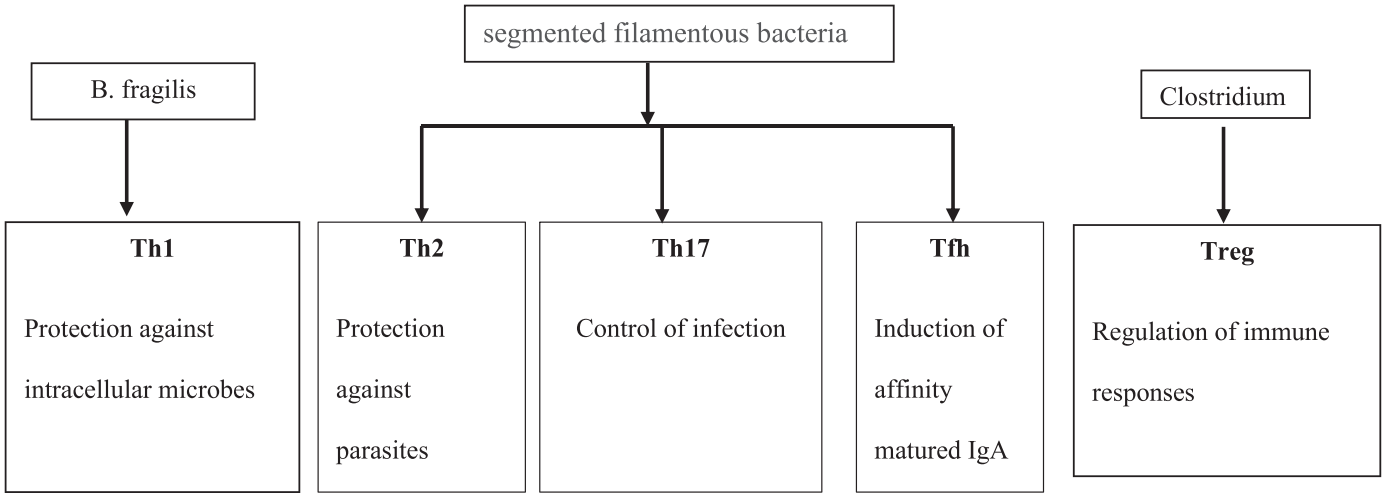

Fig. 1. : Influence of gut microbiota in intestinal CD4 T cells: (1) B fragilis helps in development of T helper 1 (Th1) cell response which is said to have protection against intracellular microbes. (2) Segmented filamentous bacteria are potent inducers of following cells, a) T helper 2 (Th2) cells function against the intestinal parasites and facilitate tissue repair through release of cytokines, b) Th17 controls infection through its action on inflammation through release of cytokines especially interleukin-17 (IL-17). c) Follicular T helper (Tfh) acts on affinity maturation of IgA and help B cells to produce antibodies. (3) Regulatory T cells or Treg cells helps in achieving immunotolerance by regulating immune responses and Clostridum species is one among acting on these.

both intrinsic and dietary variables (He et al., 2018; Moran-Ramos et al., 2020). Age-specific variances may also hold the key to understanding the effects of the human gut microbiome on health (Greenhalgh et al., 2016). A few addition to age-related changes in the GIT microbiota of healthy persons, additional elements such as environment, social context, gender, host genetics, food, and antibiotic use may also have a significant impact on the GIT microbiome's composition (Dethlefsen et al., 2008). Few of the important factors are discussed below.

3.3.1. Age

Chronic, low-grade, systemic inflammation is one of the hallmarks of ageing. It is unknown why levels of cytokines in the tissues and circulation rise with age, despite the fact that age-associated inflammation affects the ageing process (Franceschi et al., 2000) by Netusha Thevaranjan et al.l (Thevaranjan et al., 2017) concludes that microbial dysbiosis develops with age, even in minimal microbiota, and that these changes are sufficient to promote age-associated inflammation. However, they were not yet been able to determine whether this is because specific species are enriched, microbe-microbe interactions change, the ageing microbiota's functional capacity changes (such as changes in the production of SCFA), or the microbiota has lost its ability to compartmentalize (Li et al., 2016).

3.3.2. Diet

Chenhong Zhang et al. evaluated the relative roles of host genetics and diet in forming the gut microbiota and regulating metabolic syndrome symptoms in mice showed that the composition of the gut microbiota closely corresponds with diet. Numerous significant gut population alterations, including the absence of *Bifidobacteria spp*., which defend the gut barrier, occurred in mice fed a diet high in fat. Overall, dietary modifications may account for 57% of the structural variation in gut microbiota, while genetic changes could only account for 12% (C. Zhang et al., 2009). This suggests that diet strongly influences how the gut microbiota develops, and that altering certain critical populations may turn healthy gut microbiota into a disease-causing entity. The "Western" diet, which is heavy in fat and sugar, disrupts the balance of the host's gut microbiome and immune system (Sekirov et al., 2010). In a humanized mouse model, GF mice were given adult human fecal microbiota as a transplant. The microbiota composition of the mice changed when they were switched from a low-fat, high-plant polysaccharide diet to a "Western" diet, resulting in an overgrowth of Firmicutes such as *Clostridium innocuum, Eubacterium dolichum, Catenibacterium mitsuokai*, and *Enterococcus spp*., as well as a significant decrease in several Bacteroides spp. (Turnbaugh et al., 2009) In mice, calorie-restricted diets prevent the growth of *Clostridium coccoides, Lactobacillus spp*., and *Bifidobacteria spp*., all of which are important butyrate producers necessary for colon homeostasis. Carbohydrate-reduced diets also result in enriched populations of bacteria from the Bacteroidetes phyla (Santacruz et al., 2009; Walker et al., 2010). Although it has not been shown in humans, it has been hypothesized that a mother's diet may affect her unborn child's microbiota like the influence of diet on the human colonic microbiota as shown in Table 1.

Table 1
Diet responsive groups of bacteria in human colonic microbiota.

Diet	Bacteria Altered	Effect on Bacteria	Reference
High fat	*Bifidobacteria* spp.	Decreased (absent)	(Walker et al., 2010)
High-fat and high-sugar	*Clostridium innocuum, Catenibacterium mitsuokai and Enterococcus* spp.	Increased	(Walker et al., 2010)
	Bacteroides spp.	Decreased	(Walker et al., 2010)
Carbohydrate-reduced	*Bacteroidetes*	Increased	(Santacruz et al., 2009)

3.3.3. Gut microbiota metabolite - short-chain fatty acids (SCFAs)

one of the gut microbiota-derived metabolites that has received the most attention, are produced from undigested carbohydrates by the phyla Bacteroidetes and Firmicutes (Yang et al., 2022). SCFAs sensitively control Th17 polarization in a context-dependent manner while inducing Th1 cells and suppressing Th2 differentiation (Park et al., 2015). Additionally, SCFAs stimulate the synthesis of IL-10 and IL-22 by effector T cells, which are important immune response mediators (Sun et al., 2018; Yang et al., 2022). The regulation of specific cd4 +T cell subtypes caused by the gut microbiota can result in either a detrimental or favorable effect when the nature of the gut microbiota changes. A SCFA highly produced by Bifidobacteria, also regulates intestinal inflammation by stimulation of G protein-coupled receptors-43 (GPR43) (Lukasova et al., 2011). Additionally, NOD-like receptors (NLRs) such leucine-rich repeat (LRR) and pyrin domain-containing protein 3 (NLRP3) are attenuated by SCFA-mediated GPR43 signalling, which lowers inflammasome activity and the IL-18 production that follows (Nowarski et al., 2015).

