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REVIEW

The modulation and mechanism of probiotic-derived polysaccharide capsules on the immune response in allergic diseases

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ABSTRACT

Allergic diseases, derived from the dysregulation of immune tolerance mechanisms, have been rising in the last two decades. Recently, increasing evidence has shown that probiotic-derived polysaccharide capsules exhibit a protective effect against allergic diseases, involving regulation of Th1/Th2 balance, induction of differentiation of T regulatory cells and activation of dendritic cells (DCs). DCs have a central role in controlling the immune response through their interaction with gut microbiota *via* their pattern recognition receptors, including Toll-like receptors and C-type-lectin receptors. This review discusses the effects and critical mechanism of probiotic-derived polysaccharide capsules in regulating the immune system to alleviate allergic diseases. We first describe the development of immune response in allergic diseases and recent relevant findings. Particular emphasis is placed on the effects of probiotic-derived polysaccharide capsules on allergic immune response. Then, we discuss the underlying mechanism of the impact of probiotic-derived polysaccharide capsules on DCs-mediated immune tolerance induction.

KEYWORDS

Allergic diseases;
dendritic cells;
immune regulation;
probiotic polysaccharides

Introduction

The prevalence of allergic diseases, including atopic dermatitis, allergic rhinitis, food allergies, and asthma, has been rising worldwide. These allergic diseases seriously affect the health and quality of life of individuals, and have become a common public health problem. Indeed, it is reported that 20-30% population of western countries are suffering from at least one type of allergic diseases (Eslami et al. 2020).

Allergic diseases are difficult to be studied and fully understand due to their complex clinical symptoms and pathogenesis. Allergic diseases are related to an adverse reaction by the immune system to allergenic source materials, including pollen, nuts, grains, milk, and salivary proteins from insects. The allergen-specific immunotherapy (SIT) is the most widely used selective and effective method for allergic diseases in clinical practice (Sicherer and Sampson 2018). The mechanism of SIT is mainly to induce the T regulatory (Treg) cell-mediated immune tolerance to allergens (Bacher and Scheffold 2018; Schmiechen, Weissler, and Frischmeyer-Guerrerio 2019). However, not all patients reach persistent clinical tolerance (Hayen et al. 2014; Willemsen 2018). Thus, current research focuses on new therapies to enhance the immune tolerance to allergens with long-lasting effects and minimize the risk of adverse reactions (Reisacher and Davison 2017). Gut microbial community imbalances have been associated with the development of allergic diseases (Aitoro et al. 2017; Kuitunen et al. 2009; Lee et al. 2020). Even though some negative or controversial evidence has also been observed (Kuitunen et al. 2009; Morisset et al. 2011; Tan-Lim and Esteban-Ipac 2018), the administration of probiotics (mainly *Lactobacillus* and *Bifidobacteria*) has been proposed as a potential approach to promote immune tolerance and alleviate allergic response through the regulation of gut microbiota composition and immune function (Basturk et al. 2020; Shu et al. 2019; B. Yang et al. 2017). Polysaccharide capsules, high molecular weight carbohydrates presented outside of the bacterial cell wall, are considered one of the important biologically active components of probiotics. The nutritional and immunological effects of polysaccharide capsules produced by *Lactobacillus* and *Bifidobacteria* have been widely investigated, including attenuating inflammation and cell apoptosis (Fanning et al. 2012; Hughes et al. 2017; Püngel et al. 2020). Recently, the administration of probiotic-derived polysaccharide capsules has been proposed as one of the potential therapeutic approaches to regulate immune response of allergic diseases. In particular, polysaccharide capsules from *Lactobacillus* and *Bifidobacteria* reduce the serum levels of allergen-specific antibodies and relieve allergic responses (*e.g.*, atopic dermatitis, food allergy, and allergic asthma) in mice (Gorska et al. 2017; Luo et al. 2020; Noda et al. 2019). These anti-allergy effects produced by probiotic-polysaccharide capsules are involved in enhancing specific mucosal immune response, improving intestinal immune barrier function, inhibiting Th2 cell polarization, and promoting Th1 cell

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differentiation (Gorska et al. 2017; Johnson, Jones, and Cobb 2015; Luo et al. 2020; Schiavi et al. 2018). However, there are limited reviews to highlight the effects and mechanisms of probiotic-derived polysaccharide capsules on the immune response in allergic diseases.

In this review, we described the recent developments and understanding of the immune response in allergic diseases, and discussed the critical role of probiotic-derived polysaccharide capsules as a therapeutic agent in regulating immune response of allergic diseases.

Cellular immunity in allergic diseases

The differentiation and function of T cells in allergic diseases

In the majority of allergic diseases, the allergic symptoms are characterized as IgE-mediated reactions, which are known as immediate type I hypersensitivity and usually develop clinical symptoms quickly after allergen exposure (Rindsjö and Scheynius 2010). $CD4^+$T cells, which play a critical role in type I hypersensitivity, can be categorized into various subsets based on the different cytokines they secrete, namely T helper 1 (Th1), Th2, Th17 and Treg cells. Th1 cells mainly secrete cytokines such as IFN-γ, IL-12 and TNF-α, while Th2 cells mostly produce cytokines including IL-4, IL-5 and IL-9. Importantly, polarized Th2 immune response is the main feature of the immune response in allergic diseases. The first stage of allergy (allergens are encountered for the first time through the epithelial barrier of the skin, airway, or gut) is the sensitization to the allergen. It causes a polarized Th2-mediated immune response, which produces a high level of IL-4. Coupled with signals from IL-4, B cells interact with Th2 cells and subsequentially secrete a high level of IgE antibody. This large amount of IgE is released into the peripheral blood and binds to mast cells or basophils through the IgE-specific receptor on their surface. In the second stage of allergy (the same allergen is reencountered later), the allergen causes degranulation of mast cells, inducing the release of histamine and other inflammatory mediators through the binding with the IgE antibody on mast cells. This process will result in rhinorrhea, itchiness, dyspnea, and anaphylaxis. Clinically, patients with allergic diseases display imbalanced Th1/Th2 immune response, which is characterized as allergen-induced Th2-skewed immune reactions in the bloodstream (a significant amount of IL-4, IL-5, and IL-13), but low level of Th1-cytokine IFN-γ (Kumar et al. 2012; Nakata et al. 2019). Similarly, allergen-specific Th2-immune response or the high level of Th2-cytokine profiles are observed in murine models of allergy (Shin et al. 2015; Jing Yang, Ren, et al. 2015).

However, Treg cells, another crucial $CD4^+$T cell, block such allergens-promoting Th2-immune reactions. Their suppressive functions are mediated by the secretion of inhibitory cytokines, such as IL-10 and TGF-β. The balance of Treg cells and Th2 cells has played a vital role in developing the allergy. Treg cells can be classified into two main subsets according to their source: the $CD4^+Foxp3^+$ natural Treg (nTreg) cells, which are differentiated from the thymus; and the induced Treg (iTreg) cells, which are differentiated from naive conventional $CD4^+Foxp3^-$T cells after exposure to antigens under certain appropriate conditions, such as T-cell receptor (TCR) stimulation, regulator cytokines (*e.g.*, TGF-β or IL-10) (Rivas and Chatila 2016). Besides, $CD4^+$type 1 regulatory T (Tr1) cells are another subset of iTreg cells characterized by the high secretion of IL-10 and expression of lymphocyte activation gene 3 (LAG-3) and CD49b on the surface without Foxp3 expression. Clinical studies have also revealed that the decreased number and functional loss of $Foxp3^+$Treg cells in the blood of children is directly related to severe allergic reactions, and increased $Foxp3^+$Treg cells induce lower atopic sensitization and asthma (Lluis et al. 2014; Tiemessen et al. 2004). The SIT, the most effective method to treat allergies, leads to the generation of $Foxp3^+$Treg and Tr1 cells in peripheral blood mononuclear cells (PBMCs) of children suffering from an allergic disease (Lou et al. 2012). Patients with a higher frequency of circulating $Foxp3^+$Treg cells show fewer allergic symptoms, and the level of $Foxp3^+$Treg cells and the gene expression of TGF-β and IL-10 in allergen-tolerant patients are higher than those in the allergy group (Krogulska et al. 2011; Noh et al. 2012). Also, the transfer of Treg cells from healthy mice to OVA-induced allergy mice reduces the serum level of OVA-specific IgE (Yamashita et al. 2012). In summary, allergic diseases apparently occur due to the allergens-induced Th2-skewed immune reactions and loss of Treg cells.

The differentiation and function of dendritic cells in allergic diseases

In the pathogenesis of allergy, the immune response is first stimulated by antigen-presenting cells, which capture and process antigens and then transfer their information to lymphocytes. Dendritic cells (DCs) are the most functional antigen-presenting cells. During antigen capture and processing, immature dendritic DCs will become mature characterized by the increased expression of surface MHC class I/II molecules and co-stimulators, such as clusters of differentiation (CD) 40, CD80, and CD86. These mature DCs eventually deliver antigen-specific information to T cells, thereby stimulating their activation. DCs isolated from PBMCs of children with milk allergy secrete more inflammatory cytokines than those from healthy children and promote the secretion of Th2 cytokines in $CD4^+$T cells in vitro (Frischmeyer-Guerrerio et al. 2011). Besides the induction of $CD4^+$T cell activation, DCs also play an essential regulatory role in developing immune tolerance. The regulatory DCs (regDCs), which produce a large number of regulatory cytokines including IL-10, TGF-β, retinoic acid (a vitamin A metabolite), and indoleamine-2,3-dioxygenase, directly promote the generation of $Foxp3^+$Treg cells from naive $CD4^+$T cells and induce immune tolerance (Jeon et al. 2012; Xie et al. 2015). Two subsets of regDCs have been extensively studied. The ones called immature DCs or semi-mature DCs are characterized by the lower expression of MHCII and co-stimulatory molecules. The other ones,

called CD11c$^+$CD103$^+$DCs, specifically express CD103 molecules on their surface and high levels of the RALDH enzyme, leading to high levels of retinoic acid through RALDH enzyme-mediated vitamin A metabolism. Studies in murine models (peanut and cow milk allergies) indicate that oral sensitization with food allergens causes a significant change in the subsets of DCs in the gut toward a much lower percentage of CD103$^+$DCs (Smit et al. 2011; J Yang, Ren, et al. 2015). However, these allergen-induced allergic responses are attenuated by an increase in the number of CD103$^+$DCs and Foxp3$^+$ Treg cells in gut lymph nodes (Meulenbroek et al. 2013; Smit et al. 2011). Overall, the studies of allergic diseases mainly focus on the regulation of DCs functions, including the induction of Treg cells differentiation and regulation of the Th1/Th2 balance, to promote immune tolerance to allergens (Figure 1). Based on the critical role of regDCs in regulating the immune response, the differentiation and function of intestinal CD103$^+$DCs have become an essential target for the study of the mechanism of allergic diseases and the design of new therapies.

