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Microbiota and Allergy: From Dysbiosis to Probiotics

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1. Introduction

The update theory of hygiene implicates the gut microbiota in the increasing prevalence of allergy. Indeed, changes have been observed in the establishment of the gut microbiota over the last fifteen years, and dysbiosis has been demonstrated in allergic subjects by numerous clinical studies comparing the microbiota in subjects from countries with high and low prevalence of allergy, or subjects with or without allergic diseases. These results support the use of pro- and prebiotics to treat or prevent allergic diseases; however, randomized controlled trials, mainly concerning atopic dermatitis, rhinitis and asthma, provide conflicting data. The mechanism of action of probiotics has not been elucidated. Nevertheless, it appears that lactobacilli and bifidobacteria may mediate immune responses in a strain-specific way, and the interactions involved seem to include dendritic cells and detection of microbe-associated molecular patterns. Although these functional foods are promising, numerous issues, including the bacterial strains and doses to use, remain to be determined.

1.1 The update theory of hygiene implicates the gut microbiota

Over recent decades, the incidence of allergic diseases has been increasing in industrialized country whereas it is stable in developing countries (Mannino *et al*., 1998). This dichotomy and the large differences in the prevalence of allergy between genetically similar populations suggest that environmental factors make a large contribution to the development of allergies (Asher *et al*., 2010). Numerous studies agree on the importance of the T-helper CD4 lymphocyte population balance (Th1, Th2, Th17, T regulatory cells), and an imbalance towards Th2 is considered to be a major factor for the onset of allergic disease. Imbalances of this type have long been associated with the absence of triggers of the Th1 immune response during childhood. Indeed, the increase in incidence of allergic diseases in industrialized countries coincides with widespread vaccination, antibiotic usage, declining family size, improvements in household amenities, and higher standards of personal cleanliness, all of which have reduced the opportunity for cross infection between children over the past century (the hygiene hypothesis, proposed by Strachan in 1989). However, the reduction of Th1 responses as a consequence of modern lifestyle cannot alone explain the high prevalence of allergic diseases in industrialized countries. Moreover, epidemiologic

studies show that the morbidity of autoimmune diseases, which are associated with a Th1 or Th17 profiles, are increasing and that helminthiasis, associated with a Th2 profile, are not associated with an increased risk of allergic disease (Bach, 2002). Recent work implicates therefore inadequate stimulation of either various regulatory T cell subsets, or Toll-like receptor (Okada *et al.*, 2010;Akdis *et al.*, 2004).

Commensal bacteria of the intestinal microbiota play a crucial role in development of the intestinal immune system and modulation of the T helper cell balance. Rautava *et al.* extended this "hygiene hypothesis" and suggested that the initial composition of the infant gut microbiota may be a key determinant in the development of atopic disease (Rautava *et al.*, 2004). Indeed, neonates are biased towards T helper type 2 responses with reference to adults (Adkins *et al.*, 2004;Protonotariou *et al.*, 2004), and the first bacteria to colonize the infant's gut are the first stimuli for post-natal maturation of the T-helper balance. The immature Th2-dominant neonatal response undergoes environment-driven maturation via microbial contact during the early postnatal period resulting in a gradual inhibition of the Th2 response and an increase of the Th1 response and prevention of allergic diseases. This hypothesis is consistent with various observations: the delayed colonization of the digestive tract associated with changes in lifestyle over the last 15 years (Campeotto *et al.*, 2007;Adlerberth and Wold, 2009); and evidence that caesarian section (Kero *et al.*, 2002;Laubereau *et al.*, 2004), prematurity (Agosti *et al.*, 2003), and exposure to antibiotics during pregnancy (McKeever *et al.*, 2002) —all factors which modify establishment of the gut microbiota— are associated with a higher risk of atopic disease.

2. The gut microbiota and its functions

The composition of microbial communities in the gut was first investigated through culture-based studies, leading to estimates of 400 to 500 different species in the adult human intestinal tract (Manson *et al.*, 2008). The dominant microbiota (10^9-10^{11} CFU.g^{-1}) is composed of obligate anaerobes, including Gram-negative bacilli such as *Bacteroides,* Gram-positive bacilli such as *Bifidobacterium, Eubacterium,* and Gram-positive cocci. The subdominant microbiota (10^6-10^8 CFU.g^{-1}) is composed of facultative anaerobes including various species of enterobacteria, notably *Escherichia coli*, and species of the *Enterococcus* and *Lactobacillus* genera. With population densities of below 10^6 CFU.g^{-1}, this microbiota is often extremely variable and transient.

