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Probiotics and allergy

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Allergy is caused by an immune reaction that is out of all proportion to the antigenic stimuli. Classical allergy is a type I hypersensitivity reaction mediated by the interaction of mast cells (and eosinophils) coated with allergen-specific IgE and a cross-linking allergen. The physiological outcome is inflammation commonly displayed by urticaria, rhinitis, vomiting and diarrhoea, depending on the route of allergen entry. In extreme reactions anaphylactic shock can result that may lead to death. Chronic allergic responses most commonly present themselves as asthma and eczema. All these symptoms are the consequence of an imbalanced immune system making an unsuitable response to an environmental or food antigen. On bacterial colonisation of the colon after birth the appropriate microbiological stimuli is essential to redress the balance of the skewed T-helper 2 immune response present in the newborn. This normal interaction between baby and microbes is thought to be compromised in the Western world, with a reduction in bifidobacteria and an increase in clostridial species, particularly in bottle-fed infants. The use of probiotic therapy to prevent allergic disease has been demonstrated in two studies using a probiotic *Lactobacillus rhamnosus GG* in neonates. A long-term reduction in allergy has been shown in the test group, with lactobacillus reducing the incidence of atopic eczema. Management of allergy through probiotics has also been demonstrated in infants, using lactobacilli to control atopic eczema and cow's milk allergy. Unfortunately, these positive results have not been repeated in studies with older children and young adults.

Probiotics: Management of allergy: Prevention of allergy: Infants

The term probiotic is derived from the Greek and literally translates as 'for-life'. Probiotics are live microbial food supplements that can change either the composition and/or the metabolic activities of the microbiota or modulate immune system reactivity in a way that benefits health. Increasingly, probiotics used as therapeutics are being paired with a prebiotic (non-digestible food ingredient that affects the host by selectively stimulating the growth and/or activities of one or a limited number of bacterial species already resident in the gut) that has been specially selected to promote the growth of that particular probiotic, giving it a growth advantage for colonisation of the colon (for review, see O'May & Macfarlane, 2005). This combination therapy is termed a symbiotic. In 1907 Metchnikoff first described the therapeutic potential of lactic acid bacteria (Metchnikoff, 1910). He proposed that lactobacilli could minimise, or prevent, the harmful effects of the putrefactive microbes that cause gastrointestinal disease.

The term probiotic was first used 50 years ago when chlorotetracycline fermentation waste was found to enhance the growth of poultry and pigs (for review, see O'May & Macfarlane, 2005). Probiotics are now commonly available over the counter and in the chiller cabinet of every supermarket as bio-yoghurts, probiotic drinks or food supplements. Many different organisms have been used as probiotics, the most common being the lactic acid bacteria lactobacilli and bifidobacteria (Table 1). Both bifidobacteria and lactobacilli are members of the commensal microflora of a healthy human colon. They can be found both on food particles in the lumen of the gut and in the mucus overlying the epithelial cell barrier, putting them in very close proximity to the human host (Macfarlane *et al*. 2004). A number of mechanisms of action for their health-promoting properties have been proposed. Improved epithelial barrier function, with either an alteration in tight junction integrity or initiation of changes in mucin composition, makes the host epithelium less accessible to pathogenic organisms. Bifidobacteria and lactobacilli have also been shown to directly suppress the attachment and growth of pathogenic bacteria and they can

Abbreviation: Th, T-helper.
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Table 1. Organisms used as probiotics (for review, see O'May & Macfarlane, 2005)

Lactobacilli	Bifidobacteria	Other species
L. acidophilus	*B. adolescentis*	*Bacillus subtilis*
L. casei	*B. animalis*	*Enterococcus faecalis*
L. crispatus	*B. bifidum*	*Enterococcus faecium*
L. delbruckii	*B. breve*	*Escherichia coli*
L. gallinarum	*B. infantis*	*Lactococcus lactis*
L. gasseri	*B. lactis*	*Leucnostoc mesenteroides*
L. johnsonii	*B. longum*	*Pediococcus acidilactici*
L. paracasei		*Pediococcus pentosaceus*
L. plantarum		*Saccharomyces boulardii*
L. reuteri		*Sporolactobacillus inulinus*
L. rhamosus		*Streptococcus thermophilis*

produce bacteriocidal substances that can directly kill competing organisms within a particular niche. Finally, it has been proposed that they have immunoregulatory activities either through recognition by cells of the immune system or through signalling of the probiotic directly to host cells (for review, see O'May & Macfarlane, 2005).

