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Gut Normal Flora (Microbiota) and Probiotic Supplementation on Autoimmune (Inflammatory) Diseases: Multiple Sclerosis

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Abstract— Due to its large numbers, the human gut microbiota has a significant role in the human body controlling some metabolic processes and other functions. The immune system has a strong relation with microbiota where each of them affects the other. Microbiota controls some of the immune functions and responses (in local intestinal or in systematic), and the immune system keeps bacterial presence without harming the body. Studies show that change in microbiota composition (dysbiosis) is associated with some autoimmune diseases, this could increase the inflammatory response or reduce it. Probiotic, which is a bacterial combination that produces metabolites, is used to restore the bacterial and immune status in the intestinal environment. In autoimmune diseases, the main target is to reduce the pro-inflammatory cell and increase the anti-inflammatory response by increasing regulatory T cells.

Index Terms— Guts, Diseases, Autoimmune, Gut Normal Flora, Inflammatory, Multiple Sclerosis, Probiotic.

1 Introduction

THE term Microbiota/Microbiome reflects the colonization of bacteria, archaea, protists, fungi, and viruses in the human body. With different sites of the body, there are different microbial communities, the human gut has a large bacterial population. These bacteria affect human health in multiple ways one of them is their interaction with the immune system. Each of the immune systems and gut microbiota regulates the other to maintain the hemostasis so that no disease occurs, and the bacteria can live in the human body. Any change in the microbiota would have a significant effect on the immune system, since that is true why not use specific combinations of bacteria called probiotics supplementation to treat autoimmune (inflammatory) disorders.

In this paper, we review the relationship between the immune system and gut microbiota, how the microbiota influences the shaping of the immune system, how the immune system contains bacterial foreign presence in the body. Then we discuss the bacterial and immune status in some diseases, and finally, we discuss some microbial changes on the immune system to reduce the severity of the autoimmune disease using probiotics.

2 Method

2.1 Data Sources

PubMed, Embase, Scopus, Web of Science, Google Scholar, and other scientific sites were searched for studies that discuss Gut Normal flora (Microbiota) and Probiotic Supplementation on Autoimmune (Inflammatory) Diseases and Multiple Sclerosis. References list from searched and retrieved resources was reviewed for applicable studies. Following is the review from the articles studied concerning the current topic.

2.2 Study Selection

Two reviewers independently examined the articles and their abstracts to eliminate duplicates, reviews, and uncontrolled trials. The trials were avoided if their outcomes were not related to probiotic combination products.

2.3 Statistical Analysis

Data from selected studies were extracted and reformed. Included studies were weighted by sample size vs. clinical improvement. The data were analyzed manually - since the number of candidate articles was small – and 28 articles were excluded on basis of title and abstract.

3 Result Analysis

A total of 65 articles were retrieved, and 37 articles were concerned related to the subjected topic. These articles were found homogenous and can be well combined and analyzed.

3.1 The Gut Microbiota

Usually, bacteria are linked to pathogenic types against the Immune system causing disease and illness, but in the case of the normal flora, this is not the whole story. The gut microbiota -normal flora- is a group of bacterial colonization in multiple sites of the human body, the largest quantities of microorganisms are in the gut -digestive tract- with a huge variety of strains and spices. Not only bacteria are found; other microorganisms including viruses, parasites, and fungi are also present and colonize the digestive tract[1].

3.2 The Microbiota Composition

Intestinal microbiotas consist of more than 1500 species from more than 50 different phyla[2]. The most abundant phyla are Bacteroidetes and Firmicutes followed by Proteobacteria, Fusobacteria, Tenericutes, Actinobacteria, and Verrucomi-

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crobia contributing 90% of the human normal flora[3]. This composition of microorganisms is affected by several factors including diet, age, antibiotic treatment, host genetics, and other factors[2].

Moving in the gastrointestinal tract the microbiota composition change, in the stomach and the small intestine there are relatively small species of bacteria[4], this change when reaching the colon which contains the largest population of the microbial ecosystem[2]. Most of the bacteria in the gut are anaerobes but, in the cecum, the density of aerobic bacteria is increased. Bacteroidetes are the most abundant family, and the species represent 30% of the bacteria, which indicates they are significant in human health[5].

3.3 Functions of Gut Mi crobiota

The gut microbiota binds to the intestinal surface and colonize, the presence of it is compared with the secretion of various substances as metabolic products, these substances affect human health either in a bad or good way.