The use of culture-independent approaches has provided novel insights into the gut microbiota community (Manson *et al.*, 2008). Many of the techniques used are based on analysis of 16S rRNA gene sequences, and studies have exploited combinations of 16S rRNA gene libraries, DNA microarrays, 16S rRNA gene fingerprinting, fluorescent *in* situ hybridization, and quantitative PCR. These culture-independent techniques have shown that the intestinal microbiota community is more complex than previously described. The proportion of bacteria in the adult intestine that can be cultured varies between 15 and 85% (Eckburg *et al.*, 2005); over 1200 bacterial species have been characterized (Rajilic-Stojanovic *et al.*, 2007), and current estimates are that there are up to 1000 bacterial species per individual and over 5000 different species in total in human intestines (Zoetendal *et al.*, 2008). Most of the gut microbiota are from only four major phyla (Tap *et al.*, 2009). *Firmicutes* and *Bacteroidetes* are the most abundant, and *Actinobacteria* - including bifidobacteria - and *Proteobacteria* are less abundant despite representing more than 1% of the total microbiota. Adult fecal microbiota has been demonstrated to be individual-specific and relatively stable

over time (Rajilic-Stojanovic *et al.*, 2009). However, even though each individual harbors a unique microbiota, a number of microbial species are present in all individuals, consistent with the existence of a universal phylogenetic core to the human intestinal microbiota (Rajilic-Stojanovic *et al.*, 2009;Tap *et al.*, 2009).

The intestinal ecosystem develops rapidly during the neonatal stage of life. The intestine is sterile at birth and is colonized by bacteria following contact with the maternal microbiota and the surrounding environment. Little is known about the factors that lead to the establishment of particular bacterial strains. Colonizing bacteria originate mainly from the mother; the maternal gut microbiota is a major source and other sources include the microbiota of the vagina, perineum, and skin. Breast milk has also been demonstrated to be a source of lactic acid bacteria (Martin *et al.*, 2009;Gueimonde *et al.*, 2007). Infants encounter numerous bacteria in the environment including the microbiota of food and the microbiota of the skin of parents, siblings and nurses. Consequently, the number of bacterial species, mainly obligate anaerobes, increases with time in the infant gut. As a result of the diversity of exposure, there is substantial inter-individual variability in the composition and patterns of bacterial colonization during the first weeks of life (Penders *et al.*, 2006c;Palmer *et al.*, 2007;Vaishampayan *et al.*, 2010). However, by the end of the first year of life, the bacterial composition in the gut converges toward an adult-like microbiota profile (Palmer *et al.*, 2007). Various external factors can affect the pattern of bacterial colonization (for review see (Adlerberth and Wold, 2009;Vael and Desager, 2009;Campeotto *et al.*, 2007). Infants born by cesarean section are deprived of contact with their mother's gut and vaginal microbiota, which decreases bacterial diversity and colonization by obligate anaerobes, particularly bifidobacteria and *Bacteroides*. The mode of infant feeding also strongly affects bacterial establishment, with a dominant colonization by bifidobacteria being a characteristic distinguishing breastfed from formula-fed infants. However, improvements in infant formulas have led to there now being only minor differences in colonization according to feeding method (Adlerberth and Wold, 2009;Campeotto *et al.*, 2007). Finally, the establishment of gut microbiota in infants in industrialized countries appears to have been affected in modern times, most likely due to improved hygiene and general cleanliness in these countries, resulting in reduced bacterial exposure (Adlerberth and Wold, 2009;Campeotto *et al.*, 2007).

Although the gut microbiota community was for several decades mostly studied to elucidate pathogenic relationships, it is now clear that most microorganism-host interactions in the gut are, in fact, commensal or even mutualistic (Bik, 2009;Dethlefsen *et al.*, 2007). This complex ecosystem has various major functions (Fujimura *et al.*, 2010). Colonic fermentation of non-digestible dietary residues and endogenous mucus supplies energy and nutritive products to the bacteria. It also plays a role in the trophic functions of the intestinal epithelium (Wong *et al.*, 2006). The barrier effect, which involves secretion of antimicrobial molecules, competition for nutrients, and attachment to ecological niches, refers to a resistance to colonization by exogenous or opportunistic bacteria present at a low level in the gut (Stecher and Hardt, 2008). Finally, the gut microbial community has a major immune function. The contribution of the gut microbiota to immune system maturation has been demonstrated by the description of major abnormalities of the immune system in germ-free mice (Smith *et al.*, 2007). Intestinal IgA-secreting plasma cells are rare in germ-free animals, and the Peyer's patches are smaller and contain fewer lymphoid follicles than those in conventional mice. The T cell content of the mucosal immune system is also low in germ-

free animals, and particularly the CD4+ cells of the lamina propria. Spleen and lymph nodes are relatively structureless with abnormal B- and T- cell zones. These morphologic features are associated with substantial functional abnormalities, such as hypogammaglobulinemia, a Th2 cell shift and defects in oral tolerance induction (Round *et al.*, 2010). Recent reviews have highlighted how the microbiota elicits innate and adaptative immune mechanisms that cooperate to protect the host and maintain intestinal homeostasis (Hooper and Macpherson, 2010;Garrett *et al.*, 2010). Colonization of germ-free mice by a single species of bacteria e.g. *Bacteroides fragilis* (Mazmanian *et al.*, 2005) or segmented filamentous bacteria (Gaboriau-Routhiau *et al.*, 2009), has been shown to be sufficient to restore the development of a multifaceted adaptative immune response. The capacity to stimulate steady-state gut T cell responses appears to be restricted to a small number of bacteria (Gaboriau-Routhiau *et al.*, 2009) and certain strains. Indeed, the immunostimulatory properties of *Bifidobacterium* are strain-specific (Medina *et al.*, 2007;Menard *et al.*, 2008) and only some strains of *Bifidobacterium* are able to induce Foxp3+ regulatory cells or be associated with protection from respiratory and oral allergy in mice (Lyons *et al.*, 2010). *B. infantis* restored the susceptibility to oral tolerance induction in germ-free mice only if the inoculation was at the neonatal stage (Sudo *et al.*, 1997). This suggests that there is a 'time window of opportunity' during the neonatal phase, consistent with observations with probiotics (Feleszko *et al.*, 2007).