3.3.4. Antibiotics

Antibiotics have without a doubt proven to be incredibly effective against a variety of bacterial species (Neuman et al., 2018) but the composition of the microbiota and its possible metabolic functions are altered by macrolides, according to a study of 142 Finnish children aged 2 to 7, compared to children not receiving antibiotics, usage of macrolides increased the abundance of members of the Bacteroidetes and Proteobacteria phyla (including Enterobacteriaceae) and decreased the abundance of Actinobacteria, including the species Bifidobacteria (Korpela et al., 2016). Even though there's not much study on adults, Dethlefsen et al., demonstrated that exposure to two courses of ciprofloxacin quickly affected the gut flora in a 10-month prospective experimental trial of three human volunteers. After 10 months, the microbiota's makeup stabilized, but in a different manner (Dethlefsen and Relman, 2011).

3.3.5. Others

Other factors include host genetics, genetics, and environmental factors like climate and pollution. Studies on the same are very few but there's positive outlook towards its negative effects on gut microbiota by the scientific and medical community. Type I diabetes (T1D), an autoimmune illness occurring with a male to female ratio of 3:2 in populations of European origin aged 15 to 40 years, is associated with the sex-biased nature of diseases, despite the fact that relatively few research has identified this connection (Gale and Gillespie, 2001). Few of other factors will be explained in the possible mechanisms of dysbiosis.

3.4. Possible mechanisms of factors influencing on gut dysbiosis leading to autoimmunity

3.4.1. Translocation of gut microbiota

"Everything has its own place and function," just like the well said proverb the gut microbiota has its own place and function. Due to above mentioned factors, there are chances that the gut microbes translocate themselves from its innate position causing further immune responses. Earlier evidence for the same have been given by Elizabeth Ogunrinde et al.l in her research where they found high levels of plasma lipopolysaccharide in first degree relatives of systemic lupus erythematosus patients which was the proof for bacterial translocation (Ogunrinde et al., 2019). Bacterial symbionts and MAMPs can enter the liver through the portal vein following translocation from the gut, It is possible to find live, metabolically active bacteria in the lung, ovary, breast, and mesenteric lymph nodes (MLNs) of healthy people (Sedman et al., 1994). Patients with chronic liver diseases, such as cirrhosis, alcoholic

liver disease (ALD), and non-alcoholic fatty liver disease (NAFLD), which are linked to increased intestinal permeability, have higher translocation of bacterial symbionts and their constituents, such as LPS (Miele et al., 2013).

3.4.2. *Bacterial metabolites induced activation of immune system*

Speaking of bacterial metabolites, SCFA will be the first one of choice. SCFAs function as anti-inflammatory through mediating IL 10 and Tregs, in its absence or altered levels causes unwanted immune responses (Gill et al., 2018). Evidence for the same has been given in case of inflammatory bowel disease (IBD) where the altered levels of SCFA production was directly linked to altered gut microbiota composition (increase in proteobacteria and reduction in firmicutes and Bacteroidetes ratio (Xu et al., 2019). Indole-3 Lactic Acid (ILA) which is said to reduce Th17 differentiation was significantly depleted in high dietary salt intake as a result of lactobacillus depletion promoting Th17 causing impactful symptoms in humans and mouse (Wilck et al., 2017). Lactobacillus catabolites like indoles are ligands for some if the aryl hydrocarbon receptors which has immunomodulatory function surrounding cytokines (Wang et al., 2019). Altered levels Secondary bile acids are also among the bacterial metabolite causing the unwanted immune responses.

3.5. *Molecular mimicry and trigger of autoimmunity*

Molecular mimicry causes due to similarities between self-antigens and bacterial antigens, cross activation of immunomodulatory cells to attack self-antigens. However, the role of host genetics in the detection of HLA-DR related antigens is crucial for molecular mimicry to trigger an autoimmune response (Z. Zhao et al., 2019).once molecular mimicry load an autoimmune response, attacks can be done on any of the sites in the human body involving both innate and adaptive immunity including Th-1, Th17, ILCs, NKT, T-Reg, and B-lymphocytes.

Example *Prevotella copri* has been hypothesized to imitate synovial membrane self-antigens by presenting antigens in RA, which encourage auto-reactive T cells to cause autoimmunity. It has been demonstrated that two prominent RA autoantigens, filamin A and N-acetylglucosamine-6-sulfatase, are identical to Prevotella generated epitopes (T. Zhao et al., 2022)..

4. Above mentioned factors all together results in autoimmunity

4.1. *Autoimmune disorders and gut microbiota*

Even though autoimmune disorders are a wide category we will be discussing a few here with the altered gut microbiota leading to autoimmune diseases as list in Table 2.

Type 1 diabetes (T1D) is a long-term autoimmune inflammatory condition that damages the pancreatic beta cells that produce insulin, which reduces the amount of insulin produced (Notkins and Lernmark, 2001, p. 1). Ninety percent of beta cells must be destroyed before clinical symptoms appear (Islam et al., 2014). T1D is very important because of the early start of the disease and its chronic nature. Human and animal studies in the past have demonstrated the importance of genetic