The immunoregulatory effects of probiotic-polysaccharide capsules on allergic diseases

Composition and biosynthesis of probiotic-polysaccharide capsules

Polysaccharide capsules, high-molecular-weight compounds produced by various intestinal bacteria, are the main immunomodulatory components of prebiotics. Polysaccharide capsules are generally related to all polysaccharides present outside the bacterial cell wall. They can be categorized as capsular form (capsular polysaccharides, CPSs) and secreted form (exopolysaccharides, EPSs). CPSs are closely connected with microbial cell surface as a capsule, while EPSs are loosely on the microbial cell surface and secreted into the fermentable environment of microbial cells (Rajoka et al. 2020; Whitfield, Wear, and Sande 2020). In general, about 17% of *Lactobacillus* and *Bifidobacterium* strains in the human gut are EPSs producing factories (Ruas-Madiedo et al. 2007). The composition of EPSs/CPSs is primarily characterized by several repeating subunits of sugars, such as xylose, fructose, rhamnose, arabinose, mannose, glucose, galactose, and some sugar derivatives, including N-acetylglucosamine and N-acetylgalactosamine in various ratios (Hsieh and Allen 2020; Rajoka et al. 2020). The ratio of monosaccharide subunits in EPSs/CPSs differs significantly among different probiotic strains (Pyclik et al. 2020). Besides, the composition and biological activities of EPSs/CPSs are closely related to the growing condition (i.e., pH, temperature, fermentation time, and medium composition) (Ciszek-Lenda et al. 2011; Gorska et al. 2017; Rajoka et al. 2020). It is reported that cultivation media with peptone/yeast extract at pH 5.0 promote EPSs production from *B. longum* ATCC 15707, and affect the ratio of sugar subunits in EPSs (galactose, glucose, and uronic acid) (Schmid, Sieber, and Rehm 2015). Similarly, cultivation medium with lactose in the absence of pH control induces production of EPSs from *B. longum* CRC 002, compared to medium added

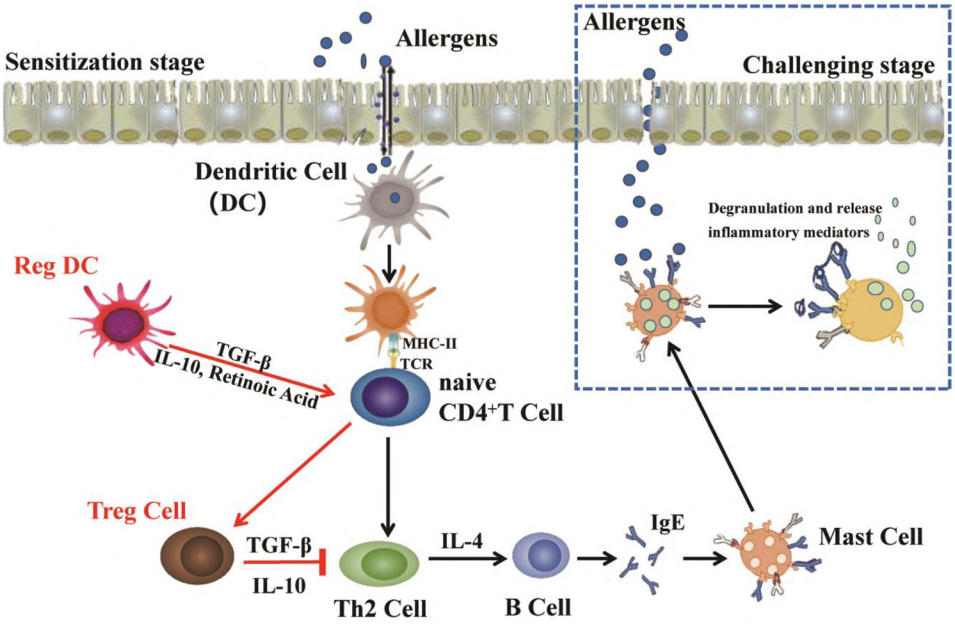

Figure 1. The immune response processes in allergen-induced allergic sensitization and challenging stage in the gut.
The exposure of allergens to DCs activates DCs to process and present allergen-specific peptides to naive CD4$^+$T cells through interaction of the MHC-II and TCR, then CD4$^+$T cells differentiate into proallergic Th2 cells. Subsequently, Th2 cells drive B cells to promote IgE class switching *via* cell contact and IL-4. IgE then binds to mast cells, causing sensitization. Following the subsequent exposure to an allergen (challenging stage), the cross-linking of the surface-bound IgE leads to mast cell degranulation with the release of primary mediators, such as histamine and inflammatory mediators, contributing to further inflammation. Additionally, another essential subset of DCs, called regDCs, secrete high levels of TGF-β, IL-10, and retinoic acid, directly mediate the conversion of T cells into Treg cells and induce the suppression of allergen-specific Th2-skewed immune responses. MHC-II, Major histocompatibility complex class II; TCR, T cell receptor; regDCs, regulatory dendritic cells.

glucose, galactose, or fructose, and the repeating unit composition of this EPSs is 2 galactose to 3 glucose (Audy et al. 2010). In this study, the expression of genes coding for EPSs is upregulated by this lactose-added cultivation medium, indicating that genes involved in EPSs biosynthesis are expressed differentially under different growing conditions.

According to their composition and biosynthesis pathways, EPSs/CPSs are classified into two groups: homopolysaccharides (HoPSs) and heteropolysaccharides (HePSs) (Zeidan et al. 2017). *Lactobacillus* and *Bifidobacterium* HoPS are composed by repeating units of a single type of monosaccharide including D-glucose or D-fructose, consist mainly in α-glucans and β-fructans, with molecular mass generally between 10^5 and 10^6 Da; HePS consist of several repeated monosaccharides subunits (D-glucose, D-galactose and L-rhamnose) and monosaccharide derivatives (N-acetyl-D-glucosamine and N-acetyl-D-galactosamine), or their phosphate/other moieties in some cases, with molecular weights ranging from 10^4 and 10^6 Da (Caggianiello, Kleerebezem, and Spano 2016; Ryan et al. 2015; Zdorovenko et al. 2009). Generally, the extracellular biosynthesis pathway and Wzx/Wzy-dependent biosynthesis pathway are two essential mechanisms for EPSs/CPSs biosynthesis in *Lactobacilli* and *Bifidobacteria* (Rajoka et al. 2020). Extracellular EPSs/CPSs biosynthesis pathway is used to synthesize HoPSs. In the beginning, a monosaccharide is added directly to an emergent sugar polymer in the cytoplasm. This elongation of the polysaccharide chain is mediated by enzymes (i.e., glucansucrase or fructansucrase). Then, the polymerized HoPSs chain is released straightly into the extracellular environment (Rajoka et al. 2020; Zannini et al. 2016). On the other hand, HePSs, a more complicated structure than HoPSs, are synthesized by Wzx/Wzy-dependent EPSs/CPSs biosynthesis pathways which require more enzymes and more significant interaction sites. The sugar units are synthesized in the cytoplasm, including phosphorylation and transportation of monosaccharides/disaccharides and the process of sugar nucleotides formation. Then, these repeating subunits are moved in the extracellular membrane from the cytoplasmic membrane facilitated by Wzx pathway. Lastly, Wzy mediated-polymerization of repeating subunits occurs, and long polymer chains are released into extracellular space (Cuthbertson et al. 2009; Schmid, Sieber, and Rehm 2015).

Both HoPSs and HePSs produced by the bacteria increase tolerance to stress environmental conditions in the host (Hsieh and Allen 2020). Besides, probiotic-polysaccharide capsules, as bio-thickeners, emulsifiers and stabilizers, contribute to the stability and progress of food products and enhance food texture and mouth-feel properties (Angelin and Kavitha 2020). In the last few years, the nutritional and immunological effects of EPSs/CPSs on human diseases have been extensively studied, such as the prevention of inflammation, inhibition of tumor growth, and attenuation of allergic responses (Gorska et al. 2017; Rajoka et al. 2020; Verma et al. 2018).

Effects of probiotic-polysaccharide capsules on T cell balance

Even though the definition of probiotics is related to the live cells, it is reported that oral administration of dead cells of *Lactobacillus* and *Bifidobacteria* can also alleviate allergic diseases (atopic dermatitis and allergic airway) in children and mice (Casaro et al. 2018; Ishida et al. 2005; Rather et al. 2021). The term postbiotic, related to non-viable cells or cell fractions, is a novel strategy that can be applied for the treatment of allergy to induce immune tolerance with less undesirable side-effects (Adams 2010; Aguilar-Toalá et al. 2018). Cell wall polysaccharide capsules are considered one of the important biological components of probiotics. Recent evidence has shown that probiotic-polysaccharide capsules reduce the serum levels of allergen-specific antibodies (IgE and IgG), suppress allergy development, and relieve atopic dermatitis, food allergy, and allergic asthma in mice (Gorska et al. 2017; Luo et al. 2020; Noda et al. 2019). EPSs/CPSs suppress allergy development through their regulatory effects on T cell responses, especially the Th1/Th2 balance. The immunological effects of *Bifidobacteria*-derived EPSs on anaphylaxis have been investigated in a murine model. In this study, EPSs from *B. breve* WBBR04 and *B. longum* WBLO01 considerably reduce the serum levels of IgE and IL-4, and relieve OVA-induced allergic responses (Luo et al. 2020). In addition, EPSs produced by *L. paracasei* IJH-SONE68 have been found to reduce the gene expression of the Th2-associated cytokine IL-4 in the ear tissue and decrease total IgE in serum in mice with allergic dermatitis (Noda et al. 2019). EPSs isolated from *L. rhamnosus* LOCK 0900 also significantly suppress the OVA-induced Th2 response polarization in spleen cells and mesenteric lymph nodes (MLNs), reduce the levels of OVA-specific IgE, and prevent OVA sensitization in mice (Gorska et al. 2017). Importantly, Treg cell-mediated immune responses are also regulated by probiotic-polysaccharide capsules (Neff et al. 2016; Speciale et al. 2019; Verma et al. 2018). The EPSs derived from the commensal bacterium *Bacteroides fragilis* have been reported to increase the percentage of Tr1 cells in lymph nodes of the lung, significantly inhibit both Th1 and Th2 responses, and limit allergic sensitization to OVA in mice (Johnson, Jones, and Cobb 2015). *B. longum* 35624 is shown to promote $Foxp3^+$Treg cell-mediated immune responses in healthy volunteers, and EPSs from *B. longum* 35624 have been found to suppress allergic responses in OVA-sensitized mice, significantly reduce IL-4 expression and eosinophil levels in the lung tissue, and increase IL-10 level (Schiavi et al. 2018). The characterization of the structural details of EPSs from *B. longum* 35624 has revealed that this EPSs are characterized by a branched hexasaccharide repeating unit containing two galactose and two glucose moieties, galacturonic acid and the unusual sugar 6-deoxy-L-talose (Altmann et al. 2016). Besides EPSs, CPSs from *Bacteroides cellulosilyticus DSM 14838* promote the proportion of Tregs in human mononuclear cells (Neff et al. 2016). Administration of the *B. bifidum* strain *PRI1* is found to increase the number of both $Foxp3^+$Treg cells and Tr1 cells in colonic lamina propria

(cLP). Furthermore, the characterization of the CPSs derived from the *B. bifidum strain* PRI1 reveals that they are a complex mixture of polysaccharides, including two main groups: a phospho-glycero-β-galactofuranan, PGβG, and a mixture with four neutral polysaccharides, namely CSGG, composed of β-1,6-glucan, β-1,4-galactan, β-1,6-galactan, β-galactofuranan and starch. These two groups of CPSs display different immune responses: CSGG is responsible for induction of Treg cells, since intraperitoneal injections of CSGG into germ-free mice for 3 weeks induces differentiation into Foxp3$^+$Treg cells in the cLP and MLN, and CSGG-treated DCs significantly increase the percentage of Foxp3$^+$Treg cells and production of IL-10 in naive CD4$^+$T cells in vitro. However, PGβG only enhances pro-inflammatory immune response by increasing the INF-γ level (Speciale et al. 2019; Verma et al. 2018). These data suggest that probiotic-polysaccharide capsules have different effects in regulating T cell immune responses depending on their chemical structures.

