Review article

Bifidobacteria: A probable missing puzzle piece in the pathogenesis of multiple sclerosis

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A B S T R A C T

Multiple sclerosis (MS) is an autoimmune disorder in which the immunopathogenesis is not fully understood. In the recent years, the role of gut microbiome in the pathogenesis of this disorder has been highlighted. *Bifidobacteria* as a component of gut microbiome might also be involved in MS pathogenesis. Being emerged in early days after birth, *bifidobacteria* have a prominent role in immune system maturation and function. Some factors like mode of delivery, breast feeding, mother's blood group and her secretory state and also environmental factors could influence its level in the early infancy, which may remain throughout lifetime. In this review, we discussed possible immunopathogenic link between the *bifidobacteria* and MS.

1. Introduction

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS), in which autoreactive immune cells attack myelin sheaths of the neurons. Pro-inflammatory immune cells like T helper type 1 (Th1) and Th17 T-cells primarily mediates pathogenesis of MS by producing pro-inflammatory cytokines (Kaskow and Baecher-Allan, 2018). On the other hand, T regulatory (Treg) cells have anti-inflammatory functions and produce inhibitory cytokines such as IL-10 and transforming growth factor-β. These inhibitory cytokines induce immune tolerance by inhibiting T helper cell proliferation (Vignali et al., 2008).

Gut microbiota approximately consist of 100 trillion cells, which is 100 times larger than the number of self-cells making up the person (Ley et al., 2006). These microbiome plays an important role in health and disease of the host (Young, 2012). The human infants gut seems to be sterile. However, in the first months of life different types of microbes (bacteria, archaea, viruses, and fungi) reside in gut. This colonization of microbes is affected by several factors including mode of delivery, gestational age, hygiene, diet and antibiotic exposure (Bhargava and Mowry, 2014). It is believed that the colonization of infants' gut is crucial and it has an important impact on the final composition of the resident microbiota in adults (Musilova et al., 2015). Notably, the influence of microbiota is not limited to local effects but also extends to remote organs, particularly the brain (Forsythe et al.,

2012).

Bifidobacteria, which are gram-positive polymorphic rods, reside gut in the first days of life. These kinds of bacteria are among the most common components of gut microbiome and are used as probiotics for human consumption (Turroni et al., 2018). These dominant bacteria influence the total metabolic activity of the gut microbiota by the mucosal cross-talk between microbes and the host (Kalliomäki et al., 2008). In this review, we discuss the role of *bifidobacteria* in the pathogenesis of MS.

2. *Bifidobacteria* and MS

The effects of *Bifidobacteria* in the MS course have been assessed both in animal models and human studies. Investigations in the experimental autoimmune encephalomyelitis (EAE) has shown the effects of *Bifidobacterium animalis* in reducing the extent of EAE symptoms (Ezendam et al., 2008). Moreover, oral administration of a probiotic cocktail including *Lactobacillus* species, *Bifidobacterium bifidum* and *Streptococcus thermophiles* has ameliorated EAE course in animal models. Such improvement was accompanied with a decline in Th1 and Th17 cells and an upsurge in Treg cells (Kwon et al., 2013). Further investigations in the EAE model have shown that a combination of *Lactobacillus* species and/or *Bifidobacterium* species either prior or after EAE initiation remedy EAE (Salehipour et al., 2017; Lavasani et al., 2010). Human studies have shown that oral administration of a

combination of *Lactobacillus* species and *Bifidobacterium* improves Expanded Disability Status Scale (EDSS) score and reduces depression and stress in MS patients (Kouchaki et al., 2017). Taken together, these investigations imply that higher relative quantities of *Bifidobacterium* taxa have beneficial effects for MS patients.