The nature of each immune reaction elicited by an individual to a particular antigen is regulated by the balance of their T-cell response at any one time. The status of each individual's T-cell response is dictated by their individual genetic predisposition and by the antigens they have met as their immune system develops. At birth there exists a natural T-helper (Th) 2 skewing of the immune response as a result of the high levels of Th2 cytokines present at the feto–maternal interface (Chaouat *et al*. 2004). Appropriate immune stimulation allows the development of a balanced immune response and resulting homeostasis.

An important source of antigenic stimulation after birth is provided by the bacteria that rapidly colonise the gastrointestinal tract of the neonate (Forchielli & Walker, 2005). At birth the colon is sterile and it acquires its own bacterial flora from its environment, with the bacteria recruited from the mother forming a large proportion of the initial colonisers (Hopkins *et al*. 2002). These colonising organisms not only provide a living barrier in the colon to protect it from invasion by pathogenic organisms, they also contribute to the stimulation of the immune response in early life (Hopkins & Macfarlane, 2002; Forchielli & Walker, 2005).

It is thought that the composition of colonising organisms is critical to the correct development of a balanced immune response. Studies in children from countries with a high incidence of allergic disease, as compared with those from countries with a low incidence, have shown a difference in colonising species, with a reduction in lactobacilli, bifidobacteria and enterococci and an increase in clostridia and *Staphylococcus aureus* in infants that developed allergy (Sepp *et al*. 1997; Bjorksten *et al*. 1999, 2001; Bottcher *et al*. 2000). It has also been shown that the distribution of species of colonising lactic acid bacteria can be associated with allergy, with infants who are atopic carrying a more-adult-like distribution of bifidobacteria when compared with matched controls without allergies. Furthermore, a comparison of formula-fed *v*. breast-fed infants has shown a lower incidence of allergies in the breast-fed infants that correlates with higher levels of bifidobacteria; formula-fed infants are known to have higher levels of clostridia (Kalliomaki *et al*. 2001*a*; Watanabe *et al*. 2003). This finding suggests that particular organisms may be able to dictate the allergic potential of an individual, and that changing the profile of bacteria early in life could possibly change that potential for atopy.

There are two potential avenues to treat allergy, either prevent the immune response from becoming Th2 skewed or manage the individual who is already atopic. In order to decide which therapy would work it is necessary to consider the target cells and molecules of the immune response that the probiotic requires to influence in order to change the allergic potential of an individual.

Allergy is a complex immune response involving cells that are *in situ* and cells that require recruitment from the circulation to the site of antigenic challenge. The cells that initiate the allergic response are the mast cells, which are situated throughout the tissues of the body and at all epithelial barriers (skin and gastrointestinal and respiratory tracts), which are sites of initial antigen exposure and also, in some cases, sites available for probiotic administration (skin and gastrointestinal tract). Furthermore, mast cells are able to recognise bacteria through expression of pattern-recognition receptors, enabling them to directly respond to probiotic bacteria (McCurdy *et al*. 2003). Mast cells secrete a wide range of pro-inflammatory mediators when activated; activation occurs by cross-linking of antigen-specific IgE bound to the surface of mast cells through a high-affinity IgE receptor. Thus, a main target molecule for therapeutics to control allergy is IgE. Production of IgE from allergen-specific B-cells has an absolute requirement for the involvement of T-cells, with a Th2-skewed cytokine profile producing high levels of the cytokine IL-4 to allow class switching of antigen-specific B-cells to IgE producers (Kotowicz & Callard, 1993). During an allergic response allergen-specific IgE, which binds to the IgE Fc receptor on the surface of mast cells, is cross-linked by interaction with the specific allergen and initiates inflammatory mediator release from the mast cell.

Another important mediator cell of allergic responses is the eosinophil. Eosinophils are not normally resident in body tissues but require recruitment from the circulation to the site of allergic challenge. This process requires a complex set of interactions that induce concomitant up-regulation of adhesion molecules on the endothelium of blood vessels and eosinophils, and the subsequent movement of these cells through the vessel wall towards the inflammatory site (Lampinen *et al*. 2004). All these interactions are regulated by the expression of cytokines and chemokines from the site of initial allergen contact.

The main probiotic organism of choice for nearly all studies of allergy therapy has been lactobacilli (Table 2).

