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REVIEW ARTICLE

Probiotics and diseases of altered IgE regulation: A short review

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Abstract

The use of probiotics has gained considerable popularity in the marketplace in the US and has been steadily increasing due to consumer interest in potential treatment of various diseases, which may be due to modulation of immune responses. The aim of this review is to present information from representative studies regarding some of the possible applications and clinical effects of probiotic use in diseases of altered immunoglobulin (IgE) regulation (allergic rhinitis (AR), asthma, atopic dermatitis (AD) and food sensitization). Reports in humans are sparse or controversial; there is currently little reliable scientific data that supports the theory that there exists a cause–effect relationship between taking probiotics and alleviation of allergic disease. Unfortunately, these findings are too variable to allow substantial conclusions as to the efficacy and effectiveness of probiotic use in these disease states.

Keywords

Asthma, IgE, Probiotics

History

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Introduction

Over the past 3 decades, increased occurrence of allergic inflammatory diseases, including asthma, AD, AR, food hypersensitivity and other immune disorders have been reported (Asher et al., 2006). The current increase in allergic disease observed in countries with Western lifestyles has been attributed to disturbed gut microbial composition (Bach, 2002), improved sanitation (the Hygiene Hypothesis) (Strachan, 1989; Tang, 2009), sterilization of food, increased use of antibiotics, smaller family sizes (Tang, 2009), as well as diet, decreases in exercise, the presence of dust mites in carpets and changes in lifestyle (Graham-Rowe, 2011).

The definition of probiotics includes the belief that ''live microorganisms that, when given in adequate amounts, may confer a health benefit on the host when consumed'' and must be a taxonomically-defined microbe (genus, species, strain) (Sanders, 2008); these may include specific bacterial strains (e.g. *Lactobacillus rhamnosus*, *Bifidobacteria bifidum*) that, when ingested, present theoretical health benefits to the individual (Betsi et al., 2008). In many parts of the world, probiotics, either alone or in conjunction with other therapeutic modalities, have been advocated for possible management of a number of disease states including gastrointestinal (GI) disturbances, cardiovascular diseases and other metabolic disorders (Scott et al., 2015; Yao et al., 2010). Studies have shown that the most common therapeutic application for probiotics was in the treatment of gastrointestinal disorders such as diarrhea (Isolauri et al., 1991; Saavedra et al., 1994). However, it has also been reported that probiotic bacteria have immune-stimulating effects (Prescott & Bjorksten, 2007).

Recent evidence suggests that probiotics can have possible therapeutic benefit in atopic disease states such as allergy, asthma, AD, eczema and related disease states (Fiocchi et al., 2015; Madhok et al., 2015; Tang et al., 2015). To this end, the World Allergy Organization (WAO) guideline panel has recommended using probiotics in (a) pregnant women at high risk for having an allergic child, (b) women who breastfeed infants at high risk of developing allergy and (c) infants at high risk of developing allergy (Fiocchi et al., 2015). However, these recommendations are conditional and supported by low quality of evidence (Fiocchi et al., 2015). Given the fact that probiotic use has increased, there is interest in improving our understanding regarding the physiology of probiotics on the immune system and its application for use in management of atopy (Yao et al., 2010). In the current report, we sought to review representative articles from the literature regarding the use of probiotics and their clinical effect on diseases of altered IgE regulation including AR, AD, asthma and food sensitization (Table 1). However, it should be noted that there exists little data to support the theoretical nature of probiotic use in humans to alleviate allergic disease.

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Effect of probiotics on the immune system

T-Regulatory and T-helper cell responses

It has been reported that probiotics may affect T-helper (T_H) responses by either direct targeting of T_H function or indirectly via T-regulatory (T_{reg}) cells (Tang, 2009). Specific bacterial strains can elicit either T_H1 cytokine production, while others can stimulate T_H2 responses or even mixed T_H1/T_H2 responses (Tang, 2009).