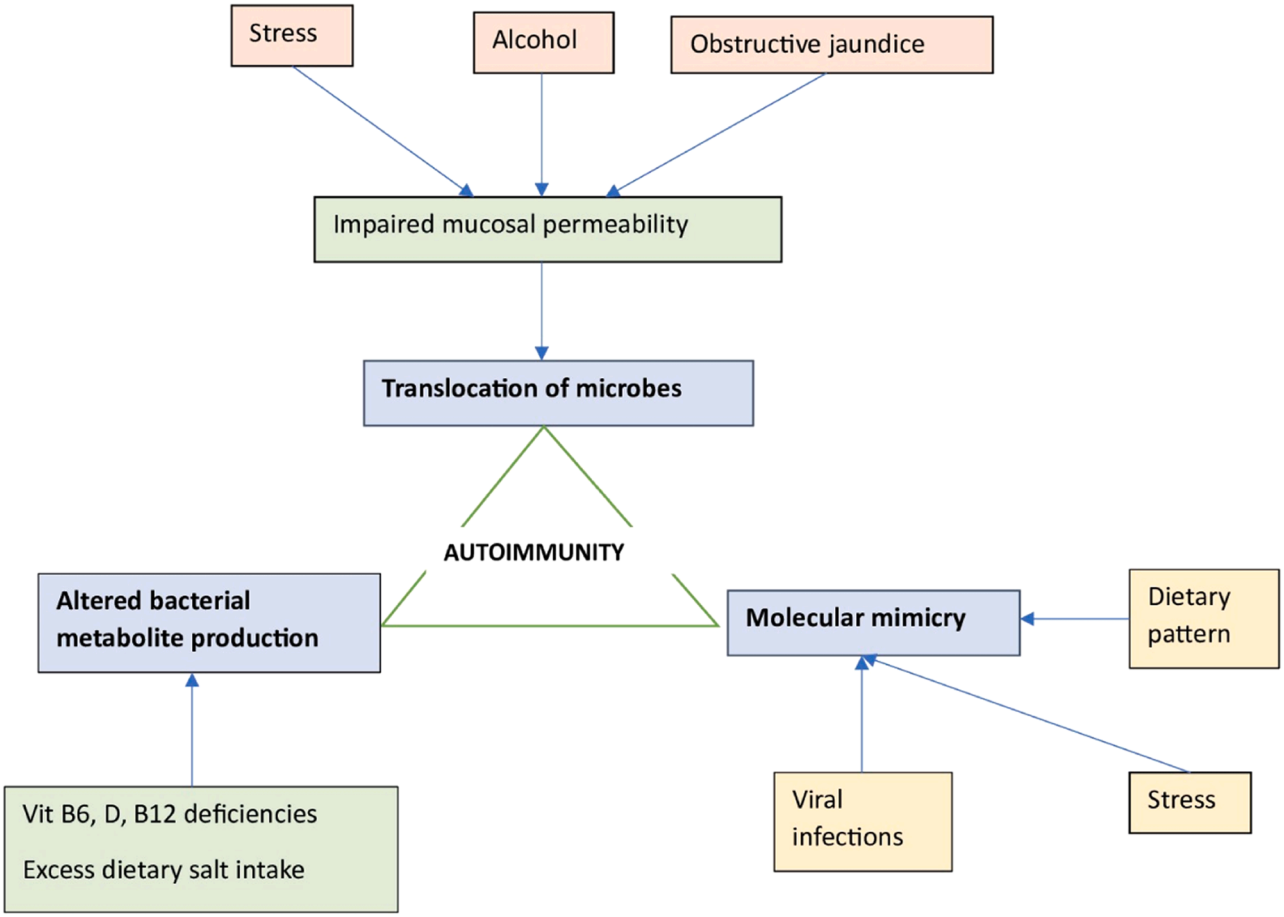

Fig. 2. : Probable mechanism of gut dysbiosis: Stress, alcohol, obstructive jaundice acts on mucosal permeability and causes in its impairment which in turn results in translocation of microbes from its innate position to out. Improper dietary pattern, stress, viral infections produce an unwanted molecular mimicry to occur which results in attacking of body cells by immune system itself. Dietary pattern resulting in deficiencies of B6, D, B12 and excess intake of salt results in altered bacterial production especially short chain fatty acids.

Table 2
List of gut microbiota responsible for autoimmune diseases.

Autoimmune diseases	Gut microbiome	Reference
Rheumatoid arthritis	Increased *Prevotella copri* and *Lactobacillus* levels Decreased *Bacteriodetes, Bifidobacteria* levels	(T.Zhao et al., 2022b)
Inflammatory bowel disease	Reduced microbial diversity Reduced abundance of firmicutes Increase in proteobacteria	(Lee and Chang, 2021)
Multiple sclerosis	higher abundance of *Akkermansia* and *Methanobrevibacter* lower abundance of Prevotella, Bacteroides	(Mirza et al., 2020)
Type 1 diabetes mellitus	Reduced microbial diversity Increase in *Bacteriodetes* Reduced *bifidobacteria*	(Zheng et al., 2018)
Systemic lupus erythematosus	Reduced Firmicutes/ Bacteroidetes Increased proteobacteria Increased *Ruminococcus*	(L.Zhang et al., 2021)

variables such as human leukocyte antigen (HLA) DQ and DRB in the aetiology of illness; however, more recent research suggests that environmental factors such gut colonising bacteria play a major role as well (Alkanani et al., 2015). Individuals with preclinical T1D have gut microbiotas that are dominated at the phylum level by Bacteroidetes, with few butyrate-producing bacteria, low community stability, and decreased bacterial and functional diversity. Nevertheless, these modifications appear to occur after to the development of autoantibodies predictive of type 1 diabetes, indicating that the gut microbiota may play a role in the development of clinical illness rather than in the first stages of β-cell autoimmunity (Knip and Siljander, 2016).

IBD is characterised by continuous colonic LP inflammation, which is caused by an overreaction to bacterial antigens, enhanced DC, and macrophage activation through TLRs (Tatiya-aphiradee et al., 2019), with excessive cytokine production and persistent inflammation, which are mostly seen in Crohn's disease and ulcerative colitis (Baumgart and Carding, 2007). The necrotic intestinal mucosal cells activate macrophages to produce IL-6 and TGF-β through STAT3 and RORγt, which induce the differentiation of Th17 cells. IL-6 and low levels of TGF-β can stimulate T cells to differentiate into Th 17. High-levels of TGF-β can inhibit the production of Th 17 cells and promote the production of Treg cells. SFB can induce Th17 cells to secrete IL-17 and IL-22 and promote intestinal inflammation. The *Clostridium* spp. resulted in the production of Tregs. *B. fragilis* induced Tregs by the IBD-related genes Atg16L1 and NOD2. *B. thetaiotaomicron* recapitulate the effects of gut microbiota and induce Tregs to influence the immune system in IBD. *Klebsiella pneumoniae* improve the induction of Th1 cell to induce the occurrence of inflammation (P. Qiu et al., 2022).

Rheumatoid arthritis (RA) is a long-term autoimmune inflammatory disease that is typified by the generation of autoantibodies and the destruction of bone in many joints (Harris, 1990). It has been shown by recent research that more than 100 genetic susceptibility loci are implicated in RA (Okada et al., 2014). It is unclear, therefore, exactly what environmental elements influence the onset of RA. Anti-citrullinated protein antibody (ACPA) immunoglobulin A (IgA) has been demonstrated to be detectable prior to the start of arthritis (Nielen et al., 2004). RA may have its origins at mucosal locations, including the gut and mouth cavity. The onset of RA may be correlated with *Porphyromonas gingivalis*, a prominent pathogenic bacteria of periodontal disorders (Lappin et al., 2013). Variations in the gut microbiota's makeup during the course of RA. In the active RA phase, the abundance of Lactobacillus *salivarius, Collinsella,* and *Akkermansia* is increased, while that of *Haemophilus spp*. is decreased. At an early stage, the levels of Prevotella copri and Lactobacillus are increased, while those of Bacteroidetes, Bifidobacteria, and *Eubacterium rectale* are decreased. Which leads to activation of B cell and T cell with results in imbalance between T cells and Th17 leads to activation B cells which progress with the production of autoantibodies (anti-citrullinated protein antibody and rheumatoid factor) (T. Zhao et al., 2022a).

Multiple sclerosis (MS) is a chronic immune-mediated disease of the brain and spinal cord, resulting in physical and cognitive impairment in young adults (Reich et al., 2018). Axonal damage and demyelination, which are the histopathological hallmarks of multiple sclerosis, are believed to result from an immune-mediated onslaught involving B cells, macrophages, CD4 + T cells, and cytotoxic CD8 + T cells on myelinated axons and the myelin sheath (Baecher-Allan et al., 2018). It is hypothesised that the pathophysiology of neurological disorders involves the gut microbiome (Cryan et al., 2020) and It's been proposed that changes to the gut microbiota might be an additional disease mechanism in multiple sclerosis since these disruptions could cause the immune system to become activated for pro-inflammatory purposes (Kadowaki and Quintana, 2020). MS and gut microbiota study shows lower presence of the genera *Bacterioides,* Parabacteroides*,* Prevotella*, and* Lactobacillus*; on the other hand, there is a higher abundance* of *Akkermansia*, *Ruminococcus*, *Blautia, and Bifidobacterium*. Endotoxemia and neuroinflammation are also giving waves of altered SCFA production *(*Altieri et al., 2023*)*. The phyla and genera changes are truly significant in all the above-mentioned conditions and hence treatment perspective should focus on balancing the gut microbiota along with the symptomatic treatment.

