



Immunomodulatory effects of probiotics: Can they be used to treat allergies and autoimmune diseases?

Narges Dargahi^a, Joshua Johnson^b, Osaana Donkor^b, Todor Vasiljevic^b, Vasso Apostolopoulos^{a,*}

^a Institute for Health and Sport, Victoria University, Melbourne, Australia

^b Institute for Sustainable Industries and Liveable Cities, Victoria University, Melbourne, Australia

ARTICLE INFO

Keywords:

Probiotics
Lactic acid bacteria
Symbiosis
Dysbiosis
Gastrointestinal tract
Inflammatory bowel disease

ABSTRACT

As a person ages, physiological, immunological and gut microbiome changes collectively result in an array of chronic conditions. According to the 'hygiene hypothesis' the increasing prevalence of immune-mediated disorders may be related to intestinal dysbiosis, leading to immune dysfunction and associated conditions such as eczema, asthma, allergies and autoimmune diseases. Beneficial probiotic bacteria can be utilized by increasing their abundance within the gastrointestinal lumen, which in turn will modulate immune cells, such as, T helper (Th)-1, Th2, Th17, regulatory T (Treg) cells and B cells, which have direct relevance to human health and the pathogenesis of immune disorders. Here, we describe the cross-talk between probiotics and the gastrointestinal immune system, and their effects in relation to inflammatory bowel disease, multiple sclerosis, allergies and atopic dermatitis.

1. Introduction

Regular ingestion of probiotic bacteria, has been used for tapping into the health benefits exerted by microbiota of the gastrointestinal tract (GIT) within a healthy subject. Use of probiotics in the form of fermented milk dates back to ancient times and in Middle Eastern traditions, with claims that Abraham's longevity was due to the consumption of fermented milk [1,2]. The physiological changes of the GIT and alterations in the gut microbiome associated with age, along with changes in life style and dietary behaviors, leads to changes to the immune system [3]. Crosstalk between gut microflora and the immune system enables a balanced gut homeostasis in healthy individuals, however, alterations in the gut ecosystem due to the aged gut or diseases, causes changes in GIT microflora homeostatic equilibrium, resulting in a number of chronic diseases [3]. In fact, there are decreased anaerobic and *Bifidobacteria* populations, and increased *Enterobacter* species in the intestine of ageing individuals [4]. Advances in the gut microbiota probiotics and its synbiotics may be beneficial to the ageing population [5]. Probiotics consumed by humans must be non-pathogenic and survive GI transit to render their health benefits [6]. Whether or not probiotic strains should be of human origin is a matter of debate; although, it is accepted that if a strain can survive and colonize the human large intestine, its origin is not important [6,7]. The survival of probiotics is crucial within the gastric acid environment, and as such,

new genes are activated to encode a number of stress proteins for their survival. Once in the lower small intestine and colon, probiotics confer health benefits (Tables 1 and 2), although there is evidence that dead cells can also induce beneficial outcomes [7].

Probiotic bacteria, mainly belong to the lactic acid bacteria (LAB) family, which are commonly found in decomposing milk products and secrete lactic acid, fermenting carbohydrates. In fact, LAB have been used in fermentation and storage of certain foods (milk, vegetables, meat) for thousands of years [8]. LAB have also been shown to contribute to the healthy microflora of the human gut [7,9]. As such, the genera *Lactobacilli* (L.) (*L. rhamnosus*, *L. helveticus*), *Bifidobacterium* (B.), *Streptococcus* (S.) and *Enterococcus* species have been used as probiotic strains, i.e. supplementing foods with live microorganisms, and subsequent improvements in a number of human health conditions [9,10]. The basis for these benefits include, the detoxification of xenobiotics [11], microbial toxins, host metabolites i.e. bile salts and food components [12], biosynthesis of vitamin K₁, folic acid, biotin, vitamin B12, an increase in the absorption of calcium, iron and magnesium, fermentation of lactose, modulation of intestinal gas production [13,14] and production of short-chain fatty acids (SCFAs; acetate, propionate, butyrate, lactate) [15–17]. SCFAs are used as a source of energy to favour the growth and differentiation of GI epithelial cells, in addition to, modulating the immune system by regulating proliferation and cytokines of T cells, T helper (Th)-17 cells and T regulatory (Treg) cells of

* Corresponding author.

E-mail address: Vasso.Apostolopoulos@vu.edu.au (V. Apostolopoulos).

<https://doi.org/10.1016/j.maturitas.2018.11.002>

Received 26 August 2018; Received in revised form 6 November 2018; Accepted 8 November 2018

0378-5122/ © 2018 Elsevier B.V. All rights reserved.

Table 1
Effects of probiotics in health and disease.

Probiotic/ probiotic strain	Beneficial applications
Probiotics in general	● Stimulate secretion of IFN-gamma and IL-10 ● Promote effective immune responses against pathogens ● Modulate host immunity
<i>Bifidobacterium</i> (B.) <i>Saccharomyces</i> (S.) <i>boulardii</i>	● Detoxify xenobiotics ● Produce mmicrobial products, toxins, host metabolites, bile salts and food components ● Improves intestinal defense against enterohaemorrhagic <i>E. coli</i> ● Regulates intestinal epithelial barrier function
<i>Lactobacilli</i> (L.) species	● Biosynthesize vitamin K₁, folic acid, biotin, B12. ● Absorption of calcium, magnesium, iron, fermentation of lactose ● Modulation of intestinal gas production ● Produce short chain fatty acids -acetate, propionate, butyrate, lactate ● Ferment indigestible dietary fibres ● Modulation of the immune responses ● Protect against cancer and allergy development ● Inhibits experimental autoimmune encephalomyelitis (EAE) in animal models of multiple sclerosis (MS) ● Prevention and treatment of MS
<i>Lactobacillus</i> recombinants	
<i>L. Plantarum</i>	
B. B94	
<i>L. acidophilus</i>	● Stimulate the innate immune system (via phagocytosis, NK cell activity)
<i>L. bulgaricus</i>	
<i>B. bifidum</i>	
<i>L. plantarum</i> A	● Increase expression of CD11c⁺ DCs and Treg cells and protection against colitis
<i>L. acidophilus</i> ATCC 4356	
<i>L. rhamnosus</i> ATCC 53,103	
<i>L. plantarum</i> WCFS1	● Upregulate CD83 and CD86 cell surface expression of antigen presenting cells (APC)
<i>L. fermentum</i> AGR1485	● Increase IL-12p70, TNF-alpha and IL-1beta
<i>L. bulgaricus</i> subsp. <i>delbrueckii</i> 11842, <i>Lactococcus lactis</i> R704	● Beneficial in allergic rhinitis and asthma
<i>B. lactis</i> BB12	
<i>L. acidophilus</i>	
<i>L. bulgaricus</i>	
<i>B. bifidum</i>	
<i>L. casei</i> Shirota	● Enhances innate immunity
<i>Bacteroides fragilis</i>	● Induce the development of gut-associated lymphoid tissues (GALT)
<i>Bacillus subtilis</i>	● Induce pre-immune antibody repertoire
<i>Clostridium</i> species	● Reduces the risk of respiratory tract infections
<i>L. rhamnosus</i> GG	● Reduces the incidence and severity of atopic dermatitis in pregnant mothers and infants
<i>B. infantis</i>	● Reduces the risk of atopic eczema and allergic sensitization in children
<i>B. infantis</i>	● Protects host against development of colitis
<i>Escherichia</i> (E.) <i>coli</i>	● Prevents <i>Salmonella typhimurium</i> infection
<i>C. subterminale</i>	● Promotes GALT development
<i>Staphylococcus epidermidis</i>	
<i>Bacteroides fragilis</i>	
<i>Bacillus subtilis</i>	
<i>F. prausnitzii</i>	● Reduces the severity of experimental colitis in mice
<i>S. thermophilus</i>	● Stimulates immune responses
<i>L. fermentum</i>	
Seven strains of <i>Bifidobacteria</i> and LAB (G17)	● Release symptoms of skin lesions in atopic dermatitis mouse model by increasing Tregs and reducing Th1/Th2 cells and associated cytokines
<i>E. coli</i>	● Suppress pathogen growth ● Secrete bacteriocin and microsin S ● Reduce eczema ● Promotes GALT development ● When fused with MOG₃₅₋₅₅ peptide, protects mice against EAE ● Improves or prevents allergic recurrences in allergic rhinitis
<i>Candida utilis</i> yeast	
<i>L. delbrueckii</i> , sub <i>bulgaricus</i>	
<i>S. thermophilus</i>	
<i>L. acidophilus</i>	
<i>Bifidobacterium</i>	
<i>B. bifidum</i>	● Reduce eczema
<i>B. lactis</i>	
<i>L. lactis</i>	

peripheral blood [12,15–17]. A non-pathogenic (probiotic) strain of *Escherichia coli* (G3/10) has been shown to suppress pathogenic bacterial growth, and secrete potent antimicrobial peptides (bacteriocin, microsin S) which are harmful to gastroenteric pathogens (i.e. *Helicobacter pylori*, *Campylobacter jejuni*, *Clostridium difficile* and *rotavirus*) [18] (Fig. 1). LAB compete with enteric pathogenic bacteria for binding to mucin (primarily MUC2) sites on the surface of epithelial cells, which may be a mechanism for inhibiting pathogenic bacteria translocating from the gut to different organs including the liver; identified as one of the benefits of some probiotic strains [19]. The impact of LAB on the

immune system has also drawn much attention in the last decade leading to their use in several pre-clinical and clinical studies in allergic and autoimmune disorders [7,20]. In 2001, the first randomized placebo controlled clinical study was published on the use of *L. rhamnosus*, to modulate immune responses in late stages of pregnancy or to newborns, (Table 3) and showed a significant decrease in the prevalence of atopic eczema [21]. In addition, using probiotic supplements alone, or in combination with vitamins and minerals have been recommended for the prevention and treatment of multiple sclerosis (MS) (Table 3) [20]; in particular, *L. plantarum* and *Bifidobacterium* B94 (BB94) were shown

Table 2
Effects of probiotics on the immune response.

Probiotic / probiotic strain	Immune stimulation outcome
Microbiota, ingested probiotics	● Maintain immune tolerance ● Activate tolerogenic DCs ● Drive regulatory T (Treg) cell differentiation ● Stimulate differential Th1, Th2, Th17, Treg cells ● Improves atopic dermatitis ● Improves allergies, inflammatory bowel disease and autoimmune disorders including multiple sclerosis
<i>Lactobacillus (L.). rhamnosus</i> <i>L. delbrueckii</i>	● Induction of tolerogenic DCs ● Reduce cell surface molecules, CD80, CD83, CD86 ● Reduce IL-12 and NF-κB ● Increase indoleamine 2,3-dioxygenase (IDO) ● Increase IL-10 ● Stimulate Treg cells
Combination of <i>L. rhamnosus</i> and <i>B. lactis</i> A mixture of probiotics (<i>L. GG</i> , <i>L. rhamnosus</i> LC705, <i>B. breve</i> , and <i>Propionibacterium freudenreichii</i> ssp. <i>Shermanii</i> JS) <i>L. s193</i> <i>L. s292</i> <i>L. reuteri</i> <i>L. casei</i> Shirota	● Ingestion during pregnancy and during breast feeding reduces risk of atopic eczema ● Increased IL-10 ● Fails to reduce the risk of atopic eczema
Combination of <i>L. reuteri</i> , <i>L. casei</i> and TNF- α <i>L. lactis</i> <i>L. acidophilus</i>	● Increase beta-8 integrin on mesenchymal DCs ● Activate differentiation of CD4 + T cells into Treg cells ● Activates Th1 and Treg cells ● Activates Th1 and Treg cells ● Decreases IgE antibody responses ● Activate splenic NK cells ● Boost innate immune system ● Stimulates TNF-α and IL-12 on human peripheral blood mononuclear cells ● Activate only Treg cells
Combination of <i>L. acidophilus</i> and <i>B. longum</i> <i>L. plantarum</i> WCFS1	● Do not activate Treg cells ● Suppresses IgE allergic responses ● Downregulates IFN-γ, IL-4 cytokines ● Upregulates IgA antibody responses ● Upregulates TGF-β and Treg cells ● Improves allergic rhinitis
LAVR1-A1 <i>L. rhamnosus</i> GG <i>L. acidophilus</i>	● Upregulates CD103⁺ DCs in the intestine ● Increases Th2 cytokines ● Upregulates Treg cells ● Induce anti-inflammatory IL-4, IL-10 and TGF-β cytokines ● Inhibit IL-12 and IFN-γ ● Increase expression of co-stimulatory cell surface markers, CD14, IL-2R, HLA-DR, ICAM-1 and CD80 on monocytes
Combination of a mixture of probiotics, zinc and the coenzyme Q10 <i>L. gasseri</i> <i>L. paracasei</i> DG <i>L. helveticus</i>	● Down regulates IgG in serum ● Decreases TNF-α, IL-1, IL-6 and IL-17 ● Decreases vascular endothelial growth factor (VEGF) ● Induces IFN-α of monocytes ● Increases TNF-α, IL-6, IL-8, CCL20 by human monocyte cell line THP-1 ● Reduces IL-17 cytokine and Th-17 cells ● Reduces IL-6 ● Increases IL-10, TGF-β and Treg cells
<i>Bifidobacterium (B.) infantis</i>	● Matures DCs ● Induces CD103⁺ tolerogenic DCs ● Induces Treg cells ● Suppresses Th2 ● Stimulates high levels of IL-10 which neutralizes IL-12 ● Stimulates high levels of TGF-β
<i>B. animalis</i>	● Reduces IL-6, IL-17, TNF-α and monocyte chemoattractant protein-1 ● Increases IL-10 ● Stimulates Treg cells
<i>B. clausii</i>	● Increases IL-10 ● Increases TGF-β ● Improves allergic responses
<i>B. bifidum</i> <i>B. lactis</i> <i>B. breve</i> <i>B. longum</i> <i>L. acidophilus</i> <i>L. gasseri</i> <i>Streptococcus (S.) thermophilus</i> Short chain fatty acids	● <i>In vivo</i>, lower number of CD4⁺ and CD8⁺ T cells. Higher Treg cells ● Mediated by short chain fatty acids ● Downregulate IL-17A ● Downregulate IL-23 ● Relieves colitis in mice ● Suppress CD40, CD80
	● Expand and differentiate Treg cells