Another evidence in favor of the protective role of *bifidobacteria* in pathogenesis of MS is Guillain Barre Syndrome (GBS). Reduced expression of *bifidobacteria* has been negatively correlated with the levels of IL-17A in CSF and plasma samples of patients with GBS (P. Shi et al., 2018). IFN-γ and IL-17 are produced by pro-inflammatory Th1 and Th17 cells, respectively, and have important roles in the pathogenesis of both MS and GBS (Loma and Heyman, 2011; Li et al., 2011). Notably, GBS like MS, is an autoimmune demyelinating disorder and the coexistence of these two syndromes in an individual's life span is reported (Etemadifar et al., 2012). Besides, Shi et al. reported lower levels of bifidobacterium infantis (*B. infantis*) in GBS patients in comparison with healthy controls in association with mRNA expression levels of RORγτ (master transcription factor of Th17) (Shi et al., 2018). Administration of *B. infantis* through gavage and rectal swab has corrected the imbalance between Th17- and Treg-related immune responses in the peripheral blood of animals with inflammatory bowel diseases (Moran et al., 2009). *Bifidobacterium* species, especially *B. infantis* can reduce RORγτ expression and probably exert a protective role in MS. In spite of these evidences, two studies have reported increased *bifidobacterium* levels among MS patients (Tremlett et al., 2016; Baum et al., 2015). Although the exact reason for the observed discrepancy regarding the role of *bifidobacterium* in MS is uncertain, there are some possible explanations. First, probiotic features of *bifidobacterium* seem to be strain specific (Russell et al., 2011), so different strains of this bacteria might have different effects. Consistent with this speculation, a previous study has shown that different strains of *bifidobacterium* can prompt dissimilar amounts of pro- and anti-inflammatory cytokines (He et al., 2002). Another reason for high inconsistency between investigations is the absence of uniform sequencing methods. The existence of numerous 16S rRNA primers which bind to different hypervariable regions in this gene might result in bias for certain taxa. Furthermore, genetics factor, nutrition, ecological location, and administration of disease-modifying drugs would alter the gut microbiome (Freedman et al., 2018). Administration of these drugs might be an important confounding factor. In the Tremlett et al. study, half of patients were under treatment with immunomodulatory drug (Tremlett et al., 2016). So, the observed higher levels of *bifidobacterium* levels among these patients might be due to the effects of these drugs.

3. Possible functions of *bifidobacteria* in MS

As described earlier, several lines of evidence imply a protective role for *bifidobacteria* in MS. Such protective role might be exerted through numerous mechanisms including changing lipid profile, induction of Treg differentiation and alteration in Th1/ Th2 balance.

3.1. Bifidobacteria and serum cholesterol levels

Elevated levels of circulating low density lipoprotein (LDL) cholesterol and total cholesterol have been associated with adverse clinical and MRI outcomes in MS (Zhornitsky et al., 2016). Notably, three *bifidobacteria* strains (*B. animalis* subspecies *lactis* MB 2409, *B. bifidum* MB 109B, and *B. longum* subspecies *longum* BL04) can reduce cholesterol and blood lipid levels (Guardamagna et al., 2014). This effect is exerted through binding of cholesterol to the bacterial cell envelope and incorporation in the membrane phospholipid bilayer. Moreover, *bifidobacteria* has bile salt hydrolase (BSH) activity, thereby limits cholesterol absorption by lowering its solubility. Furthermore, BSH degrades bile salts, reduces bile salt re-uptake to the liver and thus enhances the amount of cholesterol needed to re-synthesize new bile salt molecules (Zanotti et al., 2015).

3.2. Bifidobacteria and short chain fatty acids (SCFAs) production

SCFAs, especially butyrate, induce Treg formation via acetylation of the Foxp3 locus-master transcription factor of TGF-β production and suppression of proinflammatory NF-kB, through inhibition of histone deacetylases (Jandhyala et al., 2015; Quivy and Van Lint, 2004). In parallel, butyrate suppress proinflammatory cytokine production from dendritic cells, thereby inducing de novo Treg generation (Arpaia et al., 2013). Non-digestible carbohydrates such as cellulose and starch, escape digestion and absorption in the small intestines, so are fermented by *bifidobacteria* through the "bifid shunt" catabolic pathway. Such pathway produces SCFAs acetate and butyrate (Sela et al., 2008). Furthermore, *bifidobacteria* can reduce lactose concentration due to increase in the acetate production. This suggest that *bifidobacteria* can change bacterial metabolism from lactate to SCFA formation (Russell et al., 2011).