3. Microbiota and allergy

The extended version of the hygiene hypothesis implicating the gut microbiota is supported by several clinical studies which have shown a relationship between allergic disease and gut microbiota. In particular, they have shown that the composition of the bacterial community in the feces differ between children who live in countries with high and low prevalence of allergy, as well between children with or without allergic diseases.

3.1 Is gut microbiota different between healthy individuals and allergic subjects? Case-control studies

Numerous studies have addressed the composition of the microbiota in healthy and allergic subjects. Some of the first studies (Bjorksten *et al.*, 1999;Sepp *et al.*, 1997) compared the microbiota between two-year old children in countries with high (Sweden) and low (Estonia) incidence of allergic diseases. Irrespective of country of residence, allergic children were colonized by fewer lactobacilli but had higher counts of aerobic bacteria, especially *Enterobacteriaceae* and staphylococci and lower counts of *Bacteroides*. A prospective study (Bjorksten *et al.*, 2001) found that children who developed atopic dermatitis and/or positive skin prick test results during the two first years of life were less often colonized with enterococci during the first month of life and with bifidobacteria during the first year of life. Furthermore, allergic infants had higher counts of clostridia at 3 months of age and lower counts of *Bacteroides* at 12 months. The prevalence of colonization with *Staphylococcus aureus* was also higher in allergic children than the reference group at 6 months old.

Case-control studies confirmed differences of the gut microbiota composition between allergic and healthy subjects but the differences identified concerned various particular genera and species, including *Bifidobacterium*, *Clostridium*, *Bacteroides*, *Lactobacillus* and *Enterobacteriaceae*. Indirect methods suggested an association between allergy and

Clostridium difficile. Allergic infants had higher fecal concentrations of the rarely detected i-caproic acid, which has been associated with the presence of *Clostridium difficile* (Bottcher *et al*., 2000) and higher *C. difficile* IgG antibody levels at one year than non-allergic infants (Woodcock *et al*., 2002). However, counting bacteria by FISH analysis indicated that colonization by *Clostridium* sp. was lower in allergic than reference subjects (Mah *et al*., 2006) and no significant difference in *Clostridium* counts were found between preschool controls and children with allergy-associated atopic eczema/dermatitis syndrome (AAEDS) and non-allergic atopic eczema/dermatitis syndrome (NAAEDS) (Kendler *et al*., 2006)
Numerous other studies reported quantitative differences in colonization with *Bifidobacterium*, a dominant genus in infant fecal microbiota which may have beneficial effects (Ventura *et al*., 2004). The prevalence of *Bifidobacterium* has been found to be similar in healthy and allergic subjects, whatever the allergic disease (Stsepetova *et al*., 2007;Waligora-Dupriet *et al*., 2011), and for atopic dermatitis (Gore *et al*., 2008), and wheezing (Murray *et al*., 2005). However, the findings of one study are discordant (Sepp *et al*., 2005) with none of the 5-year-old children with atopic dermatitis and only one child with bronchial asthma colonized with bifidobacteria. Besides, low levels of bifidobacterial colonization have been observed in infants suffering from atopic dermatitis (Kirjavainen *et al*., 2001;Watanabe *et al*., 2003;Mah *et al*., 2006) and in infants suffering from atopic dermatitis and wheezing; note that these results have been contradicted by studies comparing healthy subjects with wheezing infants without other symptoms (Murray *et al*., 2005) and with patients suffering from both atopic dermatitis and food allergy (Penders *et al*., 2006a).

3.2 Does dysbiosis precede allergic symptoms? Prospective studies

Some prospective studies report that modifications of the composition of the intestinal microbiota can be detected before any atopic syndrome, suggesting that bacteria implicated in the maturation of the immune system may be important. The bacterial fatty acid profile in fecal samples differed significantly between 3-week-old infants in whom atopy was and was not developing. The stools of atopic subjects had more clostridia and tended to have fewer bifidobacteria than those of non atopic subjects, resulting in a reduced ratio of bifidobacteria to clostridia (Kalliomaki *et al*., 2001a). The Koala Birth Cohort Study in the Netherlands confirmed these results by showing that gut dysbiosis precedes the manifestation of atopic symptoms and atopic sensitization (Penders *et al*., 2007). In particular, *C. difficile* was associated with all atopic symptoms and sensitization. The presence of *Escherichia coli* was associated with a higher risk of developing (non-atopic) eczema, this risk increasing with increasing *E. coli* counts; infants colonized with *C. difficile* were at higher risk of developing atopic dermatitis, recurrent wheeze and allergic sensitisation. As *E. coli* was only associated with eczema and *C. difficile* was associated with all atopic outcomes, the underlying mechanisms may be different. Colonization with clostridia, including *C. difficile*, was associated with allergy development up to age 2 years in several studies (Kalliomaki *et al*., 2001a;Bjorksten *et al*., 2001;Penders *et al*., 2007) but not in others (Adlerberth *et al*., 2007;Sjogren *et al*., 2009;Songjinda *et al*., 2007). Fecal colonization at age 3 weeks with *Clostridium coccoides* subcluster XIVa species has been described as an early indicator of possible asthma later in life (Vael *et al*., 2008;Vael *et al*., 2011). However, Verhulst *et al*. (2008) found an association between antibiotics, anaerobic bacteria and wheezing during the first year of life, but increasing levels of *Clostridium* were protective against wheezing. These studies considered different *Clostridium* species and the genus *Clostridium* is a very