Effects of probiotic-polysaccharide capsules on DC activation

DCs have been identified as essential regulators in immunological response through their effects on T cell response. The impacts of EPSs/CPSs on DCs include promoting DCs maturation (increased expression of MHCII, CD40, CD80, and CD86), enhancing the cytokine secretion of IL-10 and IL-12, and increasing gene expression and activity of RALDH (Matsuzaki et al. 2018; Tang et al. 2015; Xiu et al. 2018). EPSs from *B. longum* 35624 have been shown to enhance the DC-mediated immune responses by inducing maturation of DCs (increasing the expression of CD80 and CD86) and regulatory cytokine IL-10 production (Schiavi et al. 2018). Co-culture of DCs with EPSs derived from *L. johnsonii* 142 induces the level of IL-10 and Th1-cytokine IL-12 in the supernatant, and promote expression of CD80 and CD86 on DCs. This *L. johnsonii* 142-derived EPSs are composed of 5-substituted galactofuranose, 3-substituted galactopyranose, and 3-substituted glucopyranose residues at a molar ratio of 1:3:1 (Górska, Sandstrőm, et al. 2016). EPSs isolated from *L. plantarum* increase the level of IL-12 and IL-10 in serum and intestinal fluid of BALB/c mice, and induce DCs to express more MHC II and CD86, which promote the proliferation of T cells. This EPSs are a complex mixture of ribose, rhamnose, arabinose, xylose, mannose, glucose, and galactose with a molar ratio of 2:1:1:10:4:205:215, respectively (Tang et al. 2015). CSGG, the component of CPSs isolated from the *B. bifidum strain* PRI1, significantly enhances the gene expression of TGF-β1, IL-10, and IL-27 in DCs, and promotes the number of Foxp3$^+$Treg cells and IL-10 level in a co-culture of CSGG-treated DCs and naive CD4$^+$T cells. Among the CSGG, the cell surface β-1-6-glucan (CSβG) has been identified as the most effective one, as 1,6-glucanase abolishes the increase in the number of Treg cells induced by CSGG in CD4$^+$T cells, but other enzymes, such as β-1,4-galactanase and β-1,6-galactanase displays little reducing activity (Speciale et al. 2019; Verma et al. 2018). The effects of different probiotic-EPSs/CPSs, capsule composition, and immune action on DC activation and T cell response are summarized in Table 1. All these results indicate that EPSs/CPSs derived from probiotics control allergic immune responses, possibly through the regulation of DC maturation and cytokine production (Figure 2).

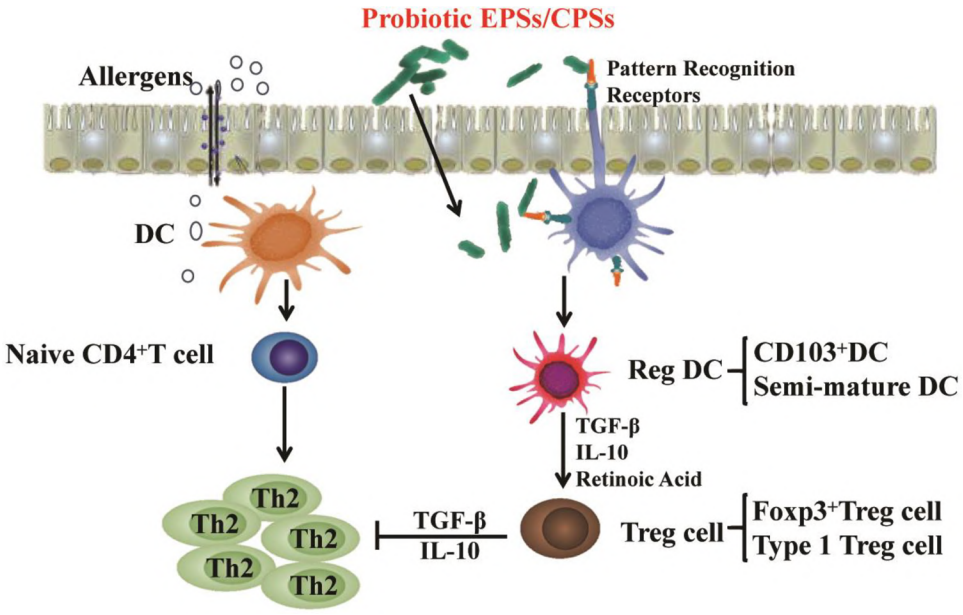

Figure 2. The effects of probiotic-polysaccharide capsules on the different populations of T cells and DCs, involved in the allergic immune response.
DCs can interact with probiotics or EPSs/CPSs through their pattern recognition receptors (PRRs), including toll-like receptors (TLRs) and C-type-lectin receptors (CLRs). This interaction results in the induction of regDC, such as CD103$^+$DC and semi-mature DC, which produce high levels of TGF-β, IL-10, and retinoic acid, directly mediating the conversion of T cells into Foxp3$^+$ Treg cells and Tr1 cells. These Treg cells reverse the allergen-specific Th2-skewed immune responses through the secretion of regulatory cytokines TGF-β, IL-10. EPSs, Exopolysaccharides; CPSs, Capsular polysaccharides; DCs, Dendritic cells; Tr1 cells, Type 1 regulatory cells; regDCs, regulatory dendritic cells.

Table 1. The regulatory effects of probiotic-EPSs/CPSs on T cell responses and DC activation.

Source of polysaccharide capsules	EPSs/CPSs	Composition	Model/Type of study	Immunoregulatory effects	References
Lactobacillus rhamnosus LOCK 0900	EPSs	Two different EPSs: a branched heteropolysaccharide with a repeating unit consisting of seven sugar residues and pyruvic acid; a pentasaccharide repeating unit and phosphorus	OVA-induced allergic response In vivo with mice	Reduces the serum levels of OVA-IgE and IgG2a; Suppresses the OVA-induced Th2-type cytokines in spleen and MLN; Decreases IgE-dependent basophil degranulation; Induces production of IL-10 and IL-12p70 in DCs	(Gorska et al. 2017)
Bifibobacterium longum 35624	EPSs	A branched hexasaccharide repeating unit consisting of two galactose and two glucose moieties, galacturonic acid and 6-deoxy-L-talose	OVA-induced allergic airway response In vivo with mice	Reduces eosinophil infiltration in lung; Reduces Th2 associated cytokine IL-4 and IL-13 gene expression in lung tissue; Promotes IL-10 level in the lung lavages; Increases CD80 expression on DCs	(Altmann et al. 2016; Schiavi et al. 2018)
Lactobacillus paracasei IJH-SONE68	EPSs	Acidic EPSs: consist primarily of mannose Neutral EPSs: consist α-1, 6-linked glycan chains made of N-acetylglucosamine (GlcNAc)	Picryl-chloride-induced delayed-type allergy In vivo with mice	Attenuates allergic responses; Reduces Th2 associated cytokine IL-4 gene expression in the ear; Decreases total IgE in serum	(Noda et al. 2018; Noda et al. 2019)
Bifidobacterium bifidum WBBI01, WBIN03, WBLO01, Bifidobacterium breve WBBR04	EPSs	Unknown	OVA-induced food allergy In vivo with mice	Decreases total IgE and IgG in serum; Inhibits the level of Th2-type cytokines and promotes the level of Th1-type cytokines in serum and the small intestine sections; Enhances the intestinal barrier integrity	(Luo et al. 2020)
Lactobacillus fermentum Lf2	EPSs	A branched repeating unit consisting of 3 different monosaccharides: β-linked glucopyranose, 1,2,3-linked glucopyranose, and 1,3-linked glucopyranose	In vivo with mice	Increases the serum level of IL-10 in mice; Induces IgA production in mice	(Elisa Carmen Ale et al. 2019; Elisa C Ale et al. 2016; Vitlic et al. 2019)
Bacillus subtilis DS991	EPSs	Mannose (88%), glucose (11.9%), N-acetylglucosamine (0.1%); Primary linkages (major): 2,6 linked Mannopyranosyl residue (31.8%), Terminal Mannopyransosyl residue (29.9%), 3 linked Mannopyranosyl residue (15%)	In vivo with mice	Induces development of M2 macrophages which inhibit T cell activation in mice	(Jones et al. 2014; Paynich, Jones-Burrage, and Knight 2017)
Bifidobacterium bifidum strain PRI1	CPSs	A phospho-glycero-β-galactofuranan (PGβG); A mixture composed of neutral polysaccharides (CSGG) composed of β-(1→6)-glucan, β-(1→4)-galactan, β-(1→6)-galactan, β-galactofuranan	OVA-induced allergic response In vivo with mice In vitro with OT-II TCR transgenic CD4+T cells	PGβG significantly promotes IFN-γ production in $CD4^+$ T cell; CSGG induces the generation of $FoxP3^+$ Tregs and production of IL-10 in $CD4^+$ T cell; Enhances gene expression of TGF-β, IL-10, and IL-27 in DCs	(Speciale et al. 2019; Verma et al. 2018)
Lactobacillus plantarum IMB19	CPSs	A linear monosaccharide repeating unit consists of 6-α-Gal-1P, 3-α-Rha, 2-α-Rha, 6 P-α-Gal, 2-α-Rha, 6-α-GlcNAc, 3-β-Glc	In vivo with mice	Enhances cytokines production of IL-6, IL-12 and IL-10 in splenocyte of mice	(Garcia-Vello et al. 2020)
Bacteroides cellulosilyticus DSM 14838	CPSs	Acetamido-amino-2,4,6-trideoxygalactose; zwitterionic	In vitro with human mononuclear cells	Promotes IL-10 production and proportions of Tregs in human mononuclear cells	(Neff et al. 2016)
Bacteroides fragilis	CPSs	Unknown	OVA-induced allergic airway In vivo with mice	Increases percentage of Tr1 cells; Inhibits both Th1 and Th2 responses in lung tissue	(Johnson, Jones, and Cobb 2015)

Abbreviations: EPSs, exopolysaccharides; CPSs, capsular polysaccharides; DCs, dendritic cells；MLN, mesenteric lymph node.