3.3. Bifidobacteria and conjugated linoleic acids (CLA) production

Leptin is a pleiotropic cytokine, which dominates Th1 cells over Th2 cells (La Cava and Matarese, 2004) and also inhibits proliferation of Treg cells (De Rosa et al., 2007). It has been reported that leptin production is significantly increased in both serum and cerebrospinal fluid (CSF) of relapsing-remitting multiple sclerosis (RRMS) patients (Matarese et al., 2005). CLA are a family of linoleic acids found mostly in dairy products derived from ruminants (Park et al., 1999). Dietary CLA has been reported to reduce leptin in Zucker diabetic fatty rats (Belury and Vanden Hauvel, 1997). Belury et al. reported that t10, c12-CLA isomer can reduce serum leptin values in human patients with type 2 diabetes (Belury et al., 2003). Notably, CLA can also be produced by *bifidobacteria*. CLA production in *bifidobacteria* vary from strain to strain (Barrett et al., 2007). It has been reported that *B. breve* NCIMB 702258 was the most efficient strain for the conversion of LA to CLA (Coakley et al., 2003). Dietary administration of *B. breve* NCIMB 702258 in combination with linoleic acid significantly increased c9,t11 CLA content in liver and eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in adipose tissue. EPA and DHA increase is in turn associated with an anti-inflammatory cytokine profile (Wall et al., 2009).

3.4. Bifidobacteria and plasma tryptophan levels

Depression is an important determinant of quality of life in MS patients that often have not been detected and treated (Feinstein, 2004; Lobentanz et al., 2004). MS patients especially who are severely depressed may have an increased risk of suicide attempt (Siegert and Abernethy, 2005). Reduced level of serotonin has been implicated in the psychopathology of depression. Serotonin synthesis in brain is dependent on the availability of tryptophan (Owens and Nemeroff, 1994). Considering the inverse relationships between the availability of plasma tryptophan and serum IL-1RA, IL-6 and IL-8 (Song et al., 1998) on one hand, and the potent stimulatory function of IFN-γ in the activation of indoleamine (Vignali et al., 2008; Ley et al., 2006)-dioxygenase (IDO), the enzyme involved in the conversion of tryptophan to kynurenine (Taylor and Feng, 1991), on the other hand, one can deduce a close association between immune activation and plasma tryptophan depletion. By suppression of IFN-γ production during immune activation, chronic *bifidobacteria* administration (especially *B. infantis*) could increase the plasma tryptophan levels (Desbonnet et al., 2008). Taken together, increased levels of pro-inflammatory cytokines in MS patients due to the reduced level of *bifidobacteria* might result in depression.

3.5. Bifidobacteria and folate production

Among all other beneficial roles of folate, it is a crucial agent in the formation of the S-adenosylmethionine (SAM) (Abbasi et al., 2018),

which may have significant implications on DNA methylation, myelination and the levels of the anti-oxidant glutathione. It has been reported that the s-adenosyl methionine levels in the CSF of MS patients are reduced in comparison with healthy controls (Lyudmer and Sadiq, 2018). *Bifidobacterium* strains including *B.adolescentis*DSM 18350, *B. adolescentis* DSM 18352, and *Bifidobacterium pseudocatenulatum*DSM 18353 have potent ability in producing folate in the intestinal environment, which is a complementary endogenous source of this vitamin. So, reduced levels of *bifidobacteria* have been correlated with reduced folic acid levels (Strozzi and Mogna, 2008).

3.6. Bifidobacteria and plasminogen

Plasminogen is a possible MS susceptibility risk factor as it is involved in the blood-brain barrier (BBB) permeability, inflammatory response, neuronal viability, and myelin degradation (Sadovnick et al., 2016). *B. bifidum, B. longum*, and *B. lactis* have significant human plasminogen-binding activity, so possibly intervene with the plasmin/plasminogen system of the human host (Candela et al., 2007). Consequently, it is possible that these species could affect MS susceptibility.

3.7. Bifidobacteria and stress responses

According to the previous studies, stress has an important role in the onset and progression of MS. Notably, its duration, severity, and frequency were the most prominent modifying factors (Mohr et al., 2004; Briones-Buixassa et al., 2015). Meanwhile, gut-related diseases can be evolved or worsen during stressful periods (De Palma et al., 2014). Moreover, there is a bidirectional communication between the CNS and the gut (Dinan and Cryan, 2012). Taken together, it is reasonable to hypothesize that stress could affect the pathogenesis of MS at least partly through dysregulation of gut microbiome. Other studies have also provided evidences for such speculation. For instance, Sudo et al. reported that *B. infantis* reduces stress responses in infant mice (Sudo et al., 2004). Furthermore, Bailey et al. have shown that rhesus monkey infants whose mothers had experienced stress during late pregnancy, had lower levels of *bifidobacteria* in comparison with non-stressed mothers (Bailey et al., 2004). Moreover, activation of hypothalamic pituitary adrenal (HPA) axis in response to stress results in cortisol production as an end product. Enhanced maternal cortisol may induce bile acid production, which could interfere with the natural development of the maternal gut microbiome during pregnancy, and therefore bacterial transmission (e.g. bifidobacteria) to offspring. In addition, maternal cortisol can cross the placenta and influence infant gut microbiome (Zijlmans et al., 2015).