Chronic autoimmune illness known as systemic lupus erythematosus (SLE) is characterized by the production of autoantibodies and immune complexes, which can harm many organs, including the kidney, skin, and central nervous system (Kaul et al., 2016). The intricate pathophysiology of SLE is conventionally believed to be strongly linked to both inherited and environmental risk factors (Tsokos, 2020). More and more data has demonstrated that intestinal infection-related dysbacteriosis, which is intimately linked to the onset of SLE, occurs in varying degrees in both SLE humans and SLE mice (Chen et al., 2021). Potential mechanisms of gut microbiota dysbiosis in SLE, *E. gallinarum* has the ability to cross the intestinal barrier and go into livers, MVs, and MLNs. In addition, *E. gallinarum* increased the expression of ERV gp70 in the liver, which aided in the promotion of systemic autoimmunity. *R. gnavus* encapsulates itself to aid in intestine colonisation and expresses a B-cell superantigen to increase the generation of IgA antibodies. Moreover, *R. gnavus* has the ability to synthesize a glucorhamnan inflammatory polysaccharide that stimulates DCs to release TNF-α via TLR4. Furthermore, *R. gnavus* has the ability to impair the function of the intestinal barrier, which raises the levels of LPS and calprotectin in sera and stool samples, respectively. The weakened intestinal barrier then makes the intestinal commensal *R. gnavus* antigen visible, which triggers the molecule's mimicking to create anti-dsDNA autoantibodies and aggravates lupus nephritis (Pan et al., 2021).

5. Conclusion

Gut microbiota as explained helps in attaining immune homeostasis in the body. Its further functions are yet another scope for study in this field. The dysbiosis or its alteration caused various factors starting from genetics to environment including lifestyle causes various autoimmune conditions. Changes in the gut microbiota affect both innate and adaptive immunity by influencing the neutrophil-activating capacity, impairing CD4 and CD8 T cells, and affecting B cells, among other immune responses. This presented mechanistic evidence for future beneficial strategies based on the gut microbiota for avoiding autoimmune illnesses, which links dysbiosis of the gut microbiota with autoimmune pathways implicated in disease development.

Author contributions

All authors have equally participated in contributions to this research article, either in terms of the concept, methodology or

validation phases of the proposed protocol. All authors have read and agreed to the published version of the manuscript.

Funding

No specific grant was given to this research by funding organizations in the public, private, or not-for-profit sectors.

CRediT authorship contribution statement

H L Nanjeshgowda: Data curation, Project administration, Validation, Writing – review & editing. **Shetty Prashanth:** Formal analysis, Supervision, Visualization. **Shetty Geetha B:** Data curation, Project administration, Validation. **Sai Abhay:** Conceptualization, Methodology, Resources, Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

All data described in the review are included in this published article.

References

Abraham, S.N., St John, A.L., 2010. Mast cell-orchestrated immunity to pathogens. Nat. Rev. Immunol. 10 (6), 440–452. https://doi.org/10.1038/nri2782.

Alkanani, A.K., Hara, N., Gottlieb, P.A., Ir, D., Robertson, C.E., Wagner, B.D., Frank, D.N., Zipris, D., 2015. Alterations in intestinal microbiota correlate with susceptibility to type 1 diabetes. Diabetes 64 (10), 3510–3520. https://doi.org/10.2337/db14-1847.

Allin, K.H., Nielsen, T., Pedersen, O., 2015. Mechanisms in endocrinology: gut microbiota in patients with type 2 diabetes mellitus. Eur. J. Endocrinol. 172 (4), R167–R177. https://doi.org/10.1530/EJE-14-0874.

Altieri, C., Speranza, B., Corbo, M.R., Sinigaglia, M., Bevilacqua, A., 2023. Gut-microbiota, and multiple sclerosis: background, evidence, and perspectives. Nutrients 15 (4), 942. https://doi.org/10.3390/nu15040942.

Alzabin, S., Venables, P.J., 2012. Etiology of autoimmune disease: past, present and future. Expert Rev. Clin. Immunol. 8 (2), 111–113. https://doi.org/10.1586/eci.11.88.

Arumugam, M., Raes, J., Pelletier, E., Paslier, D.L., Yamada, T., Mende, D.R., Fernandes, G.R., Tap, J., Bruls, T., Batto, J.M., Bertalan, M., Borruel, N., Casellas, F., Fernandez, L., Gautier, L., Hansen, T., Hattori, M., Hayashi, T., Kleerebezem, M., Zeller, G., 2011. Enterotypes of the human gut microbiome. Nature 473 (7346), 174–180. https://doi.org/10.1038/NATURE09944.

Bachem, A., Makhlouf, C., Binger, K.J., de Souza, D.P., Tull, D., Hochheiser, K., Whitney, P.G., Fernandez-Ruiz, D., Dähling, S., Kastenmüller, W., Jönsson, J., Gressier, E., Lew, A.M., Perdomo, C., Kupz, A., Figgett, W., Mackay, F., Oleshansky, M., Russ, B.E., Bedoui, S., 2019. Microbiota-derived short-chain fatty acids promote the memory potential of antigen-activated CD8+ T cells. Immunity 51 (2), 285–297.e5. https://doi.org/10.1016/j.immuni.2019.06.002.

Baecher-Allan, C., Kaskow, B.J., Weiner, H.L., 2018. Multiple sclerosis: mechanisms and immunotherapy. Neuron 97 (4), 742–768. https://doi.org/10.1016/j.neuron.2018.01.021.

Baumgart, D.C., Carding, S.R., 2007. Inflammatory bowel disease: Cause and immunobiology. Lancet 369 (9573), 1627–1640. https://doi.org/10.1016/S0140-6736(07)60750-8.

Belkaid, Y., Hand, T.W., 2014. Role of the microbiota in immunity and inflammation. Cell 157 (1), 121–141. https://doi.org/10.1016/j.cell.2014.03.011.

Bernink, J.H., Peters, C.P., Munneke, M., te Velde, A.A., Meijer, S.L., Weijer, K., Hreggvidsdottir, H.S., Heinsbroek, S.E., Legrand, N., Buskens, C.J., Bemelman, W.A., Mjösberg, J.M., Spits, H., 2013. Human type 1 innate lymphoid cells accumulate in inflamed mucosal tissues. Nat. Immunol. 14 (3), 221–229. https://doi.org/10.1038/ni.2534.

Bischoff, S.C., 2009. Physiological and pathophysiological functions of intestinal mast cells. Semin. Immunopathol. 31 (2), 185–205. https://doi.org/10.1007/s00281-009-0165-4.

Botía-Sánchez, M., Alarcón-Riquelme, M.E., Galicia, G., 2021. B Cells and Microbiota in Autoimmunity. Article 9 Int. J. Mol. Sci. 22 (9). https://doi.org/10.3390/ijms22094846.

Chen, B., Jia, X.-M., Xu, J.-Y., Zhao, L.-D., Ji, J.-Y., Wu, B.-X., Ma, Y., Li, H., Zuo, X.-X., Pan, W.-Y., Wang, X.-H., Ye, S., Tsokos, G.C., Wang, J., Zhang, X., 2021. An Autoimmunogenic and proinflammatory profile defined by the gut microbiota of patients with untreated systemic lupus erythematosus. Arthritis Rheumatol. 73 (2), 232–243. https://doi.org/10.1002/art.41511.