The mechanisms of probiotic-polysaccharide capsule-mediated immune regulation against allergic diseases

The host and intestinal microbiota interactions involve complex crosstalk between various microbial molecules and host receptors. The pattern recognition receptors (PRRs) on DCs, which detect microorganisms-associated molecular patterns (MAMPs), are crucial for the interaction between DCs and intestinal microbiota. This interaction between MAMPs and PRRs causes the activation of various downstream signaling pathways, which determine different immune responses (production of cytokines and chemokines) (Caggianiello, Kleerebezem, and Spano 2016). Several classes of PRRs that recognize intestinal bacteria have been reported, such as toll-like receptors (TLRs) and C-type-lectin receptors (CLRs) (Castro-Bravo et al. 2018). Some bioactive compounds derived from bacterial cell wall, including polysaccharide capsules, are involved in the mechanisms of the interaction between bacteria and host receptors. The binding of polysaccharide capsules to host receptors results in the stable adherence of bacteria to cells, thereby inducing immunological regulation (Caggianiello, Kleerebezem, and Spano 2016). To date, polysaccharide capsules have been associated with the functions of DCs, activation of natural killer cells and macrophage, induction of cytokines production and polarization of T cell response following interaction with TLRs and/or other PRRs.

Regulation of TLRs signaling by probiotic-polysaccharide capsules

TLRs, an ancient family of PRRs, are recognized as homologues of Drosophila Toll proteins and play a key role in detecting various substances and then initiating and activating the immune system (Trebichavsky et al. 2009). Each TLR interacts with different MAMPs, such as polysaccharide capsules, lipopolysaccharide (LPS), CpG DNA. Their interaction triggers different signaling pathways that result in the production of various cytokines (K. Chen et al. 2007; Palazzo et al. 2008; Trebichavsky et al. 2009). Among these receptors, TLR2 and TLR4 are the most widely investigated and have a fundamental role in mediating the immunoregulatory effects of probiotic bacteria. Upon interaction with their ligands, TLR2/4 activates a series of signaling pathways that trigger immune response (Albuquerque-Souza et al. 2019; Wachi et al. 2014). There are two possible pathways of ligand binding-mediated signaling, the myeloid differentiation primary response gene 88 (MyD88)-dependent signaling pathway and MyD88-independent TIR-domain-containing adapter-inducing interferon-β (TRIF) pathway. Most TLRs-mediated signaling pathways are MyD88-dependent, while TRIF is unique to TLR3 and TLR4-mediated signaling pathways (T. Yang et al. 2020). Both MyD88-dependent and MyD88 independent signaling pathways induce IκB kinase (IKK)-β phosphorylation, which leads to degradation of I-κB, and promotes the translocation of nuclear factor kappa B (NF-κB) from the cytoplasm to the nucleus (Bagchi et al. 2007; Mitchell 2016). In addition, the MyD88-dependent signaling pathway also mediates the activation of mitogen-activated protein kinase (MAPK), including p38, ERK, and JNK, which results in the production of immune cytokines. Both NF-κB and MAPK signaling pathways are activated in DCs, macrophages, and IECs after activation of TLR2 (Murofushi et al. 2015; Nocerino et al. 2019; Xiu et al. 2018). On the other hand, TLR2-deficient DCs have been found to secrete lower IL-10 and TGF-β, and $CD11c^+$DCs isolated from TLR2 knockout mice show a significant loss of Treg cell-inducing activity compared with wild-type (WT) DCs (Verma et al. 2018). Notably, TLR4 knockout mice are susceptible to allergy, as indicated by the findings that challenge with peanut allergen induces much higher levels of both allergen-specific IgE and histamine in plasma of TLR4 knockout mice than those in plasma of TLR4 WT mice (Bashir et al. 2004). Stimulation of the TLR4-TRIF pathway (MyD88 independent signaling pathway) can protect against the development of allergic airways in mice (Shalaby et al. 2017).

The effects of probiotics and EPSs/CPSs on the functions of DCs are mainly mediated by TLRs and their downstream signaling pathways. In vitro studies show that *L. acidophilus* X37 induces the expression of CD40 and CD86 and the production of TNF-α and IL-6 in bone marrow-derived dendritic cells (BMDCs) through interaction with TLR2. TLR2 knockout blocks *B. longum* Q46-increased secretion of IL-10 in BMDCs compared with WT DCs (Zeuthen, Fink, and Frøkiaer 2008). *L. casei* Lbs2 treatment enhances the proportion of $CD103^+$DCs and $FoxP3^+$Treg cells in MLNs of mice, and these Lbs2 induced-regulatory responses are found to be dependent on TLR2 signaling in DCs (Thakur et al. 2016). The gene expression of TLR2 and TLR4 in splenocytes of mice are upregulated by *L. casei Zhang*, and the increase of the number of $CD103^+$DCs and Treg cells by *L. casei Zhang* is found to be dependent on the activation of the NF-κB signaling pathway (Fu et al. 2020). In addition, the microbiota-activated TLR2/4 is reported to be responsible for IgA production in B cells, which are associated with the development of immune tolerance (Mezouar et al. 2018). Moreover, neonatal mono-colonization with *B. longum* in germ-free mice prevents allergic sensitization through the induction of immune tolerance mediated by TLR2/MyD88 signaling pathways. In vitro, *B. longum* induces low maturation status of BMDCs and production of IL-10 in a TLR2/MyD88/MAPK-dependent manner (Schwarzer et al. 2013). CSGG, an CPSs derived from the *B. bifidum strain* PRI1, increases TLR2 expression in DCs. Compared with WT DCs, CSGG-treated $CD11c^+$DCs isolated from TLR2 knockout mice show a significant reduction in Treg-inducing activity (Verma et al. 2018). CPSs (polysaccharide A), produced by the intestinal commensal *Bacteroides fragilis,* induce IL-12 production in BMDCs, but not in $TLR2^{-/-}$ and $MyD88^{-/-}$ BMDCs (Wang et al. 2006). Moreover, this CPSs induced-conversion of $Foxp3^+$ Treg from $CD4^+$T cells are also dependent on the TLR-2 mechanism. The administration of polysaccharide A from *Bacteroides fragilis* increases the population of $Foxp3^+$ Treg induction and IL-10 production in C57BL/6 WT, but not

in TLR2 deficient mice (Round and Mazmanian 2010). Besides, the cytokines production and mRNA expression of TLR4 in RAW 264.7 macrophages are increased by EPSs from *Bifidobacterium animalis* RH, which are suppressed when TLR4 is blocked by its antibody (Liu et al. 2017). These experiments reveal strain-specific immunomodulatory properties of CPSs/EPSs in host interaction, suggesting that the activity of whole bacteria and CPSs/EPSs induce the development of DCs and Treg cells through the TLR2/4-mediated mechanism (Figure 3). Interestingly, *L. plantarum* WCFS1 upregulates TLR2-mediated NF-κB activation in HEK-293 cell lines stably expressing TLR2. Moreover, EPSs (L919/A or L919/B) produced by *L.casei* LOCK 0919 promote the *L. plantarum* WCFS1 induced-IL-10 production in BMDCs, but TLR2 and TLR4 are not involved in the immunomodulatory effect of L919/A and L919/B (Górska, Hermanova, et al. 2016; Górska et al. 2014). These findings indicate that other family of PRRs, not only TLR2/4, would interact probiotic-EPSs to activate intracellular signaling pathways in DCs.

Modulation of DC-SIGN signaling by probiotic-polysaccharide capsules

The CLRs are another family of PRRs, which have a critical role in the binding and uptake of microbial components in DCs. DC-specific intracellular adhesion molecule-grabbing non-integrin (DC-SIGN) is one of the crucial CLRs, mainly expressed in myeloid and monocyte-derived DCs, and primarily interacts with unique structures with high mannose or fucose-terminated glycan. DC-SIGN has been reported as a central player in regulating DC adhesion, migration, and activation of T cell-mediated immune response. Activation of DC-SIGN-mediated signaling on DCs promotes IL-10 production in DCs, the generation of Treg cells, and Th1 cell response in co-culture of DCs and $CD4^+$T cells (Bergman et al. 2004). The blocking of DC-SIGN, TLR2, and TLR4 has been shown to decrease the expression of maturation markers in DCs and their production of IL-10 and TGF-β, which reduces the capacity of DCs to induce the expansion of $Foxp3^+$Treg cells (Cvetkovic et al. 2020). Additionally, *F.*

