Mini Review
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Prebiotics and probiotics in allergy: potential mechanisms of prebiotics' and probiotics' actions in allergy – (part 1)

Abstract

The prevalence of allergic diseases is increasing from the last half of XXth century. This increase has been thought to be due to different factors e.g. diet as well as decreased microbial exposure (hygiene hypothesis). Gastrointestinal microbiota contributes to microbial contact during infancy and is one of the most important stimulatory factors for immature Th2–dominant neonatal immune system. Since tendency to allergy development begin to manifest early in life, there has been apparent curiosity for the possible profits of adjusting the intestinal microbiota by using pre– and/or pro–biotics. Alteration of the intestinal micro flora by giving particular non–digestible carbohydrates/fibers has received a lot of interest since the introduction of the Prebiotics concept by Gibson in 1995 and Probiotics concept by the works of Metchnikoff and Tissier.

Probiotic is an oral supplement or a food product that contains a sufficient number of viable microorganisms to adapt the microbiota of the individual and has the potential for beneficial health effects. Even though the favorable effects of pre– and pro–biotics on various atopic diseases have been considered for a long time, little is identified about how pre– and pro–biotics modify the immune system and atopic disease development. In this first part of the article, our objective is to explain the possible mechanisms of pre– and pro–biotics' effects in the prevention and therapy of different allergic disease. The author thinks that better comprehension of the actions of various probiotic species on innate and adaptive immune system and further research in near future to understand into the etio–pathogenesis of the diverse manifestations of allergy are necessary for the confirmation of particular species having anti–allergic potential.

Keywords: prebiotics, probiotic, allergy, atopy

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Introduction

The prevalence of allergic diseases is increasing from the last half of XXth century. This increase is thought to be caused by different factors e.g. diet as well as decreased microbial exposure (hygiene hypothesis).[1] The infant's immune system is liable to develop a T–helper 2 (Th2) type response during early childhood. Thus, immature immune system should go through maturation by means of steady diminution of Th2 and mounting Th1 pathways. Immature Th2–pathway predominant infantile immune responses have to endure environment–driven maturation thru microbial exposure during postnatal episode to avert allergy development.[2,3]

Gastrointestinal microbiota contributes to microbial contact during infancy and is one of the most important stimulatory factors for immature Th2–dominant neonatal immune system. Since tendency to allergy development begin to manifest early in life, there has been apparent curiosity for the possible profits of adjusting the intestinal microbiota by using pre– and/or pro–biotics.[4] In this first part of the article, our objective is to explain the possible mechanisms of pre– and pro–biotics' effects in the prevention and therapy of different allergic diseases. In the second part of this article, the beneficial effects of pre– and pro–biotics in allergy will be told under the light of recent literature.

Definition of prebiotics

Alteration of the intestinal micro flora by giving particular non–digestible carbohydrates/fibers has received a lot of interest since the introduction of the prebiotic concept by Gibson in 1995.[5] Prebiotics are described as 'non–digestible food ingredient *(fermentable oligosaccharides)* that benefits the individual by selectively stimulating the favorable expansion and/or activity of one or more indigenous probiotics e.g. *Bifidobacterium* and *Lactobacillus* in the colon and thus improve individual's health'.[5,6]

Dietary prebiotics consist of mixture of short–chain galacto–oligosaccharides (scGOS) and long–chain fructo–oligosaccharides (lcFOS). The most extensively studied prebiotics are the fructans (inulin, FOS) and GOS which, owing to their chemical structure, are indigestible in the intestine and are fermented by anaerobic bacteria in the gut. For example, FOS, which are non–digestible polymers of fructose found naturally in artichokes, leeks, asparagus, onions and bananas, stimulate the growth of faecal Bifidobacteria in healthy human subjects.[6]

What are potential mechanisms of prebiotics' actions in the prevention/therapy of allergy?