The gut microbiota plays a significant function in the body including; protection against pathogen by colonizing in the mucosal membrane preventing any external pathogen from attaching along with its ability to produce antimicrobial substances, it also helps in the digestion of some molecules thus help in diet, it controls the epithelial cell proliferation and differentiation, has a role on insulin resistance and its secretion, affect the brain-gut axis thus affect the neurological functions and it also plays important role in immune system development and enhances[6].

The immune Control over Gut Microbiota

a. Control over the bacterial location.

The key point in the relationship between the immune system and the microbiome is maintaining homeostasis, the immune system must have control over the gut bacteria otherwise disease may occur[7].

Due to the number of bacteria in the intestine; intestinal immunity faces a unique challenge in maintaining its control over microbiota, it must control the exposer of this bacteria to other body tissues.

The containing happens in two levels: one, minimizing the contact between the bacteria and the epithelial cells of the intestine. Second, by preventing its leakage from the intestine and reach the systematic immune compartment[7], see Fig. 1.

First: Minimize the interaction between the bacteria and epithelial cells.

The intestinal wall is contributed by goblet cells, these cells produce a large amount of mucin glycoprotein giving the intestine a thick layer. Colon, for example, has two mucin layers due to a large number of bacteria there, the outer layer holds the bacteria while the inner layer is resistant to bacterial penetration[8]. In the small intestine, there are no two layers of mucin, but the bacterial presence is controlled by an antibacterial protein produced from intestinal epithelial cells such as RegIIIγ which is an antimicrobial lectin that limits the bacterial penetration of the intestinal mucosa[9].

Another component that helps in preventing bacterial infection throw the epithelial cells is the immunoglobulin A (IgA). IgA is specific for the intestinal bacteria, it is produced after a small number of bacteria pass the epithelial layer and are caught by the dendritic cells underlying the epithelial layer[10]. This dendritic cell then reaches the Peyer's patches

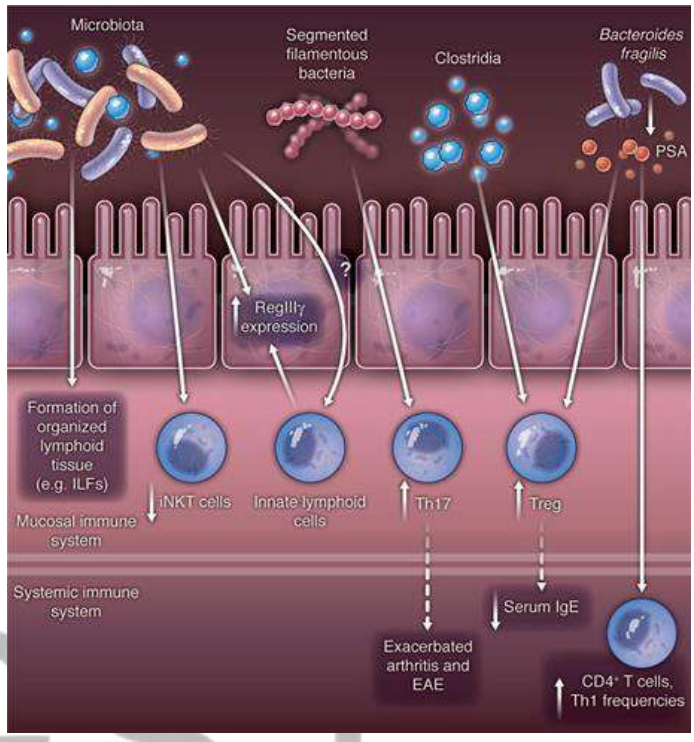

Fig 1: The way of immune control over gut microbiota location, Reprinted with permission from Ref. 7

to interact with T and B cells. This process produces the activated B cells (plasma cells) which migrate to the lamina propria to secret IgA which gets the secretory piece when passing the epithelial cell and becomes IgAs[11].

Second: Prevent the bacteria from reaching the systematic immune.

Although the bacteria are contained in the lumen of the intestine, its huge number makes the escape possible, but these escaped bacteria are phagocytosed in the lamina propria by the phagocytic cells (Dendritic cells) and then migrate to the closest lymph node. The bacteria cannot move furthermore than the first lymph node and since the dendritic cell reach the lymph node it activates th e adaptive immunity (T and B cells) [10]. Lymphoid cells -especially cell-producing Interleukin (IL)-22- that reside in the lamina propria also play a role by releasing cytokines profile, thus prevent bacterial escape [12]. Also, the presence of IgA is crucial in preventing bacterial escape, in the mice that lack IgA there was a significant increment in serum IgG against the normal flora (gut microbiota) indicating that the bacteria reach systematic immunity[13].

b. Control over microbiota composition.