heterogeneous group comprising several different clusters (Stackebrandt *et al.*, 1999). Indeed, it seems unlikely that all members of this genus exert the same effects on the human immune system (Penders *et al.*, 2007).

Children not developing allergy before age 2 years have been shown to be more frequently colonized with bifidobacteria than children developing allergy (Bjorksten *et al.*, 2001), but this decreased prevalence of *Bifidobacterium* in children suffering allergies was not confirmed in all studies (Songjinda *et al.*, 2007;Penders *et al.*, 2006a;Adlerberth *et al.*, 2007). Differences in patterns of colonization by bifidobacteria species have also been observed but no clear consensus exists. Young *et al* (2004) compared the populations of bifidobacteria in feces from children aged 25 to 35 days in Ghana (which has a low prevalence of atopy), New Zealand, and the United Kingdom (high-prevalence countries): almost all fecal samples from Ghana contained *Bifidobacterium longum* subsp *infantis* whereas those from the children living in the other countries did not. The authors suggested that place of birth influences the patterns of bifidobacterial species present. *B. adolescentis* has been found in the fecal microbiota of both allergic infants (Ouwehand *et al.*, 2001;He *et al.*, 2001) and non-allergic infants (Sjogren *et al.*, 2009). Similarly, *B. catenulatum/pseudocatenulatum* has been isolated from both allergic (Gore *et al.*, 2008) and non-allergic infants (Stsepetova *et al.*, 2007). Some authors report that restricted *Bifidobacterium* diversity is linked with allergy (Stsepetova *et al.*, 2007) but again, this was not confirmed in other studies at the species (Sjogren *et al.*, 2009;Waligora-Dupriet *et al.*, 2011) or strain level (Waligora-Dupriet *et al.*, 2011). It has been suggested that the intrinsic properties of bacterial strains may be pertinent. Indeed, *in vitro*, bifidobacterial species differentially affected expression of cell surface markers and cytokine production by dendritic cells harvested from cord blood. *B. bifidum*, *B. longum*, and *B. pseudocatenulatum*, species commonly detected in children in New Zealand and the United Kingdom increased the expression of the dendritic-cell activation marker CD83 and induce IL-10 production, whereas *B. infantis*, a species commonly isolated in Ghana, does not (Young *et al*, 2004). By contrast, heat-inactivated *B. longum* subsp *longum* and *B. adolescentis*, known as adult-type bifidobacteria, were significantly stronger inducers of pro-inflammatory cytokine (IL-12 and TNF-alpha) production by a murine macrophage cell line than *B. bifidum, B. breve,* and *B. longum* subsp *infantis* usually isolated from infants (He *et al.*, 2002). The Th1 stimulation profile induced by *B. adolescentis* (Karlsson *et al.*, 2004;He *et al.*, 2002) may intensify pathology in allergic infants (He *et al.*, 2002). However, the properties of intestinal bifidobacteria are highly strain-dependent (Matto *et al.*, 2004), and this is particularly true of immunostimulatory properties (Menard *et al.*, 2008;Medina *et al.*, 2007).

Bacteroidaceae are also associated with allergic development, although, as for clostridia and bifidobacteria, findings are contradictory. Indeed, *Bacteroides* colonization of the gut was not found to be linked to allergy in several studies (Adlerberth *et al.*, 2007;Kalliomaki *et al.*, 2001a; Bjorksten *et al.*, 2001; Sjogren *et al.*, 2009), but colonization with the *B. fragilis* group at age 3 weeks has been associated with a higher risk of developing asthma later in life (Vael *et al.*, 2008;Vael *et al.*, 2011). A high level of *Bacteroides* colonization positively correlated with IgE in children with atopic dermatitis (Kirjavainen *et al.*, 2002). Moreover, fecal *Bacteroides* strains induced high levels of Th2 cytokine production by peripheral blood monocyte cells from patients suffering from Japanese Cedar Pollinosis (Odamaki *et al.*, 2007).

Discrepancies between studies might be the consequence of the methods used to study the gut microbiota. Indeed, in the same study, some differences were observed with FISH but

that were not detected by bacterial cultivation (Kalliomaki *et al.*, 2001a). These discrepancies are such that it is not possible to conclude about the association of particular species, genera or groups with the development of allergy, although it seems that the diversity of the gut microbiota is a major determinant in allergy risk. Interestingly, a large recent study did not find any relationships between the presence of various particular bacteria and allergy development up to 18 months of age (Adlerberth *et al.*, 2007), but showed that infants who developed allergy had a lower diversity in their gut microbiota at one week of age (Wang *et al.*, 2008).