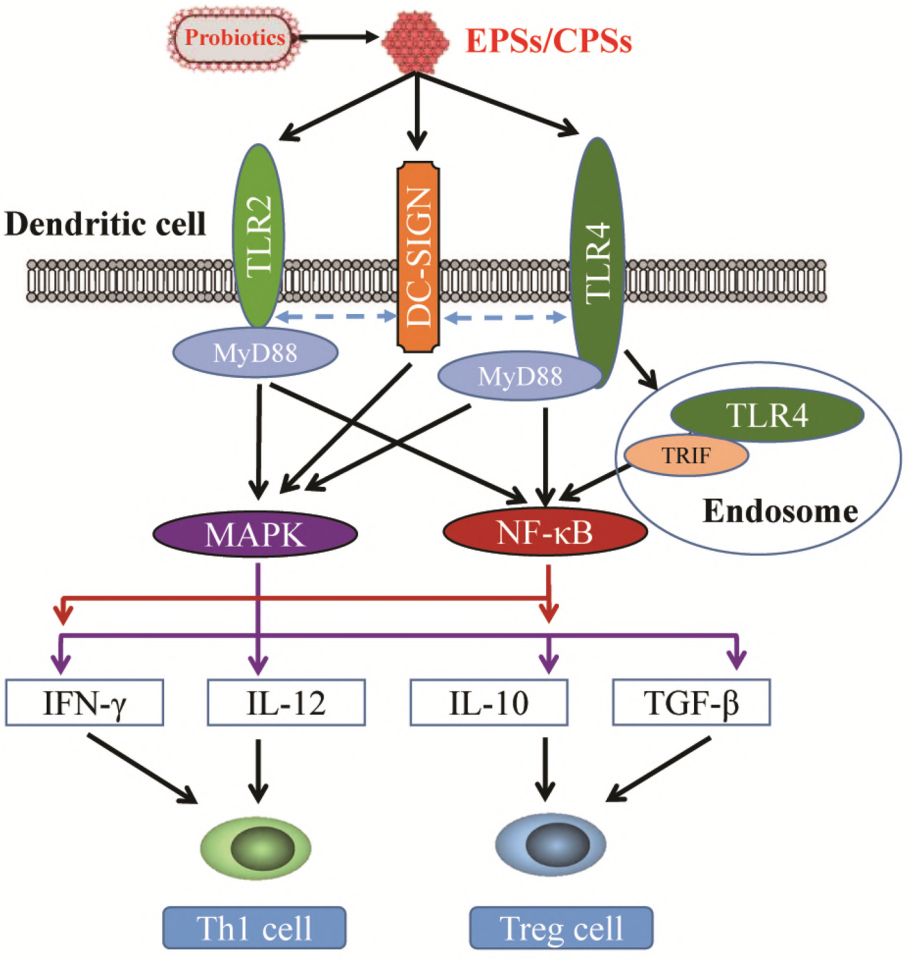

Figure 3. Proposed mechanisms of the probiotic-polysaccharide capsules' effects on DC-mediated allergic immune responses.
The effects of EPSs/CPSs on DC-regulated Th1 and Treg cell responses are mediated by TLR2/4 and their downstream signaling pathways. TLR2 and TLR4 can induce the activation of MAPK or NF-κB in DCs through the MyD88-mediated pathways, leading to the production of various cytokines and triggering Th1 or Treg responses. TLR4 initiates the MyD88-mediated pathway at the plasma membrane, and its endocytosis activates the TRIF-signaling pathway. These regulatory effects of TLR4 can be amplified by DC-SIGN. EPSs, Exopolysaccharides; DC, dendritic cell; DC-SIGN, DC-specific intracellular adhesion molecule-grabbing non-integrin; TLR, Toll-like receptor; MAPK, Mitogen-activated protein kinase; NF-κB, Nuclear factor kappa B.

hepatica glycoconjugates are shown to suppress T cells proliferation and drive the development of Treg cells *via* their interaction with DC-SIGN on DCs (Rodríguez et al. 2017). It has been reported that *L reuteri* and *L casei* bind the DC-SIGN to increase the generation of Treg cells in vitro, and blocking antibodies to DC-SIGN inhibits the increase of the number of Treg cells induced by these probiotic bacteria (Smits et al. 2005). All these findings suggest that DC-SIGN activation can prime DCs to induce the Treg cell-mediated immune response.

EPSs from *L. plantarum* WCFS1 could modulate the DCs mediated-immune response through binding to DC-SIGN (Meijerink et al. 2010). Bacterial EPSs bind to DC-SIGN and induce IL-10 production in DCs, and these effects are blocked by the DC-SIGN specific inhibitor (Geurtsen et al. 2009). Capsular polysaccharide A (PSA), the CPSs of *Bacteroides fragilis*, is a ligand for the DC-SIGN. PSA-incubated DCs increase in $CD4^+$T cell proliferation, which is inhibited by blocking DC-SIGN on DCs (Bloem et al. 2013). Recent studies revealed possible crosstalk between DC-SIGN and TLRs. DC-SIGN has been identified as an essential receptor in regulating immune response by assisting TLR-induced activation (Y. Chen, Huang, and Xu 2020; Feng et al. 2018). The cooperation of TLR2/4 and DC-SIGN receptors is critical for the production of IL-10 and TGF-β in DCs and DC-induced expansion of $Foxp3^+$ Treg cells (Cvetkovic et al. 2020; Xiao et al. 2019). Thus, the crosstalk between DC-SIGN and TLRs in the probiotic-EPSs/CPSs-modulated immune response needs to be further investigated.

Conclusion and perspectives

According to the available clinical and animal studies, DC-mediated T cells differentiation is an essential process in the pathogenesis of allergic diseases. Recently, several therapeutic strategies have been developed to prevent and treat allergies. Among the exciting strategies, probiotic-derived EPSs/CPSs are important immune regulators with potential anti-allergic effects. Recent evidence reveals the protective effects of probiotic-EPSs/CPSs on allergic diseases, including regulation of Th1/Th2 balance, induction of Treg cells, DCs activation. However, the detailed understanding of the underlying mechanism by which probiotic-derived EPSs/CPSs regulate DCs (especially $CD103^+$DCs) differentiation and function in allergy is lacking. Therefore, a detailed understanding of how the biological activities of probiotic-derived EPSs/CPSs affect PPRs on DCs and their downstream signaling pathways need to be achieved through further studies.

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References

Adams, C. A. 2010. The probiotic paradox: Live and dead cells are biological response modifiers. *Nutrition Research Reviews* 23 (1):37–46. doi: 10.1017/S0954422410000090.

Aguilar-Toalá, J., R. Garcia-Varela, H. Garcia, V. Mata-Haro, A. González-Córdova, B. Vallejo-Cordoba, and A. Hernández-Mendoza. 2018. Postbiotics: An evolving term within the functional foods field. *Trends in Food Science & Technology* 75:105–14. doi: 10.1016/j.tifs.2018.03.009.

Aitoro, R., L. Paparo, A. Amoroso, M. Di Costanzo, L. Cosenza, V. Granata, C. Di Scala, R. Nocerino, G. Trinchese, M. Montella, et al. 2017. Gut microbiota as a target for preventive and therapeutic intervention against food allergy. *Nutrients* 9 (7):672. doi: 10.3390/nu9070672.

Albuquerque-Souza, E., D. Balzarini, E. S. Ando-Suguimoto, K. H. Ishikawa, M. R. Simionato, M. Holzhausen, and M. P. Mayer. 2019. Probiotics alter the immune response of gingival epithelial cells challenged by Porphyromonas gingivalis. *Journal of Periodontal Research* 54 (2):115–27. doi: 10.1111/jre.12608.

Ale, E. C., M. J. Perezlindo, P. Burns, E. Tabacman, J. A. Reinheimer, and A. G. Binetti. 2016. Exopolysaccharide from Lactobacillus fermentum Lf2 and its functional characterization as a yogurt additive. *The Journal of Dairy Research* 83 (4):487–92. doi: 10.1017/S0022029916000571.

Ale, E. C., M. J.-B. Bourin, G. H. Peralta, P. G. Burns, O. B. Ávila, L. Contini, J. Reinheimer, and A. G. Binetti. 2019. Functional properties of exopolysaccharide (EPS) extract from Lactobacillus fermentum Lf2 and its impact when combined with Bifidobacterium animalis INL1 in yoghurt. *International Dairy Journal* 96:114–25. doi: 10.1016/j.idairyj.2019.04.014.

Altmann, F., P. Kosma, A. O'Callaghan, S. Leahy, F. Bottacini, E. Molloy, S. Plattner, E. Schiavi, M. Gleinser, D. Groeger, et al. 2016. Genome analysis and characterisation of the exopolysaccharide produced by Bifidobacterium longum subsp. longum 35624™. *PloS One* 11 (9):e0162983. doi: 10.1371/journal.pone.0162983.

Angelin, J., and M. Kavitha. 2020. Exopolysaccharides from probiotic bacteria and their health potential. *International Journal of Biological Macromolecules* 162:853–65. doi: 10.1016/j.ijbiomac.2020.06.190.

Audy, J., S. Labrie, D. Roy, and G. Lapointe. 2010. Sugar source modulates exopolysaccharide biosynthesis in Bifidobacterium longum subsp. longum CRC 002. *Microbiology* 156 (3):653–64. doi: 10.1099/mic.0.033720-0.

Bacher, P., and A. Scheffold. 2018. The effect of regulatory T cells on tolerance to airborne allergens and allergen immunotherapy. *The Journal of Allergy and Clinical Immunology* 142 (6):1697–709. doi: 10.1016/j.jaci.2018.10.016.

Bagchi, A., E. A. Herrup, H. S. Warren, J. Trigilio, H.-S. Shin, C. Valentine, and J. Hellman. 2007. MyD88-dependent and MyD88-independent pathways in synergy, priming, and tolerance between TLR agonists. *Journal of Immunology (Baltimore, MD: 1950)* 178 (2):1164–71. doi: 10.4049/jimmunol.178.2.1164.

Bashir, M. E. H., S. Louie, H. N. Shi, and C. Nagler-Anderson. 2004. Toll-like receptor 4 signaling by intestinal microbes influences susceptibility to food allergy. *Journal of Immunology (Baltimore, MD: 1950)* 172 (11):6978–87. doi: 10.4049/jimmunol.172.11.6978.

Basturk, A., İ. Isik, A. Atalay, and A. Yılmaz. 2020. Investigation of the efficacy of Lactobacillus rhamnosus GG in infants with cow's milk protein allergy: a randomised double-blind placebo-controlled trial . *Probiotics and Antimicrobial Proteins* 12 (1):138–43. doi: 10.1007/s12602-019-9516-1.

Bergman, M. P., A. Engering, H. H. Smits, S. J. Van Vliet, A. A. Van Bodegraven, H.-P. Wirth, M. L. Kapsenberg, C. M. Vandenbroucke-Grauls, Y. Van Kooyk, and B. J. Appelmelk. 2004. Helicobacter pylori modulates the T helper cell 1/T helper cell 2 balance through phase-variable interaction between lipopolysaccharide and DC-SIGN. *The Journal of Experimental Medicine* 200 (8):979–90. doi: 10.1084/jem.20041061.

Bloem, K., J. J. García-Vallejo, I. M. Vuist, B. Cobb, S. J. Van Vliet, and Y. Van Kooyk. 2013. Interaction of the capsular polysaccharide A from Bacteroides fragilis with DC-SIGN on human dendritic cells is necessary for its processing and presentation to T cells. *Frontiers in Immunology* 4:103. doi: 10.3389/fimmu.2013.00103.

Caggianiello, G., M. Kleerebezem, and G. Spano. 2016. Exopolysaccharides produced by lactic acid bacteria: From health-promoting benefits to stress tolerance mechanisms. *Applied Microbiology and Biotechnology* 100 (9):3877–86. doi: 10.1007/s00253-016-7471-2.

Casaro, M., A. Crisma, A. Vieira, G. Silva, E. Mendes, W. Ribeiro, F. Martins, and C. Ferreira. 2018. Prophylactic Bifidobacterium adolescentis ATTCC 15703 supplementation reduces partially allergic airway disease in Balb/c but not in C57BL/6 mice. *Beneficial Microbes* 9 (3):465–76. doi: 10.3920/BM2017.0073.

Castro-Bravo, N., J. M. Wells, A. Margolles, and P. Ruas-Madiedo. 2018. Interactions of surface exopolysaccharides from Bifidobacterium and Lactobacillus within the intestinal environment. *Frontiers in Microbiology* 9:2426. doi: 10.3389/fmicb.2018.02426.

Chen, K., J. Huang, W. Gong, P. Iribarren, N. M. Dunlop, and J. M. Wang. 2007. Toll-like receptors in inflammation, infection and cancer. *International Immunopharmacology* 7 (10):1271–85. doi: 10.1016/j.intimp.2007.05.016.