Microbiota composition is affected by many factors such as diet and nutrition, and it was shown that the immune system products also affect the microbiota composition. Certain antibacterials produced by cells lining the intestine (epithelial

cells) affect the composition, one example is the α- defensin which is an antibacterial peptide produced by the Paneth cells in the small intestine epithelia. In the mice model, when there is a defect in the human α- defensin-5 incorporated in mice gene (over-expression or under-expression) there was no change in the number of microbiota but the change was in the bacterial community composition[7].

Defect in the immune system can also affect the microbiota composition, such as in an experiment performed in mice lack T-bet transcription factor (from Tbx21 -/-) which regulate the inflammatory response of the innate and the adaptive immune system and the Rag2 -/- which lack the adaptive immunity it shows a development of ulcerative colitis in a microbiota manner[14]. The change in the immune system induces a change in the microbiota the causes microbiota "dysbiotic" causing the disease. In another experiment with mice lacking TLR5 – a flagellin receptor for bacteria-, the mice have metabolic syndrome with insulin resistance, hyperlipidemia, and an increase in fat deposition combined with the alteration on the microbiome composition[15].

4 Discussion

Mice with defected NLRP6 component – an inflammatory component secreted from epithelial cells – exhibit alteration in microbiota composition. These alterations increase the abundance of Bacteroidetes phylum which enhance the chemicals' susceptibility and increase the intestinal inflammatory cell recruitment causing colitis[16]. This all indicates that the immune system manages the microbiota ecosystem in its composition, diversity, and location [7], in Table 1.

TABLE 1
IMMUNE SYSTEM DEFECT IN MICE MODELS AND ITS EFFECT ON THE INTESTIINAL STATUS

Immune response defect in	RESULT
α- defensin	Change in the microbiota composition
Tbx21 and Rag2	Develop ulcerative colitis
TLR5	Metabolic syndrome developed
NLRP6	Increase in Bacteroidetes phylum, increase susceptibility to chemicals and increase inflammatory cell recruitment to intestinal site.

4.1 The effect of microbiota on the immune system, immune system shaping, and homeostasis.

Microbiota also affects the immune system (the local intestinal immune system and the systematic immune response) and has a role in maintaining balance in the human body. Using a germ-free model (animals grew up in a sterile environment with no exposure to any microorganisms), scientists can determine the role of microbiota[17] , see Fig. 2.

Microbiota and immune cells

a. Microbiota and innate immune cells

Antigen-presenting cells (APCs):

In the intestine, the APCs have a significant role in protecting

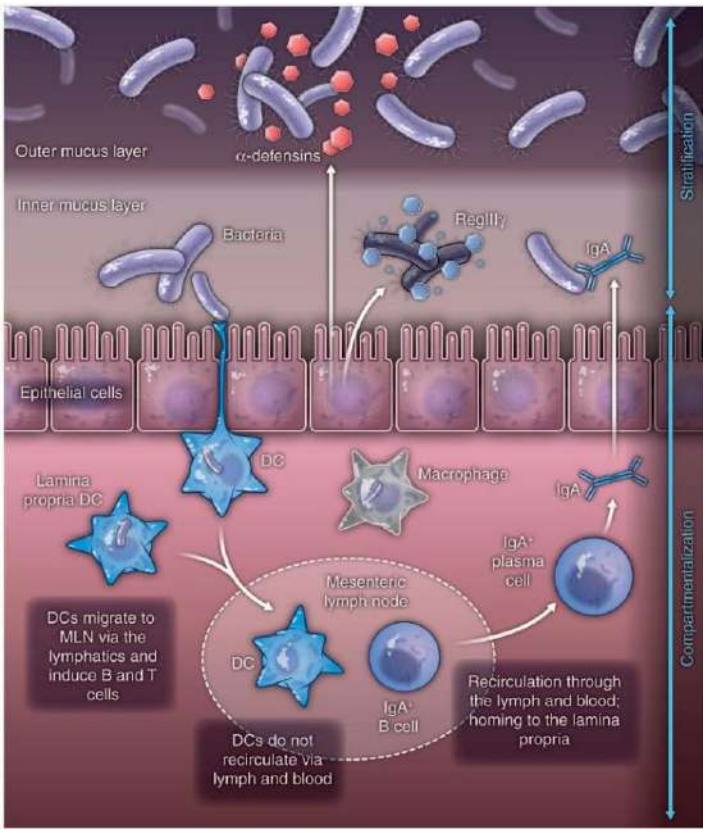

Fig 2: : Microbiota and innate immune cell interactions, Reprinted with permission from Ref. [7]

the body against pathogens while getting immune tolerance to normal gut microbiota. The dendritic cells in Peyer's patches produce a high level of IL-10 compared with the splenic dendritic cells that had been activated with a similar condition[18]. For macrophages, the cells develop a unique phenotype "inflammation energy" with a low ability to induce inflammation. The intestinal macrophages do not generate pro-inflammatory cytokines when the cells encounter microbial ligands binding to the Toll-like receptor on its surface. The APCs in the germ-free mice model show a decrease in the number of intestinal dendritic cells but not the systematic, while for gut macrophages the number was normal [17].