Despite prospective studies showing that modifications of the gut microbiota composition can be detected before any atopic syndrome, these epidemiological studies cannot demonstrate which of these factors appears first. Atopy could be linked to a mucosal state favoring some bacterial populations to the detriment of others. In a mouse model of food allergy, mice with high and low anaphylaxis scores showed differences in intestinal microbiota composition: high responders exhibited less staphylococcus colonization (Rodriguez *et al.*, 2011). The composition of the intestinal bacteria fluctuated significantly during the pollen season in adults with IgE-dependent pollinosis, with colonization by the *Bacteroides fragilis* group increasing with pollen dispersal, especially at the end of the pollen season (Odamaki *et al.*, 2007). It is clear that the cause-and-effect relationship between the composition of the microbiota and allergic diseases remains to be determined.

4. Probiotics and allergic diseases

Despite discrepancies between studies, there is mounting evidence of a relationship between the intestinal microbiota and allergy. It therefore follows that a modulation of the gut microbiota may help prevent allergic diseases and this notion supports the use of probiotics, prebiotics and synbiotics. Probiotics are currently defined as "live microorganisms which when administered in adequate amounts confer a health benefit on the host" (FAO/WHO, 2001; FAO/WHO 2001, 2002). The most widely used probiotics are lactic acid bacteria, specifically *Lactobacillus* and *Bifidobacterium* species (Williams, 2010). The yeast *Saccharomyces boulardii* is also used. Although the efficacy of probiotics is sometimes debatable, they offer substantial potential benefits to health and are safe for human use.

The mechanisms of action of "probiotic" strains in allergic diseases may include modulation of the gut microbiota, maturation of the gut barrier, stimulation of the immune system and immunomodulation. However, the effects of probiotics described in experimental models need to be confirmed for human use through randomized controlled trials. We conducted bibliographic searches in the PubMed/Medline database for the following terms (all field): allergy AND probiotic*", and results limited to randomized controlled trials identified 99 publications.

4.1 Clinical impact of probiotics in atopic/allergic diseases

4.1.1 Probiotics in the treatment of atopic dermatitis

Fifty studies have evaluated clinical consequences of probiotics in the treatment of atopic dermatitis (AD) in infants and children, and between them have studied about 1100 subjects. AD is a chronic highly pruritic inflammatory skin disease including IgE- and non-IgE-mediated mechanisms. It commonly occurs during early infancy but can persist or even start in adulthood. It includes a wide clinical spectrum from minor forms to major

symptoms including erythrodermic rash and can be associated with other atopic diseases such as food allergy, asthma, and allergic rhinitis. To evaluate the effects of probiotics on AD, a rigorous definition of study participants is necessary. The diagnosis of AD is currently based on diagnostic criteria scales developed by Hanifin and Rafka in 1980 and by the "United Kingdom Working party" in 1994 (*in* Roguedas-Contios and Misery, 2011). It is equally important that diseases outcome measures used in treatment studies are both valid and reliable. Three of the various eczema outcome measures have been shown to be reliable: SCORing Atopic Dermatitis (SCORAD), the Eczema Area and Severity Index (EASI) and the Patient Oriented Eczema Measure (POEM). SCORAD is commonly used in studies of probiotics. It combines an estimation of the intensity and extent of the eczema with a subjective itch. However, it assesses a clinical state of the disease at a particular time point without taking into account overall severity or evolution of the disease (Société Française de Dermatologie, 2005). Some quality of life scales are also used, for example the Infant Dermatitis Quality Of Life (IDQOL), Dermatitis Family Impact (DFI), and Dermatitis Family Impact Questionnaire (DFIQ) scores (Gerasimov *et al.*, 2010; Weston *et al.*, 2005) scores.

