

Probiotics and prebiotics in allergy prevention and treatment: future prospects

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Background

Healthy babies are sterile prior to birth. During delivery and in the first days of life bacteria rapidly colonize the gut. Most of the human lymphoid tissue is located in and around the GI tract and the bacterial colonization of its mucosa is a key immunological stimulus for the development of the immune system. The significance of colonization for the development of a protective immune system is illustrated by experimental studies in which sterile mice lack sufficient development of lymphoid tissue, immune effector cells and molecules [1].

Colonization of the sterile gut by commensal bacteria is also essential for tolerance induction to oral allergens. Commensals stimulate the gut's lymphoid tissue with their cell wall components, such as lipopolysaccharide from Gram-negative bacteria and peptidoglycan from Gram-positive and Gram-negative bacteria. Breast milk contains a pattern recognition receptor, CD14, to which commensals bind. As a result of binding, immune cells differentiate into the Th1 type, production of regulatory cytokines (i.e., IL-10 and TGF- β) is upregulated, and Th2-type immunity as a promoter of allergy is downregulated [2].

The 'gold standard' of early baby nutrition is human milk. Breastfeeding was associated with a reduced prevalence of allergy in numerous epidemiological studies. Breast milk promotes colonization of the gut with nonpathogenic commensal bacteria (probiotics). Bifidobacterium as

probiotic representatives, thus are more prevalent in the stool of breastfed infants, whereas *Clostridiaceae* as representatives of more pathogenic bacteria are more abundant among formula-fed infants. Epidemiological studies from the 1990s showed an association of higher counts of probiotic bacteria and less pathogenic bacteria in the stool of less allergic populations. In a prospective study of infants, it was shown that early gut colonization with nonprobiotic clostridia is associated with the development of allergy later in life [3].

Past

Based on epidemiological observations randomized, placebo-controlled intervention trials investigated the potential of supplementary probiotics in the primary prevention of allergy, mainly in infants at heightened risk for atopic dermatitis.

In a pioneering Finnish study, allergic families with perinatal supplementation of the mothers' and infants' diet with live *Lactobacillus GG* demonstrated a 50% reduced prevalence of early atopic dermatitis in children, but no effect on disease severity or allergic sensitization [4,5]. Replication of these results was attempted in Germany with a similar study design and the same probiotic. The study was negative in regard to eczema occurrence and severity, but wheezing was more common in the intervention group [6]. In a study among infants at high atopy risk, a preventive effect of *Lactobacillus reuteri* on infant eczema was not confirmed, apart from lower eczema prevalence in a subgroup of infants who

were allergic sensitized and had allergic mothers [7]. In another trial high-risk infants received postnatal *Lactobacillus acidophilus*; no effect was seen on the risk of eczema, but the rate of allergic sensitization and wheeze was higher in the active group [8]. Further studies with different species and strains have been published with heterogeneous outcome.

Probiotics seem not to be a reliably effective therapy in established allergic disease. In two controlled studies improvement of eczema was only observed in subpopulations with allergic sensitization [9,10]. A further study showed no significant improvement of moderate-to-severe eczema under treatment with *Lactobacillus*, except 8 weeks after treatment had been finished [11]. A study in infants with mild-to-moderate eczema offering *Lactobacillus GG* as eczema treatment was negative [12]. More studies have been published on this issue, but there seems to be no clinically relevant therapeutic effect against allergy.

Recent developments

More recently, research has concentrated on oligosaccharides, which account for approximately 10% of the solid human milk components and which stimulate the growth of probiotic bacteria (prebiotics). Whereas the probiotic approach adds one or two species to a spectrum of hundreds of species in the gut flora, the prebiotic approach aims at fertilization of the intestinal ecosystem. Functional imitates of the naturally occurring prebiotics, galacto- and fructo-oligosaccharides (GOS/FOS), stimulate intestinal growth of *Bifidobacteria* as a marker of probiotics in a dose-dependent fashion and transform the microbiota profile of formula-fed infants towards that of breastfed infants [13].

A combination strategy (hydrolyzed whey formula plus GOS/FOS) was performed in infants at high risk for eczema; infants who received hydrolysate plus prebiotic had significantly less frequent eczema and recurrent wheeze up to 2 years of age than infants who received just the hydrolysate [14,15].

In an experimental model, addition of a functional imitate of human milk acidic oligosaccharides to GOS/FOS prior to allergic sensitization resulted in more effective suppression of Th2-dependent allergic airway disease than with GOS/FOS alone [16].

Recently, first results of a large multicenter trial became available in which among infants at standard risk for atopic dermatitis a formula supplemented with prebiotics was tested against unsupplemented formula and against breastfeeding as gold standard. Breastfed infants were less likely to develop atopic dermatitis than unsupplemented formula-fed infants and, if atopic dermatitis occurred, their eczema was less severe. Infants who were randomized to receive supplementation with GOS/FOS/acidic oligosaccharides of their standard formula had, in comparison with standard formula alone, an approximately 50% proportional hazard reduction for eczema occurrence – almost identical to that of the breastfed infants [17]. To date, there are no published trials investigating the therapeutic potential of prebiotics alone against allergy.

To summarize, the currently available evidence, controlled therapy trials against atopic dermatitis are largely negative. Explorative analyses in a few studies indicate a possible therapeutic potential of probiotics for IgE-sensitized atopic dermatitis patients. This

question could be answered in specifically designed and sufficiently powered trials. The evidence from controlled prebiotic trials indicates preventive potential early in life. Ongoing studies will answer whether the protective effect lasts beyond infancy and includes respiratory allergy.

Future perspectives

Is the probiotic concept for allergy prevention and therapy outdated? To derive a general conclusion from the trials currently available is difficult, because not only the study designs and regimens differ, but also strains and species investigated. A disease-specific combination of synergistic probiotic bacteria might establish more successfully a probiotic niche in the gut and combine different antiallergic properties for better efficacy. A preclinical study that identified candidates for such an immunomodulating cocktail revealed a transiently reduced eczema incidence during the first 3 months of life although the infants received probiotics and prebiotics until their first birthday [18].

An alternative approach is to genetically engineer nonpathogenic bacteria that produce therapeutic peptides or proteins. In an experimental model for food allergy, a genetically modified *Lactococcus lactis* strain was orally administered that delivered messenger IL-10 to the gut [19]. Treatment of mice with this strain after exposure to the model allergen induced antigen-specific IL-10-secreting CD3⁺ cells in Peyer's plaques and resulted in a mitigation of the allergic reaction to the model allergen. Genetically improved probiotics could be also an elegant strategy for the prevention of atopic dermatitis. Until the safety of genetically modified probiotics is established, great caution should prevail in this regard.

The prebiotic approach seems to be a powerful tool for the prevention of atopic dermatitis. Whether there is a role for prebiotics in the therapy of established allergic disease remains to be elucidated. Further research options are the therapeutic use of bacterial metabolites or fermentation products, polyunsaturated fatty acids, possibly in combination with probiotics, prebiotics or hypoallergenic formula. Clinical studies in this direction are underway.

Considerable progress has been made in regard to a functional 'perfect' human milk substitute for those infants who cannot be sufficiently breastfed and future research will hopefully lead to even more effective strategies to prevent and treat allergy. From a clinical point of view, it seems too early to give general recommendations for the preventive and therapeutic use of probiotics and prebiotics as food supplements against atopic dermatitis. In the meantime, every reasonable effort should be made to promote the gold standard: human milk.

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