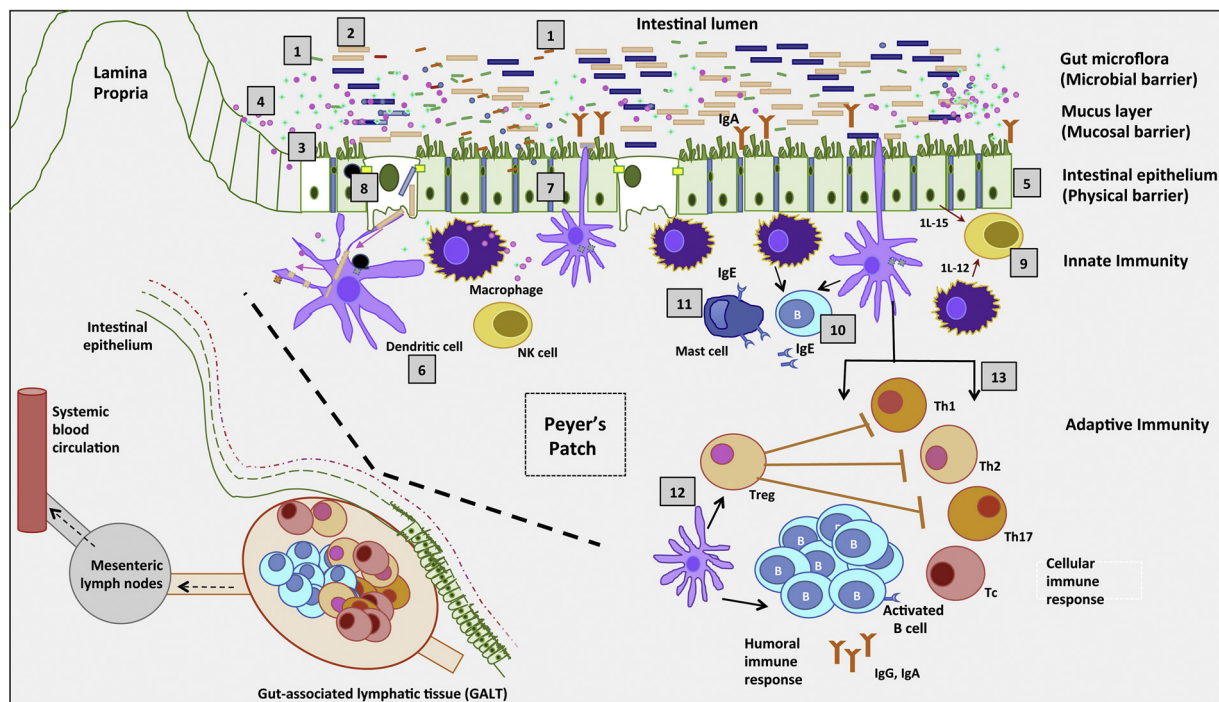


Fig. 1. The immunological complexity of the gut associated lymphoid tissue (GALT) and its interaction and activation with probiotics and gut microbiota. Probiotic and commensal microflora (1) collaboratively perform barrier function and compete with microbial pathogens (2) for nutrients and adhesion to the epithelial surface (3). Probiotics stimulate mucin secretion by goblet cells which protects the mucosal barrier. Antimicrobial peptides (4) such as, bacteriocin and microsin S by probiotics have antagonistic effects against pathogens. Probiotics can also induce mucosal epithelial cells (5) to secrete defensins. Dendritic cells (DCs) (6) endocytose bacterial products either via extending into the enteric lumen throughout epithelial tight junctions (7), or via bacterial transit through microfold M cells (8), or via pinocytosis of probiotics/microflora by epithelial cells (5). The innate immune response (natural killer (NK) cells), are triggered by IL-12 secreted by macrophage/DCs and IL-15 by epithelial cells (9). Immune response to extracellular pathogens via B cells are activated by macrophage/DC and secrete IgE (10) which stimulate mast cells (11) contributing to innate immunity. Adaptive immune responses are triggered by DCs, macrophages, and epithelial cells which process and present probiotics that stimulate regulatory T (Treg) cells (12) and tolerogenic TGF β , IL-10 cytokines leading to suppression of IgA secretion and effector T helper (Th)-1, Th2, Th17 and cytotoxic T (Tc) cell responses (13). If pathogens bypass the epithelial barrier, pathogenic peptides presented by DC/macrophages trigger a series of immune responses; Th1 and Th17 pro-inflammatory and Th2 anti-inflammatory responses which can lead to pathogenicity of the immune system such as inflammation, allergic reactions, autoimmune disorders, and cancer. Such disorders can be modulated with probiotics supplementation. Thus, probiotics confer an array of benefits on epithelial barrier activities and the ensuing responses of the underlying mucosal immune and GALT systems.

to positively impact the spatial memory and learning of rats [20]. Herein, we describe the effects of probiotics to immune cells and their use in allergic and autoimmune disorders.

2. Methodology

Searches were conducted using PubMed, Google Scholar and Medline using the following key terms: Probiotics OR lactic acid bacteria AND human health, probiotics OR lactic acid bacteria AND immune disorders OR allergies AND therapy, probiotics OR lactic acid bacteria AND immune cells, probiotics OR lactic acid bacteria AND immune cells differentiation, probiotics OR lactic acid bacteria AND inflammation, probiotics AND inflammatory diseases, probiotics AND Inflammatory bowel disease, probiotics OR lactic acid bacteria AND multiple sclerosis, probiotics AND atopic dermatitis. Studies from all years were included, specifically those published within the last 10 years. Additionally, terms such as therapeutic, health benefits, and specific immune cells (i.e. monocytes, T cells, natural killer cells, and dendritic cells) were searched in the context of probiotic effects and gastrointestinal microflora. Some review articles and their reference lists were also searched to identify related articles. Over 1000 papers were retrieved and the most relevant were included in this article.

3. Cross talk between probiotics, intestinal epithelium and immune development

The beneficial effects of probiotics was first explained by the

'hygiene hypothesis', suggesting a lack of exposure to microbial stimuli early in childhood was the major factor behind allergic reactions [22,23]. Probiotics and intestinal microflora interact and confer an array of positive effects on the epithelial layer to maintain gastrointestinal and systemic health, by interacting with the gut-associated lymphoid tissues (GALT) which mediate oral tolerance and mucosal immunity [24]. Within the GALT are Peyer's patches, specialized areas of the intestinal immune system consisting of numerous lymphoid follicles surrounded by specialized epithelial cells of the mucosa-associated lymphoid tissues (M-cells), which are involved in the translocation of most antigens and bacteria, including probiotics, from the intestinal lumen into the patches [25] (Fig. 1, Table 1). Interestingly, specific bacteria in the intestinal microflora, such as combination of *Bacteroides fragilis* and *Bacillus subtilis*, can induce the development of GALT and pre-immune antibody repertoire [24]. Germ-free mice, that lack intestinal bacteria, display major immune deficiencies, such as, structural lymphoid deficiencies in the spleen and Peyer's patches and lymph nodes, with no germinal zones [26]. Yet, after exposure to microbial antigenic stimuli such as, *Salmonella paratyphi*, germinal zones are developed, and antibodies are present in the circulation [26]. In addition, germ-free mice show abnormal T cells, intraepithelial lymphocytes, macrophages and dendritic cells (DCs). However, colonization with commensal flora early in life allows proper development of immune cells [27–29]. Thus, establishing a balanced gut microflora and maintaining it by adequate exposure to commensal bacteria at birth and early in childhood provides challenges to the immune system by infections or other immune insults resulting in impacts on the

Table 3
Effects of probiotics on gastrointestinal tract, allergies and autoimmune diseases.

Type of disease	Probiotic bacteria	Form of used bacteria	Study model: Animal / Human trial <i>In vitro</i> / <i>In vivo</i>	Outcome (primary and secondary effects)	Ref
Gastroenteric infections	Non-pathogenic <i>Escherichia</i> (<i>E. coli</i> G3/10)	Oral injection of live bacteria	Human trial: Probiotic treatment of irritable bowel syndrome in children	Stops gastroenteric pathogens <i>H. pylori</i> , <i>C. jejuni</i> , <i>C. difficile</i> and rotavirus) by producing microcin Reduces abdominal pain score (APS) and general symptom score (GSS)	[18]
Functional gastrointestinal disorders	<i>E. coli</i> G3/10 <i>E. coli</i> G4/9 <i>E. coli</i> G5 <i>E. coli</i> G6/7 <i>E. coli</i> G8 <i>E. coli</i> MDS42 genotypes present in probiotic drug <i>L. rhamnosus</i>	Live wild type in the form of probiotic drug Synbioflor 2 (DSM17252)	Human study: Treats functional gastrointestinal disorders; particularly IBS in adults and children (298 patients with IBS -lower abdominal symptoms)		
Atopic eczema		Oral injection of live bacteria	Clinical studies: Pregnant mothers and their newborn infants Animal study: rat model	Reduces the incidence of atopic eczema in newborns at high-risk Improved spatial memory and learning	[21]
Multiple sclerosis (MS)	<i>L. plantarum</i> and <i>Bifidobacterium</i> B94 (BB94)	Live with/ without vitamins			[20]
Allergy to Albumin	<i>Lactobacillus</i> (<i>L. acidophilus</i> strain L-92	Oral administration of heat-killed lyophilized bacteria	Mouse model of Ovalbumin Allergy Splenocytes and	Modified total and OVA-specific serum IgE levels Prevents allergic asthma by differential stimulation of immune responses	[61]
Allergic asthma	<i>S. thermophilus</i> , <i>L. fermentum</i> and yeast (<i>zymosan</i> and <i>Saccharomyces cerevisiae</i>) <i>Bacillus clausii</i>	Oral feeding administration	Animal study: mice		[101,102]
Allergies and recurrent	<i>Bacillus clausii</i>	Oral feeding <i>B. clausii</i> spores	Children (fluids collected from nasal lavage)	Modulates cytokine profiles (Increases IL-10 and TGF-beta), induces Treg cells	[105]
Respiratory infections	<i>Bacillus clausii</i>	Oral feeding <i>B. clausii</i> spores	Children	Prevents recurrent respiratory infections and shortens duration	[107]
Atopic dermatitis	<i>B. animalis</i> subsp. <i>lactis</i> Bb12 <i>L. rhamnosus</i> GG <i>L. acidophilus</i> La-5 <i>L. rhamnosus</i> GG	Oral injection of live bacteria as probiotic milk Oral ingestion of live bacteria	Pregnant women and their children	Reduced incidence of atopic dermatitis and reduced Th22 cells	
Allergic rhinitis, atopic dermatitis, eczema or asthma			Pregnant women with strong family history of allergic rhinitis, eczema or asthma	Significant delay in atopic dermatitis in infants within 1 st six months of life due to increased levels of IL-10	[112]
Atopic eczema atopic eczema, allergic rhinitis, or asthma	<i>L. rhamnosus</i> GG and <i>B. lactis</i>	Oral ingestion of bacteria as capsules/capsules content dissolved in water (for infants)	Pregnant and breastfeeding mothers or infants	Reduces risk of atopic eczema and allergic sensitization in children	[21]
Experimental colitis and dysbiosis	<i>F. prausnitzii</i>	Oral consumption of live bacteria	Mouse model	Anti-inflammatory effects and reduction of severity of colitis	[118]
Crohn's disease (CD) and ulcerative colitis (UC)	<i>Clostridium</i> strains <i>Clostridium</i> strains	Oral consumption of live bacteria Colonization of GF mice with fecal material from mice colonized with 46 <i>Clostridium</i> strains	Mouse model Gnotobiotic mice model	Protects against colitis by suppressing effector responses and inducing Tregs Protects against colitis and resistance to systemic IgE responses	[79] Delete 120 Delete 79
Colitis and subsequent IBD caused by <i>Citrobacter rodentium</i>	<i>L. plantarum</i> A, <i>L. acidophilus</i> ATCC 4356 and <i>L. rhamnosus</i> ATCC 53,103 <i>Bacteroides fragilis</i>	Oral feeding of live bacteria Oral feeding of live bacteria	Mouse model of <i>C. rodentium</i> -induced colitis Mouse germ free model	Colonize the gut and protects against invasive <i>C. rodentium</i> Protects against colitis by over expression of Treg cells mediated by bacterial capsular polysaccharide antigen (PSA) to TLR2	[123] [124]
Colitis	All microflora in fecal microbiota	Live bacteria fecal microbiota transplantation	Human colitis patients	Relieves colitis symptoms by restoring composition of intestinal microbiota	[126]
Crohn's disease (CD) and ulcerative colitis (UC)	<i>Bifidobacteria</i>	Live bacteria co-cultured with PBMC or dendritic cells			[127]