Probiotics have been shown to predominantly affect dendritic cells (DC) and T_{reg} cell activity (Tang, 2009). In myeloid and plasmacytoid DC, bifidobacteria induces production of interleukin (IL)-10 and down-regulates expression of CD80 and CD40 (co-stimulatory molecules) on DC (Hart et al., 2004; Tang, 2009). Specific *Lactobacillus* bacteria affect T_{reg} cells by generating semi-mature DC and increased expression of CD80 and CD40, while not affecting IL-10 production. Studies of von der Weid

Table 1. Summary of representative probiotics used to treat immune-based diseases.

Disease	Probiotic	Source
Allergic Rhinitis	*Lactobacillus paracasi*	Peng & Hsu (2005); Wang et al. (2004)
	Lactobaillus casei	Giovannini et al. (2007)
	Bacillus clausii	Ciprandi et al. (2005a, b)
	Lactobacillus johsonii	Lue et al. (2012)
Asthma	*Lactobacillus acidophilus*	Wheeler et al. (1997)
	Lactobacillus rhamnosus	Rose et al. (2012)
Atopic Dermatitis	*Lactobacillus salivarius*	Drago et al. (2011)
	Bifidobacterium breve	Lemoli et al. (2012)
	Lactobacills rhamnosus	Sistek et al. (2006)
	Bifidobacterium lactis	Sistek et al. (2006)
Food Sensitization	*Bifidobacterium breve**	Lau (2013)
	*Streptococcus thermophiles**	Lau (2013)
	Lactobacillus acidophilus ADO31	Kim et al. (2008)
	Lactobacillus brevis HY7401	Lee et al. (2013)
	Lactobacillus casei strain Shirota	Shida et al. (2002)

*In cow milk formula.

et al. (2001) demonstrated that lactic acid bacteria, such as *Lactobacillus paracasei* NCC2461, inhibited CD4+ T_H cell production of T_H1 and T_H2 cytokines (e.g. interferon [IFN]-γ, IL-4, IL-5), while inducing specific regulatory cytokines (e.g. transforming growth factor [TGF]-β, IL-10). It should be mentioned that specific bifidobacteria or lactobacillus bacteria may also exhibit the opposite effect on T_{reg} cell function and have inhibitory effects (Tang, 2009). Studies by Christensen et al. (2002) showed that *B. lactis* down-regulated production of TGF-β, while *L. reuteri* inhibited *L. casei*-induced DC production of cytokines and up-regulation of CD80 and CD40 co-stimulatory markers. Thus, these results suggest that probiotics may directly or indirectly target T-cells and can elicit a T_H1, T_H2 or mixed T_H1/T_H2 response (Tang, 2009).

Antibody effects

Probiotic bacteria can also enhance IgA immune responses to both oral and parenteral antigens (Tang, 2009). Studies have reported higher numbers of cow milk-specific IgA-secreting cells in infants who drank cow milk formula supplemented with probiotic *Lactobacillus rhamnosus* GG (LGG) and *Bifidobacterium lactis* Bb-12, compared with placebo-treated infants (Pohjavouri et al., 2004; Tang, 2009). Kaila et al. (1992) observed that an increased number of children with acute rotavirus diarrhea who were given LGG had increased levels of rotavirus-specific IgA antibody-secreting cells compared with control children. In infants supplemented with fermented infant formula (*Bifidobacterium longum-infantis* [*B. longum-infantis*] and *B. breve*), anti-poliovirus IgA responses to poliovirus vaccine (challenge) were higher compared to those seen in control infants given standard formula (Mullie et al., 2004; Tang, 2009). However, Mullie et al. concluded that the effect observed on the immune system may be achieved either through the bifidogenic effect of the formula (through *B. longum*/*B. infantis* and *B. breve* stimulation) or directly linked to certain compounds, such as peptides (Mullie et al., 2004). Thus, these results suggest that certain probiotics may affect IgA levels in infants.