3.8. Bifidobacteria and obesity

Obesity as an important risk factor for MS susceptibility (Gianfrancesco and Barcellos, 2016), is associated with lower levels of *bifidobacteria* in gut (Gao et al., 2015). Obese pregnant woman had decreased numbers of *bifidobacteria* spp. in comparison with normal weight pregnant woman (Santacruz et al., 2009). In addition, the number of *bifidobacterium* has been higher in children with normal weight in comparison with obese children (Kalliomäki et al., 2008). Previous studies have concluded that breast-fed infants have 13–22% reduced possibility of obesity in childhood and the duration of breast-feeding is inversely associated with the risk of overweight (Arenz et al., 2004; Harder et al., 2005). *Bifidobacteria*, particularly *B. breve, B. infantis*, and *B. longum*, represent the gut microbiota constitution of the healthy breastfed newborns (Vaughan et al., 2002). It is believed that *bifidobacteria* comprise an internal link between breastfeeding and weight development (Kalliomäki et al., 2008). Thus, the microbiota profile in favor of a higher number of *bifidobacteria* in infancy may provide protection against overweight and obesity development (Marques et al., 2010). Consequently, *bifidobacteria* can control the

obesity and in this way affect the susceptibility to MS.

3.9. Bifidobacteria and γ-aminobutyric acid (GABA) production

GABA is an inhibitory neurotransmitter that is involved in several critical functions of the CNS. GABA receptors are present in immune cells and treatment with GABA reduces inflammatory cytokine production in peripheral macrophages (Reyes-García et al., 2007). It has been reported that GABA levels decrease in patients with RRMS, and its reduced levels were associated with impairment of cognitive performance in these patients (Cao et al., 2018). Furthermore, MS patients have lower levels of GABA in their fecal samples in comparison to healthy controls (Yalçınkaya et al., 2016). According to Yunes et al. *bifidobacteria* species are the most efficient GABA-producers among gut-derived bacteria (Yunes et al., 2016). For instance, *B.dentium* produces GABA via GadB enzyme, which decarboxylate glutamate (Pokusaeva et al., 2017).

3.10. Bifidobacteria and protection against infection

Bifidobacteria can prevent infections by pathogenic bacteria such as Helicobacter pylori (Russell et al., 2011), which has been shown to be overrepresented in MS patients in comparison with control subjects (Gavalas et al., 2015).

4. Factors associated with *bifidobacteria* levels

4.1. Breast/formula feeding

Beneficial bacteria in the intestinal tract, such as *bifidobacteria*, give rise to improved health conditions for years or even a lifetime. Despite the important role of this bacteria in gut microbiome, appearance of it in some infants can be significantly delayed (Mitsuoka, 1992). *Bifidobacteria* in some formula-fed infants can be nondetectable. In contrary, it can comprise 90% of total microbiota in some exclusively breast-fed infants (Harmsen et al., 2000). On the other hand, formula-fed infants have a higher diversity of microbial species than that of breast-fed infants, although this higher diversity is apparently beneficial in adults, it is not necessarily more beneficial in infant's gut (Zivkovic et al., 2013).

4.2. Mode of delivery

The mode of infant delivery has more important effect on the bacterial colonization process than the type of feeding the infant receives (Biasucci et al., 2010). It was observed that colonization by *bifidobacteria* in infants born by cesarian section may be delayed by 1 month (Grölund et al., 1999). Maghzi et al. reported that cesarian section can increase MS risk in women. Also, the mean age at onset is lower in women born with cesarean section in comparison with patients born by vaginal delivery (Maghzi et al., 2012). Because the early intestinal microbiota is considered to be crucial for the development of the immune system (Scholtens et al., 2012), the delayed appearance of *bifidobacteria* and/or great diversity of microbial species in infants born through cesarean section might explain higher incidence rate of MS in these infants.