(continued on next page)

Table 3 (continued)

Type of disease	Probiotic bacteria	Form of used bacteria	Study model: Animal / Human trial <i>In vitro</i> / <i>In vivo</i>	Outcome (primary and secondary effects)	Ref
CD and UC	<i>Bifidobacteria</i>	Live bacteria co-cultured with PBMC or DCs	Peripheral blood mononuclear cells (PBMC)-dendritic cells (DCs) from Chrohn's disease (CD) children	DCs showed high uptake of bacterial particles, higher TNF-alpha, no effect on IFN-gamma and IL-17, UC	[127]
Necrotizing enterocolitis	Mixture of <i>B. infantis</i> , <i>S. thermophilus</i> , <i>B. bifidus</i> and <i>L. acidophilus</i>	Oral feeding of live bacteria	PBMCs of healthy and adult patients with CD, UC	DCs from healthy and CD, UC adults did not show significant changes	[27]
Experimental allergic encephalomyelitis (EAE) in mice	<i>Candida utilis</i>	Oral feeding of live bacteria	Extremely low birth weight neonatal rats	Beneficially improves caveolin-1 and nitric oxide signalling and growth factors in the terminal ileum	
EAE in mice	Recombinant <i>Lactobacilli</i> expressing myelin antigens	Oral feeding and intranasal administration of PLP ₁₃₉₋₁₅₁ and MBP	EAE mouse model	Protects mice against the development and clinical symptoms of EAE	[131]
EAE in mice	<i>Lactobacillus</i> and <i>Bifidobacterium</i>	Oral feeding	EAE in Lewis rats	Inhibited EAE	[132]
EAE in mice	<i>L. helveticus</i>	Intraperitoneal injection	EAE mouse model	Delays EAE onset and clinical score significantly	[134]
EAE in mice	VSL#3	Bidbm breve	EAE mouse model	Reduces the incidence and clinical score of EAE	[135]
EAE in mice	<i>L. casei</i> Shirota, <i>L. casei</i> 393, <i>L. reuteri</i> , <i>L. paracasei</i> , <i>B. breve</i> and <i>B. animalis</i>	Lacto-mix: Lctb paracasei, Lctb plantarum, Lctb delbrueckii, LGG, Lctb GG	EAE mouse model	Reduces the clinical score and EAE activity by, increasing IL-10, TGF-beta and Treg cells	[71]
EAE-induced with guinea pig- spinal cord homogenate	<i>L. casei</i> Shirota	Oral feeding of live bacteria (started before EAE)	Infant Lewis rats with EAE	Represses EAE neurological symptoms development (not statistically significant)	[71]
EAE-induced with guinea pig-MBP	<i>L. casei</i> Shirota	Oral feeding of live bacteria (started before EAE)	Infant Lewis rats with EAE	Represses EAE neurological symptoms development (statistically significant)	[71]
EAE-induced with guinea pig-MBP	<i>L. casei</i> Shirota and <i>B. breve</i> strain Yakult (BbY)	Oral feeding of live bacteria (started before EAE)	Infant Lewis rats with EAE	Represses EAE neurological symptoms development (statistically significant)	[71]
Multiple Sclerosis (MS)	<i>Lactobacillus</i> , <i>Bifidobacterium</i> and <i>Streptococcus</i>	Oral feeding of live bacteria	Human: MS patients	Decrease abundance of <i>Akkermansia</i> and <i>Blautia</i> bacteria, Decreases inflammatory monocytes, MHC-II and CD80	[136]
MS	<i>L. acidophilus</i> , <i>L. casei</i> , <i>B. bifidum</i> and <i>L. fermentum</i>	Oral feeding of live bacteria in capsules	Human: MS patients	Improve disability status scale, depression and anxiety symptoms and reduced C-reactive protein, plasma oxidative and malondialdehyde	[137]

microbiome population, colonization, and host health.

Both probiotics and commensal bacteria enforce the functions of the mucosal barrier of the GIT epithelia, induce mucus secretion, and stimulate secretion of IgA which neutralizes pathogens inside the lumen (Fig. 1) [13]. Correspondingly, cross talk between epithelial cells and residing epithelial immune cells are mediated and enforced by probiotics, and contribute to their effector functions [6]. Probiotics are also able to induce expression of adhesion molecules, similarly important for regulatory function of residing immune cells. Probiotics stimulate the innate immune system, antigen presenting cells (APC) and natural killer (NK) cells in both mice and humans [30]. Adaptive immunity is stimulated by probiotics, such that IgG and IgA antibodies are produced in response to probiotic consumption, as demonstrated with *L. acidophilus*, *L. bulgaricus* and *B. bifidum* (Fig. 1) [31,32]. In addition, macrophages, CD8⁺ T cells, Treg cells and cytokines (i.e. interferon (IFN)-gamma and interleukin (IL)-10) are stimulated by probiotics [33]. APCs exposed to probiotics or commensal bacteria, present harmless peptides to T cells and subsequently induce Treg cells, to produce anti-inflammatory cytokines including, transforming growth factor beta (TGF-beta), IL-10 and retinoic acid. In addition, Treg cells suppress effector Th1, Th17 and cytotoxic T (Tc) cells and IgA secretion [34]. However, if APCs present invasive pathogenic peptides, it leads to the initiation of effector, pro-inflammatory Th1/Th17 responses. Thus, probiotic bacteria can control the ‘on/off switch’ of immune responses in a strain-dependent manner, modulating the host immune system at the mucosal level. Lack of sufficient probiotic bacteria and their subsequent stimulatory impact on the immune system, leads to inadequate or inappropriate immune modulation. Insufficient probiotic bacteria alone, or inadequacy, together with stimulation of immune system by invasive pathogens (which bypass the mucosal barrier), mediate a range of immunopathogenic disorders such as, allergies, asthma, atopic disorders, inflammatory bowel diseases (IBD), cancer, type-2 diabetes and autoimmune disorders (Table 1) [6,35–37].

4. Probiotic organisms and immune cells

Probiotic bacteria have numerous beneficial immune and health effects. They not only enhance the bioavailability of nutrients and moderate health, they also aid in regulating the gastrointestinal ecosystem and stimulate immunomodulatory properties to a number of immune cells (Table 1, Figs. 1 and 2).

4.1. Dendritic cells

DCs play a key role in directing immune responses to self and non-self antigens. Upon endocytosis of antigens, DCs mature functionally and phenotypically. As mature cells, they prime T cells towards Th1 or Th2 phenotypes, however, in their immature state (tolerogenic DCs) they cause the deletion of T cells or stimulation of Treg cells (Fig. 2, Table 2) [38]. The intestinal microbiota and ingested probiotics can interact with the host's innate and adaptive immune system, regulating cell differentiation in the gut which is involved in sustaining immune tolerance. In particular, microbiota are able to activate distinct tolerogenic DCs in the gut and consequently drive Treg cell differentiation [39]. DCs also endocytose probiotics and present short antigenic peptides to T cells, stimulating Th1, Th2, Th17 and/or Treg cells. Due to these roles, in recent years considerable focus has been directed towards the anti-inflammatory properties of probiotics e.g. *L. rhamnosus* and *L. delbrueckii* and the induction of tolerogenic DCs and their effect on the stimulation of Treg cells [40]. In particular, significantly reduced co-stimulatory cell surface molecules (CD80, CD83, CD86), IL-12 and NF-kappa B were noted and increased expression of indoleamine 2,3-dioxygenase (IDO) and IL-10, suggesting that probiotics are able to modify properties of DCs to modulatory cells, which may contribute to immune tolerance and immune balance [41]. Recently, two novel *Lactobacillus* probiotics strains (s193 and s292) isolated from Funazushi

(a traditional Japanese fermented food) were shown to increase beta-8 integrin on mesenchymal DCs which strongly activated CD4⁺ T cell differentiation into Treg cells; monoclonal antibodies against beta-8 integrin are able to block the differentiation of Treg cells [42]. DCs co-cultured with *L. reuteri* and *L. casei*, although displaying different cytokine profiles (IFN-gamma production), activate both Th1 and Treg cells. However, DCs stimulated with *L. reuteri* and *L. casei* and combined with TNF-alpha stimulate only Treg cells [9]. On the other hand, DCs exposed to *L. lactis* do not stimulate Treg cells, showing the importance of the *Lactobacilli* strain used in the ensuing immune response. Oral administration of *B. infantis* in mice stimulates DCs to a maturation state and CD103⁺ tolerogenic DCs accumulate in the GALT, induce Treg cells and suppress Th2-biased responses [43]. Given the roles of DCs and the intestinal residing DCs in endocytosing bacteria, it is clear that DCs play a central part in immune homeostasis in the healthy intestine and in the pathology of IBD [44,45]. Thus, understanding the effect of stromal cells and microbial signals on DC function are important as the manipulating regime of DCs through probiotics, nutrition and microbiota, leading to therapeutic modalities against inflammatory diseases, which still require further research

4.2. Monocytes and macrophages

Monocytes are present in the peripheral blood which then differentiate to tissue macrophages and myeloid lineage DCs. Intestinal microbiota and ingested probiotics can interact with macrophages for beneficial immune effects [44]. In fact, IL-12 secreted by macrophages stimulates CD4⁺ T cells and NK cells to secrete IFN-gamma, resulting in the generation of pro-inflammatory Th1 cells. Interestingly, IFN-gamma and IL-12 production seem to be controlled in a positive feedback loop, as IFN-gamma in turn, stimulates production of IL-12. This loop of IFN-gamma and IL-12 production can be deleterious, as it may result in uncontrollable expression of cytokines and possible shock. However, co-culturing peripheral blood mononuclear cells (PBMCs) with selected bacteria (LAVRI-A1, *L. rhamnosus* GG, *Bifidobacteria* and *L. acidophilus*) induces anti-inflammatory cytokines IL-4, IL-10 and TGF-beta [46,47]. These cytokines inhibit the production of IL-12, IFN-gamma and other pro-inflammatory cytokines which are beneficial for autoimmune and allergic responses. In addition, probiotics from dairy source such as LAB *L. gasseri* strains could induce IFN-alpha production by monocytes with *L. gasseri* DSM20243 T [48], and 3 strains of LAB (*L. delbrueckii* ssp. *bulgaricus*, *B. bifidum*, *L. acidophilus*, trilac) being the most potent [49]. In addition, CD4⁺ T cell proliferative responses, high levels of IL-10 and TNF-alpha (not IL-12 and IFN-gamma) are induced, as well as increased expression of cell surface markers (CD14, CD80, HLA-DR, ICAM-1, IL-2 receptor) [49]. The probiotic *L. paracasei* DG commonly used in commercial probiotic products, shows immunostimulatory properties by increasing the expression of TNF-alpha, IL-6, IL-8 and CCL20 by human monocyte cell line, THP-1 [50]. Similarly, it has recently been demonstrated that *S. thermophilus* induced differential cytokine secretion of human monocyte U937 cell line; IL-4 and IL-10 secretion important for anti-inflammatory responses, TNF-alpha and IL-6 necessary for stimulation of the innate immune response, as well as CXCL8 (IL-8) and GM-CSF required for cell recruitment at sites of inflammation [Ref.]. Hence, the use of commensal LAB results in an anti-inflammatory profile and activation of monocytes, which is beneficial in suppressing pathogenic-induced pro-inflammatory responses in microbiota (via IL-10 production) and simultaneous induction of antimicrobial effects (via TNF-alpha stimulation and monocyte induction).

4.3. NK cells

NK cells play a keyrole in innate immunity and are cytotoxic to tumors. NK cells have a regulatory role in the development of allergic respiratory disease. *L. casei* subspecies Shirota (S) administered in mice intraperitoneally, or intravenously leads to activated splenic NK cells,