Chirdo, F.G., Millington, O.R., Beacock-Sharp, H., Mowat, A.M., 2005. Immunomodulatory dendritic cells in intestinal lamina propria. Eur. J. Immunol. 35 (6), 1831–1840. https://doi.org/10.1002/eji.200425882.

Clarke, T.B., Davis, K.M., Lysenko, E.S., Zhou, A.Y., Yu, Y., Weiser, J.N., 2010. Recognition of peptidoglycan from the microbiota by Nod1 enhances systemic innate immunity. Nat. Med. 16 (2), 228. https://doi.org/10.1038/nm.2087.

Cryan, J.F., O'Riordan, K.J., Sandhu, K., Peterson, V., Dinan, T.G., 2020. The gut microbiome in neurological disorders. Lancet Neurol. 19 (2), 179–194. https://doi.org/10.1016/S1474-4422(19)30356-4.

Davidson, A., Diamond, B., 2001. Autoimmune diseases. N. Engl. J. Med. 345 (5), 340–350. https://doi.org/10.1056/NEJM200108023450506.

Dethlefsen, L., Relman, D.A., 2011. Incomplete recovery and individualized responses of the human distal gut microbiota to repeated antibiotic perturbation. Proc. Natl. Acad. Sci. USA 108 (SUPPL. 1), 4554–4561. https://doi.org/10.1073/PNAS.1000087107/SUPPL_FILE/SD01.TXT.

Dethlefsen, L., Huse, S., Sogin, M.L., Relman, D.A., 2008. The pervasive effects of an antibiotic on the human gut microbiota, as revealed by deep 16S rRNA. PLoS Biol. 6 (11), e280 https://doi.org/10.1371/JOURNAL.PBIO.0060280.

Diehl, G.E., Longman, R.S., Zhang, J.-X., Breart, B., Galan, C., Cuesta, A., Schwab, S.R., Littman, D.R., 2013. Microbiota restricts trafficking of bacteria to mesenteric lymph nodes by CX(3)CR1(hi) cells. Nature 494 (7435), 116–120. https://doi.org/10.1038/nature11809.

Franceschi, C., Bonafè, M., Valensin, S., Olivieri, F., De Luca, M., Ottaviani, E., De Benedictis, G., 2000. Inflamm-aging: an evolutionary perspective on immunosenescence. Ann. N. Y. Acad. Sci. 908 (1), 244–254. https://doi.org/10.1111/J.1749-6632.2000.TB06651.X.

Gale, E.A.M., Gillespie, K.M., 2001. Diabetes and gender. Diabetologia 44 (1), 3–15. https://doi.org/10.1007/S001250051573/METRICS.

Gill, P.A., van Zelm, M.C., Muir, J.G., Gibson, P.R., 2018. Review article: short chain fatty acids as potential therapeutic agents in human gastrointestinal and inflammatory disorders. Aliment. Pharmacol. Ther. 48 (1), 15–34. https://doi.org/10.1111/apt.14689.

Greenhalgh, K., Meyer, K.M., Aagaard, K.M., Wilmes, P., 2016. The human gut microbiome in health: establishment and resilience of microbiota over a lifetime. Environ. Microbiol. 18 (7), 2103–2116. https://doi.org/10.1111/1462-2920.13318.

Gury-BenAri, M., Thaiss, C.A., Serafini, N., Winter, D.R., Giladi, A., Lara-Astiaso, D., Levy, M., Salame, T.M., Weiner, A., David, E., Shapiro, H., Dori-Bachash, M., Pevsner-Fischer, M., Lorenzo-Vivas, E., Keren-Shaul, H., Paul, F., Harmelin, A., Eberl, G., Itzkovitz, S., Amit, I., 2016. The spectrum and regulatory landscape of intestinal innate lymphoid cells are shaped by the microbiome. Cell 166 (5), 1231–1246.e13. https://doi.org/10.1016/j.cell.2016.07.043.

Harris, E.D., 1990. Rheumatoid arthritis. pathophysiology and implications for therapy. N. Engl. J. Med. 322 (18), 1277–1289. https://doi.org/10.1056/NEJM199005033221805.

Hayashi, F., Means, T.K., Luster, A.D., 2003. Toll-like receptors stimulate human neutrophil function. Blood 102 (7), 2660–2669. https://doi.org/10.1182/blood-2003-04-1078.

He, Y., Wu, W., Zheng, H.M., Li, P., McDonald, D., Sheng, H.F., Chen, M.X., Chen, Z.H., Ji, G.Y., Zheng, Z.D.X., Mujagond, P., Chen, X.J., Rong, Z.H., Chen, P., Lyu, L.Y., Wang, X., Wu, C.B., Yu, N., Xu, Y.J., Zhou, H.W., 2018. Regional variation limits applications of healthy gut microbiome reference ranges and disease models. Nat. Med. 24 (10), 1532–1535. https://doi.org/10.1038/S41591-018-0164-X.

Honda, K., Littman, D.R., 2012. Micro Infect. Dis. Inflamm. https://doi.org/10.1146/annurev-immunol-020711-074937.

Hooks, K.B., O'Malley, M.A., 2017. Dysbiosis and its discontents. mBio 8 (5). https://doi.org/10.1128/MBIO.01492-17.

Iacob, S., Iacob, D.G., Luminos, L.M., 2018. Intestinal microbiota as a host defense mechanism to infectious threats. Front. Microbiol. 9, 3328 https://doi.org/10.3389/fmicb.2018.03328.

Islam, S.T., Srinivasan, S., Craig, M.E., 2014. Environmental determinants of type 1 diabetes: a role for overweight and insulin resistance. J. Paediatr. Child Health 50 (11), 874–879. https://doi.org/10.1111/jpc.12616.

Iwasaki, A., Kelsall, B.L., 1999. Freshly Isolated Peyer's patch, but not spleen, dendritic cells produce interleukin 10 and induce the differentiation of T helper type 2 cells. J. Exp. Med. 190 (2), 229–240.

Kadowaki, A., Quintana, F.J., 2020. The gut–CNS axis in multiple sclerosis. Trends Neurosci. 43 (8), 622–634. https://doi.org/10.1016/j.tins.2020.06.002.

Kau, A.L., Ahern, P.P., Griffin, N.W., Goodman, A.L., Gordon, J.I., 2011. Human nutrition, the gut microbiome and the immune system. Nature 474 (7351), 327–336. https://doi.org/10.1038/nature10213.

Kaul, A., Gordon, C., Crow, M.K., Touma, Z., Urowitz, M.B., van Vollenhoven, R., Ruiz-Irastorza, G., Hughes, G., 2016. Systemic lupus erythematosus. Nat. Rev. Dis. Prim. 2, 16039 https://doi.org/10.1038/nrdp.2016.39.

Knip, M., Siljander, H., 2016. The role of the intestinal microbiota in type 1 diabetes mellitus. Article 3 Nat. Rev. Endocrinol. 12 (3). https://doi.org/10.1038/nrendo.2015.218.

Korpela, K., Salonen, A., Virta, L.J., Kekkonen, R.A., Forslund, K., Bork, P., de Vos, W.M., 2016. Intestinal microbiome is related to lifetime antibiotic use in Finnish pre-school children. Article 1 Nat. Commun. 7 (1). https://doi.org/10.1038/ncomms10410.