Chen, Y., J. Huang, and C. Xu. 2020. Lipopolysaccharide-induced DC-SIGN/TLR4 crosstalk activates NLRP3 inflammasomes via MyD88-independent signaling in gastric epithelial cells. *Experimental Cell Research* 396 (1):112292. doi: 10.1016/j.yexcr.2020.112292.

Ciszek-Lenda, M., B. Nowak, M. Sróttek, A. Gamian, and J. Marcinkiewicz. 2011. Immunoregulatory potential of exopolysaccharide from Lactobacillus rhamnosus KL37: effects on the production of inflammatory mediators by mouse macrophages. *International Journal of Experimental Pathology* 92 (6):382–91. doi: 10.1111/j.1365-2613.2011.00788.x.

Cuthbertson, L., I. L. Mainprize, J. H. Naismith, and C. Whitfield. 2009. Pivotal roles of the outer membrane polysaccharide export and polysaccharide copolymerase protein families in export of extracellular polysaccharides in gram-negative bacteria. *Microbiology and Molecular Biology Reviews: MMBR* 73 (1):155–77. doi: 10.1128/MMBR.00024-08.

Cvetkovic, J., N. Ilic, A. Gruden-Movsesijan, S. Tomic, N. Mitic, E. Pinelli, and L. Sofronic-Milosavljevic. 2020. DC-SIGN signalling induced by Trichinella spiralis products contributes to the tolerogenic signatures of human dendritic cells. *Scientific Reports* 10 (1):1–14. doi: 10.1038/s41598-020-77497-x.

Eslami, M., A. Bahar, M. Keikha, M. Karbalaei, N. Kobyliak, and B. Yousefi. 2020. Probiotics function and modulation of the immune system in allergic diseases. *Allergologia et Immunopathologia* 48 (6):771–88. doi: 10.1016/j.aller.2020.04.005.

Fanning, S., L. J. Hall, M. Cronin, A. Zomer, J. MacSharry, D. Goulding, M. O. Motherway, F. Shanahan, K. Nally, G. Dougan, et al. 2012. Bifidobacterial surface-exopolysaccharide facilitates commensal-host interaction through immune modulation and pathogen protection. *Proceedings of the National Academy of Sciences of the United States of America* 109 (6):2108–13. doi: 10.1073/pnas.1115621109.

Feng, D., Y. Wang, Y. Liu, L. Wu, X. Li, Y. Chen, Y. Chen, C. Xu, K. Yang, et al. 2018. DC-SIGN reacts with TLR-4 and regulates inflammatory cytokine expression via NF-κB activation in renal tubular epithelial cells during acute renal injury. *Clinical and Experimental Immunology* 191 (1):107–15. doi: 10.1111/cei.13048.

Frischmeyer-Guerrerio, P., A. L. Guerrerio, K. Chichester, A. Bieneman, R. Hamilton, R. A. Wood, and J. T. Schroeder. 2011. Dendritic cell and T cell responses in children with food allergy. *Clinical and Experimental Allergy: Journal of the British Society for Allergy and Clinical Immunology* 41 (1):61–71. doi: 10.1111/j.1365-2222.2010.03606.x.

Fu, L., M. Xie, C. Wang, Y. Qian, J. Huang, Z. Sun, H. Zhang, and Y. Wang. 2020. Lactobacillus Casei Zhang alleviates shrimp tropomyosin-induced food allergy by switching antibody isotypes through the NF-κB-dependent immune tolerance. *Molecular Nutrition & Food Research* 64 (10):1900496. doi: 10.1002/mnfr.201900496.

Garcia-Vello, P., G. Sharma, I. Speciale, A. Molinaro, S.-H. Im, and C. D. Castro. 2020. Structural features and immunological perception of the cell surface glycans of Lactobacillus plantarum: A novel rhamnose-rich polysaccharide and teichoic acids. *Carbohydrate Polymers* 233:115857. doi: 10.1016/j.carbpol.2020.115857.

Geurtsen, J., S. Chedammi, J. Mesters, M. Cot, N. N. Driessen, T. Sambou, R. Kakutani, R. Ummels, J. Maaskant, H. Takata, et al. 2009. Identification of mycobacterial alpha-glucan as a novel ligand for DC-SIGN: involvement of mycobacterial capsular polysaccharides in host immune modulation. *Journal of Immunology (Baltimore, MD: 1950)* 183 (8):5221–31. doi: 10.4049/jimmunol.0900768.

Górska, S., C. Sandström, J. Wojas-Turek, J. Rossowska, E. Pajtasz-Piasecka, E. Brzozowska, and A. Gamian. 2016. Structural and immunomodulatory differences among lactobacilli exopolysaccharides isolated from intestines of mice with experimentally induced inflammatory bowel disease. *Scientific Reports* 6 (1):37613–6. doi: 10.1038/srep37613.

Gorska, S., M. Schwarzer, D. Srutkova, P. Hermanova, E. Brzozowska, H. Kozakova, and A. Gamian. 2017. Polysaccharides L900/2 and L900/3 isolated from Lactobacillus rhamnosus LOCK 0900 modulate allergic sensitization to ovalbumin in a mouse model. *Microbial Biotechnology* 10 (3):586–93. doi: 10.1111/1751-7915.12606.

Górska, S., M. Schwarzer, W. Jachymek, D. Srutkova, E. Brzozowska, H. Kozakova, and A. Gamian. 2014. Distinct immunomodulation of bone marrow-derived dendritic cell responses to Lactobacillus plantarum WCFS1 by two different polysaccharides isolated from Lactobacillus rhamnosus LOCK 0900. *Applied and Environmental Microbiology* 80 (20):6506–16. doi: 10.1128/AEM.02104-14.

Górska, S., P. Hermanova, J. Ciekot, M. Schwarzer, D. Srutkova, E. Brzozowska, H. Kozakova, and A. Gamian. 2016. Chemical characterization and immunomodulatory properties of polysaccharides isolated from probiotic Lactobacillus casei LOCK 0919. *Glycobiology* 26 (9):1014–24. doi: 10.1093/glycob/cww047.

Hayen, S. M., A. I. Kostadinova, J. Garssen, H. G. Otten, and L. E. Willemsen. 2014. Novel immunotherapy approaches to food allergy. *Current Opinion in Allergy and Clinical Immunology* 14 (6):549–56. doi: 10.1097/ACI.0000000000000109.

Hsieh, S. A., and P. M. Allen. 2020. Immunomodulatory roles of polysaccharide capsules in the intestine. *Frontiers in Immunology* 11:690. doi: 10.3389/fimmu.2020.00690.

Hughes, K. R., L. C. Harnisch, C. Alcon-Giner, S. Mitra, C. J. Wright, J. Ketskemety, D. Van Sinderen, A. J. Watson, and L. Hall. 2017. Bifidobacterium breve reduces apoptotic epithelial cell shedding in an exopolysaccharide and MyD88-dependent manner. *Open Biology* 7 (1):160155. doi: 10.1098/rsob.160155.

Ishida, Y., F. Nakamura, H. Kanzato, D. Sawada, N. Yamamoto, H. Kagata, M. Oh-Ida, H. Takeuchi, and S. Fujiwara. 2005. Effect of milk fermented with Lactobacillus acidophilus strain L-92 on symptoms of Japanese cedar pollen allergy: A randomized placebo-controlled trial. *Bioscience, Biotechnology, and Biochemistry* 69 (9):1652–60. doi: 10.1271/bbb.69.1652.

Jeon, S. G., H. Kayama, Y. Ueda, T. Takahashi, T. Asahara, H. Tsuji, N. M. Tsuji, H. Kiyono, J. S. Ma, T. Kusu, et al. 2012. Probiotic Bifidobacterium breve induces IL-10-producing Tr1 cells in the colon. *PLoS Pathogens* 8 (5):e1002714. doi: 10.1371/journal.ppat.1002714.

Johnson, J. L., M. B. Jones, and B. A. Cobb. 2015. Bacterial capsular polysaccharide prevents the onset of asthma through T-cell activation. *Glycobiology* 25 (4):368–75. doi: 10.1093/glycob/cwu117.

Jones, S. E., M. L. Paynich, D. B. Kearns, and K. L. Knight. 2014. Protection from intestinal inflammation by bacterial exopolysaccharides. *Journal of Immunology (Baltimore, MD: 1950)* 192 (10):4813–20. doi: 10.4049/jimmunol.1303369.

Krogulska, A., M. Borowiec, E. Polakowska, J. Dynowski, W. Młynarski, and K. Wasowska-Królikowska. 2011. FOXP3, IL-10, and TGF-β genes expression in children with IgE-dependent food allergy. *Journal of Clinical Immunology* 31 (2):205–15. doi: 10.1007/s10875-010-9487-1.

Kuitunen, M., K. Kukkonen, K. Juntunen-Backman, R. Korpela, T. Poussa, T. Tuure, T. Haahtela, and E. Savilahti. 2009. Probiotics prevent IgE-associated allergy until age 5 years in cesarean-delivered children but not in the total cohort. *The Journal of Allergy and Clinical Immunology* 123 (2):335–41. doi: 10.1016/j.jaci.2008.11.019.

Kumar, S., A. K. Verma, M. Das, and P. D. Dwivedi. 2012. Molecular mechanisms of IgE mediated food allergy. *International Immunopharmacology* 13 (4):432–9. doi: 10.1016/j.intimp.2012.05.018.

Lee, K. H., Y. Song, W. Wu, K. Yu, and G. Zhang. 2020. The gut microbiota, environmental factors, and links to the development of food allergy. *Clinical and Molecular Allergy* 18 (1):1–11. doi: 10.1186/s12948-020-00120-x.

Liu, L., H. Li, R.-H. Xu, and P.-L. Li. 2017. Expolysaccharides from Bifidobacterium animalis RH activates RAW 264.7 macrophages through toll-like receptor 4. *Food and Agricultural Immunology* 28 (1):149–61. doi: 10.1080/09540105.2016.1230599.

Lluis, A., M. Depner, B. Gaugler, P. Saas, V. I. Casaca, D. Raedler, S. Michel, J. Tost, J. Liu, J. Genuneit, Protection Against Allergy: Study in Rural Environments Study Group, et al. 2014. Increased regulatory T-cell numbers are associated with farm milk exposure and lower atopic sensitization and asthma in childhood. *The Journal of Allergy and Clinical Immunology* 133 (2):551–559. e510. doi: 10.1016/j.jaci.2013.06.034.

Lou, W., C. Wang, Y. Wang, D. Han, and L. Zhang. 2012. Responses of CD4+ CD25+ Foxp3+ and IL-10-secreting type IT regulatory cells to cluster-specific immunotherapy for allergic rhinitis in children. *Pediatric Allergy and Immunology* 23 (2):141–50. doi: 10.1111/j.1399-3038.2011.01249.x.

Luo, M., M. Gan, X. Yu, X. Wu, and F. Xu. 2020. Study on the regulatory effects and mechanisms of action of bifidobacterial exopolysaccharides on anaphylaxes in mice. *International Journal of Biological Macromolecules* 165 (Pt A):1447–54. doi: 10.1016/j.ijbiomac.2020.09.224.