Table 2. Probiotics used in allergy

Organism	Allergic condition
Lactobacillus rhamnosus GG	Asthma
	Rhinitis
	Eczema
	Food allergy
Bifidobacter lactis	Atopic eczema
Lactobacillus paracasei	Allergic rhinitis
Lactobacillus reuteri	Atopic dermatitis

They are relatively easy to grow and store when compared with bifidobacteria and are less fastidious about their environment; thus they can colonise all along the gastrointestinal tract. On investigation of their immune modulatory properties it has been shown that different species and strains can induce different cytokine patterns in dendritic cells *in vitro* (Christensen *et al*. 2002; Hart *et al*. 2004). Mono-association of rats with different species of lactobacilli has shown that Th1 *v*. Th2 skewing is dependant on the species of lactobacilli used (Ibnou-Zekri *et al*. 2003). It has also been demonstrated that one species can inhibit cytokine responses induced by another species and that low inducers can inhibit high inducers, allowing an immune balance to be reached with a mixture of different colonising species (Christensen *et al*. 2002). In human studies it is possible to investigate either prevention of allergy with at-birth colonisation, targetting immune priming and induction of homeostasis, or management of the disease at any age, allowing a reduction of symptoms by targetting effector cells and molecules, as detailed earlier.

Randomised placebo-controlled double-blind clinical trials have investigated the ability of probiotics to prevent the induction of allergy. A decrease in the severity of atopic dermatitis has been found using a double-probiotic therapy of *Lactobacillus rhamosus GG* and *Bifidobacter lactis* (*n* 13 and *n* 14, respectively) given in conjunction with a milk-free diet over 2 months to young children with cow's milk allergy (Majamaa & Isolauri, 1997). *L. rhamosus GG* has been shown to modulate phagocyte receptor levels in individuals sensitised to cow's milk (Pelto *et al*. 1998), demonstrating a modulation of the innate immune response by a probiotic.

More recently, it has also been demonstrated that children with IgE-mediated atopic dermatitis induced by cow's milk allergy have a reduced interferon-γ response that can be markedly increased by treatment with *L. rhamosus GG*, thereby providing a strengthened Th1 cytokine response that could potentially reduce the Th2-mediated allergic potential in these individuals (Pohjavuori *et al*. 2004).

Kalliomaki *et al*. (2001*b*) have extended these studies, recruiting 159 expectant mothers with either a first-degree relative or partner with atopic disease. Groups were randomised and given *L. rhamosus* GG or placebo prenatally, continued through breast-feeding and given to the infant for the first 6 months after birth. The infants were followed up at 2 (Kalliomaki *et al*. 2001*b*) and 4 years (Kalliomaki *et al*. 2003) and assessed for the incidence of atopic dermatitis. It was found that the incidence of atopic dermatitis in the probiotic group was 23% compared with 46% in the placebo at both the 2-year and 4-year follow up, strongly suggesting an extent of disease prevention in high-risk infants. However, this study raises a number of questions. The prevalence of atopic dermatitis in the placebo group is very high when compared with similar studies. Furthermore, the score for severity of atopic dermatitis is very low in the placebo group (mean 10·4; maximum score 103) and the reduction in severity is minor in the probiotic group (mean 9·8). In addition, on measuring the objective markers of atopy, including skin prick testing to selected foods and environmental allergens, total serum IgE or levels of allergen-specific IgE (milk, egg, cat, house dust mite), there are no differences between the two groups. Furthermore, the prevalence of cow's milk allergy is doubled in the probiotic group (six of twenty-nine subjects) when compared with the placebo (three of thirty-one subjects).

Several mechanisms have been proposed to explain these results of this study. It has been shown that the levels of transforming growth factor β (immune-modulating cytokine) are doubled in breast milk from mothers receiving a probiotic as compared with placebo (2885 pg/ml *v*. 1340 pg/ml; Rautava *et al*. 2002). There are also enhanced levels of the immune-modulatory cytokine IL-10 in children with atopic dermatitis given *L. rhamosus GG* (Pessi *et al*. 2000), and positive modulation of the microbiota has been reported in probiotic-fed individuals in these studies (Kirjavainen *et al*. 2001). These findings suggest that a modulation in the microflora and an increase in immune-modulatory cytokines in both the mother and infants lead to a reduction in the potential of the infant for atopic dermatitis, but not in IgE-specific allergic responses. A further study (Rosenfeldt *et al*. 2003) in infants and children (1–13 years) with established atopic dermatitis treated with *L. rhamnosus* and *L. reuteri* for 6 weeks has shown no difference in the score for severity of atopic dermatitis when compared with treatment with a placebo. However, when only the children with at least one positive skin prick test and elevated IgE levels are analysed there is a reduction in the score for severity of atopic dermatitis and in eosinophil cationic protein levels, and no changes in IL-2, IL-4, IL-10 and interferon-γ levels in mitogen-stimulated peripheral blood mononuclear cells. Thus, in young subjects with specific disease a beneficial effect is observed with the use of a particular combination of probiotics.