Neutrophils:

The germ-free mice model shows neutropenia alongside the improved superoxide anion and nitric oxide generation, decreased in the phagocytosis function in the peripheral blood of the GF mice [17]. The change of the neutrophil status cannot happen when the microbiota is introduced to the animal. The gut microbiota also affects the bone marrow neutrophils, the peptidoglycan of the gut microbiota is recognized by the cyto-

solic receptor-nucleotide oligomerization domain 1 (NOD1), which enhances the killing activity of the bone marrow neutrophils[19].

Natural Killer:

Natural killers are an immune cell that detects and eliminates converted and virally infected cells either by generating interferon-gamma (IFN-γ) or by perforin molecules. In the gut mucosa, there are two types of NK cells both show the natural cytotoxicity receptor NKp46 (Np46+) [20]. One of these types is similar to the normal NK cells but the other has lower activity in secreting IFN-γ with no perforin. These normal gut NKs also express the nuclear hormone receptor retinoic acid receptor-related orphan receptor gamma t (RORγt) with the production of interleukin- 22 (IL-22) [17]. In the germ-free mice, the NKp46+ were absent, this suggests that microbiota may play role in IL-22+ NKp46+ cells differentiation[21].

Mast cells:

In the normal GI tract, the mast cells are representing 2-3% of the lamina propria (LP) cells with regulatory functions as controlling the blood flow and the coagulation cases, the peristalsis movement of the smooth mussels in the intestines [17]. In germ-free mice, the number of intestinal mast cells decreases while the number of systematic mast cells were increased in the blood [22]. This result indicates that the gut microbiota has a role in the migration of mast cells from blood to the intestine by the induction of CXC chemokine receptor 2 (CXCR2) from the intestinal epithelial cells (IECs) depending on the MyD88 adaptor molecule in the TLR signaling pathway (the main pathway in sensing common cells microbiota and trigger several responses to maintain host-microbial homeostasis) [17].

Intestinal Epithelial cells:

The epithelial cells of the small intestine are the primary physical barrier against the bacteria, separating the lumen from the underlying sterile tissue. This layer of cells also has immune effects like secreting antimicrobial peptides, some cytokines, and chemokines[17]. Using the TLR-MyD88 pathway the microbiota activates the repair of damaged intestinal epithelial and enhances the induction of antimicrobial proteins such as RegIIIγ. This expression is activated by lipopolysaccharides (LPS) of the microbiota or by flagellin[11].

In the germ-free mice, there was a reduction in the proliferation rate of the intestinal epithelial and low expression of the antimicrobial genes. This supports the relationship between the gut microbiota as stimuli for some pathways required in the immune response[17].

b. Microbiota and innate immune cells

T cells:

In the intestine CD4+ (T helper) cells are the most abundant type, and by the stimuli effect four subclasses are formed Th1, Th2, Th17, Treg. Th1 is important in immunity against intracellular infection, Th2 for extracellular infection, and Treg is important in maintaining the balance while any defect in its function can beacon autoimmune disease as for Th17 and Th1. The microbiota affects Th cells inside (intestinal immunity) and outside (systematic immunity) [7].

Polysaccharide A (PSA) of Bacteroides fragilis induces the systematic Th1 development leading to the suppression of Th17 by the production of IL-10 and it also activates the TLR2 of Treg that reduces mucosal damage making Bacteroides fragilis successful normal flora. Segmented filamentous bacteria (SFB) can pass throw the mucus layer of the intestine, the bacteria reach Th17 in the underlying area, and then it induces its activity which promotes the healing of the epithelial layer. Clostridial strains (IV and XIVa) induces Treg (anti-inflammatory) and increases the IL-10[23]. The gut microbiota DNA also can induce the TLR9 signaling pathway which is important in maintaining homeostasis and limit the Treg conversion.

The Treg in the intestinal lamina propria is unique due to its activation with TGF-β and rhetoric acid (unlike other Treg cells that are induced un the thymus) so it is called inducible T reg (iTreg) and it could produce IL-10 [7].