4.3. Blood group

Another factor that can influence infant's gut bacterial profile is mother's *fucosyltransferase 2* (*FUT2*) gene and secretor state. Lewis et al. reported that infants fed by non-secretor mothers are delayed in the appearance of microbiota dominated by *bifidobacteria* (Lewis et al., 2015). Human milk oligosaccharides (HMOs) are the third most abundant component of breast milk after lactose and lipids (Boehm and Stahl, 2007). Free HMOs and their related glycoconjugates that are described as human milk glycans (HMGs) are non-digestible sugars, so
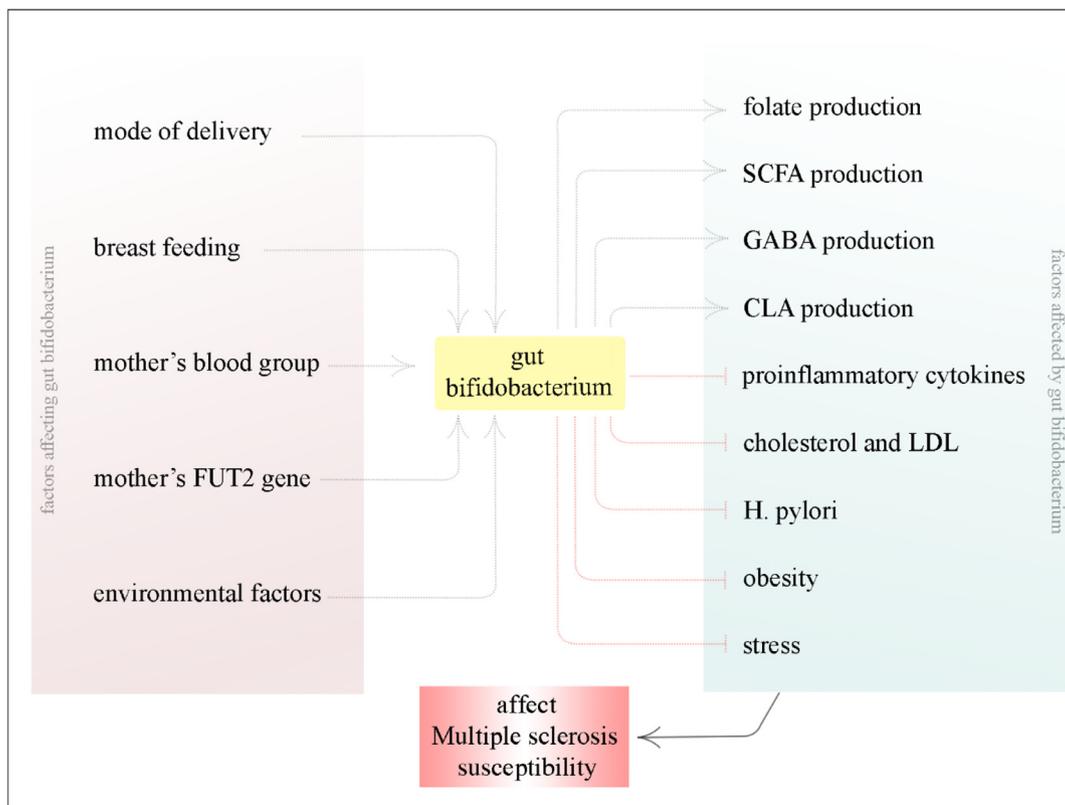
Fig. 1. Factors affecting gut microbiome and factors affected by it and their role in MS pathogenesis.

pass undigested through the small intestine. These non-digestible sugars in the infant's gut serve as bifidogenic factor and can increase the adhesion and efficacy of *bifidobacteria* (Sarkar and Mandal, 2016). Breast milk of secretor mothers are enriched in fucosylated oligosaccharides, specifically several isomers that contain 2′ fucose. *Bifidobacteria* are one of the limited members of gut microbes that can cleave fucose from secretor HMGs, which is a necessary step to access the rest of the molecule (Zivkovic et al., 2013). So HMG fucosylation may be a pathway to enrich specific *bifidobacteria* in infant gut. Therefore, mother's secretary state might influence MS susceptibility through gut *bifidobacteria* level. Furthermore, it has been reported that ABO blood group affects the relative abundances of gut microbiota, and blood group O subjects have higher diversity or clustering of the genus *bifidobacterium* in comparison with blood group AB subjects (Mäkivuokko et al., 2012). HMO fucosylation, on the other hand, is highly dependent on the mother's Lewis blood group status (Bode, 2015), which may alter the infants gut microbiota and exert protective or predisposing effects on some diseases like MS (Fig. 1).