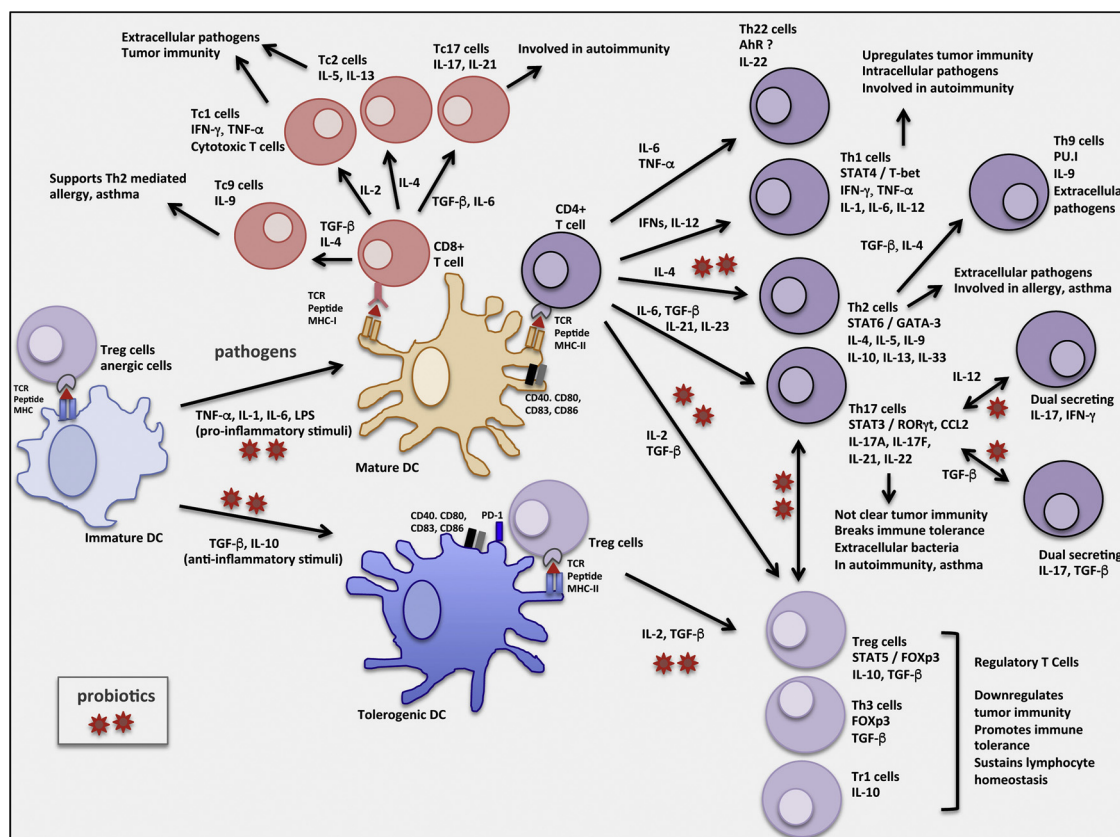


Fig. 2. Immunomodulatory effects of probiotics stimulating T helper (Th)-1, Th2, Th17 cells or T regulatory (Treg) cells. Immature dendritic cells (DC) either mature following pro-inflammatory stimuli (IL-1, IL-6, lipopolysaccharide (LPS), TNF- α or pathogens) or become tolerogenic DCs in the presence of anti-inflammatory stimuli TGF- β and IL-10. The differentiation of immature DCs into mature or tolerogenic DCs is also regulated in the presence of probiotics. Mature DCs confer an array of stimulatory functions whereby they stimulate Th or Treg cells depending on the cytokine produced. Mature DCs interact with naïve CD4 + T cells and depending on the resulting cytokine produced by the CD4 + T cells they differentiated into either, (i) inflammatory Th1 (secrete IL-1, IL-6, IL-12, IFN- γ , TNF- α) or Th17 (secrete IL-17A, IL-17F, IL-21, IL-22) cells; (ii) anti-inflammatory Th2 (secrete IL-4, IL-5, IL-9, IL-10, IL-13, IL-33) or Th9 (secrete IL-9) cells; (iii) regulatory Treg (secrete IL-10, TGF- β), Th3 (secrete TGF- β) or Tr1 (secrete IL-10) cells or (iv) Th22 cells which secrete IL-22. In addition, Th17 cells can be further divided into dual secreting cells of either IL-17, IFN- γ or IL-17, TGF- β . Probiotics have been shown to regulate Treg cells and/or Th2 cells depending on the strain and disease. Tolerogenic DCs interact with T cells and can directly stimulate Treg cells in the presence of IL-2 and TGF- β (or probiotics). Furthermore, mature DCs stimulate CD8 + T cells into Tc1, Tc2, Tc9 or Tc17 cells however, it is not clear whether probiotics are involved in their differentiation / stimulation.

peritoneal exudate cells and thoracic exudate cells, respectively, but not via oral administration. In contrast, *L. casei* S administered orally to newborn mice is able to activate splenic NK cells [51]. Thus, oral consumption of probiotics, such as *L. casei*, early in life boosts the innate immune system [27]. In human PBMCs, *L. casei* S stimulates pro-inflammatory cytokines IL-12 and TNF- α ; the type of immune response required for a DC-NK cell interaction and defence mechanism [52]. Another study showed that *Lactobacillus* strains were able to stimulate IL-12 secretion by DCs, resulting in activation of NK cells and subsequent secretion of IFN- γ , which not only leads to innate immune responses, but also activation of the adaptive immune responses [9]. Upon stimulation by *Bifidobacterium*, high levels of IL-10 is produced which neutralizes IL-12 induced by *Lactobacillus* strains [9]. This suggests that co-administration of probiotics might not be favorable when used for immunomodulatory therapeutic methods for NK-DC mediated type of immune responses. Results from such studies suggest that *Lactobacillus* strains may initiate cellular immune responses whilst *Bifidobacterium* strains can induce polarization towards anti-inflammatory and Treg cells. Thus, *Bifidobacterium* might be the probiotic of choice to be used to manage or prevent inflammatory immune disorders such as, allergies and autoimmune conditions, although, *Lactobacillus* strains may be beneficial for anti-tumor immunity. In addition, LAB have been shown to stimulate T/NK cells via induction of IL-12/IFN- γ , whereas, other strains can either suppress or boost Treg/

Th2 responses via IL-4, IL-5 and IL-10 [53]. Understanding the cytokine profiles induced following probiotic exposure and their immune modulating properties can provide a clear path for managing immunopathologies [6,54]. These studies infer that host innate immune responses are important in relation to the development of some diseases and inducing it by probiotic bacteria can help to enhance immunity and health. Therefore, *L. casei* strains have established safety and functional characteristics and are extensively used in probiotic dairy products, and have long been used as staple food ingredients in many countries including Japan and Europe.

4.4. Regulatory T cells

Evidence that Treg cells play an active role in immune tolerance was established in the 1970s [55], at the time they were referred to as suppressor T cells. During the late 1980's research into the role of these cells in immune tolerance dwindled, however the identification of cell-surface markers in the mid-1990s led to a resurgence in interest [56]. In 1994, Tregs were described as key cells in the establishment of oral tolerance [57], and were proposed as a potential target for the treatment/prevention of diseases that are caused by over reaction of the immune system (i.e. autoimmunity, inflammatory metabolic diseases, asthma and allergy) all of which have exhibited a global increase, especially in western countries [58,59]. Tregs are responsible for the

state of unresponsiveness of the immune system to specific antigens (self-peptides); a process known as immune tolerance, which is critical for the maintenance of immune homeostasis [60].

There is accumulating evidence which suggests probiotics are not only beneficial for the treatment of Th1 or Th2 mediated inflammatory disorders, but are also able to induce beneficial Treg cells to modulate immune balance (Fig. 2). For instance, *L. acidophilus* strain L-92 suppresses IgE allergic responses to an antigen model in mice, as well as downregulating the secretion of IFN-gamma, IL-4 and IL-10, and significantly increase the levels of IgA, TGF-beta and Treg cells [61]. *L. plantarum* WCFS1 is also associated with CD103⁺ DC infiltration in the intestine, increases Th2 cytokines and is involved in the generation of Treg cells in mice [62]. More recently, the combination of probiotics, zinc, and coenzyme Q10 synergistically reduced rheumatoid inflammation in mice by significantly downregulating IgG in serum, decreased the expression of pro-inflammatory cytokines (IL-1, IL-6, IL-17, TNF-alpha) and vascular endothelial growth factor in the joint synovium and upregulated Treg cells [63]. *L. casei* administration in mice with *E. coli* induced intestinal inflammation is associated with CD4⁺CD25⁺Foxp3⁺ Treg cells in the spleen and mesenteric lymph nodes with corresponding decreased CD4⁺IL-17⁺ Th17 cells and RORγt mRNA levels [64]. Thus, *L. casei* could have possible therapeutic implications against intestinal inflammation by modulating the Treg/Th17 balance. However, intragastric administration of *L. casei* BL23 stimulates the expression of CD4⁺Foxp3⁺ Treg cells and RORγt⁺ Th17 cells, termed type-3 Treg cells which are believed to control luminal inflammatory disorders by suppressing inflammation [65].

LAB from *Bifidobacteria* strains, can also prime expression of TGF-beta and IL-10, and increase the number of Treg cells, which is associated with suppressive function/tolerance [66]. Similarly, administration of *B. animalis* subsp. *lactis* 420 (B420) or *L. salivarius*-33 (Ls-33) to mice shows reduced levels of pro-inflammatory cytokines TNF-alpha, IL-6, IL-17 and monocyte chemoattractant protein-1 (MCP-1) and skews towards IL-10 anti-inflammatory cytokine profile and generation of Treg cells [67]. Likewise, *B. infantis* 14.518 fed with shrimp allergies, show DC-dependent stimulation of Treg cells [43]. It is clear that an array of probiotics exert their beneficial effects and mediate an immune balance by their stimulation of Treg cells.

SCFAs produced by commensal microbiota following fermentation of dietary fibers, have also been shown to expand and differentiate intestinal Treg cells [68]. In particular, butyrate initiates the differentiation of Tregs [69] as well as suppressing the onset of colon cancer and reducing allergic responses in the lung of mice [69,70]. In mouse models of asthma and colitis (newborn and mature) which were orally subjected to a mixture *L. casei*, *L. lactis*, *L. acidophilus*, *B. bifidum* and *B. lactis* daily, showed a lower proportion of CD4⁺ and CD8⁺ T cells and higher Treg cells; these effects were shown to be mediated by SCFAs (acetate, propionate and butyrate) [71]. However, in other studies it was noted that butyrate induces the expression of the transcription factor T-bet resulting in IFN-gamma secreting T cells and not Treg cells. Thus, butyrate may exert either beneficial or detrimental effects on the mucosal immune system. Further studies are required to determine the dose of butyrate and its mechanism by which it induces beneficial Treg cells.

4.5. Th17 cells

Th17 cells secrete IL-17 (IL-17 A), IL-17 F, and IL-22 and eliminate external pathogens mainly at epithelial mucosal sites [72,73]. At mucosal sites, secretion of anti-microbial defensins is dependent on the stimulatory activities of IL-17, IL-22 and differentiation and stimulation of neutrophils which is dependent on these cytokines. However, it is believed that excessive or persistent responses of Th17 cells can drive the onset of inflammatory diseases, and as such, Th17 cells together with Th1 cells, are generally responsible for the pathophysiology of autoimmune diseases, asthma, allergy and the development and

progression of tumors [74,75]. Similar to human Th17 cells, murine Th17 cells also play a critical role in numerous mouse autoimmune disease models such as, experimental autoimmune encephalomyelitis (EAE) [76,77].

Intestinal microflora are shown to regulate and maintain the quantity and function of DCs, through which they are able to differentially modulate naïve CD4⁺ T cell responses towards specific Th cell populations (Fig. 2). Studies in germ free mice show that the number of CX3CR1⁺ DCs is reduced which favorably induces naïve CD4⁺ T cell differentiation towards Th1 and Th17 [78]. In addition, filamentous bacteria affect the whole microflora of the GIT immune system which subsequently stimulate Th17 cells residing in lamina propria [79]. The number of Th17 cells in the GIT lamina propria is associated with the presence of microbiota, thus, in germ free mice, the percentage of Th17 cells is very low [80]. As such, the severity of EAE symptoms and autoimmune arthritis are reduced due to lower levels of Th17 cells and lower IL-17 and IFN-gamma [81,82]. On the contrary, colonization of segmented filamentous bacteria which induce high levels of local Th17 cells in the lamina propria, prevents diabetes in non-obese diabetic mice [83]. Thus, Th17 cells and IL-17 play differential roles depending on the disease model. Commensal microbiota are also able to stimulate secretion of IL-25 (IL-17E) in the GIT that prevents expression of IL-23; without IL-23, pathogenic Th17 cells cannot survive [84].

Numerous animal models as well as clinical trials have established beneficial effects of probiotics in IBD due to anti-inflammatory properties as a result of down-regulating the expression of IL-17 [85,86]. Several studies with colitis-induced mouse models have shown that the probiotics *B. longum* subsp. *infantis*, *B. breve*, *L. acidophilus*, *L. gasseri* A5, *B. longum* and *S. thermophilus* ST28, are able to down-regulate the production of IL-17 leading to relief of colitis symptoms [87–90]. Two individual studies determined the effect of blocking IL-17 by using novel immunosuppressive drugs 4SC-101 [91] and vidofludimus [92] to compare with probiotic effects; drugs similarly alleviated severe colitis in mice by targeting IL-17 and confirmed the suppressive mechanisms of probiotics. IL-23 which is also associated with development, maintenance and polarization of Th17, is another activator for inflammatory conditions [93]; in fact, suppressing the IL-23/IL-17 axis, is now a promising target for probiotic treatments in the prevention and management of IBD [90]. Studies on the effects of *B. breve* and *L. rhamnosus* GG on colitis-induced mouse models revealed that LPS-induced IL-23 expression by intestinal cells, was reduced by these probiotics [87,90].

In vitro studies using intestinal epithelial cell lines, *B. longum* subsp. *infantis* JCM 1222 was shown to suppress the expression of co-stimulatory cell surface molecules, CD40 and CD80 as well as IL-17 A at mRNA and protein levels [88]. In another comparative study on the effect of *B. breve* and *L. rhamnosus* GG, in human intestinal HT-29/B6 or T84 cells and PBMCs, reduced CD40 and IL-17 A mRNA expression induced by LPS stimulation [87]. Similarly, *B. longum* subsp. *infantis* [88] is able to reduce the expression of RORγt and simultaneously suppress IL-17 A production following oral administration in a mouse model of colitis. Due to the vital role of RORγt as a specific transcription factor for differentiation of Th17 cells, it can be a promising candidate to target for probiotic therapeutics in inhibiting Th17 cells and subsequent alleviation of inflammatory conditions. Furthermore, feeding of *L. acidophilus* or *B. clausii* in ovariectomized mice for 6 weeks was able to skew Th17 cells towards a Treg phenotype by reducing pro-inflammatory IL-6, IL-17 and TNF-alpha and increasing expression of IL-10 [94,95]. Hence, there is an increasing value of the use of probiotics as a driver of treating many inflammatory disorders by skewing Treg/Th17 balance.