Immune stimulating effects of probiotics

In recent decades, an increase in the prevalence of autoimmune and allergic disorders has been reported (Tang, 2009). Development of allergic disease has been associated with less exposure to microbial stimuli due to a Westernized lifestyle, increased use of antibiotics, sterilization of food, reduced gut colonization with *lactobacilli* and *bifidobacteria* (Pohjavouri et al., 2004), as well as reduction in gut microbial diversity (Sjogren et al., 2009; Wang et al., 2008).

In the newborn intestine, microbial colonization is necessary for normal immune development (Tang, 2009). Intestinal bacteria are also required for the development of the gut and immune system (Macpherson & Harris, 2004; Round & Mazmanian, 2009), as well as for mucosal (T_H1) and T_{reg} cell responses (Atarashi et al., 2011; Gaboriau-Routhiau et al., 2009; Ivanov et al., 2009). It is important to maintain healthy intestinal microflora for regulation of gut inflammatory responses and maintenance of oral tolerance to environmental and self-antigen and food allergens (Tang, 2008, 2009); altered intestinal microflora has been associated with increased risk of development of atopic disease (Tang, 2008).

In vitro and *in vivo* studies have shown that probiotic bacteria also have immune-stimulating effects (Prescott & Bjorksten, 2007). It has been suggested that microbial stimuli might play a role in the maturation of adaptive T-cell immunity (West et al., 2011). However, the role of probiotics in prevention of allergic disease remains controversial and warrants further investigation (Weaver & Hatton, 2009; West et al., 2011). The studies of West et al. described the effects of feeding the probiotic *Lactobacillus paracasei* subsp. *paracasei* F19 (LF 19) to healthy infants in relation to T-cell maturation (West et al., 2011). Those findings indicated that feeding LF19 to weaning infants decreased T_H0 responses, but increased T_H1 and T_H17 responses. After 9 months of LF19 intake, these infants had stronger capacity to mount T_H cell responses for tetanus toxoid (TT) IgG antibody production and produced a higher level of IL-17 A (which plays a role in immune protection to extracellular bacteria (Peck & Mellins, 2010) in response to TT stimulation compared with the control (placebo) group. Thus, these results suggest that probiotics might play a role in maturation of T-cell function in adaptive immune responses that may have clinical benefits. However, it is unknown whether these observed differences have implications for the development of future allergic disease.

Gut microbacteria

Improved hygiene has been shown to alter early microbial exposure by reducing childhood infection, thus suggesting a possible cause for the rise in allergic diseases (Kalliomaki et al., 2001). Thus, it has been hypothesized that exposure to commensal microflora may provide immune protection against atopy. To this end, it has been hypothesized that the deleterious effects of the Hygiene Hypothesis (decreased suppression of self-reactive T-cells, resulting in increased autoimmunity and increased incidence of asthma, allergy, atopy, etc.), purportedly a result of

ubiquitous sterility resulting from environmental exposure to antibacterial soaps, detergents, diet, etc., can be prevented by supplementation with probiotics inclusion in the diet (Cabana, 2011). Kalliomaki et al. (2001) reported differences in the neonatal gut microflora that precedes development of atopy, thus suggesting an important role of the balance of intestinal bacterial necessary for the maturation of immunity to a non-atopic state. Since gut microbiota plays a role in immune development as well as health, there is much interest in the therapeutic potential of probiotics for asthma and other altered IgE-related disorders (Azad & Lozyrskyj, 2012; Forsythe, 2011). Thus, these findings suggest that the composition of the intestinal mircrobiota is important in the long-term development of allergies (Yamanaka et al., 2003), which is in agreement with the ''hygiene hypothesis'' (Strachan, 1989).