Matsuzaki, C., C. Takagaki, Y. Higashimura, Y. Nakashima, K. Hosomi, J. Kunisawa, K. Yamamoto, and K. Hisa. 2018. Immunostimulatory effect on dendritic cells of the adjuvant-active exopolysaccharide from Leuconostoc mesenteroides strain NTM048. *Bioscience, Biotechnology, and Biochemistry* 82 (9):1647–51. doi: 10.1080/09168451.2018.1482195.

Meijerink, M., S. Van Hemert, N. Taverne, M. Wels, P. De Vos, P. A. Bron, H. F. Savelkoul, J. Van Bilsen, M. Kleerebezem, and J. M. Wells. 2010. Identification of genetic loci in Lactobacillus plantarum that modulate the immune response of dendritic cells using comparative genome hybridization. *PloS One* 5 (5):e10632. doi: 10.1371/journal.pone.0010632.

Meulenbroek, L. A., B. C. Van Esch, G. A. Hofman, C. F. Den Hartog Jager, A. J. Nauta, L. E. Willemsen, C. A. Bruijnzeel-Koomen, J. Garssen, E. Van Hoffen, and L. M. Knippels. 2013. Oral treatment with β-lactoglobulin peptides prevents clinical symptoms in a mouse model for cow's milk allergy. *Pediatric Allergy and Immunology: Official Publication of the European Society of Pediatric Allergy and Immunology* 24 (7):656–64. doi: 10.1111/pai.12120.

Mezouar, S., Y. Chantran, J. Michel, A. Fabre, J.-C. Dubus, M. Leone, Y. Sereme, J.-L. Mège, S. Ranque, B. Desnues, et al. 2018. Microbiome and the immune system: From a healthy steady-state to allergy associated disruption. *Human Microbiome Journal* 10:11–20. doi: 10.1016/j.humic.2018.10.001.

Mitchell, W. M. 2016. Efficacy of rintatolimod in the treatment of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME). *Expert Review of Clinical Pharmacology* 9 (6):755–70. doi: 10.1586/17512433.2016.1172960.

Morisset, M., C. Aubert-Jacquin, P. Soulaines, D. Moneret-Vautrin, and C. Dupont. 2011. A non-hydrolyzed, fermented milk formula reduces digestive and respiratory events in infants at high risk of allergy. *European Journal of Clinical Nutrition* 65 (2):175–83. doi: 10.1038/ejcn.2010.250.

Murofushi, Y., J. Villena, K. Morie, P. Kanmani, M. Tohno, T. Shimazu, H. Aso, Y. Suda, K. Hashiguchi, T. Saito, et al. 2015. The toll-like receptor family protein RP105/MD1 complex is involved in the immunoregulatory effect of exopolysaccharides from Lactobacillus plantarum N14. *Molecular Immunology* 64 (1):63–75. doi: 10.1016/j.molimm.2014.10.027.

Nakata, J., T. Hirota, H. Umemura, T. Nakagawa, N. Kando, M. Futamura, Y. Nakamura, and K. Ito. 2019. Additive effect of Lactobacillus acidophilus L-92 on children with atopic dermatitis concomitant with food allergy. *Asia Pacific Allergy* 9 (2):e18. doi: 10.5415/apallergy.2019.9.e18.

Neff, C. P., M. E. Rhodes, K. L. Arnolds, C. B. Collins, J. Donnelly, N. Nusbacher, P. Jedlicka, J. M. Schneider, M. D. McCarter, M. Shaffer, et al. 2016. Diverse intestinal bacteria contain putative zwitterionic capsular polysaccharides with anti-inflammatory properties. *Cell Host & Microbe* 20 (4):535–47. doi: 10.1016/j.chom.2016.09.002.

Nocerino, R., M. Di Costanzo, G. Bedogni, L. Cosenza, Y. Maddalena, C. Di Scala, G. Della Gatta, L. Carucci, L. Voto, S. Coppola, et al. 2019. Dietary treatment with extensively hydrolyzed casein formula containing the probiotic Lactobacillus rhamnosus GG prevents the occurrence of functional gastrointestinal disorders in children with cow's milk allergy. *The Journal of Pediatrics* 213:137–142. e132. doi: 10.1016/j.jpeds.2019.06.004.

Noda, M., N. Sultana, I. Hayashi, M. Fukamachi, and M. Sugiyama. 2019. Exopolysaccharide produced by Lactobacillus paracasei IJH-SONE68 prevents and improves the picryl chloride-induced contact dermatitis. *Molecules* 24 (16):2970. doi: 10.3390/molecules24162970.

Noda, M., S. Sugimoto, I. Hayashi, N. Danshiitsoodol, M. Fukamachi, and M. Sugiyama. 2018. A novel structure of exopolysaccharide produced by a plant-derived lactic acid bacterium Lactobacillus paracasei IJH-SONE68. *Journal of Biochemistry* 164 (2):87–92. doi: 10.1093/jb/mvy048.

Noh, J., G. Noh, H. S. Kim, A.-R. Kim, and W. S. Choi. 2012. Allergen-specific responses of CD19(+)CD5(+)Foxp3(+) regulatory B cells (Bregs) and CD4(+)Foxp3(+) regulatory T cell (Tregs) in immune tolerance of cow milk allergy of late eczematous reactions. *Cellular Immunology* 274 (1–2):109–14. doi: 10.1016/j.cellimm.2012.01.005.

Palazzo, M., S. Gariboldi, L. Zanobbio, G. F. Dusio, S. Selleri, M. Bedoni, A. Balsari, and C. Rumio. 2008. Cross-talk among Toll-like receptors and their ligands. *International Immunology* 20 (5):709–18. doi: 10.1093/intimm/dxn027.

Paynich, M. L., S. E. Jones-Burrage, and K. L. Knight. 2017. Exopolysaccharide from Bacillus subtilis induces anti-inflammatory M2 macrophages that prevent T Cell-Mediated Disease. *Journal of Immunology (Baltimore, MD: 1950)* 198 (7):2689–98. doi: 10.4049/jimmunol.1601641.

Püngel, D., A. Treveil, M. J. Dalby, S. Caim, I. J. Colquhoun, C. Booth, J. Ketskemety, T. Korcsmaros, D. van Sinderen, M. A. Lawson, et al. 2020. Bifidobacterium breve UCC2003 exopolysaccharide modulates the early life microbiota by acting as a potential dietary substrate. *Nutrients* 12 (4):948. doi: 10.3390/nu12040948.

Pyclik, M., D. Srutkova, M. Schwarzer, and S. Górska. 2020. Bifidobacteria cell wall-derived exo-polysaccharides, lipoteichoic acids, peptidoglycans, polar lipids and proteins–their chemical structure and biological attributes. *International Journal of Biological Macromolecules* 147:333–49.

Rajoka, M. S. R., Y. Wu, H. M. Mehwish, M. Bansal, and L. Zhao. 2020. Lactobacillus exopolysaccharides: New perspectives on engineering strategies, physiochemical functions, and immunomodulatory effects on host health. *Trends in Food Science & Technology* 103:36–48. doi: 10.1016/j.tifs.2020.06.003.

Rather, I. A., B.-C. Kim, L.-C. Lew, S.-K. Cha, J. H. Lee, G.-J. Nam, R. Majumder, J. Lim, S.-K. Lim, Y.-J. Seo, et al. 2021. Oral administration of live and dead cells of Lactobacillus sakei proBio65 alleviated atopic dermatitis in children and adolescents: A randomized, double-blind, and placebo-controlled study. *Probiotics and Antimicrobial Proteins* 13 (2):315–26. doi: 10.1007/s12602-020-09654-7.

Reisacher, W. R., and W. Davison. 2017. Immunotherapy for food allergy. *Current Opinion in Otolaryngology & Head and Neck Surgery* 25 (3):235–41. doi: 10.1097/MOO.0000000000000353.

Rindsjö, E., and A. Scheynius. 2010. Mechanisms of IgE-mediated allergy. *Experimental Cell Research* 316 (8):1384–9. doi: 10.1016/j.yexcr.2010.02.038.

Rivas, M. N., and T. A. Chatila. 2016. Regulatory T cells in allergic diseases. *The Journal of Allergy and Clinical Immunology* 138 (3):639–52. doi: 10.1016/j.jaci.2016.06.003.

Rodríguez, E., H. Kalay, V. Noya, N. Brossard, C. Giacomini, Y. Van Kooyk, J. J. García-Vallejo, and T. Freire. 2017. Fasciola hepatica glycoconjugates immuneregulate dendritic cells through the Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin inducing T cell anergy. *Scientific Reports* 7 (1):46748. doi: 10.1038/srep46748.

Round, J. L., and S. K. Mazmanian. 2010. Inducible Foxp3+ regulatory T-cell development by a commensal bacterium of the intestinal microbiota. *Proceedings of the National Academy of Sciences of the United States of America* 107 (27):12204–9. doi: 10.1073/pnas.0909122107.

Ruas-Madiedo, P., J. A. Moreno, N. Salazar, S. Delgado, B. Mayo, A. Margolles, and G. Clara. 2007. Screening of exopolysaccharide-producing Lactobacillus and Bifidobacterium strains isolated from the human intestinal microbiota. *Applied and Environmental Microbiology* 73 (13):4385–8. doi: 10.1128/AEM.02470-06.

Ryan, P., R. Ross, G. Fitzgerald, N. Caplice, and C. Stanton. 2015. Sugar-coated: Exopolysaccharide producing lactic acid bacteria for food and human health applications. *Food & Function* 6 (3):679–93. doi: 10.1039/c4fo00529e.

Schiavi, E., S. Plattner, N. Rodriguez-Perez, W. Barcik, R. Frei, R. Ferstl, M. Kurnik-Lucka, D. Groeger, R. Grant, J. Roper, et al. 2018. Exopolysaccharide from Bifidobacterium longum subsp. longum 35624™ modulates murine allergic airway responses. *Beneficial Microbes* 9 (5):761–73. doi: 10.3920/BM2017.0180.

Schmid, J., V. Sieber, and B. Rehm. 2015. Bacterial exopolysaccharides: Biosynthesis pathways and engineering strategies. *Frontiers in Microbiology* 6:496. doi: 10.3389/fmicb.2015.00496.

Schmiechen, Z. C., K. A. Weissler, and P. A. Frischmeyer-Guerrerio. 2019. Recent developments in understanding the mechanisms of food allergy. *Current Opinion in Pediatrics* 31 (6):807–14. doi: 10.1097/MOP.0000000000000806.

Schwarzer, M., D. Srutkova, I. Schabussova, T. Hudcovic, J. Akgün, U. Wiedermann, and H. Kozakova. 2013. Neonatal colonization of germ-free mice with Bifidobacterium longum prevents allergic sensitization to major birch pollen allergen Bet v 1. *Vaccine* 31 (46):5405–12. doi: 10.1016/j.vaccine.2013.09.014.