The age range of subjects included varies between studies: around weaning (median 5 months old) (Brouwer *et al.*, 2006;Isolauri *et al.*, 2000;Kirjavainen *et al.*, 2003;Viljanen *et al.*, 2005b;Gruber *et al.*, 2007), around 1 year old (Weston *et al.*, 2005;Folster-Holst *et al.*, 2006), and around 5 years old (Rosenfeldt *et al.*, 2003, 2004; Sistek *et al.*, 2006; Woo *et al.*, 2010). Seven of these publications describe effects of *Lactobacillus rhamnosus* GG LGG in infants but report contradictory results (Brouwer *et al.*, 2006;Isolauri *et al.*, 2000;Kirjavainen *et al.*, 2003;Viljanen *et al.*, 2005b;Gruber *et al.*, 2007;Folster-Holst *et al.*, 2006;Nermes *et al.*, 2011). Two of them (Isolauri *et al.*, 2000;Kirjavainen *et al.*, 2003) showed a significant decrease of the SCORAD score, but both these studies included only small groups of infants (27 and 35). Moreover, the heat-inactivated LGG used in Kirjavainen's study induced adverse gastrointestinal symptoms and diarrhea leading to the recruitment of patients being stopped after the pilot phase (Kirjavainen *et al.*, 2003). Six other studies, similar in terms of subjects included and protocol, did not find any improvement in SCORAD scores following LGG supplementation (Folster-Holst *et al.*, 2006;Brouwer *et al.*, 2006;Gruber *et al.*, 2007;Viljanen *et al.*, 2005b;Nermes *et al.*, 2011;Rose *et al.*, 2010). Other probiotic strains have been studied, and *Bifidobacterium lactis* Bb12 (Isolauri *et al.*, 2000), *L. sakei* KCTC 10755B0 and *L. fermentum* VRI-003 (Weston *et al.*, 2005) induced significant decreases in SCORAD scores. In the last of these studies, the effects of *L. fermentum* VRI-003 were found to persist two months after the end of supplementation. Four studies used a *L. rhamnosus* strain (not LGG) alone (Brouwer *et al.*, 2006) or mixed with *L. reuteri* (Rosenfeldt *et al.*, 2003) or with other *Lactobacillus sp.* and *Bifidobacterium sp.* (Viljanen *et al.*, 2005b;Sistek *et al.*, 2006). These studies did not detect significant SCORAD score improvement although in the crossover study of Rosenfeldt *et al* (2003), which included children older than those in the other studies, patients felt better according to their subjective evaluations. Nevertheless, a pronounced decrease in SCORAD score was observed in patients with a positive skin prick-test response and increased IgE levels (Viljanen *et al.*, 2005b;Rosenfeldt *et al.*, 2003;Sistek *et al.*, 2006). The administration of a probiotic mixture containing *L. acidophilus* DDS-1, *B. lactis* UABLA-12, and fructo-oligosaccharide was associated with a significant clinical improvement in children with AD and in particular a large decrease in SCORAD score and increase in quality of life score relative to the placebo group (Gerasimov *et al.*, 2010). This was not the case with a mixture of *B. breve* M-16V and galacto-/fructooligosaccharide (Immunofortis) (van der Aa *et al.*, 2010), even though this synbiotic mixture seemed to prevent asthma-like symptoms in infants with

AD (van der Aa *et al.*, 2011). To conclude, investigations of probiotics for the treatment of AD provide promising results, but are not conclusive, as confirmed by meta-analyzes (Lee *et al.*, 2008;Osborn and Sinn, 2007) such that they do not provide sufficient basis to recommend the use of such products.

4.1.2 Probiotics in the treatment of rhinitis and respiratory allergic diseases

Eleven studies have evaluated clinical effects of probiotics in the treatment of allergic diseases of the respiratory tract, *i.e.* rhinitis and asthma, and altogether included about 890 subjects.

Lactobacillus paracasei-33, whether or not heat-inactivated, improved quality of life of patients with allergic rhinitis: both frequency and intensity of symptoms were significantly lower in the LP-33 group than the placebo group, after the 30-day treatment (Wang *et al.*, 2004;Peng & Hsu, 2005). Likewise, *Lactobacillus casei* DN114 001 decreased the occurrence of rhinitis episodes and improved the health status of children with allergic rhinitis (Giovannini *et al.*, 2007). For patients with Japanese cedar pollen allergy, LGG and *Lactobacillus gasseri* TMC0356 reduced nasal symptoms (Kawase *et al.*, 2009), and *B. longum* BB536 was able to relieve eye symptoms (Ishida *et al.*, 2005;Xiao *et al.*, 2007). The degree of eosinophil infiltration into the respiratory mucosa correlates directly with the intensity of allergic rhinitis and can be used as an objective marker of the disease. A mixture of *L. acidophilus* NCFMTM and *B. lactis* Bl-04 reduced nasal eosinophil infiltration (Ouwehand *et al.*, 2009) as did *Bacillus clausii* which also reduced the number of days on which antihistamine was used in children with allergic rhinitis due to pollen sensitization (Ciprandi *et al.*, 2005a). However, *L. rhamnosus* ATCC53103 was not beneficial to teenagers and young adults allergic to birch pollen or ingested apple and who had intermittent symptoms of atopic allergy and/or mild asthma (Helin *et al.*, 2002). Similarly, *L. casei* Shirota was not found to reduce symptoms of Japanese cedar pollen allergy (Tamura *et al.*, 2007), although the strain did reduce serum concentrations of IL-5, IL-6, IFN-γ and specific IgE in subjects with allergic rhinitis (Ivory *et al.*, 2008). In children with recurrent wheeze and an atopic family history, LGG had no clinical effect on asthma-related events, and only a small effect on allergic sensitization (Rose *et al.*, 2010); likewise, long-term consumption of fermented milk containing *L. casei* had no detectable effect in asthmatic children (Giovannini *et al.*, 2007)

4.1.3 Probiotics in the primary prevention of allergic diseases

The prevention of allergy through an early administration of probiotics is appealing.