5. Probiotics, allergy and autoimmune diseases

Studies in animal and in human clinical trials suggest that probiotics have the potential to prevent or treat allergies (atopic dermatitis and

allergic rhinitis) and autoimmune diseases (IBD and MS). Based on the ‘hygiene hypothesis’, it is believed that any change to the human GIT and microflora results in increased risk of such diseases. Regulation of gut microbiota by the consumption of probiotics has been shown to influence the development of the mucosal and systemic immune response (Figs. 1 and 2) that alter immune homeostasis and immune profile and positively affect allergies and autoimmune disorders.

5.1. Probiotics and allergies

Food allergy is described as the activation of mast cells or basophils and production of IgE in response to specific food proteins [96]. This can be in the form of life-threatening food hypersensitivity reactions with symptoms usually appearing within minutes of exposure; a condition quite distinct from food intolerances, such as Coeliac disease [97,98]. Around 1–2% of adults and 5–7% of children suffer from some type of food allergy, which its prevalence has significantly increased over the last 20 years [99]. Although allergy symptoms are manageable with medications, no cure is available for food allergy except for strictly avoiding allergy triggering food. Interestingly, it is now widely accepted that early life exposure to bacteria such as probiotics, results in activation of APCs that leads to immune homeostasis and subsequent reduction in allergies. Probiotics are able to differentially stimulate the immune system to express pro- and anti-inflammatory cytokines in a strain-dependent manner. As previously discussed, probiotics have been shown to modulate immune responses *in vitro* and *in vivo* to skew immune responses towards Th1/Th2 and Treg phenotypes, which is essential in managing and preventing immune-mediated pathologies, including allergies [100]. Oral consumption of killed *L. casei* Shirota has been reported to stimulate the production of Th1 cytokines, resulting in decreased stimulation of allergic IgE antibodies against ovalbumin (OVA) in experimental allergic mouse models with allergy to OVA [51]. Thus, the use of probiotic bacteria to shift mucosal immunity towards Th1 responses supports their use as a viable approach for the treatment of allergic disorders [51]. Oral feeding of *S. thermophilus*, *L. fermentum* and yeast (such as zymosan and *Saccharomyces cerevisiae*) [101,102], also, differentially stimulate immune responses. In one study for example, mice were fed with yeast or *L. fermentum*, then fed with OVA, and vaccinated with OVA [51]. The probiotic-exposed mice responded more efficiently to vaccination with OVA than mice with no pre-feeding of either probiotics or OVA, or the mice which were only given OVA. Nevertheless, vaccination in mice that were given either yeast or *L. fermentum* followed by yeast and OVA or *L. fermentum* and OVA showed significantly suppressed antibody responses as a result of vaccination with OVA. This suggests that, although feeding the antigen alone appears to prime the onset of immune responses, co-feeding the same antigen with probiotics can repress allergic responses due to suppressing both cellular and humoral immunity [51]. Similarly, studies showing the effects of probiotic treatment (*L. casei*, *L. lactis*, *L. acidophilus*, *B. bifidum* and *B. lactis*) on the suppression in mice of experimental OVA-induced asthma, an allergic airway disease model, either at the time of birth or at later developmental stages, resulted in decreased numbers of Th1, Th2 and CD8⁺T cells in the airways compared to control mice [103]. This data may provide insights into an effective treatment approach for controlling allergic reactions.

In humans, *B. longum* and *L. acidophilus* in milk or yogurt, if used as probiotics powder, capsules, or even heat-killed bacteria, can alleviate the severity of the clinical scales of allergic rhinitis and asthma symptoms compared to placebo [104]. In children with allergies and recurrent respiratory infections, *B. clausii* was shown to beneficially modulate cytokine profiles, and induce Treg cells in parallel with increased levels of IL-10 and TGF-beta [105]. Similarly, PBMC from subjects with allergic rhinitis who consumed yogurt or skimmed milk (containing *L. delbrueckii*, sub *bulgaricus* and *S. thermophilus*, *L. acidophilus* and *Bifidobacterium*) showed higher IFN-gamma responses and improved symptom score [106]. All these suggest the use of probiotics as

a novel approach in allergic conditions due to their great potency in polarizing T cells in the gut towards Treg cells.

5.2. Probiotics and atopic dermatitis

Atopic dermatitis is a chronic inflammatory skin disorder which is predominantly noted in infants and toddlers. Although the acute phase of atopic dermatitis is dominated by Th2 (IL-4, IL-5, IL-13) and Th22 cells, during the chronic phase, Th1 cells (IFN-gamma and IL-12) take the lead, resulting in atopic dermatitis [107,108]. In a mouse model of atopic dermatitis, consumption of a mixed of 7 strains of *Bifidobacterium* and LAB for 8 weeks resulted in reduced atopic skin irritation and increased Treg cells [108]. In another study, Treg cells were increased locally in the skin of mice following supplementation of *L. casei* [109]. Similarly, an increase in Treg cells were noted in the spleen after *L. reuteri* supplementation in mouse models with asthma [110]. In addition, Tregs have been shown to be induced from human PBMCs following exposure to probiotic species (*L. acidophilus*, *B. lactis*, and *L. plantarum*) with *L. acidophilus* being the most potent [9,111].

In humans, a randomized controlled study of probiotic consumption (*B. animalis* subsp. *lactis* Bb-12, *L. rhamnosus* GG, and *L. acidophilus* La-5) in pregnant women and their children, showed reduced incidence of atopic dermatitis and reduced Th22 cells [107]. Additionally, ingestion of *L. rhamnosus* GG alone in pregnant women with strong family history of allergic rhinitis, eczema or asthma, showed significant delay in developing atopic dermatitis in their infants during the first six months of delivery, which correlated to increased levels of IL-10 [112]. Likewise, the combination of *L. rhamnosus* GG and *B. lactis* throughout pregnancy and breastfeeding reduces the risk of atopic eczema and allergic sensitization in children [21], whereas a mixture of probiotics (*Lactobacillus* GG, *B. breve*, *L. rhamnosus* LC705, and *Propionibacterium freudenreichii* ssp. *Shermanii* JS) failed to reduce the risk of atopic eczema, due to the strain dependency of probiotic bacteria [21]. In a systematic review and meta-analysis studies of pediatric atopic dermatitis it was noted that probiotics are effective in preventing this condition [113]. Furthermore, cutaneous exposure to a lysate of probiotics (*Vitreoscilla filiformis*) alleviates skin inflammation and induces IL-10 secreting tolerogenic DCs and Treg cells and reduces Th1 pro-inflammatory cells and their cytokines [114].

5.3. Probiotics and inflammatory bowel disease

IBD, including Crohn's disease (CD) and ulcerative colitis (UC), is a major human health problem [115]. IBD is a group of chronic inflammatory disorders of the GIT, which is currently incurable and results in intestinal inflammation, severe diarrhoea, fatigue, pain and subsequent weight loss. A link has been established between insufficient intestinal probiotics (dysbiosis) and the development of CD and UC [116]. In fact, mucosal-associated microbiota of twin individuals with CD has been shown to have lower abundance of *Faecalibacterium prausnitzii* and significantly higher levels of *E. coli*, compared to corresponding healthy twin siblings [117]. Such dysbiosis of intestinal microbiota is believed to contribute to pathophysiology of CD and UC through an imbalance between intestinal microbiota and mucosal immunity, leading to inflammation in the intestine. Interestingly, experimental colitis, in mice, caused by dysbiosis, is corrected by consuming *F. prausnitzii* orally, which leads to anti-inflammatory effects and reduction of severity of colitis [118]. Consumption of probiotics in general has been increasingly used as a means of preventing and/or managing CD and UC by restoring damaged intestinal mucosal barrier [119]. In fact, suppression of effector responses and induction of Treg cells has been shown in mice, following consumption of *Clostridium* strains, and their consumption in early life is also beneficial in the protection against colitis [79,120]. Consumption of *B. infantis* by mice results in increased number of Treg cells and leads to prevention of *Salmonella typhimurium* infection. Furthermore, *Bifidobacteria* increases

gastrointestinal defense against enterohaemorrhagic pathogenic *E. coli* by generating acetate [121]. Recently it was shown that SCFAs produced through the fermentation of indigestible dietary fibers by *Bifidobacteria* and other anaerobic bacteria [103] resulted in the differentiation of colonic Treg cells. *L. rhamnosus* and *B. infantis* protected the host against the development of colitis via the effect of their SCFAs products on the immune system [122]. Additionally, *L. casei*, *L. lactis*, *L. acidophilus*, *B. bifidum* and *B. lactis* also generate SCFAs (acetate, propionate and butyrate) which induce the differentiation of Treg cells in the colon, subsequently suppressing the development of DSS-induced experimental colitis in mice [88].

Interestingly, while *Citrobacter rodentium* can cause colitis and subsequently IBD, commensal microflora of the gut can provide protection against invasive pathogens like *C. rodentium* through colonization of the host gut [123]. In a mouse model of *C. rodentium*-induced colitis, administration of *L. plantarum* A, *L. acidophilus* ATCC 4356 and *L. rhamnosus* ATCC 53103 increased expression of CD11c⁺ DCs and Treg cells, whilst down-regulating pro-inflammatory cytokines (IL-17, IFN- γ and TNF- α) and protection against colitis [124]. Hence, for individuals experiencing gut dysbiosis, probiotics and gut microbiome are therapeutic interventions for restoring gut microbial equilibrium and balancing the immune system for better health [125]. To this end, fecal microbiota transplantation has shown to be effective in colitis patients through rapid restoration of intestinal microbiota composition. The specific mechanisms are not clear, however, the intestinal microbiota is restored to be similar to that of the donor [126].

Bifidobacteria have also been shown to contribute to intestinal homeostasis and help to diminish inflammation. *Bifidobacteria* mixture was tested on DC functionality from different sources; children with IBD, DCs from PBMCs of patients with CD, UC, and healthy controls. DCs were pre-treated with probiotics and incubated with *E. coli* fluorochrome-conjugated particles or DQ-ovalbumin (DQ-OVA) [127]. Following incubation with probiotics, DCs from CD children had a higher uptake of bacterial particles and DQ-OVA processing; whereas DCs from the other 2 groups showed no significant changes. DCs from CD children also showed higher TNF- α and no effect on IFN- γ and IL-17 [127]. This shows that *Bifidobacteria* can significantly increase antigen uptake and processing of DCs which are from patients with CD, in whom DCs demonstrate a decreased autophagic function. Probiotics had a lesser effect on antigen uptake or autophagy by DCs sourced from CD/UC and healthy people. Enhanced antigen sampling and processing could be a viable approach to solving innate immunity deficiency in GIT and a method to reducing uncontrolled bacterial growth in the intestine of IBD children.

Probiotics have also shown to be effective against specific infections in infants and children, including infectious diarrhoea, traveller's diarrhoea, and infants necrotizing enterocolitis and *Helicobacter pylori* [54]. Neonates with extremely low birth weight due to necrotizing enterocolitis have marked reduced incidence and severity following probiotics consumption, in particular combinations of, *B. infantis*, *S. thermophilus*, *B. bifidus* and *L. acidophilus* [27]. Caveolin-1 regulates nitric oxide (NO) signaling which is responsible for the pathogenesis of necrotizing enterocolitis, and in formula-fed neonatal rats, the intestinal caveolin-1 and NO signalling are deficient [27]. Probiotics fed to babies, improves the survival of the microorganism in the intestine and beneficially improves caveolin-1 and NO signalling and growth factors in the terminal ileum.

5.4. Probiotics and multiple sclerosis

Chronic inflammation has been generally accepted as a common hallmark of neuro-degenerative diseases, such as, MS, Alzheimer's disease and Parkinson's disease [76,128,129]. Gut microbiota associate with central nervous system (CNS) [130], as there is cross-talk between the GIT, the CNS and the immune system, known as the gut-brain axis. Any dysfunction in the gut-brain axis is associated with the

pathogenesis of a number of diseases inside and outside the GIT.

EAE, an animal model of human MS has been used to study the effects of probiotic microorganisms on CNS. One of the safe and appropriate ways to induce tolerance towards peripheral T-cell in autoimmune diseases like MS, is the oral administration of specific autoantigens [131,132]. A food based probiotic yeast, *Candida utilis*, fused with an immunodominant myelin epitope (MOG₃₅₋₅₅)-peptide as carrier, when administered in mice, protects mice against the development and clinical symptoms of EAE [131]. In addition, administration of heat-inactivated *C. utilis* also resulted in reduction of disease severity in animals which indicated that tolerance effect is independent of viability of the yeast. Rechallenge with MOG₃₅₋₅₅ resulted in decreased disease severity associated with reduced cellular inflammation in the spinal cord, demyelination, lower T cell proliferation and higher Treg cells in the lymph nodes. These results showed that using a food-grade fungus, *C. utilis*, with surface-infused immunogenic MOG₃₅₋₅₅ peptide is effective in modulating immune responses and can successfully stimulate oral tolerance against this epitope in EAE [131]. Similarly, oral and intranasal administration of recombinant *Lactobacilli* expressing myelin antigens also showed reduced EAE [132]. Furthermore, a panel of recombinant *Lactobacilli* were constructed to produce some of human and guinea pig myelin proteins and peptides, such as proteolipid protein peptide 139–151 (PLP₁₃₉₋₁₅₁) and myelin basic protein (MBP) and. The effect of these *Lactobacillus* recombinants on inducing intranasal and oral tolerance in EAE animal models were studied. Soluble cell extracts of *Lactobacillus* transformants were given to Lewis rats intranasally three times prior to induction of EAE. In order to induce oral tolerance, animals were given live recombinant *Lactobacilli* for 20 days. Within 10 days of first oral consumption, rats were induced for EAE induction. Using extracts containing guinea pig MBP₇₂₋₈₅ peptide epitope intranasally inhibited EAE in Lewis rats significantly. It seems that *Lactobacilli* with myelin infused-antigens are able to reduce EAE if intranasally and orally administered [131,132]. This and other studies offer novel approaches for mucosal tolerance induction by mucosal administration of recombinant yeast or *Lactobacilli* expressing relevant autoantigens, which may be applicable in autoimmune disease such as MS.