Further studies have presented less-promising results. Helin *et al*. (2002) treated birch (*Betula verrucosa*) pollen allergy with *L. rhamosus* given 2·5 months before the pollen season, 1 month during the season and for 2 months after the season. They assessed allergic rhinitis, both respiratory and eye symptoms, and were unable to demonstrate any difference in symptoms between the probiotic and placebo groups. In addition, the probiotic group used more medication over the birch-pollen season compared with the placebo group ($P = 0{\cdot}06$). Another study (Wang *et al*. 2004) that has assessed the effect of *L. paracasei* on perennial allergic rhinitis of at least 1 year duration and specific IgE for house dust mite has shown no clinical improvement of symptoms, although the probiotic group did report an improvement in quality of life.

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Both these studies have unsuccessfully attempted to treat existing allergy in adults with IgE-mediated disease and previous exposure to the specific allergen over an extended period of time.

This limited number of studies raises a number of issues concerning the use of probiotics to manage allergy. It is clear that in adult subjects with clearly-defined IgE-mediated respiratory symptoms probiotic therapy has, to date, shown no ability to reduce their clinical symptoms (Helin *et al*. 2002; Wang *et al*. 2004). However, studies in Finland (Kalliomaki *et al*. 2001*b*, 2003) strongly suggest that if probiotics are given prenatally and immediately after birth there may be some benefit in preventing the induction of an allergic phenotype later in life (≤ 4 years of age) in high-risk children. Rosenfeldt *et al*. (2003) have reported successful treatment of atopic dermatitis in infants and children with IgE-mediated cow's milk allergy. A further study by this group (Rosenfeldt *et al*. 2004) suggests a possible mechanism for reduction of atopic dermatitis in these patients. They have reported a reduction in gastrointestinal symptoms and a positive association between the level of intestinal permeability and the severity of atopic dermatitis in these patients.

There are two mechanisms whereby proteins can traverse the epithelial barrier of the gastrointestinal tract. Transcellular movement of antigen through the epithelial cell by endocytosis is mediated by interferon-γ (Buning *et al*. 2005), allowing effective presentation of food antigens to the immune response and inducing oral tolerance and not inappropriate immune reactivity to that antigen. Interferon-γ has been shown to be reduced in infants with cow's milk allergy (Pohjavuori *et al*. 2004). Antigen can also cross the epithelium by a paracellular route through tight junctions that allow passive but selective movement of molecules through epithelial barriers. This paracellular pore is variable and tightly regulated by a complex group of intracellular and transcellular proteins that are directly linked to the actin cytoskeleton of each cell in the epithelial monolayer. It has been shown that probiotics can also strengthen the paracellular transport of molecules, rendering the gut 'less leaky' (Baumgart & Dignass, 2002; Qin *et al*. 2005). Symptoms of allergy to food antigen require that the antigen reaches and stimulates the immune response. Thus, that antigen must be able to exit the gut in its native state and enter an immune environment that allows induction of an immune response. In a normal situation there is oral tolerance, a state of specific systemic hyporesponsiveness to the food that is eaten (Mowat *et al*. 2004). However, if that antigen is delivered in an inappropriate manner through the gut, induction of allergy or immune responsiveness to that antigen can occur (Furrie *et al*. 1994, 2004). Probiotics may be able to subtly alter the transport of antigen across the epithelium while increasing Th1-type cytokines, therefore re-establishing oral tolerance and removing the allergic stimuli.

In summary, probiotics have demonstrated an ability to prevent the induction of allergic symptoms, particularly that of atopic dermatitis, in high risk infants. However this cannot be readily repeated in individuals already exposed to a particular allergen especially with respiratory symptoms. The ability of probiotics to regulate the induction of atopic dermatitis may be due to their ability to strengthen the mucosal barrier and prevent the circulation of undigested food proteins into the periphery of susceptible individuals, thus preventing stimulation of that particular antigen specific immune response.

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