B cells:

Most of the B cells in the intestinal site are in the Peyer's patches with the ability to produce immunoglobulins (Ig), most of the Ig produced are the IgA in the mucous layer. The IgA here has no memory response; thus, the type of IgA differs according to the bacterial composition in lamina propria. In germ-free mice, there was a reduced number of IgA in lamina propria [17].

The effect of Gut microbiota on the systematic immune system:

The gut microbiota affects the systematic immune cells, for instance, the Clostridia clusters IV and XIVa increase the iTreg and affect the systematic inflammatory response that reduces the serum IgE thus less inflammatory response and less tissue damage.

Bacteroides fragilis as mentioned earlier have PSA that shows that it has a function in the development of T- cell response. The induction of Bacteroides fragilis in germ-free mice causes increment in the CD4+ cells count. The PSA also increases Th1 in serum [7].

4.2 Gut microbiota and host intestinal environmental changes.

The effect of microbiota is not only on the immune system it also affects the metabolism in our body, knowing that the microbiota influences the health state of an individual helps in choosing proper treatment and understand the status of the immune system.

A metabolic syndrome is a group of abnormalities in the body -including insulin resistance, obesity, dyslipidemia, and hypertension - may be caused by other factors such as diet, lifestyle, emotional states like stress and depression but recently the role of the gut microbiome and its composition enter the explanation after the explanation of immune system- microbiota relation [24].

In mice with defects in some microbial molecule (like flagellin) sensing by the intestinal immunity features of metabolic syndrome were observed. Also in mice lack of NLRP3 or NLRP6 (pattern recognition receptor) has a reduction in intestinal inflammation due to the overgrowth of *Prevotellaceae* and *Porphyromonadaceae* members of the *Bacteroidetes* [7].

4.3 Gut microbiota in Autoimmune and inflammatory disorder

Gut microbiota shows to be affecting both innate and adaptive immunity beyond the local gut immune system affecting the body stability, any changes in the gut microbiota composition will lead to a significant impact on the immune system causing autoimmune and inflammatory disorders. Examples of some disorders that have been linked with the gut microbiota: Inflammatory bowel disease (IBD), Diabetes type 1, Systematic upus erythematosus, and Multiple sclerosis[25].

Gut microbiota and Multiple sclerosis:

Multiple sclerosis (MS) is an autoimmune inflammatory neurological disorder categorized by demyelination on neuron cells. Symptoms include weakness, loss of vision, dizziness, cognitive impairment, depression, and bowel discomfort. This disease is characterized by the increased inflammatory response, the destruction of myelin sheaths, the multiplication of astrocytes, microglial activation, gliosis, axonal degeneration. Myelin component in the neurons is targeted by the immune system, this attack is mediated by CD4+ cells (T helper) specifically Th1 cells (interferon- γ producing T cells) and/or Th17 (IL-17 producing T cell) this leads to the degradation of the brain axon along with the axon of the multiple sclerosis patients[26]. As shown earlier, gut microbiota is important for the immune system both intestinal and systematic with a specific effect on the T helper cell, its regulation, pro-inflammatory, and anti-inflammatory activity, antioxidant, and a metabolic effect[27].

There is strong evidence about the connection between gut health and the central nervous system (CNS) a term called the gut-brain axis. An alteration in this axis more specifically an alteration in the gut will induce inflammation that affects the brain and nerves as is shown in MS animals and humans.

All this gives a new way to think about the treatment strategy, a change in diet or some supplementation could help in reducing the severity. This disease causes neuroinflammation, in a study of 20 patients with MS shows a decrease in Faecalibacterium, Prevotella, and Anaerostipes bacteria[27].

Another study performed on 60 patients with multiple sclerosis shows microbiota alterations in the MS, an increase in the Methanobrevibacter and Akkermansia, and decreases in Butyricimonas compared with the control group. The change in the microbial composition is associated with variation in the expression of genes involved in dendritic cell maturation, interferon signaling, and NF-κB signaling pathway in circulating T cells and monocytes. the patients have elevated methane breathing compared with control due to the increase inMethanobrevibacter[28].

As the researchers found changes in the human gut microbiome in MS that is associated with changes in the immune transcriptome and treatment. Strategies for the MS treatment are expected to include therapeutic interventions that affect the microbiome for example probiotics, fecal transplantation, and delivery of constituents of organisms isolated from the microbiome, yet this requires more work to be established in the future. The characterization of the gut microbiome in MS could provide biomarkers for evaluating disease activity and could theoretically be a possibility to prevent MS in young at-risk populations [28].