Allergic rhinitis (AR) or asthma

Studies have shown that probiotics may be useful in the treatment or prevention of AR (Azad & Lozyrskyj, 2012; Singh & Das, 2010). However, there exist no conclusive studies for the treatment of asthma with probiotics (Sanz, 2011). Wang et al. (2004) showed that ingestion of fermented milk containing *Lactobacillus paracasi* 33 (LP 33) for 30 days could effectively and safely improve the quality-of-life of patients with AR and perhaps serve as an alternative treatment for AR. In agreement with those studies, Peng and Hsu (2005) also demonstrated that ingestion of live LP 33 might improve the quality-of-life for patients with perennial AR induced by house-dust mite. However, another study showed that long-term consumption of fermented milk containing *Lactobacillus casei* might improve the health status of children with AR, but had no effect on those that were asthmatic (Giovannini et al., 2007).

Ciprandi et al. (2005a, b) reported that another probiotic, *Bacillus clausii*, might exert immunomodulating activity in allergic children by affecting cytokine patterns (decreasing interleukin [IL]-4 levels and increasing IFNγ, TGFβ and IL-10 levels) in allergic subjects and that it could positively affect children with AR. Others have demonstrated that addition of *Lactobacillus johnsonii* (Lj) EM1 to levocetirizine for treatment of AR in children aged 7–12 years was more effective than treatment with levocetirizine alone; this difference persisted for 3 months after subjects discontinued Lj EM1 (Lue et al., 2012).

In contrast, Wheeler et al. (1997) noted that treatment of adult asthmatic patients with *L. acidophilus* did not have any positive/beneficial effects (Wheeler et al., 1997). Other studies reported that probiotics had no effect on asthma development (Azad & Lozyrskyj, 2012; Dotterud et al., 2010) or airway inflammation (Azad & Lozyrskyj, 2012; Kukkonen et al., 2011). Furthermore, Rose et al. (2012) reported that, among young children with recurrent wheeze and with family history of atopy, oral *L. rhamnosus* (LGG) had no clinical effect on asthma-related events or atopic dermatitis (AD), but had mild effects on allergic sensitization. Stockert et al. (2007) showed that Traditional Chinese Medicine (laser acupuncture) and probiotics (living non-pathogenic *Enterococcus faecalis*) had a beneficial clinical effect on bronchial hyper-reactivity in school age children with intermittent or mild persistent asthma and might be a useful treatment in the prevention of acute respiratory exacerbations. Thus, the results demonstrate that probiotics have little beneficial effect in children with AR and no effect in children or adults with asthma.

Atopic dermatitis (AD) and eczema

AD is a chronic, relapsing pruritic inflammatory disorder of skin (Wuthrich, 1999), characterized by xerosis, pruritus and eczema (Drago et al., 2011). It has been suggested that AD might serve as a portal for the development of IgE-mediated atopic manifestations (Isolauri, 2004). Specific probiotic strains from healthy gut have been shown to have both anti-pathogenic and anti-inflammatory (allergic) potential; thus use of probiotics in the prevention of AD has been investigated (Isolauri, 2004). While probiotics have been reported to reduce the severity of AD in infants and children (Sistek et al., 2006), few studies have focused on adults (Drago et al., 2011). However, the mechanisms of action of the probiotics or their ability to act as immunomodulants in AD are unknown.

Drago et al. (2011) reported that, in adult patients with AD, oral administration of *Lactobacillus salivarius* LS01 was well tolerated and improved the clinical manifestation of AD and the dermatology life quality index. Further, after 4 months of treatment, there was a significant reduction in cytokine production by peripheral blood mononuclear cells (PBMC) [T_H1 cytokines (IL-12, IFNγ) and T_H1/T_H2 ratios (IL-12 + IFNγ/IL-4 + IL-5)] only in the patients treated with placebo (maltodextrin) (Drago et al., 2011). In agreement with these studies, Lemoli et al. (2012) showed that adult patients with AD who were treated with a mixture of the probiotics LS01 and *Bifidobacterium breve* (BR03) showed improvement of clinical parameters (SORAD index and DLQ index improvement) from baseline.