Kunii, J., Takahashi, K., Kasakura, K., Tsuda, M., Nakano, K., Hosono, A., Kaminogawa, S., 2011. Commensal bacteria promote migration of mast cells into the intestine. Immunobiology 216 (6), 692–697. https://doi.org/10.1016/j.imbio.2010.10.007.

Lang, P.A., Lang, K.S., Xu, H.C., Grusdat, M., Parish, I.A., Recher, M., Elford, A.R., Dhanji, S., Shaabani, N., Tran, C.W., Dissanayake, D., Rahbar, R., Ghazarian, M., Brüstle, A., Fine, J., Chen, P., Weaver, C.T., Klose, C., Diefenbach, A., Ohashi, P.S.,

2012. Natural killer cell activation enhances immune pathology and promotes chronic infection by limiting CD8+ T-cell immunity. Proc. Natl. Acad. Sci. 109 (4), 1210–1215. https://doi.org/10.1073/pnas.1118834109.
Lappin, D.F., Apatzidou, D., Quirke, A.-M., Oliver-Bell, J., Butcher, J.P., Kinane, D.F., Riggio, M.P., Venables, P., McInnes, I.B., Culshaw, S., 2013. Influence of periodontal disease, porphyromonas gingivalis and cigarette smoking on systemic anti-citrullinated peptide antibody titres. J. Clin. Periodontol. 40 (10), 907–915. https://doi.org/10.1111/jcpe.12138.
Lee, M., Chang, E.B., 2021. Inflammatory Bowel Diseases (IBD) and the microbiome—searching the crime scene for clues. Gastroenterology 160 (2), 524–537. https://doi.org/10.1053/j.gastro.2020.09.056.
Lerner, A., Jeremias, P., Matthias, T., 2015. The world incidence and prevalence of autoimmune diseases is increasing. Article 4 Int. J. Celiac Dis. 3 (4). https://doi.org/10.12691/ijcd-3-4-8.
Li, H., Qi, Y., Jasper, H., 2016. Preventing age-related decline of gut compartmentalization limits microbiota dysbiosis and extends lifespan. Cell Host Microbe 19 (2), 240–253. https://doi.org/10.1016/J.CHOM.2016.01.008.
Littman, D.R., Pamer, E.G., 2011. Role of the commensal microbiota in normal and pathogenic host immune responses. Cell Host Microbe 10 (4), 311–323. https://doi.org/10.1016/J.CHOM.2011.10.004.
Lukasova, M., Malaval, C., Gille, A., Kero, J., Offermanns, S., 2011. Nicotinic acid inhibits progression of atherosclerosis in mice through its receptor GPR109A expressed by immune cells. J. Clin. Investig. 121 (3), 1163–1173. https://doi.org/10.1172/JCI41651.
Mann, E.R., Li, X., 2014. Intestinal antigen-presenting cells in mucosal immune homeostasis: crosstalk between dendritic cells, macrophages and B-cells. World J. Gastroenterol.: WJG 20 (29), 9653–9664. https://doi.org/10.3748/wjg.v20.i29.9653.
Martinez, J.E., Kahana, D.D., Ghuman, S., Wilson, H.P., Wilson, J., Kim, S.C.J., Lagishetty, V., Jacobs, J.P., Sinha-Hikim, A.P., Friedman, T.C., 2021. Unhealthy lifestyle and gut dysbiosis: a better understanding of the effects of poor diet and nicotine on the intestinal microbiome. Front. Endocrinol. 12, 649. https://doi.org/10.3389/FENDO.2021.667066/BIBTEX.
Miele, L., Marrone, G., Lauritano, C., Cefalo, C., Gasbarrini, A., Day, C., Grieco, A., 2013. Gut-liver axis and microbiota in NAFLD: Insight pathophysiology for novel therapeutic target. Curr. Pharm. Des. 19 (29), 5314–5324.
Mirza, A., Forbes, J.D., Zhu, F., Bernstein, C.N., Van Domselaar, G., Graham, M., Waubant, E., Tremlett, H., 2020. The multiple sclerosis gut microbiota: a systematic review. Mult. Scler. Relat. Disord. 37, 101427 https://doi.org/10.1016/j.msard.2019.101427.
von Moltke, J., Ji, M., Liang, H.-E., Locksley, R.M., 2016. Tuft-cell-derived IL-25 regulates an intestinal ILC2-epithelial response circuit. Nature 529 (7585), 221–225. https://doi.org/10.1038/nature16161.
Montaldo, E., Juelke, K., Romagnani, C., 2015. Group 3 innate lymphoid cells (ILC3s): origin, differentiation, and plasticity in humans and mice. Eur. J. Immunol. 45 (8), 2171–2182. https://doi.org/10.1002/eji.201545598.
Moran-Ramos, S., Lopez-Contreras, B.E., Villarruel-Vazquez, R., Ocampo-Medina, E., Macias-Kauffer, L., Martinez-Medina, J.N., Villamil-Ramirez, H., León-Mimila, P., Del Rio-Navarro, B.E., Ibarra-Gonzalez, I., Vela-Amieva, M., Gomez-Perez, F.J., Velazquez-Cruz, R., Salmeron, J., Reyes-Castillo, Z., Aguilar-Salinas, C., Canizales-Quinteros, S., 2020. Environmental and intrinsic factors shaping gut microbiota composition and diversity and its relation to metabolic health in children and early adolescents: a population-based study. Gut Microbes 11 (4), 900–917. ⟨https://doi.org/10.1080/19490976.2020.1712985/SUPPL_FILE/KGMI_A_1712985_SM3571.ZIP⟩.
Mu, Q., Edwards, M.R., Swartwout, B.K., Cabana Puig, X., Mao, J., Zhu, J., Grieco, J., Cecere, T.E., Prakash, M., Reilly, C.M., Puglisi, C., Bachali, P., Grammer, A.C., Lipsky, P.E., Luo, X.M., 2020. Gut microbiota and bacterial DNA suppress autoimmunity by stimulating regulatory B cells in a murine model of lupus. Front. Immunol. 11, 593353 https://doi.org/10.3389/fimmu.2020.593353.
Neuman, H., Forsythe, P., Uzan, A., Avni, O., Koren, O., 2018. Antibiotics in early life: dysbiosis and the damage done. FEMS Microbiol. Rev. 42 (4), 489–499. https://doi.org/10.1093/FEMSRE/FUY018.
Nielen, M.M.J., van Schaardenburg, D., Reesink, H.W., van de Stadt, R.J., van der Horst-Bruinsma, I.E., de Koning, M.H.M.T., Habibuw, M.R., Vandenbroucke, J.P., Dijkmans, B.A.C., 2004. Specific autoantibodies precede the symptoms of rheumatoid arthritis: a study of serial measurements in blood donors. Arthritis Rheum. 50 (2), 380–386. https://doi.org/10.1002/art.20018.
Notkins, A.L., Lernmark, A., 2001. Autoimmune type 1 diabetes: resolved and unresolved issues. J. Clin. Investig. 108 (9), 1247–1252. https://doi.org/10.1172/JCI14257.
Nowarski, R., Jackson, R., Gagliani, N., de Zoete, M.R., Palm, N.W., Bailis, W., Low, J.S., Harman, C.C.D., Graham, M., Elinav, E., Flavell, R.A., 2015. Epithelial IL-18 equilibrium controls barrier function in colitis. Cell 163 (6), 1444–1456. https://doi.org/10.1016/j.cell.2015.10.072.
Ogunrinde, E., Zhou, Z., Luo, Z., Alekseyenko, A., Li, Q.-Z., Macedo, D., Kamen, D.L., Oates, J.C., Gilkeson, G.S., Jiang, W., 2019. A link between plasma microbial translocation, microbiome, and autoantibody development in first-degree relatives of systemic lupus erythematosus patients. Arthritis Rheumatol. 71 (11), 1858. https://doi.org/10.1002/art.40935.
Ohkubo, T., Tsuda, M., Suzuki, S., El Borai, N., Yamamura, M., 1999. Peripheral blood neutrophils of germ-free rats modified by in vivo granulocyte–colony-stimulating factor and exposure to natural environment. Scand. J. Immunol. 49 (1), 73–77. https://doi.org/10.1046/j.1365-3083.1999.00456.x.