4.4 Probiotic treatment approach in treating inflammatory and immune diseases.

Effects of probiotics on the immune dysregulation and autoimmune disease:

The effect of probiotic treatment has shown its efficiency in treating systematic disorders including inflammatory and autoimmune disorders such as Irritable Bowel Diseases, due to "ulcerative colitis and Crohn's disease, multiple sclerosis, rheumatoid arthritis", and others[25]. Probiotics help in reducing inflammation depending on the bacterial strain used in the treatment. The probiotics have effects in two ways; they may increase the immune response that will help for patients with immunodeficiency disease, and it may reduce the immune response in inflammatory and autoimmune diseases[29].

Mechanism of action of probiotics:

Probiotics can affect all compartments of the gut, "including the luminal microbiome, mucus barrier, the microbe- and cell-free (kill zone) of the epithelium, lymphocyte, and plasma cell-rich lamina propria, the vascular and neural elements of the lamina propria, the underlying smooth muscles which control motility, and the mesenteric lymph nodes that communicate with the systemic immune system" [25]. As in the case of microbiota, the probiotic can modulate the local and systematic metabolites [25], see Fig. 3.

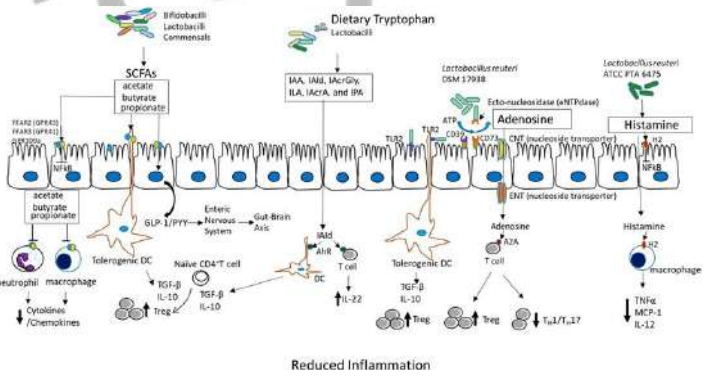

Fig 3: the anti-inflammatory function of probiotic metabolites in human, Reprinted with permission from Ref. [25]

Some metabolites that are produced by probiotic bacteria:

a. Short-chain fatty acid (SCFA)production in the colon.

The short-chain fatty acids include acetate, propionate, and butyrate, which are produced by normal flora (microbiota) bacteria (such as Facecalibacterium prausnitizii, Eubacterium rectale, Eubacterium hallii, and Ruminococcus bromii) and by many probiotics [25]. Lactobacilli produce mainly lactate then it has further metabolizing reactions by Firmicutes phylum (which includes Lachnospiraceae, Ruminococcaceae, Erysipelotrichaceae, and Clostridiaceae) a strictly anaerobic bacteria that produce butyrate[30]. Another bacteria is Bifidobacteria which use a fermentation reaction to produce SCFAs, when the carbohydrates are in small quantities the SCFAs are produced mainly acetate and formate, on the other hand, acetate and lactate are produced when carbohydrates are available in

large quantities [25].

Mechanism of SCFAs:

SCFAs are important to maintaining metabolic homeostasis in the colonocytes and protecting against external harm. Butyrate form of SCFAs protects the human gut from the development of colorectal cancer (CRC) and it increases colon peristalsis, diminishes inflammation, induces apoptosis by inhibition of histone deacetylation, and prevents the progression of tumor cells (Table 2). Free fatty acid receptors (FFARs), and G-protein-coupled receptors (GPRs) are two specific SCFAs receptors in the colon.

Both FFAR3 (GPR41) and FFAR2 (GPR43) on colon cells control gut colon motility. In the intestine, SCFAs can bind and activate FFAR2 and/or FFAR3 this induces glucagon-like protein-1 (GLP-1) and peptide tyrosine tyrosine (PYY) release into the basolateral milieu. GLP-1 and PYY activate enteric or primary afferent neurons in pelvic and vagal networks. Due to activation, the neural information moves to the central nervous system (CNS), affecting host metabolic energy outflow. SCFAs also reduce neutrophil cytokine production, while reducing macrophage nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling, giving an anti-inflammatory action. The Butyrate could induce differentiation of Tregs, the key role of intestinal inflammation [25].

b. Tryptophan metabolism–aryl hydrocarbon receptor activation

L-Tryptophan (Trp) has an important role in intestinal immunity the tolerance and active state. Studies show that Trp metabolites from humans (such as kynurenines, serotonin, and melatonin) and bacterial sources (such as indole, indolic acid, skatole, and tryptamine) have a significant effect, in Table 2. Aryl hydrocarbon receptor (AhR) that concede to be Trp receptor is a cytosolic ligand-activated transcription factor in dendritic cells and T cells thus AhR shows a vital role in preserving gut immune tolerance and barrier function. The AhR role was confirmed by the finding that AhR-null mice with colitis induced by dextran sodium sulfate (DSS) have severe symptoms and mortality[31].