4.4. Caffeine consumption

There is some evidence that high consumption of coffee can reduce MS susceptibility. Coffee contains many biological substances of which caffeine, a stimulant of the CNS, is the most studied one (Hedström et al., 2016). By protecting against blood-brain barrier leakage, caffeine consumption exerts protective effects in animal model of Alzheimer's disease (Chen et al., 2010). In animal model of MS, caffeine can reduce neuroinflammation and demyelination by up-regulating adenosine A1 receptors (Tsutsui et al., 2004). It was reported that consumption of coffee increases the population of *bifidobacterium* without affecting the population of the dominant microbiota. Moreover, coffee consumption can specifically increase metabolic activity of *bifidobacteria* (Jaquet et al., 2009), indicating that its consumption might have some prebiotic effects. This bifidogenic effects may be due

to the existence of galactomannans and melanoidins in coffee beverages (Morales et al., 2012; Pokusaeva et al., 2011). Therefore, coffee may exert protective effects against MS susceptibility at least in part by increasing *bifidobacteria* population.

4.5. Antibiotics

Antibiotics are another environmental factor that could reduce gut *bifidobacteria* level. The effects differ between antibiotics and usually most gut microorganisms return to their normal levels within weeks of exposure. However, excessive use of antibiotics (mainly amoxicillin) (Penders et al., 2006) in infancy, may alter the outcome of immune development and thus potentially predispose to certain inflammatory diseases in later life (Marques et al., 2010). On the other hand, antibiotics consumption may lead to an increased risk for the development of obesity later in life by affecting the composition of the gut microbiota (Bäckhed et al., 2004).

4.6. Birth order

Infants who have older siblings have significantly higher proportion of *bifidobacteria* on their gut in comparison with first children (Penders et al., 2006). In parallel, it has been reported that children with many older siblings have lower risk of certain allergic diseases (Strachan, 2000). This sibling effect maybe be an indicator of early-life infections, and has been assumed to be mediated by commensal gut microbiotic composition (Penders et al., 2006).

5. *Bifidobacteria* and immune system

Gut microbiota and vertebrates have co-evolved over the eras, therefore normal functioning of the digestive and immune systems depends on the presence of symbionts. Different species of gut microbiota exert potent effects on shaping of the immune composition of the

host. Meanwhile, there are reciprocal interactions between gut microbiome and immune system. For instance, MyD88 deficiency in mice results in higher levels of *bacteroidetes* phylum in the gut, and this microbiota inhibits the development of diabetes, perhaps through immunomodulation (Maslowski and Mackay, 2010). Interestingly, Van der Waaij et al. reported reduced relative thymus weight in germ-free mice in comparison with conventional mice (Van der Waaij, 1986).

Bifidobacteria, as the most common bacteria in the infant gut, could play a major role in the development of the body's immune system. By induction of IL-12 and IL-10 expression in dendritic cells in the local gut, *bifidobacteria* could prime naive CD4+ T cells differentiation toward Th1 cells and regulatory T cell lineage, respectively. Therefore, *bifidobacteria* could drive protection against infection, and also modulate the effector response by means of Th1 cells and Treg cells, respectively (Dong et al., 2010).

Cell surface β-glucan/galactan (CSGG) polysaccharides of *B. bifidum* are key components in induction of Treg. This induction is mediated by phenotypic conversion of conventional DCs to regulatory DCs (regDCs) (Verma et al., 2018). RegDCs have lower levels of co-stimulatory molecules (CD80, CD86, CD40), down-regulated expression of proinflammatory cytokines (IL-12), up-regulated expression of inhibitory molecules (PDL1, CD95L, IDO) and anti-inflammatory cytokines (TGF-β, IL-10). Furthermore, regDCs promote immunological tolerance by Treg cells induction, inhibition of T cell responses and induction of T cell apoptosis (Liu and Cao, 2015).