Prior literature has reported that probiotics may reduce severity of AD in infants and children. Sistek et al. (2006) reported that the combination of the probiotics *Lactobacillus rhamnosus* and *Bifidobacterium lactis* improved AD in food-sensitized children. In addition, Wickens et al. (2008) found that supplementation with the probiotic *Lactobacillus rhamnosus* HN001, but not *B. animalis subsp lactis strain HN019* reduced the prevalence of eczema but not atopy by 2 years-of-age and that the protective effect of HN001 against eczema (when given for the first 2 years of life) extended the protection until the age of 4 (2 years after stopping probiotic supplementation) (Wickens et al., 2012). Thus, this probiotic may have appropriate indication as a preventative intervention for some types of high-risk infants.

Probiotic supplementation in mothers and children (younger than 3 years) has been shown to prevent development and reduce severity of AD (Foolad, 2013). The probiotic *Lactobacillus rhamnosus GG* was effective in long-term prevention of AD development, while γ-linolenic acid reduced severity of AD. It was also demonstrated that supplementation with prebiotics and blackcurrant seed oil (γ-linolenic acid and ω-3 combination) reduced the development of AD (Foolad, 2013). Thus, certain types of nutrient supplementation may be beneficial in improving AD. However, the biological signaling pathways and mechanisms that are triggered by the probiotics in the treatment of AD require further investigation. Thus, the results show that probiotics may reduce severity of AD in infants, but further studies in adults are warranted.

Food allergy and sensitization and oral tolerance

Regarding food allergy and sensitization, the use of probiotics, prebiotics, hydrolyzed formula and bacterial lysates in infancy had no effect on food sensitization, but did reduce the incidence of AD (Lau, 2013). Studies by Lau demonstrated that using *Bifidobacterium breve* and *Streptococcus thermophiles* in cow milk formula resulted in a slight reduction of food sensitization at 12 months-of-age. However, the study needed further investigation and the success was restricted to certain populations. Studies in mouse models have shown that, in ovalbumin (OVA)-sensitized mice, treatment with *Lactobacillus acidophilus* ADO31 and *Bifidobacterium lactis* ADO11 might be useful in the prevention of food allergy (Kim et al., 2008). Others have reported that the

oral administration of *Lactobacillus brevis* HY7401 in OVA-sensitized mice might be useful to promote anti-allergic processes through oral administration, possibly due to the induction of T_H1 cytokine and inhibition of T_H2 cytokines (Lee et al., 2013).

There are few animal models available for the investigation of IgE responses to orally ingested allergens and the mechanisms remains elusive (Shida et al., 2000). However, those authors demonstrated that oral administration of OVA to transgenic mice led to an increase in the levels of both antigen-specific IgE and total IgE in sera. The authors concluded that the orally-ingested antigen elicited a response by a sub-population of T-cells that produced high levels of T_H2-type cytokines (that promote IgE secretion) (Shida et al., 2000). Later studies by Shida et al. (2002) reported that, in their mouse model, addition of *Lactobacillus casei* strain Shirota (LcS) to allergen-sensitized murine splenocyte cultures suppressed IgE and IgG1 responses. However, no studies have shown the effect of this probiotic in humans. Thus, these results suggest that probiotics may have some positive use in a mouse model of food sensitization or oral tolerance; however, studies remain elusive and inconclusive in humans.

Conclusions

In this review, we have summarized representative articles regarding treatment of AR, AD, asthma or food allergy with probiotic supplementation in both mice and humans. In general, the ''benefits'' of probiotic use in humans are either unknown or limited and there is very little high quality data from human studies that support the theory that there may exist a cause/effect relationship between taking probiotics and alleviation of allergic disease. Caution must be used at interpreting results and drawing correct conclusions regarding strains, methods and applications of the probiotic in question. Further studies in humans using standardized criteria are necessary to investigate the benefits of probiotics in both health and disease state and to establish therapeutic applications and guidelines.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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