Four studies investigating probiotic supplementation begun during pregnancy. The first study to be published was by the team of Isolauri and reported promising results on preventive effects of LGG (Kalliomaki *et al.*, 2001b). LGG was given prenatally to 132 mothers who had at least one first-degree relative (or partner) with atopic eczema, allergic rhinitis, or asthma, and postnatally for 6 months to their infants. Two years later, the frequency of atopic eczema in infants given probiotics was half that of those on placebo (Kalliomaki *et al.*, 2001b). The reduction was greatest for infants who were exclusively breastfed, and therefore who did not receive the probiotic directly until 3 months of age (LGG being given to the mother) (Rautava *et al.*, 2002a). Administration of probiotics to the mother during pregnancy and breast-feeding appeared to be a safe and effective method for enhancing the immunoprotective potential of breast milk and preventing atopic eczema in the infant. The protective effect of LGG extended beyond infancy until 7 years old

(Kalliomaki *et al*., 2003; 2007). Infants most likely to benefit from probiotics might be those with an elevated cord blood IgE concentration (Rautava *et al*., 2002a), despite such high IgE levels not appearing as a risk factor for atopic diseases (Bergmann *et al*., 1998). However, LGG had no impact on sensitization: there was no difference between LGG and placebo groups at 2, 4 and 7 year old as concerns the numbers of infants with high levels of specific IgE and/or positive prick test results (Kalliomaki *et al*., 2001b; 2003; 2007).

The preventive effect of LGG was not confirmed in a similar study by Kopp *et al.* (2008) with 94 mother-infant couples. The discrepancies between the data of Kalliomaki *et al* and the data of Kopp *et al* cannot be explained by the minor differences between the study designs, but could be linked to the study populations. The German cohort (Kopp *et al*) was at higher risk of allergy than the Finnish cohort (Kalliomaki *et al*), the infants had older siblings, and the genetic contexts were different. Two other preventive studies considered prenatal and postnatal supplementation with probiotics. An investigation of *L reuteri* ATCC55730 supplementation for infants with a family history of allergic disease did not confirm a preventive effect against infant eczema but found a decreased prevalence of IgE-associated eczema during the second year. The effect was larger in the subgroup of children of allergic mothers (Abrahamsson *et al*., 2007). Infants receiving *L rhamnosus* HN001 had a significantly lower risk of eczema than infants receiving placebo, but this was not the case for *B animalis* subsp *lactis* and there was no significant effect of these two strains on atopy (Wickens *et al*., 2008). Taylor *et al* (2006a; 2006b; 2007a; 2007b) and of Soh *et al* (2009) studied newborns given, from birth to 6 months of life, *L. acidophilus* LAVRI-A1 (178 infants) and a mixture of *L. rhamnosus* LPR and *B. longum* BL999 (253 infants), respectively, and did not find any reduction of the risk of AD in high-risk infants as assessed from the numbers of patients affected, SCORAD score or IgE sensitization. Moreover, *L. acidophilus* was associated with increased allergen sensitization (Taylor *et al*., 2007a). Likewise, supplementation with LGG during pregnancy and early infancy did not alter the severity of atopic dermatitis in affected children and was associated with an increased rate of recurrent episodes of wheezing and bronchitis (Kalliomaki *et al*., 2003; 2007; Kopp *et al*., 2008).

4.2 Mechanisms of probiotic action in atopic/allergic diseases in human

Although no unambiguous clinical benefits were observed in several studies, probiotics may nevertheless have useful effects on microbiota composition, the immune system and the gut barrier in infants and in children.

4.2.1 Effects of probiotics on microbiota composition

Any effects of probiotic microorganisms on health and well-being may potentially be due, at least in part, to modulation of the intestinal microbiota. However, few of the studies on probiotics and allergic diseases assessed the consequences of probiotic use on gut microbiota composition. From the available evidence, it seems that probiotics have no impact on microbiota. In the treatment of rhinitis with *L. acidophilus* NCFMTM, fecal probiotic cell counts correlated positively with fecal acetic, propionic and butyric acid concentrations (Ouwehand *et al*., 2009), suggesting that the presence of *L. acidophilus* NCFMTM increases microbial fermentation in the colon. However, the colonization pattern did not differ between groups that consumed the probiotic strains and placebo. Similarly, no modification of the gut microbiota was observed following LGG supplementation in infants with AD (Kirjavainen *et al*, 2003). The fecal microbiota fluctuated in subjects with Japanese

cedar pollinosis during the pollen season and supplementation with BB536 yogurt modulated the microbiota in a manner that may possibly contribute to the alleviation of allergic symptoms (Odamaki *et al*, 2007).

4.2.2 Gut immunity and barrier effect

Probiotics may modulate local immune systems. Treatment with LGG resulted in a trend towards elevated fecal IgA levels, and this effect was significant in IgE-associated cow-milk allergy infants, suggesting maturation of intestinal immunity and triggering of a mechanism to protect the gut from the offending food (Viljanen *et al.*, 2005a). In older subjects with a mature immune system and suffering from allergic rhinitis, fecal IgA concentrations increased in the placebo group during the pollen season; this increase was prevented by *L. acidophilus* NCFMTM (Ouwehand *et al.*, 2009).