In mice, administration of *Lactobacillus* or *Bifidobacterium* strains result in less severe EAE clinical scores, recovery of myelin content in the spinal cord, increased levels of TGF- β and Treg cells compared to control mice [133]. Administration of a mixture of the two strains induced a more significant delay in EAE onset and clinical score, along with significant decreased mononuclear infiltration into the central nervous system, as well as elevated CD4⁺CD25⁺Foxp3⁺ expressing Treg cells in the spleen and lymph nodes of mice [134]. Likewise, intraperitoneal injection of *L. helveticus* in mice significantly reduced the incidence and clinical score of EAE, which correlated with reduced Th17 cells and IL-6 (an essential cytokine for Th17 differentiation) [135]. *L. casei* Shirota, *L. casei* 393, *L. reuteri*, *L. paracasei*, *B. breve* and *B. animalis* also reduce disease activity by increasing IL-10, TGF- β and Treg cells. [71].

Oral administration of probiotics (*Lactobacillus*, *Bifidobacterium* and *Streptococcus*) in 9 MS patients and 13 control subjects, twice a day for 8 weeks, resulted in decreased abundance of *Akkermansia* and *Blautia*, known to be associated with dysbiosis in MS patients, and increased abundance of *Lactobacillus* and *Bifidobacterium* [136]. In addition, decreased number of inflammatory monocytes, and decreased expression of MHC-II and co-stimulatory molecule CD80 were noted. In a randomized, placebo-controlled study, 60 patients with MS were also given a probiotic capsule containing *L. acidophilus*, *L. casei*, *B. bifidum* and *L. fermentum* for 12 weeks. Subsequently, expanded disability status scale, as well as depression and anxiety symptoms were improved, c-reactive protein (inflammatory marker), plasma oxidative metabolites and malondialdehyde (markers of oxidative stress) were reduced [137]. Thus, probiotics have been shown to modulate symptoms of disease in mice (EAE model) and in MS patients, and warrants further research

into the use of probiotics as an adjunct treatment in humans with MS, however, there is a need for further animal and human studies to understand the effects of probiotics to human health.

6. Conclusion

Probiotics have been shown to alter immune responses, and induce tolerance in both animal models and humans. The rapidly growing knowledge of microbiome-host interactions has revealed new avenues for understanding the immunopathological basis of many diseases. Evidence is slowly emerging, that one of the approaches for maintaining or restoring immune balance and, thereby preventing or treating diseases, is through the use of probiotics in the form of fermented foods or probiotic supplements. The mechanism by which probiotics affect individual's health is multidimensional and has been the focus of many studies. The prevailing evidence suggests that probiotics keep the immune system in check, by differentially modulating cellular (Th1, Th2, Th17, Treg, Tc) and humoral (B cells) immune responses specific to the probiotic strain(s) and disease pathophysiology. However, current knowledge still lacks most pieces of the puzzle for a complete picture that explains the mechanisms by which probiotics improve general health and diseases, specifically in regards to treating or preventing allergies, gastrointestinal and immune disorders. There seems to be a lack of adequate research on the effects of probiotics on the central nervous system, such as autoimmune diseases, specifically MS, and additional *in vivo* and *in vitro* research on MS is required to provide sound evidence and detailed information for the beneficial effects of probiotics.

Contributors

Narges Dargahi wrote, reviewed and edited the article.

Joshua Johnson reviewed and edited the article.

Osaana Donkor reviewed and edited the article.

Todor Vasiljevic reviewed and edited the article.

Vasso Apostolopoulos wrote, reviewed and edited the article.

Conflict of interest

The authors declare that they have no conflict of interest.

Funding

No funding was received specifically for this review.

Ethical approval

No ethics was required for this review article.

Provenance and peer review

This article has undergone peer review.

References

- [1] F.B. Ahtesh, L. Stojanovska, V. Apostolopoulos, Anti-hypertensive peptides released from milk proteins by probiotics, *Maturitas* 115 (2018) 103–109.
- [2] T. Vasiljevic, N.P. Shah, Probiotics—From Metchnikoff to bioactives, *Int. Dairy J.* 18 (2008) 714–728.
- [3] E. Biagi, L. Nylund, M. Candela, R. Ostan, L. Bucci, E. Pini, et al., Through ageing, and beyond: gut microbiota and inflammatory status in seniors and centenarians, *PLoS One* 5 (2010).
- [4] K. Tihiainen, A.C. Ouwehand, N. Rautonen, Human intestinal microbiota and healthy ageing, *Ageing Res. Rev.* 9 (2010) 107–116.
- [5] E. Biagi, S. Rampelli, S. Turroni, S. Quercia, M. Candela, P. Brigidi, The gut microbiota of centenarians: signatures of longevity in the gut microbiota profile, *Mech. Ageing Dev.* 165 (2017) 180–184.
- [6] H. Hardy, J. Harris, E. Lyon, J. Beal, A.D. Foey, Probiotics, prebiotics and immunomodulation of gut mucosal defences: homeostasis and immunopathology, *Nutrients* 5 (2013) 1869–1912.
- [7] A. Ljungh, T. Wadstrom, Lactic acid bacteria as probiotics, *Curr. Issues Intest. Microbiol.* 7 (2006) 73–90.
- [8] J.A. Reis, A.T. Paula, S.N. Casarotti, A.L.B. Penna, Lactic acid bacteria antimicrobial compounds: characteristics and applications, *Food Eng. Rev.* 4 (2012) 124–140.
- [9] S. de Roock, M. van Elk, M.O. Hoekstra, B.J. Prakken, G.T. Rijkers, I.M. de Kleer, Gut derived lactic acid bacteria induce strain specific CD4+ T cell responses in human PBMC, *Clin. Nutr.* 30 (2011) 845–851.
- [10] M.J. Butel, Probiotics, gut microbiota and health, *Médecine et Maladies Infectieuses* 44 (2014) 1–8.
- [11] C.F. Maurice, H.J. Haier, P.J. Turnbaugh, Xenobiotics shape the physiology and gene expression of the active human gut microbiome, *Cell* 152 (2013) 39–50.
- [12] E. Kiseleva, G. Novik, Probiotics as Immunomodulators: Substances, Mechanisms and Therapeutic Benefits, (2013).
- [13] A.J. Macpherson, N.L. Harris, Interactions between commensal intestinal bacteria and the immune system, *Nat. Rev. Immunol.* 4 (2004) 478–485.
- [14] S. Salminen, A. von Wright, A.C. Ouwehand (Ed.), *Lactic Acid Bacteria: Microbiological and Functional Aspects*, 3rd ed., Marcel Dekker, Inc, New York, 2004.
- [15] M. Asarat, V. Apostolopoulos, T. Vasiljevic, O. Donkor, Short-chain fatty acids produced by synbiotic mixtures in skim milk differentially regulate proliferation and cytokine production in peripheral blood mononuclear cells, *Int. J. Food Sci. Nutr.* 66 (2015) 755–765.
- [16] M. Asarat, V. Apostolopoulos, T. Vasiljevic, O. Donkor, Short-chain fatty acids regulate cytokines and Th17/Treg cells in human peripheral blood mononuclear cells in vitro, *Immunol. Invest.* 45 (2016) 205–222.
- [17] M. Asarat, T. Vasiljevic, V. Apostolopoulos, O. Donkor, Short-Chain fatty acids regulate secretion of IL-8 from human intestinal epithelial cell lines in vitro, *Immunol. Invest.* 44 (2015) 678–693.
- [18] A. Zschüttig, K. Zimmermann, J. Blom, A. Goesmann, C. Pöhlmann, F. Gunzer, Identification and characterization of microcin S, a new antibacterial peptide produced by probiotic *Escherichia coli* G3/10, *PLoS One* 7 (2012).
- [19] V. Giannelli, V. Di Gregorio, V. Iebba, M. Giusto, S. Schippa, M. Merli, et al., Microbiota and the gut-liver axis: bacterial translocation, inflammation and infection in cirrhosis, *World J. Gastroenterol.* 20 (2014) 16795–16810.
- [20] M. Goudarzvand, S. Rasouli Koohi, Z. Khodaii, S.S. Moghadam, Probiotics *Lactobacillus plantarum* and *Bifidobacterium B94*: cognitive function in demyelinated model, *Med. J. Islamic Repub. Iran* 30 (2016).
- [21] M. Kalliomäki, S. Salminen, H. Arvilommi, P. Kero, P. Koskinen, E. Isolauri, Probiotics in primary prevention of atopic disease: A randomised placebo-controlled trial, *Lancet* 357 (2001) 1076–1079.
- [22] G. Clarke, S.M. O'Mahony, T.G. Dinan, J.F. Cryan, Priming for health: gut microbiota acquired in early life regulates physiology, brain and behaviour, *Acta Paediatr. Int. J. Paediatr.* 103 (2014) 812–819.
- [23] D. Kelly, T. King, R. Aminov, Importance of microbial colonization of the gut in early life to the development of immunity, *Mutat. Res. – Fundam. Mol. Mech. Mutagen.* 622 (2007) 58–69.
- [24] K.J. Rhee, P. Sethupathi, A. Driks, D.K. Lanning, K.L. Knight, Role of commensal bacteria in development of gut-associated lymphoid tissues and preimmune antibody repertoire, *J. Immunol.* 172 (2004) 1118–1124.
- [25] M.S. Britti, M. Roselli, A. Finamore, N. Merendino, E. Mengheri, Regulation of immune response at intestinal and peripheral sites by probiotics, *Biologia* 61 (2006) 735–740.
- [26] M. Pollard, N. Sharon, Responses of the Peyer's patches in germ-free mice to antigenic stimulation, *Infect. Immun.* 2 (1970) 96–100.
- [27] A. D'Souza, L. Fordjour, A. Ahmad, C. Cai, D. Kumar, G. Valencia, et al., Effects of probiotics, prebiotics, and synbiotics on messenger RNA expression of caveolin-1, NOS, and genes regulating oxidative stress in the terminal ileum of formula-fed neonatal rats, *Pediatr. Res.* 67 (2010) 526–531.
- [28] A.M. Williams, C.S.J. Probert, R. Stepankova, H. Tlaskalova-Hogenova, A. Phillips, P.W. Bland, Effects of microflora on the neonatal development of gut mucosal T cells and myeloid cells in the mouse, *Immunology* 119 (2006) 470–478.
- [29] M. Yamamoto, R. Yamaguchi, K. Munakata, K. Takashima, M. Nishiyama, K. Hioki, et al., A microarray analysis of gnotobiotic mice indicating that microbial exposure during the neonatal period plays an essential role in immune system development, *BMC Genomics* 13 (2012).
- [30] A. Mortha, A. Diefenbach, Natural killer cell receptor-expressing innate lymphocytes: more than just NK cells, *Cell. Mol. Life Sci.* 68 (2011) 3541–3555.
- [31] V. Delcenserie, D. Martel, M. Lamoureux, J. Amiot, Y. Boutin, D. Roy, Immunomodulatory effects of probiotics in the intestinal tract, *Curr. Issues Mol. Biol.* 10 (2008) 37–54.
- [32] J. Michalkiewicz, M. Krotkiewski, L. Gackowska, M. Wyszomirska-Golda, A. Helmin-Basa, D. Dzierzanowska, et al., Immunomodulatory effects of lactic acid bacteria on human peripheral blood mononuclear cells, *Microb. Ecol. Health Dis.* 15 (2003) 185–192.
- [33] L.N. Fink, L.H. Zeuthen, H.R. Christensen, B. Morandi, H. Frøkiær, G. Ferlazzo, Distinct gut-derived lactic acid bacteria elicit divergent dendritic cell-mediated NK cell responses, *Int. Immunol.* 19 (2007) 1319–1327.
- [34] S.Z. Josefowicz, R.E. Niec, H.Y. Kim, P. Treuting, T. Chinen, Y. Zheng, et al., Extrathymically generated regulatory T cells control mucosal T H 2 inflammation, *Nature* 482 (2012) 395–399.
- [35] A. Aumeunier, F. Grela, A. Ramadan, Bardel E. Van LP, A.G. Alcala, et al., Systemic toll-like receptor stimulation suppresses experimental allergic asthma and autoimmune diabetes in NOD mice, *PLoS One* 5 (2010).
- [36] P. Knight, B.J. Campbell, J.M. Rhodes, Host-bacteria interaction in inflammatory