Okada, Y., Wu, D., Trynka, G., Raj, T., Terao, C., Ikari, K., Kochi, Y., Ohmura, K., Suzuki, A., Yoshida, S., Graham, R.R., Manoharan, A., Ortmann, W., Bhangale, T., Denny, J.C., Carroll, R.J., Eyler, A.E., Greenberg, J.D., Kremer, J.M., Plenge, R.M., 2014. Genetics of rheumatoid arthritis contributes to biology and drug discovery. Nature 506 (7488), 376–381. https://doi.org/10.1038/nature12873.
de Oliveira, G.L.V., Leite, A.Z., Higuchi, B.S., Gonzaga, M.I., Mariano, V.S., 2017. Intestinal dysbiosis and probiotic applications in autoimmune diseases. Immunology 152 (1), 1–12. https://doi.org/10.1111/IMM.12765.
Pan, Q., Guo, F., Huang, Y., Li, A., Chen, S., Chen, J., Liu, H., Pan, Q., 2021. Gut microbiota dysbiosis in systemic lupus erythematosus: novel insights into mechanisms and promising therapeutic strategies. Front. Immunol. 12. ⟨https://www.frontiersin.org/articles/10.3389/fimmu.2021.799788⟩.
Park, J., Kim, M., Kang, S.G., Jannasch, A.H., Cooper, B., Patterson, J., Kim, C.H., 2015. Short-chain fatty acids induce both effector and regulatory T cells by suppression of histone deacetylases and regulation of the mTOR-S6K pathway. Mucosal Immunol. 8 (1), 80–93. https://doi.org/10.1038/mi.2014.44.
Platt, A.M., Mowat, A.M., 2008. Mucosal macrophages and the regulation of immune responses in the intestine. Immunol. Lett. 119 (1–2), 22–31.
Qin, Y., Bao, X., Zheng, M., 2023. CD8+ T-cell immunity orchestrated by iNKT cells. Front. Immunol. 13. ⟨https://www.frontiersin.org/articles/10.3389/fimmu.2022.1109347⟩.
Qiu, P., Ishimoto, T., Fu, L., Zhang, J., Zhang, Z., Liu, Y., 2022. The gut microbiota in inflammatory bowel disease. Front. Cell. Infect. Microbiol. 12, 733992 https://doi.org/10.3389/fcimb.2022.733992.
Qiu, Y., Jiang, Z., Hu, S., Wang, L., Ma, X., Yang, X., 2017. Lactobacillus plantarum enhanced IL-22 production in natural killer (NK) cells that protect the integrity of intestinal epithelial cell barrier damaged by enterotoxigenic Escherichia coli. Article 11 Int. J. Mol. Sci. 18 (11). https://doi.org/10.3390/ijms18112409.
Reich, D.S., Lucchinetti, C.F., Calabresi, P.A., 2018. Multiple sclerosis. N. Engl. J. Med. 378 (2), 169–180. https://doi.org/10.1056/NEJMra1401483.
Renz, H., Brandtzaeg, P., Hornef, M., 2012. The impact of perinatal immune development on mucosal homeostasis and chronic inflammation. Nat. Rev. Immunol. 12 (1), 9–23. https://doi.org/10.1038/NRI3112.
Rinninella, E., Raoul, P., Cintoni, M., Franceschi, F., Abele, G., Miggiano, D., Gasbarrini, A., Mele, M.C., 2019. microorganisms what is the healthy gut microbiota composition? A changing ecosystem across age. Environ., Diet., Dis. 7, 14. https://doi.org/10.3390/microorganisms7010014.
Santacruz, A., Marcos, A., Wärnberg, J., Martí, A., Martin-Matillas, M., Campoy, C., Moreno, L.A., Veiga, O., Redondo-Figuero, C., Garagorri, J.M., Azcona, C., Delgado, M., García-Fuentes, M., Collado, M.C., Sanz, Y., 2009. Interplay between weight loss and gut microbiota composition in overweight adolescents. Obesity 17 (10), 1906–1915. https://doi.org/10.1038/OBY.2009.112.
Sedman, P.C., Macfie, J., Sagar, P., Mitchell, C.J., May, J., Mancey-Jones, B., Johnstone, D., 1994. The prevalence of gut translocation in humans. Gastroenterology 107 (3), 643–649. https://doi.org/10.1016/0016-5085(94)90110-4.
Sekirov, I., Russell, S.L., Caetano M Antunes, L., Finlay, B.B., 2010. Gut microbiota in health and disease. Physiol. Rev. 90 (3), 859–904. https://doi.org/10.1152/PHYSREV.00045.2009.
Shimizu, K., Asakura, M., Shinga, J., Sato, Y., Kitahara, S., Hoshino, K., Kaisho, T., Schoenberger, S.P., Ezaki, T., Fujii, S., 2013. Invariant NKT cells induce plasmacytoid dendritic cell (DC) cross-talk with conventional DCs for efficient memory CD8+ T cell induction. J. Immunol. 190 (11), 5609–5619. https://doi.org/10.4049/jimmunol.1300033.
Smythies, L.E., Shen, R., Bimczok, D., Novak, L., Clements, R.H., Eckhoff, D.E., Bouchard, P., George, M.D., Hu, W.K., Dandekar, S., Smith, P.D., 2010. Inflammation anergy in human intestinal macrophages is due to smad-induced IκBα expression and NF-κB inactivation. J. Biol. Chem. 285 (25), 19593–19604. https://doi.org/10.1074/jbc.M109.069955.
Steinman, R.M., 2012. Decisions about dendritic cells: past, present, and future. Annu. Rev. Immunol. 30, 1–22. https://doi.org/10.1146/annurev-immunol-100311-102839.
Sun, M., Wu, W., Chen, L., Yang, W., Huang, X., Ma, C., Chen, F., Xiao, Y., Zhao, Y., Ma, C., Yao, S., Carpio, V.H., Dann, S.M., Zhao, Q., Liu, Z., Cong, Y., 2018. Microbiota-derived short-chain fatty acids promote Th1 cell IL-10 production to maintain intestinal homeostasis. Nat. Commun. 9, 3555 https://doi.org/10.1038/s41467-018-05901-2.
Supajatura, V., Ushio, H., Nakao, A., Akira, S., Okumura, K., Ra, C., Ogawa, H., 2002. Differential responses of mast cell Toll-like receptors 2 and 4 in allergy and innate immunity. J. Clin. Investig. 109 (10), 1351–1359. https://doi.org/10.1172/JCI14704.
Suzuki, T., 2013. Regulation of intestinal epithelial permeability by tight junctions. Cell. Mol. Life Sci. 70 (4), 631–659. https://doi.org/10.1007/s00018-012-1070-x.
Tatiya-aphiradee, N., Chatuphonprasert, W., Jarukamjorn, K., 2019. Immune response and inflammatory pathway of ulcerative colitis. J. Basic Clin. Physiol. Pharmacol. 30 (1), 1–10. https://doi.org/10.1515/jbcpp-2018-0036.
Thevaranjan, N., Puchta, A., Schulz, C., Naidoo, A., Szamosi, J.C., Verschoor, C.P., Loukov, D., Schenck, L.P., Jury, J., Foley, K.P., Schertzer, J.D., Larché, M.J., Davidson, D.J., Verdú, E.F., Surette, M.G., Bowdish, D.M.E., 2017. Age-associated microbial dysbiosis promotes intestinal permeability, systemic inflammation, and macrophage dysfunction. Cell Host Microbe 21 (4), 455–466.e4. https://doi.org/10.1016/J.CHOM.2017.03.002.
Tsokos, G.C., 2020. Autoimmunity and organ damage in systemic lupus erythematosus. Nat. Immunol. 21 (6), 605–614. https://doi.org/10.1038/s41590-020-0677-6.
Turnbaugh, P.J., Ridaura, V.K., Faith, J.J., Rey, F.E., Knight, R., Gordon, J.I., 2009. The effect of diet on the human gut microbiome: a metagenomic analysis in humanized gnotobiotic mice. Sci. Transl. Med. 1 (6) https://doi.org/10.1126/SCITRANSLMED.3000322/SUPPL_FILE/3000322_TABLES_S1_S16.ZIP.