Probiotics have also been reported to decrease the levels of fecal inflammatory markers, but this is controversial: findings differ between studies and strains used. Treatment of AD with LGG was associated with a decrease of TNF-α and α-antitrypsin levels suggesting that LGG may alleviate inflammation in the gut. Indeed, TNF-α is a proinflammatory cytokine for both Th1- and Th2-type cells, and a marker of local inflammation. The presence of α-antitrypsin indicates protein loss in the intestine and is a marker of mucosal integrity. These results were not confirmed in the studies by Folster-Holt *et al* (2006) and Brouwer *et al* (2006) who did not observe any differences in α-antitrypsin, or calprotectin, or eosinophilic cationic protein levels between infants receiving or not receiving LGG. Accumulation of eosinophilic cationic protein at sites of allergic inflammation demonstrates local eosinophil degranulation in the gut. Specific lactobacilli (*L. rhamnosus* 19070-2 and *L reuteri* DSM 12246) might reverse increased small intestinal permeability (such permeability is involved in the pathogenesis of atopic dermatitis) thereby stabilizing the intestinal barrier function and decreasing gastrointestinal symptoms in children with AD (Rosenfeldt *et al.*, 2004).

4.2.3 Th1/Th2 balance

Certain strains of *Lactobacillus* and *Bifidobacterium* can modulate cytokine production.

Bacillus clausii modulated the cytokine pattern in the nasal mucosa in allergic children with recurrent respiratory infections. In particular, *B. clausii* restored physiological Th1 polarization and induced T-regulatory cell responses, as documented by increased levels of IL-10 and tumor growth factor (TGF)-β after treatment (Ciprandi *et al.*, 2005b). TGF-β is a regulatory cytokine which may be responsible for a decrease in local inflammation (Shull *et al.*, 1992). Interestingly, Rautava *et al* (2002b) observed high TGF-β2 concentrations in breast-milk from mothers who had received LGG for prevention of allergic disease. The authors concluded that, first, direct supplementation of infant after birth is not necessary, and second that probiotics could increase the protective effects of breast milk.

The effects on the Th1-Th2 balance of probiotic strains used for the treatment of AD in early infancy have been evaluated in several studies. Pohjavuori *et al.* (2004) were able to demonstrate greater IFN-γ production in anti-CD3/anti-CD28-stimulated *in vitro* peripheral blood mononuclear cells (PBMC) from infants treated with LGG than placebo. A different modulatory effect was observed with a mix of four bacterial strains including LGG: a significant increase in secretion of IL-4 in infants with cow milk allergy. By contrast, production of the predominant Th1 cytokine INF-γ, and the Th2 cytokines IL-4 or IL-5 after polyclonal or specific anti-CD3/anti-CD28 stimulation, was unaffected by supplementation

with *L rhamnosus*, *LGG* (Brouwer *et al.*, 2006) or a lactobacillus mix (Rosenfeldt *et al.*, 2003). A decrease in circulating IgA-, IgG- and IgM-secreting cells and an increase in memory B cells during LGG supplementation has been described (Nermes *et al.*, 2011).
The oral administration of particular probiotic strains to patients with atopic dermatitis can modulate the cytokine pattern *in vivo* at site other than the intestine. *L. casei* Shirota reduced serum concentrations of IL-5, IL-6, IFN-γ and specific IgE in subjects with allergic rhinitis (Ivory *et al.*, 2008) but was not found to be effective in reducing the symptoms of Japanese cedar pollen allergy (Tamura *et al.*, 2007). Probiotics can be involved in both antagonistic and synergistic relationships with each other, and with members of the gut ecosystem. Indeed, mixtures of bacteria induced a response in human dendritic cells different to those of the component bacteria in isolation: antagonistic immunosuppressive effects were observed with certain strains of *Lactobacillus* and *Bifidobacterium* but synergistic effects were observed when these *Lactobacillus* and *Bifidobacterium* strains were combined with *E. coli* and *K. pneumoniae* strains (Zeuthen *et al.*, 2006).

5. Conclusion

Despite some promising results, the role of probiotics in the treatment and the prevention of allergy and related diseases has not been clearly demonstrated. Indeed, clinical trials provide various contradictory findings that do not allow probiotic supplementation to be included in the guidelines for the management of allergic diseases. These conflicting data may be however attributable to the differences between studies. The populations studied have been very diverse in terms of size, age, sensitization and allergic disease, environment, and genetic background. Study designs included different probiotics in term of strains, preparations (alive/ killed; one strain/mixture/synbiotics), doses, duration of supplementation, and period of administration (prental/postnatal). In addition to these issues, progress in our basic knowledge of probiotic strains, in strain selection, and in understanding their mechanisms of action is needed to give credibility to the health claims made for probiotics and especially for the design of efficacious therapeutic agents.

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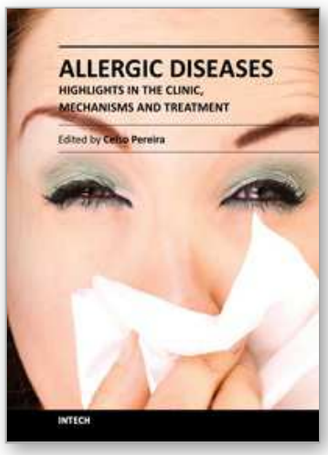
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