Shalaby, K. H., S. Al Heialy, K. Tsuchiya, S. Farahnak, T. K. Mcgovern, P. A. Risse, W. K. Suh, S. T. Qureshi, and J. G. Martin. 2017. The TLR4-TRIF pathway can protect against the development of experimental allergic asthma. *Immunology* 152 (1):138–49. doi: 10.1111/imm.12755.

Shin, H. S., H.-J. See, S. Y. Jung, D. W. Choi, D.-A. Kwon, M.-J. Bae, K.-S. Sung, and D.-H. Shon. 2015. Turmeric (Curcuma longa) attenuates food allergy symptoms by regulating type 1/type 2 helper T cells (Th1/Th2) balance in a mouse model of food allergy. *Journal of Ethnopharmacology* 175:21–9. doi: 10.1016/j.jep.2015.08.038.

Shu, S.-A., A. W. Yuen, E. Woo, K.-H. Chu, H.-S. Kwan, G.-X. Yang, Y. Yang, and P. S. Leung. 2019. Microbiota and food allergy. *Clinical Reviews in Allergy & Immunology* 57 (1):83–97. doi: 10.1007/s12016-018-8723-y.

Sicherer, S. H., and H. A. Sampson. 2018. Food allergy: A review and update on epidemiology, pathogenesis, diagnosis, prevention, and management. *The Journal of Allergy and Clinical Immunology* 141 (1):41–58. doi: 10.1016/j.jaci.2017.11.003.

Smit, J., M. Bol-Schoenmakers, I. Hassing, D. Fiechter, L. Boon, R. Bleumink, and R. Pieters. 2011. The role of intestinal dendritic cells subsets in the establishment of food allergy. *Clinical and Experimental Allergy: Journal of the British Society for Allergy and Clinical Immunology* 41 (6):890–8. doi: 10.1111/j.1365-2222.2011.03738.x.

Smits, H. H., A. Engering, D. van der Kleij, E. C. de Jong, K. Schipper, T. M. M. van Capel, B. A. J. Zaat, M. Yazdanbakhsh, E. A. Wierenga, Y. van Kooyk, et al. 2005. Selective probiotic bacteria induce IL-10-producing regulatory T cells in vitro by modulating dendritic cell function through dendritic cell-specific intercellular adhesion molecule 3-grabbing nonintegrin. *The Journal of Allergy and Clinical Immunology* 115 (6):1260–7. doi: 10.1016/j.jaci.2005.03.036.

Speciale, I., R. Verma, F. D. Lorenzo, A. Molinaro, S.-H. Im, and C. D. Castro. 2019. Bifidobacterium bifidum presents on the cell surface a complex mixture of glucans and galactans with different immunological properties. *Carbohydrate Polymers* 218:269–78. doi: 10.1016/j.carbpol.2019.05.006.

Tang, Y., W. Dong, K. Wan, L. Zhang, C. Li, L. Zhang, and N. Liu. 2015. Exopolysaccharide produced by Lactobacillus plantarum induces maturation of dendritic cells in BALB/c mice. *PloS One* 10 (11):e0143743. doi: 10.1371/journal.pone.0143743.

Tan-Lim, C. S. C., and N. a R. Esteban-Ipac. 2018. Probiotics as treatment for food allergies among pediatric patients: A meta-analysis. *World Allergy Organization Journal* 11 (1):25. doi: 10.1186/s40413-018-0204-5.

Thakur, B. K., P. Saha, G. Banik, D. R. Saha, S. Grover, V. K. Batish, and S. Das. 2016. Live and heat-killed probiotic Lactobacillus casei Lbs2 protects from experimental colitis through Toll-like receptor 2-dependent induction of T-regulatory response. *International Immunopharmacology* 36:39–50. doi: 10.1016/j.intimp.2016.03.033.

Tiemessen, M. M., A. G. Van Ieperen-Van Dijk, C. A. Bruijnzeel-Koomen, J. Garssen, E. F. Knol, and E. Van Hoffen. 2004. Cow's milk-specific T-cell reactivity of children with and without persistent cow's milk allergy: key role for IL-10 . *The Journal of Allergy and Clinical Immunology* 113 (5):932–9. doi: 10.1016/j.jaci.2003.12.016.

Trebichavsky, I., V. Rada, A. Splichalova, and I. Splichal. 2009. Cross-talk of human gut with bifidobacteria. *Nutrition Reviews* 67 (2):77–82. doi: 10.1111/j.1753-4887.2008.00141.x.

Verma, R., C. Lee, E.-J. Jeun, J. Yi, K. S. Kim, A. Ghosh, S. Byun, C.-G. Lee, H.-J. Kang, G.-C. Kim, et al. 2018. Cell surface polysaccharides of Bifidobacterium bifidum induce the generation of Foxp3+ regulatory T cells. *Science Immunology* 3 (28):eaat6975. doi: 10.1126/sciimmunol.aat6975.

Vitlic, A., S. Sadiq, H. I. Ahmed, E. C. Ale, A. G. Binetti, A. Collett, P. N. Humpreys, and A. P. Laws. 2019. Isolation and characterization of a high molecular mass β-glucan from Lactobacillus fermentum Lf2 and evaluation of its immunomodulatory activity. *Carbohydrate Research* 476:44–52. doi: 10.1016/j.carres.2019.03.003.

Wachi, S., P. Kanmani, Y. Tomosada, H. Kobayashi, T. Yuri, S. Egusa, T. Shimazu, Y. Suda, H. Aso, M. Sugawara, et al. 2014. Lactobacillus delbrueckii TUA4408L and its extracellular polysaccharides attenuate enterotoxigenic Escherichia coli-induced inflammatory response in porcine intestinal epitheliocytes via Toll-like receptor-2 and 4 . *Molecular Nutrition & Food Research* 58 (10):2080–93. doi: 10.1002/mnfr.201400218.

Wang, Q., R. M. Mcloughlin, B. A. Cobb, M. Charrel-Dennis, K. J. Zaleski, D. Golenbock, A. O. Tzianabos, and D. L. Kasper. 2006. A bacterial carbohydrate links innate and adaptive responses through Toll-like receptor 2. *The Journal of Experimental Medicine* 203 (13):2853–63. doi: 10.1084/jem.20062008.

Whitfield, C., S. S. Wear, and C. Sande. 2020. Assembly of bacterial capsular polysaccharides and exopolysaccharides. *Annual Review of Microbiology* 74:521–43. doi: 10.1146/annurev-micro-011420-075607.

Willemsen, L. E. 2018. Novel immunotherapy approaches to food allergy. *Immunomodulatory Effects of Non-Digestible Oligosaccharides in Peanut Allergy* 14 (6):47.

Xiao, L., W. R. van De Worp, R. Stassen, C. van Maastrigt, N. Kettelarij, B. Stahl, B. Blijenberg, S. A. Overbeek, G. Folkerts, J. Garssen, et al. 2019. Human milk oligosaccharides promote immune tolerance via direct interactions with human dendritic cells. *European Journal of Immunology* 49 (7):1001–14. doi: 10.1002/eji.201847971.

Xie, F. T., J. S. Cao, J. Zhao, Y. Yu, F. Qi, and X. C. Dai. 2015. IDO expressing dendritic cells suppress allograft rejection of small bowel transplantation in mice by expansion of Foxp3+ regulatory T cells. *Transplant Immunology* 33 (2):69–77. doi: 10.1016/j.trim.2015.05.003.

Xiu, L., H. Zhang, Z. Hu, Y. Liang, S. Guo, M. Yang, R. Du, and X. Wang. 2018. Immunostimulatory activity of exopolysaccharides from probiotic Lactobacillus casei WXD030 strain as a novel adjuvant in vitro and in vivo. *Food and Agricultural Immunology* 29 (1):1086–105. doi: 10.1080/09540105.2018.1513994.

Yamashita, H., K. Takahashi, H. Tanaka, H. Nagai, and N. Inagaki. 2012. Overcoming food allergy through acquired tolerance conferred by transfer of Tregs in a murine model. *Allergy* 67 (2):201–9. doi: 10.1111/j.1398-9995.2011.02742.x.

Yang, B., L. Xiao, S. Liu, X. Liu, Y. Luo, Q. Ji, P. Yang, and Z. Liu. 2017. Exploration of the effect of probiotics supplementation on intestinal microbiota of food allergic mice. *American Journal of Translational Research* 9 (2):376–85.

Yang, J., F. Ren, H. Zhang, L. Jiang, Y. Hao, and X. Luo. 2015. Induction of regulatory dendritic cells by Lactobacillus paracasei L9 prevents allergic sensitization to bovine β-lactoglobulin in mice. *Journal of Microbiology and Biotechnology* 25 (10):1687–96. doi: 10.4014/jmb.1503.03022.

Yang, J., H. Zhang, L. Jiang, H. Guo, X. Luo, and F. Ren. 2015. Bifidobacterium longum BBMN68-specific modulated dendritic cells alleviate allergic responses to bovine β-lactoglobulin in mice. *Journal of Applied Microbiology* 119 (4):1127–37. doi: 10.1111/jam.12923.

Yang, T., S. Zang, Y. Wang, Y. Zhu, L. Jiang, X. Chen, X. Zhang, J. Cheng, R. Gao, H. Xiao, et al. 2020. Methamphetamine induced neuroinflammation in mouse brain and microglial cell line BV2: Roles of the TLR4/TRIF/Peli1 signaling axis. *Toxicology Letters* 333:150–8. doi: 10.1016/j.toxlet.2020.07.028.

Zannini, E., D. M. Waters, A. Coffey, and E. K. Arendt. 2016. Production, properties, and industrial food application of lactic acid bacteria-derived exopolysaccharides. *Applied Microbiology and Biotechnology* 100 (3):1121–35. doi: 10.1007/s00253-015-7172-2.

Zdorovenko, E. L., V. V. Kachala, A. V. Sidarenka, A. V. Izhik, E. P. Kisileva, A. S. Shashkov, G. I. Novik, and Y. A. Knirel. 2009. Structure of the cell wall polysaccharides of probiotic bifidobacteria Bifidobacteriumbifidum BIM B-465. *Carbohydrate Research* 344 (17):2417–20. doi: 10.1016/j.carres.2009.08.039.

Zeidan, A. A., V. K. Poulsen, T. Janzen, P. Buldo, P. M. Derkx, G. Øregaard, and A. R. Neves. 2017. Polysaccharide production by lactic acid bacteria: From genes to industrial applications. *FEMS Microbiology Reviews* 41 (Supp_1):S168–S200. doi: 10.1093/femsre/fux017.

Zeuthen, L. H., L. N. Fink, and H. Frøkiaer. 2008. Toll-like receptor 2 and nucleotide-binding oligomerization domain-2 play divergent roles in the recognition of gut-derived lactobacilli and bifidobacteria in dendritic cells. *Immunology* 124 (4):489–502. doi: 10.1111/j.1365-2567.2007.02800.x.