Due to the loss in AhR, the mice were more susceptible to toxins and external pathogens. Both the host and bacterial Trp metabolites stimulate AhR and AhR-dependent gene expression, including IL-6, IL-22, prostaglandin G/H synthase 2 (PTGS2), vascular endothelial growth factor A (VEGFA), cytochrome P450 1A1 (CYP1A1), and mucin 2 (Muc2) in the intestine" [25]. This helps in modulating intestinal homeostasis, the effect of this product is both individually and additively.

Other Trp products are the indolic acid derivatives ("indole-3-acetic acid (IAA), indole-3-aldehyde (IAId), indole acryloyl glycine (IAcrGly), indole lactic acid (ILA), indole acrylic acid (IAcrA), and indolyl propionic acid (IPA)") influences the intestinal immunity homeostasis [31]. Some examples are Clostridium sporogenes that can convert Trp into IPA, which protects mice from colitis from DSS by enhancing the anti-inflammatory cytokine IL-10 creation after lipopolysaccharide (LPS) stimulation and decreases TNF-alpha creation.

Another example is the probiotic supplementation of Bifidobacteria infantis, which elevates the plasma Trp level along with the kynurenic acid level in mice thus it decreases proinflammatory immune response[32]. Also, the probiotic Lactobacillus reuteri can produce IAld when there is sufficient Trp that activates ILC3 cells to produce IL-22 via AhR, which helps in antifungal resistance and mucosal protection from inflammation [33].

c. Transforming growth factor-beta (TGF-β) and Tregs

TGF-β has a role in the intestinal mucosa, it affects the IgA production from B-cells and Treg activation. TGF-β has a signaling pathway that activates SMAD2 and SMAD3 transcription factor[25], SMAD3 enhances Foxp3 expression in Treg, and in the thymic precursor the Foxp3 helps in the conversion of naïve T cells into inducible Treg (iTreg), it also protects the existing Treg from apoptosis [34]. In an animal model, Lactobacillus gasseri SBT2055 induces TGF-β expression in dendritic cells and activates TLR2 signaling to produce IgA in the small intestine[35].

Probiotic VSL #3-generated TGF-β also enhances food allergy inflammation for the mouse model of peanut sensitization by induction of Tregs in the gut mucosa[36]. The TGF-β1signal is upregulated when administrating B. breve to preterm infants, thus decreases the inflammation and allergic reactions[25].

d. Nucleoside (adenosine) signaling.

A study performed on the "scurfy" mice model (the mice have a genetic deficiency in Treg as an autoimmune inflammatory disease, the mice have low Foxp3+ Treg cells that rise gut microbial dysbiosis) which is similar to human immune dysregulation, polyendocrinopathy, and enteropathy, with X-linked inheritance (IPEX), shows that the remodeling of gut microbiota by L. reuteri bacteria upgrade the microbiota–adenosine-inosine receptor 2A (A2A) axis, that inhibits TH1 and TH2 cell differentiation to reduce inflammation in the liver, lungs, gut, and skin[37]. L. reuteri 17938 can change the metabolomic profile disrupted due to Treg deficiency, and the reducing serum levels of the purine metabolite inosine, and downstream products xanthine and hypoxanthine.

TABLE 2
SOME EXAMPLES OF GUT MICROBIOTA-DERIVED METABOLITES AND THEIR BENEFICIAL EFFECTS ON HUMAN HEALTH, REPRINTED WITH PERMISSION FROM REF. [2]

Metabolite	Pathway	Microbial agent	Health benefits
Butyrate	Carbohydrate metabolism	Clostridia	Enhanced intestinal barrier function
		Faecalibacterium prausnitzii	Regulate intestinal macrophage function
		Coprococcus catus	Suppression of colonic inflammation
		Anaerostipes hadrus	Improvements in insulin sensitivity
Indole	Tryptophan metabolism	Lactobacillus spp	Maintenance of host-microbe homeostasis at mucosal surfaces via IL-22
		Bifidobacterium longum	Increased barrier function
		Bacteroides fragilis	Modulation of host metabolism
Indole-3- aldehyde	Tryptophan metabolism	Lactobacillus spp.	Maintenance of mucosal homeostasis and intestinal barrier function via increased IL-22 production
			Protection against intestinal inflammation in mouse models of colitis
Propionate	Tryptophan metabolism	Clostridium sporogenes	Maintenance of intestinal barrier function and mucosal homeostasis
			Increased production of antioxidant and neuroprotectant products