- bowel disease, *Br. Med. Bull.* 88 (2008) 95–113.
- [37] S.J. Ott, S. Schreiber, Reduced microbial diversity in inflammatory bowel diseases [1], *Gut* 55 (2006) 1207.
 - [38] R.M. Steinman, D. Hawiger, M.C. Nussenzweig, Tolerogenic dendritic cells, *Annu. Rev. Immunol.* 21 (2003) 685–711.
 - [39] B. Foligne, G. Zoumpoulou, J. Dewulf, A. Ben Younes, F. Chareyre, J.C. Sirard, et al., A key role of dendritic cells in probiotic functionality, *PLoS One* 2 (2007) e313.
 - [40] M.J. Smelt, B.J. de Haan, P.A. Bron, I. van Swam, M. Meijerink, J.M. Wells, et al., L. Plantarum, L. salivarius, and L. Lactis attenuate Th2 responses and increase treg frequencies in healthy mice in a strain dependent manner, *PLoS One* 7 (2012).
 - [41] S.A. Esmaeili, M. Mahmoudi, Z. Rezaeiyazdi, M. Sahebari, N. Tabasi, A. Sahebkar, et al., Generation of tolerogenic dendritic cells using lactobacillus rhamnosus and lactobacillus delbrueckii as tolerogenic probiotics, *J. Cell. Biochem.* (2018).
 - [42] Y. Okada, Y. Tsuzuki, T. Takeshi, H. Furuhashi, M. Higashiyama, C. Watanabe, et al., Novel probiotics isolated from a Japanese traditional fermented food, funazushi, attenuates DSS-induced colitis by increasing the induction of high integrin α h β 8-expressing dendritic cells, *J. Gastroenterol.* 53 (2018) 407–418.
 - [43] L. Fu, J. Song, C. Wang, S. Fu, Y. Wang, Bifidobacterium infantis potentially alleviates shrimp tropomyosin-induced allergy by tolerogenic dendritic cell-dependent induction of regulatory T cells and alterations in gut microbiota, *Front. Immunol.* 8 (2017).
 - [44] J. Farache, E. Zigmund, G. Shakh, S. Jung, Contributions of dendritic cells and macrophages to intestinal homeostasis and immune defense, *Immunol. Cell Biol.* 91 (2013) 232–239.
 - [45] A.J. Stagg, A.L. Hart, S.C. Knight, M.A. Kamm, Interactions between dendritic cells and bacteria in the regulation of intestinal immunity, *Best Pract. Res.: Clin. Gastroenterol.* 18 (2004) 255–270.
 - [46] O.N. Donkor, M. Ravikumar, O. Proudfoot, S.L. Day, V. Apostolopoulos, G. Paukovics, et al., Cytokine profile and induction of T helper type 17 and regulatory T cells by human peripheral mononuclear cells after microbial exposure, *Clin. Exp. Immunol.* 167 (2012) 282–295.
 - [47] O.N. Donkor, N.P. Shah, V. Apostolopoulos, T. Vasiljevic, Development of allergic responses related to microorganisms exposure in early life, *Int. Dairy. J.* 20 (2010) 373–385.
 - [48] H. Kitazawa, Y. Tomioka, K. Matsumura, H. Aso, M. Mizugaki, T. Itoh, et al., Expression of mRNA encoding IFN α in macrophages stimulated with Lactobacillus gasseri, *FEMS Microbiol. Lett.* 120 (1994) 315–321.
 - [49] P. Gutkowski, K. Madaliński, M. Grek, H. Dmernańska, M. Syczewska, J. Michalkiewicz, Effect of orally administered probiotic strains lactobacillus and bifidobacterium in children with atopic asthma, *Central-Eur. J. Immunol.* 35 (2010) 233–238.
 - [50] S. Balzaret, V. Taverniti, S. Guglielmetti, W. Fiore, M. Minuzzo, H.N. Ngo, et al., A novel rhamnose-rich hetero-exopolysaccharide isolated from lactobacillus paracasei DG activates THP-1 human monocyte cells, *Appl. Environ. Microbiol.* 83 (2017).
 - [51] T. Matsuzaki, J. Chin, Modulating immune responses with probiotic bacteria, *Immunol. Cell Biol.* 78 (2000) 67–73.
 - [52] K. Shida, T. Suzuki, J. Kiyoshima-Shibata, S. Shimada, M. Nanno, Essential roles of monocytes in stimulating human peripheral blood mononuclear cells with lactobacillus casei to produce cytokines and augment natural killer cell activity, *Clin. Vaccine Immunol.* 13 (2006) 997–1003.
 - [53] H. Dong, I. Rowland, P. Yaqoob, Comparative effects of six probiotic strains on immune function in vitro, *Br. J. Nutr.* 108 (2012) 459–470.
 - [54] D. Wolvers, J.M. Antoine, E. Myllyluoma, J. Schrezenmeir, H. Szajewska, G.T. Rijkers, Guidance for substantiating the evidence for beneficial effects of probiotics: prevention and management of infections by probiotics, *J. Nutr.* 140 (2010) 698S–712S.
 - [55] R.K. Gershon, K. Kondo, Cell interactions in the induction of tolerance: the role of thymic lymphocytes, *Immunology* 18 (1970) 723.
 - [56] S. Sakaguchi, N. Sakaguchi, M. Asano, M. Itoh, M. Toda, Immunologic self-tolerance maintained by activated T cells expressing IL-2 receptor α -chains (CD25). Breakdown of a single mechanism of self-tolerance causes various autoimmune diseases, *J. Immunol.* 155 (1995) 1151–1164.
 - [57] Y. Chen, V.K. Kuchroo, Inobe J-i, D.A. Hafler, H.L. Weiner, Regulatory T cell clones induced by oral tolerance: suppression of autoimmune encephalomyelitis, *Science* 265 (1994) 1237–1240.
 - [58] C. McKenzie, J. Tan, L. Macia, C.R. Mackay, The nutrition-gut microbiome-physiology axis and allergic diseases, *Immunol. Rev.* 278 (2017) 277–295.
 - [59] A.N. Thorburn, L. Macia, C.R. Mackay, Diet, metabolites, and "Western-lifestyle" inflammatory diseases, *Immunity* 40 (2014) 833–842.
 - [60] H. Zeng, R. Zhang, B. Jin, L. Chen, Type 1 regulatory T cells: A new mechanism of peripheral immune tolerance, *Cell Mol. Immunol.* 12 (2015) 566–571.
 - [61] A. Torii, S. Torii, S. Fujiwara, H. Tanaka, N. Inagaki, H. Nagai, Lactobacillus acidophilus strain L-92 regulates the production of Th1 cytokine as well as Th2 cytokines, *Allergol. Int.* 56 (2007) 293–301.
 - [62] M. Bermudez-Brito, T. Borghuis, C. Daniel, B. Pot, B.J. de Haan, M.M. Faas, et al., L. plantarum WCF51 enhances Treg frequencies by activating DCs even in absence of sampling of bacteria in the Peyer Patches, *Sci. Rep.* 8 (2018) 1785.
 - [63] S.Y. Lee, S.H. Lee, J. Jhun, H.B. Seo, K.A. Jung, C.W. Yang, et al., A combination with probiotic complex, zinc, and coenzyme Q10 attenuates autoimmune arthritis by regulation of Th17/Treg balance, *J. Med. Food* 21 (2018) 39–46.
 - [64] K. Wang, H. Dong, Y. Qi, Z. Pei, S. Yi, X. Yang, et al., Lactobacillus casei regulates differentiation of Th17/Treg cells to reduce intestinal inflammation in mice, *Can. J. Vet. Res.* 81 (2017) 122–128.
 - [65] N.G. Cortes-Perez, D. Lozano-Ojalvo, M.A. Maiga, S. Hazebrout, K. Adel-Patient, Intragastric administration of Lactobacillus casei BL23 induces regulatory FoxP3+ ROR γ T+ T cells subset in mice, *Beneficial Microbes* 8 (2017) 433–438.
 - [66] L.L. Zhang, X. Chen, P.Y. Zheng, Y. Luo, G.F. Lu, Z.Q. Liu, et al., Oral bifidobacterium modulates intestinal immune inflammation in mice with food allergy, *J. Gastroenterol. Hepatol.* 25 (2010) 928–934.
 - [67] C.A. Danilo, E. Constantopoulos, L.A. McKee, H. Chen, J.A. Regan, Y. Lipovka, et al., Bifidobacterium animalis subsp. Lactis 420 mitigates the pathological impact of myocardial infarction in the mouse, *Beneficial Microbes* 8 (2017) 257–269.
 - [68] K. Atarashi, T. Tanoue, K. Oshima, W. Suda, Y. Nagano, H. Nishikawa, et al., Treg induction by a rationally selected mixture of clostridia strains from the human microbiota, *Nature* 500 (2013) 232–236.
 - [69] N. Singh, A. Gurav, S. Sivaprakasam, E. Brady, R. Padia, H. Shi, et al., Activation of Gpr109a, receptor for niacin and the commensal metabolite butyrate, suppresses colonic inflammation and carcinogenesis, *Immunity* 40 (2014) 128–139.
 - [70] A. Trompette, E.S. Gollwitzer, K. Yadava, A.K. Sichelstiel, N. Sprenger, C. Ngom-Bru, et al., Gut microbiota metabolism of dietary fiber influences allergic airway disease and hematopoiesis, *Nat. Med.* 20 (2014) 159–166.
 - [71] Ö Öner, G.-E. Azize, Probiotics for autoimmune diseases: is there a benefit? *Contemp. Pediatr.* (2012) 153–180.
 - [72] P.R. Mangan, L.E. Harrington, D.B. O'Quinn, W.S. Helms, D.C. Bullard, C.O. Elson, et al., Transforming growth factor- β induces development of the Th17 lineage, *Nature* 441 (2006) 231–234.
 - [73] Y. Zheng, P.A. Valdez, D.M. Danilenko, Y. Hu, S.M. Sa, Q. Gong, et al., Interleukin-22 mediates early host defense against attaching and effacing bacterial pathogens, *Nat. Med.* 14 (2008) 282–289.
 - [74] I. Kryczek, A.T. Bruce, J.E. Gudjonsson, A. Johnston, A. Aphale, L. Vatan, et al., Induction of IL-17+ T cell trafficking and development by IFN- γ : mechanism and pathological relevance in psoriasis, *J. Immunol.* 181 (2008) 4733–4741.
 - [75] C.M. Wilke, K. Bishop, D. Fox, W. Zou, Deciphering the role of Th17 cells in human disease, *Trends Immunol.* 32 (2011) 603–611.
 - [76] N. Dargahi, M. Katsara, T. Tselios, M.E. Androutsou, M. De Courten, J. Matsoukas, et al., Multiple sclerosis: immunopathology and treatment update, *Brain Sciences* 7 (2017).
 - [77] M. Zhao, Y. Tan, Q. Peng, C. Huang, Y. Guo, G. Liang, et al., IL-6/STAT3 pathway induced deficiency of RFX1 contributes to Th17-dependent autoimmune diseases via epigenetic regulation, *Nat. Commun.* 9 (2018).
 - [78] J.H. Niess, G. Adler, Enteric flora expands gut lamina propria CX3CR1+ dendritic cells supporting inflammatory immune responses under normal and inflammatory conditions, *J. Immunol.* 184 (2010) 2026–2037.
 - [79] K. Atarashi, J. Nishimura, T. Shima, Y. Umesaki, M. Yamamoto, M. Onoue, et al., ATP drives lamina propria Th17 cell differentiation, *Nature* 455 (2008) 808–812.
 - [80] I.I. Ivanov, F. Frutos Rdl, N. Manel, K. Yoshinaga, D.B. Rifkin, R.B. Sartor, et al., Specific microbiota direct the differentiation of IL-17-producing T-helper cells in the mucosa of the small intestine, *Cell Host Microbe* 4 (2008) 337–349.
 - [81] H.S. Lee, S.Y. Han, E.A. Bae, C.S. Huh, Y.T. Ahn, J.H. Lee, et al., Lactic acid bacteria inhibit proinflammatory cytokine expression and bacterial glycosaminoglycan degradation activity in dextran sulfate sodium-induced colitic mice, *Int. Immunopharm.* 8 (2008) 574–580.
 - [82] H.J. Wu, I.I. Ivanov, J. Darce, K. Hattori, T. Shima, Y. Umesaki, et al., Gut-residing segmented filamentous bacteria drive autoimmune arthritis via T helper 17 cells, *Immunity* 32 (2010) 815–827.
 - [83] M.A. Kriegel, E. Sefik, J.A. Hill, H.J. Wu, C. Benoist, D. Mathis, Naturally transmitted segmented filamentous bacteria segregate with diabetes protection in nonobese diabetic mice, *Proc. Natl. Acad. Sci. U. S. A.* 108 (2011) 11548–11553.
 - [84] C. Zaph, Y. Du, S.A. Saenz, M.G. Nair, J.G. Perrigoue, B.C. Taylor, et al., Commensal-dependent expression of IL-25 regulates the IL-23-IL-17 axis in the intestine, *J. Exp. Med.* 205 (2008) 2191–2198.
 - [85] L.R. Fitzpatrick, Novel pharmacological approaches for inflammatory bowel disease: targeting key intracellular pathways and the IL-23/IL-17 axis, *Int. J. Inflammation* 2012 (2012).
 - [86] S. Tanabe, Y. Kinuta, Y. Saito, Bifidobacterium infantis suppresses proinflammatory interleukin-17 production in murine splenocytes and dextran sodium sulfate-induced intestinal inflammation, *Int. J. Mol. Med.* 22 (2008) 181–185.
 - [87] D. Ghadimi, U. Helwig, J. Schrezenmeir, K.J. Heller, M. de Vrese, Epigenetic imprinting by commensal probiotics inhibits the IL-23/IL-17 axis in an in vitro model of the intestinal mucosal immune system, *J. Leukocyte Biol.* 92 (2012) 895–911.
 - [88] E. Miyauchi, T. Ogita, J. Miyamoto, S. Kawamoto, H. Morita, H. Ohno, et al., Bifidobacterium longum alleviates dextran sulfate sodium-induced colitis by suppressing IL-17A response: involvement of intestinal epithelial costimulatory molecules, *PLoS One* 8 (2013).
 - [89] T. Ogita, Y. Tani, H. Morita, T. Suzuki, S. Tanabe, Suppression of Th17 response by streptococcus thermophilus ST28 through induction of IFN- γ , *Int. J. Mol. Med.* 28 (2011) 817–822.
 - [90] E. Owaga, R.H. Hsieh, B. Mugendi, S. Masuku, C.K. Shih, J.S. Chang, Th17 cells as potential probiotic therapeutic targets in inflammatory bowel diseases, *Int. J. Mol. Sci.* 16 (2015) 20841–20858.
 - [91] L.R. Fitzpatrick, L. Deml, C. Hofmann, J.S. Small, M. Groepel, S. Hamm, et al., 4SC-101, a novel immunosuppressive drug, inhibits IL-17 and attenuates colitis in two murine models of inflammatory bowel disease, *Inflamm. Bowel Dis.* 16 (2010) 1763–1777.
 - [92] L.R. Fitzpatrick, J.S. Small, R. Doblhofer, A. Ammendola, Vidofludimus inhibits colonic interleukin-17 and improves hapten-induced colitis in rats by a unique dual mode of action, *J. Pharmacol. Exp. Ther.* 342 (2012) 850–860.
 - [93] L. Chen, Y. Zou, J. Peng, F. Lu, Y. Yin, F. Li, et al., Lactobacillus acidophilus suppresses colitis-associated activation of the IL-23/Th17 axis, *J. Immunol. Res.*