Walker, A.W., Ince, J., Duncan, S.H., Webster, L.M., Holtrop, G., Ze, X., Brown, D., Stares, M.D., Scott, P., Bergerat, A., Louis, P., McIntosh, F., Johnstone, A.M., Lobley, G.E., Parkhill, J., Flint, H.J., 2010. Dominant and diet-responsive groups of bacteria within the human colonic microbiota, 2, 5 ISME J. 2011 5 (2), 220–230. https://doi.org/10.1038/ismej.2010.118.

Wang, G., Huang, S., Wang, Y., Cai, S., Yu, H., Liu, H., Zeng, X., Zhang, G., Qiao, S., 2019. Bridging intestinal immunity and gut microbiota by metabolites. Cell. Mol. Life Sci.: CMLS 76 (20), 3917–3937. https://doi.org/10.1007/s00018-019-03190-6.

Wilck, N., Matus, M.G., Kearney, S.M., Olesen, S.W., Forslund, K., Bartolomaeus, H., Haase, S., Mähler, A., Balogh, A., Markó, L., Vvedenskaya, O., Kleiner, F.H., Tsvetkov, D., Klug, L., Costea, P.I., Sunagawa, S., Maier, L., Rakova, N., Schatz, V., Müller, D.N., 2017. Salt-responsive gut commensal modulates TH17 axis and disease. Nature 551 (7682), 585–589. https://doi.org/10.1038/nature24628.

Williams, A.M., Probert, C.S.J., Stepankova, R., Tlaskalova-Hogenova, H., Phillips, A., Bland, P.W., 2006. Effects of microflora on the neonatal development of gut mucosal T cells and myeloid cells in the mouse. Immunology 119 (4), 470–478. https://doi.org/10.1111/j.1365-2567.2006.02458.x.

Xu, H., Liu, M., Cao, J., Li, X., Fan, D., Xia, Y., Lu, X., Li, J., Ju, D., Zhao, H., 2019. The dynamic interplay between the gut microbiota and autoimmune diseases. J. Immunol. Res. 2019, 7546047 https://doi.org/10.1155/2019/7546047.

Yang, W., Yu, T., Cong, Y., 2022. CD4+ T cell metabolism, gut microbiota, and autoimmune diseases: implication in precision medicine of autoimmune diseases. Precis. Clin. Med. 5 (3), pbac018 https://doi.org/10.1093/pcmedi/pbac018.

Zhang, C., Zhang, M., Wang, S., Han, R., Cao, Y., Hua, W., Mao, Y., Zhang, X., Pang, X., Wei, C., Zhao, G., Chen, Y., Zhao, L., 2009. Interactions between gut microbiota, host genetics and diet relevant to development of metabolic syndromes in mice, 2, 4 ISME J. 2010 4 (2), 232–241. https://doi.org/10.1038/ismej.2009.112.

Zhang, D., Frenette, P.S., 2019. Cross talk between neutrophils and the microbiota. Blood 133 (20), 2168–2177. https://doi.org/10.1182/blood-2018-11-844555.

Zhang, L., Qing, P., Yang, H., Wu, Y., Liu, Y., Luo, Y., 2021. Gut microbiome and metabolites in systemic lupus erythematosus: link, mechanisms and intervention. Front. Immunol. 12, 686501 https://doi.org/10.3389/fimmu.2021.686501.

Zhao, Q., Elson, C.O., 2018. Adaptive immune education by gut microbiota antigens. Immunology 154 (1), 28–37. https://doi.org/10.1111/imm.12896.

Zhao, T., Wei, Y., Zhu, Y., Xie, Z., Hai, Q., Li, Z., Qin, D., 2022a. Gut microbiota and rheumatoid arthritis: from pathogenesis to novel therapeutic opportunities. Front. Immunol. 13. ⟨https://www.frontiersin.org/articles/10.3389/fimmu.2022.1007165⟩.

Zhao, T., Wei, Y., Zhu, Y., Xie, Z., Hai, Q., Li, Z., Qin, D., 2022b. Gut microbiota and rheumatoid arthritis: from pathogenesis to novel therapeutic opportunities. Front. Immunol. 13, 1007165 https://doi.org/10.3389/fimmu.2022.1007165.

Zhao, Z., Ren, J., Dai, C., Kannapell, C.C., Wang, H., Gaskin, F., Fu, S.M., 2019. Nature of T cell epitopes in lupus antigens and HLA-DR determines autoantibody initiation and diversification. Ann. Rheum. Dis. 78 (3), 380–390. https://doi.org/10.1136/annrheumdis-2018-214125.

Zheng, P., Li, Z., Zhou, Z., 2018. Gut microbiome in type 1 diabetes: a comprehensive review. Diabetes/Metab. Res. Rev. 34 (7), e3043 https://doi.org/10.1002/dmrr.3043.

Zhu, X., Zhu, J., 2020. CD4 T helper cell subsets and related human immunological disorders. Int. J. Mol. Sci. 21 (21), 8011. https://doi.org/10.3390/ijms21218011.

Zhu, Y.P., Padgett, L., Dinh, H.Q., Marcovecchio, P., Blatchley, A., Wu, R., Ehinger, E., Kim, C., Mikulski, Z., Seumois, G., Madrigal, A., Vijayanand, P., Hedrick, C.C., 2018. Identification of an early unipotent neutrophil progenitor with pro-tumoral activity in mouse and human bone marrow. Cell Rep. 24 (9), 2329–2341.e8. https://doi.org/10.1016/j.celrep.2018.07.097.