Tregs have a strong role in controlling inflammatory effector T cells (Th1, Th2, and TH17). And the proinflammatory function of these T cells is regulated by the interaction of adenosine (that is produced by T reg) when it binds to the receptor A2Aon the inflammatory effector T cells. When Tregs are absent the adenosine is converted to its metabolites one of which is inosine that may replace the effect of adenosine to interact with the A2A receptor and inhibit Th cell differentiation. When mice with low Tregs with inosine their wase inhibition of multi origin inflammation (decrease Th1/Th2 and its cytokines) [25].

e. Histamine signaling.

The immunogenic effects of lactobacilli introduction are strain-dependent and metabolite-dependent. A strain called L.rhamnosus can secrete low levels of histamine that has an immunosuppressive effect, other strain called L. saerimneri secretes high histamine levels causes gut inflammation. reuteri 6475 and ATCC and PTA strains the histamine produced work on H2 receptor on macrophage result the decrease in TNF-α, MCP-1, IL-12 [25].

4.5 Probiotics supplementation in multiple sclerosis

As reviewed in this paper the microbial presence affects the immune system, the experiments in both human and animal models show evidence that the administration of probiotic supplementation compromises gut dysbiosis and reduces inflammation by increasing mucosal secretion, preventing the destruction of tight junctions' proteins between epithelial cells.

When the LPS from the bacteria bind to toll-like receptors (TLR 2 and 4) on the endothelial cells, dendritic cells, and macrophages it induces inflammation in case of dysbiosis. The probiotics reduce the pathogenic LPS and decrease the differentiation rate of T cells into Th1 and Th17 and Th2 which induces inflammation. In a mice model of EAE oral probiotic supplementation provoked TGF-β and IL-10 increasing Treg number. This reaction is combined with increasing in Foxp3.

Eventually, the Th1/Th2 and Th17/Treg can be regulated by increasing Foxp3 and GATA3 versus the decrease of T-bet and ROR- γt expression as the primitive molecular immune suppression mechanism moving toward the Th2 and Treg thus reduces inflammation. More accurate, there was a decrement of inflammatory cells the secretion of IFN-γ, IL-17, GM-CSF, and TNFα, while the construction of IL-10 because of an improved population of CD4+CD25+Foxp3+T-regs was enhanced due to the increase of the anti-inflammatory cells. Also, it was confirmed that the oral administration of probiotics might decrease the MOG-reactive T-cell proliferation and pro-inflammatory cytokine levels and a rise in the IL-10+ or/and Foxp3+T-reg cells [27] , in Fig. 4.

5. SUMMARY

The second genome (microbiota) may have the key for treating many untreatable diseases giving us the key to control the untreatable changes in the human body just like MS in the future. Further studies are required to detect the perfect strain combination for each immune disorder. To have the power to control the immune system and reduce its severity in autoimmune diseases is such incredible hope.

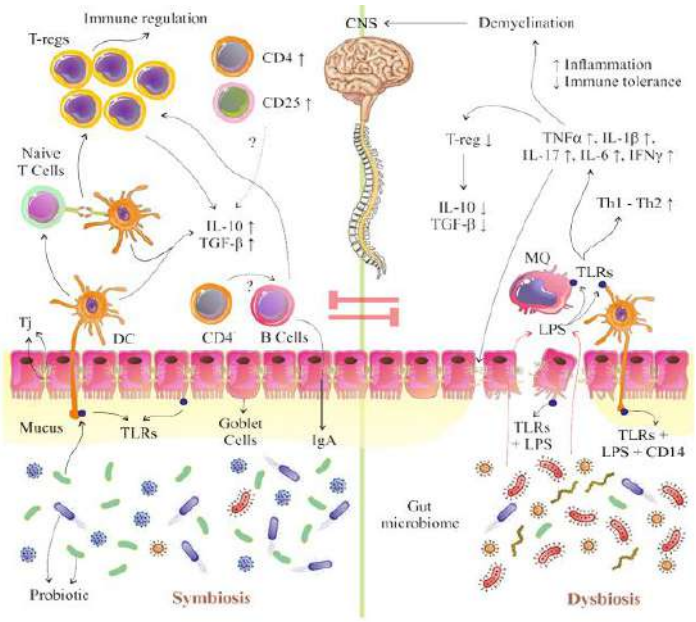

Fig 4: the immune status in dysbiosis and the probiotic presence in MS, Reprinted with permission from Ref. [27]

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