- 2015 (2015).
- [94] H.Y. Dar, S. Pal, P. Shukla, P.K. Mishra, G.B. Tomar, N. Chattopadhyay, et al., *Bacillus clausii* inhibits bone loss by skewing treg-Th17 cell equilibrium in post-menopausal osteoporotic mice model, *Nutrition* 54 (2018) 118–128.
 - [95] H.Y. Dar, P. Shukla, P.K. Mishra, R. Anupam, R.K. Mondal, G.B. Tomar, et al., *Lactobacillus acidophilus* inhibits bone loss and increases bone heterogeneity in osteoporotic mice via modulating treg-Th17 cell balance, *Bone Rep.* 8 (2018) 46–56.
 - [96] A.D. Kraneveld, S. Sagar, J. Garssen, G. Folkerts, The two faces of mast cells in food allergy and allergic asthma: The possible concept of yin yang, *Biochimica et Biophysica Acta (BBA)* 1822 (2012) 93–99.
 - [97] P. Hajeb, J. Selamat, A contemporary review of seafood allergy, *Clin. Rev. Allergy Immunol.* 42 (2012) 365–385.
 - [98] A.L. Lopata, M.F. Jeebhay, Airborne seafood allergens as a cause of occupational allergy and asthma, *Curr. Allergy Asthma Rep.* 13 (2013) 288–297.
 - [99] A.W. Burks, M. Tang, S. Sicherer, A. Muraro, P.A. Eigenmann, M. Ebisawa, et al., ICON: food allergy, *J. Allergy Clin. Immun.* 129 (2012) 906–920.
 - [100] C. Barberi, S. Campana, C. De Pasquale, M. Rabbani Khorasgani, G. Ferlazzo, I. Bonaccorsi, T cell polarizing properties of probiotic bacteria, *Immunol. Lett.* 168 (2015) 337–342.
 - [101] V.M.B. Fonseca, T.M.S. Milani, R. Prado, V.L.D. Bonato, S.G. Ramos, F.S. Martins, et al., Oral administration of saccharomyces cerevisiae UFMG A-905 prevents allergic asthma in mice, *Respirology* 22 (2017) 905–912.
 - [102] K. Sadakane, T. Ichinose, M. Nishikawa, H. Takano, T. Shibamoto, Co-exposure to zymosan A and heat-inactivated Asian sand dust exacerbates ovalbumin-induced murine lung eosinophilia, *Allergy Asthma Clin. Immunol.* 12 (2016).
 - [103] C.F. Nunes, J.S. Nogueira, P.H.O. Vianna, B.T. Ciambarella, P.M. Rodrigues, K.R. Miranda, et al., Probiotic treatment during neonatal age provides optimal protection against experimental asthma through the modulation of microbiota and T cells, *Int. Immunol.* 30 (2018) 155–169.
 - [104] H. Vliagofitis, V.D. Kouranos, G.I. Betsi, M.E. Falagas, Probiotics for the treatment of allergic rhinitis and asthma: systematic review of randomized controlled trials, *Ann. Allergy Asthma Immunol.* 101 (2008) 570–579.
 - [105] G. Ciprandi, A. Vizzaccaro, I. Cirillo, M.A. Tosca, *Bacillus clausii* exerts immunomodulatory activity in allergic subjects: a pilot study, *Eur. Ann. Allergy Clin. Immunol.* 37 (2005) 129–134.
 - [106] G. Yang, Z.Q. Liu, P.C. Yang, Treatment of allergic rhinitis with probiotics: an alternative approach, *North. Am. J. Med. Sci.* 5 (2013) 465–468.
 - [107] A.D.B. Rø, M.R. Simpson, T.B. Rø, O. Storrø, R. Johnsen, V. Videm, et al., Reduced Th22 cell proportion and prevention of atopic dermatitis in infants following maternal probiotic supplementation, *Clin. Exp. Allergy* 47 (2017) 1014–1021.
 - [108] J.H. Shin, M.J. Chung, J.G. Seo, A multistrain probiotic formulation attenuates skin symptoms of atopic dermatitis in a mouse model through the generation of CD4+ Foxp3+ T cells, *Food Nutr. Res.* 60 (2016).
 - [109] R.E. Hoeppli, D. Wu, L. Cook, M.K. Levings, The environment of regulatory T cell biology: cytokines, metabolites, and the microbiome, *Front. Immunol.* 6 (2015).
 - [110] S.L. Russell, M.J. Gold, B.P. Willing, L. Thorson, K.M. McNagny, B.B. Finlay, Perinatal antibiotic treatment affects murine microbiota, immune responses and allergic asthma, *Gut Microbes* 4 (2013) 158–164.
 - [111] S. De Roock, M. Van Elk, M.E.A. Van Dijk, H.M. Timmerman, G.T. Rijkers, B.J. Prakken, et al., Lactic acid bacteria differ in their ability to induce functional regulatory T cells in humans, *Clin. Exp. Allergy* 40 (2010) 103–110.
 - [112] J.P. Chouraqui, C. Dupont, A. Bocquet, J.L. Bresson, A. Briend, D. Darmaun, et al., Feeding during the first months of life and prevention of allergy, *Archives de pediatrie* 15 (2008) 431–442.
 - [113] J. Lee, D. Seto, L. Bielory, Meta-analysis of clinical trials of probiotics for prevention and treatment of pediatric atopic dermatitis, *J. Allergy Clin. Immunol. Pract.* 121 (2008) 116–21 e11.
 - [114] T. Volz, Y. Skabytska, E. Guenova, K.M. Chen, J.S. Frick, C.J. Kirschning, et al., Nonpathogenic bacteria alleviating atopic dermatitis inflammation induce IL-10-producing dendritic cells and regulatory Tr1 cells, *J. Invest. Dermatol.* 134 (2014) 96–104.
 - [115] Z. Vadasz, T. Rainis, A. Nakhleh, T. Haj, J. Bejar, K. Halasz, et al., The involvement of immune semaphorins in the pathogenesis of inflammatory bowel diseases (IBDs), *PloS One* 10 (2015).
 - [116] Z. Xun, Q. Zhang, T. Xu, N. Chen, F. Chen, Dysbiosis and ecotypes of the salivary microbiome associated with inflammatory bowel diseases and the assistance in diagnosis of diseases using oral bacterial profiles, *Front. Microbiol.* 9 (2018).
 - [117] B. Willing, J. Halfvarson, J. Dicksved, M. Rosenquist, G. Järnerot, L. Engstrand, et al., Twin studies reveal specific imbalances in the mucosa-associated microbiota of patients with ileal crohn's disease, *Inflamm. Bowel Dis.* 15 (2009) 653–660.
 - [118] C.L. Sokol, G.M. Barton, A.G. Farr, R. Medzhitov, A mechanism for the initiation of allergen-induced T helper type 2 responses, *Nat. Immunol.* 9 (2008) 310–318.
 - [119] T.A. Oelschlaeger, Mechanisms of probiotic actions – a review, *Int. J. Med. Microbiol.* 300 (2010) 57–62.
 - [120] T. Chiba, H. Seno, Indigenous clostridium species regulate systemic immune responses by induction of colonic regulatory T cells, *Gastroenterology* 141 (2011) 1114–1116.
 - [121] S. Fukuda, H. Toh, K. Hase, K. Oshima, Y. Nakanishi, K. Yoshimura, et al., Bifidobacteria can protect from enteropathogenic infection through production of acetate, *Nature* 469 (2011) 543–549.
 - [122] H. van der Kleij, C. O'Mahony, F. Shanahan, L. O'Mahony, J. Bienenstock, Protective effects of *Lactobacillus rhamnosus* [corrected] and *Bifidobacterium infantis* in murine models for colitis do not involve the vagus nerve, *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 295 (2008) R1131–7.
 - [123] Y. Jiang, G. Yang, F. Meng, W. Yang, J. Hu, L. Ye, et al., Immunological mechanisms involved in probiotic-mediated protection against *Citrobacter rodentium*-induced colitis, *Beneficial Microbes* 7 (2016) 397–407.
 - [124] E. Nikoopour, B. Singh, Reciprocity in microbiome and immune system interactions and its implications in disease and health, *Inflam. Allergy – Drug. Targets* 13 (2014) 94–104.
 - [125] F. Bäckhed, M. Fraser Claire, Y. Ringel, E. Sanders Mary, R.B. Sartor, M. Sherman Philip, et al., Defining a healthy human gut microbiome: current concepts, future directions, and clinical applications, *Cell Host Microbe* 12 (2012) 611–622.
 - [126] W.R. Brown, Fecal microbiota transplantation in treating *clostridium difficile* infection, *J. Dig. Dis.* 15 (2014) 405–408.
 - [127] C. Strisciuglio, E. Miele, F.P. Giugliano, S. Vitale, M. Andreozzi, A. Vitale, et al., Bifidobacteria enhance antigen sampling and processing by dendritic cells in pediatric inflammatory bowel disease, *Inflamm. Bowel Dis.* 21 (2015) 1491–1498.
 - [128] K. Mikkelsen, L. Stojanovska, K. Tangalakis, M. Bosevski, V. Apostolopoulos, Cognitive decline: A vitamin B perspective, *Maturitas* 93 (2016) 108–113.
 - [129] N. Nemazannikova, K. Mikkelsen, L. Stojanovska, G.L. Blatch, V. Apostolopoulos, Is there a link between Vitamin B and multiple sclerosis? *Med. Chem.* 14 (2018) 170–180.
 - [130] R. Catanzaro, M. Anzalone, F. Calabrese, M. Milazzo, M. Capuana, A. Italia, et al., The gut microbiota and its correlations with the central nervous system disorders, *Panminerva Med.* 57 (2015) 127–143.
 - [131] C. Buerth, A.K. Mausberg, M.K. Heininger, H.P. Hartung, B.C. Kieseier, J.F. Ernst, Oral tolerance induction in experimental autoimmune encephalomyelitis with *candida utilis* expressing the immunogenic MOG35-55 peptide, *PloS One* 11 (2016).
 - [132] C.B.M. Maassen, J.D. Laman, C. Van Holten-Neelen, L. Hoogteijling, L. Groenewegen, L. Visser, et al., Reduced experimental autoimmune encephalomyelitis after intranasal and oral administration of recombinant *lactobacilli* expressing myelin antigens, *Vaccine* 21 (2003) 4685–4693.
 - [133] A. Consonni, C. Cordiglieri, E. Rinaldi, R. Marolda, I. Ravanelli, E. Guidesi, et al., Administration of bifidobacterium and lactobacillus strains modulates experimental myasthenia gravis and experimental encephalomyelitis in Lewis rats, *Oncotarget* 9 (2018) 22269–22287.
 - [134] Z. Salehipour, D. Haghmorad, M. Sankian, M. Rastin, R. Nosratabadi, M.M. Soltan Dallal, et al., Bifidobacterium animalis in combination with human origin of *Lactobacillus plantarum* ameliorate neuroinflammation in experimental model of multiple sclerosis by altering CD4+ T cell subset balance, *Biomed. Pharmacother.* 95 (2017) 1535–1548.
 - [135] M. Yamashita, K. Ukibe, Y. Matsubara, T. Hosoya, F. Sakai, S. Kon, et al., *Lactobacillus helveticus* SBT2171 attenuates experimental autoimmune encephalomyelitis in mice, *Front. Microbiol.* 8 (2017) 2596.
 - [136] S.K. Tankou, K. Regev, B.C. Healy, E. Tjon, L. Laghi, L.M. Cox, et al., A probiotic modulates the microbiome and immunity in multiple sclerosis, *Ann. Neurol.* (2018).
 - [137] E. Kouchaki, O.R. Tamtaji, M. Salami, F. Bahmani, R. Daneshvar Kakhaki, E. Akbari, et al., Clinical and metabolic response to probiotic supplementation in patients with multiple sclerosis: a randomized, double-blind, placebo-controlled trial, *Clin. Nutr.* 36 (2017) 1245–1249.