Using an *in vitro* model of human peripheral blood mononuclear cell (PBMC), Dong et al. reported that *B. longum* and *B. bifidum* have high capacity for induction of anti-inflammatory cytokines especially IL-10 (Dong et al., 2012). The effects of *bifidobacteria* species in promoting IL-10 secretion might vary even within a certain strain. Studies have demonstrated dissimilar immunomodulatory effects of *B. longum* strains which might be originated from differences in the existence or abundance of CpG motifs in their DNAs, since it is proved that some of these motifs have a more prominent immunomodulatory impacts compared with others (Medina et al., 2007). The anti-inflammatory functions of IL-10 could be helpful in the treatment of inflammatory conditions or diseases (Kekkonen et al., 2008). Further, it has been reported that treatment of mice and intestinal epithelial cell line Colon-26 cells with *B. longum* reduces the expression of Th1- and Th17- specific cytokines (Miyauchi et al., 2013). Therefore, this bacterium has an anti-inflammatory effect in mice.

Hart et al. reported that some *bifidobacteria* species including *B. breve* and *B. infantis* have the ability to reduce the level of CD40 expression on DC (Hart et al., 2004). Signaling through CD40 has a critical role in IL-12 production by DC, which play a significant role in Th1 cell lineage differentiation (Wenner et al., 1996). CD40, also, has a major role in connecting innate to adaptive immunity and for both CD4+ and CD8+ T cell responses (S-i et al., 2004). MS-derived APCs secrete more IL-12 in response to T cells, in a CD40-dependent manner (Balashov et al., 1997).

6. Conflicting results

Despite evidences of the anti-inflammatory effects of *bifidobacterium*, some studies have reported its pro-inflammatory effects. Previous studies have reported that *bifidobacteria* could reduce the proportion of DCs expressing CD80 without affecting the level of those expressing CD86 (Hart et al., 2004). These ligands could bind to both CD28 (stimulatory) and CTLA-4 (inhibitory) receptors on T cells; but the relative expression levels of CD80 and CD86 on DCs could dictate the balance between stimulatory and inhibitory outcomes by modifying the potency of Treg (Zheng et al., 2004). CD80 ligand has a high affinity for CTLA-4 in comparison with CD86, and only CD80 could induce inhibition function of CTLA-4 (Manzotti et al., 2002). Furthermore, CD80 and CTLA-4 could prevent graft rejection in transplant models (Yamada et al., 2001). In conclusion, *bifidobacteria* may be able to

suppress CTLA-4 receptors on T cells through reducing CD80 expression.

Further, it has been reported that *bifidobacteria*, especially *B. adolescentis*, similar to segmented filamentous bacteria (SFB), could induce intestinal Th17 cells in the murine (Tan et al., 2016). In this study it was stated that *B. adolescentis* deteriorated autoimmune arthritis in a mouse model by increasing Th17 cell population (Tan et al., 2016).

In spite of these apparently pro-inflammatory functions of some *bifidobacterial* species, especially *B. adolescentis* (Tan et al., 2016) and *B. bifidum* (López et al., 2010), it has been proposed that, these beneficial probiotics may moderately induce Th17 cells differentiation in the steady-state circumstances, since these cells and their cytokines are important for proper host defense. But in the pathogenic conditions, they may suppress pro-inflammatory Th17 cells (Tanabe, 2013).

7. Conclusions

Gut microbiome has an established role in the pathogenesis of some human diseases. *Bifidobacteria* are among strains with substantial roles in regulation of immune response. Based on the observed associations between the lower frequency of *bifidobacteria* in gut and some MS risk factors, one can deduce a protective role of *bifidobacteria* in MS. Moreover, some *in vitro* studies have shown anti-inflammatory roles of some *bifidobacterium* strains. Moreover, a pilot study has assessed the effect of a probiotic cocktail in MS patients and healthy individuals. The administered cocktail which contained a number of probiotics including three strains of *bifidobacterium* (*B. longum* DSM 24736, *B. infantis* DSM 24737, and *B. breve* DSM 24732) could elicit an anti-inflammatory peripheral immune response (Tankou et al., 2018). The inconsistent results originated from some studies might be due to strain-specific features, lack of standardized methods for identification of strains and the presence of genetic/ ecological factors or administration of disease-modifying therapies. So based on the safety of administration of probiotics in human subjects, *bifidobacteria* might be a putative candidates for modulation of immune responses in MS patients.

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