Supplementation of GOS/FOS in infants causes stimulation of a Bifidogenic intestinal microflora; improved intestinal physiology, possibly less infections as well as allergy development.[7,8] Moreover, this fermentation of non–digestible dietary fiber/carbohydrate by the Bifidobacterium species causes the production of valuable fermentation metabolites such as short chain fatty acids (SCFA) e.g. acetate, proprionate and butyrate, which have immunomodulatory and anti–inflammatory characteristics.[9]

Furthermore the effects of SCFA are as follows: –

Acidification: Acidification of the gastrointestinal microenvironment which is damaging to certain pathogenic bacteria strains e.g. bacteroides, clostridia and coliforms.[10] Acidification also favors to increase mucin production. Consequently, mucin is to decrease pathogenic bacterial colonisation and translocation.[11]

SCFA receptors: Thru binding to SCFA receptors (G protein coupled receptors), the prebiotic may interact with receptors on immune cells in the gut–associated lymphoid tissues (GALT).[12] Butyrate, the principal fuel for colonic epithelial cells, decreases the requirement of glutamine for epithelial cells, thus sparing more glutamine for immune system cells in the body such as in GALT, thereby enhancing immune system reactivity.[13]

SCFA: Several studies showed that SCFA have direct immunomodulatory properties.[14] Butyrate may also modify epithelial cell gene expression, for example IL–8 and monocyte chemoattractant protein 1, and this in turn would change the signaling of the epithelial cell to the mucosal immune system.[15,16] SCFA cause an altered lymphocyte numbers in the spleen and intestinal mucosa in addition to cytokine formation.[17] They also can stimulate IFN–γ and IL–10 production.[18] The particular scGOS/lcFOS preparation decreased kappa and lambda immunoglobulin levels in plasma of infants at high risk for allergy development in contrast to infants receiving placebo formula.[19]

Galectin–9: Galectins, expressed by intestinal epithelial cells, are soluble–type lectins identifying β–galactoside including glycans over the cell surface. One of the galectins, galectin–9 was demonstrated to control mast cell degranulation as well as T–cell differentiation. In a study; after dietary supplementation with a mixture of scGOS/lcFOS and probiotic Bifidobacterium breve, serum galectin–9 levels were detected to be elevated in mice and humans. This increased level was consistent with lowered acute allergic skin reaction and mast cell degranulation. Additionally, this pre– and pro–biotic mixture was demonstrated to augment Th1– and Treg–cell differentiation in lymph nodes and in peripheral blood mononuclear cell cultures exposed to galectin–9.[20]

Briefly; concerning the immuno modulatory effect of prebiotics, hypothetical mechanisms of the effects are as follows: They are considered to boost the activity of lactic acid bacteria, e.g. Lactobacilli and Bifidobacteria, which have immuno modulatory capability. A second mechanism of effect is that fermentation of prebiotics by lactic acid bacteria augments SCFA production which performs as energy material for colon epithelial cells. SCFAs have also important positive impacts on intestinal epithelial cell function, including maintenance of metabolism, proliferation, differentiation and promotion a low pH of the gut environment, favoring beneficial microbes with a simultaneous decline in pathogenic bacterial growth.

Description of probiotics

Probiotic is an oral supplement or a food product that contains a sufficient number of viable microorganisms to adjust the microbiota of the individual and has the potential for beneficial health effects.[1,2] Therefore, probiotics are defined as 'live microorganisms that, when given in sufficient amounts, confer a health benefit on the individual.[21] Currently the most common probiotic foodstuffs contain Bifidobacteria and/or Lactobacilli, but also may contain other lactic acid bacteria such as lactococci and streptococci. The non–lactic acid probiotic bacteria group also includes Escherichia coli Nissle 1917, Bacillus coagulans and the yeast Saccharomyces (boulardii and cerevisiae).[22]

What are potential mechanisms of probiotics' actions in the prevention / therapy of allergy?

Even though the favorable effects of probiotics on various atopic diseases have been considered for a long time, little is identified about how probiotics modify the immune system and atopic disease development. These mechanisms of probiotics' effects in the prevention and therapy of atopic diseases have been recently explained by us in detail somewhere else.[1,2] Here, some major mechanisms are briefly mentioned.

Intestine–stabilizing effect (Intestinal Barrier Maturation): Besides affording maturational signals for the GALT, probiotics control the production of pro– and anti–inflammatory cytokines in the intestine. Probiotics can thwart the inflammatory progression by alleviating the intestinal microenvironment and the permeability barricade of the gut, and by augmenting the degradation of antigens/ allergens in gut and changing their immunogenicity.[23] This intestine–stabilizing effect was supposed to be elucidated by the enhancement by probiotics of the immunological barrier of the gut via intestinal IgA responses, particularly.[24]

Immune response modulation (Th1/Th2 Balance and Th17 Cell Suppression): Some lactic acid bacteria probiotics can alter the cytokine profiles released by peripheral blood mononuclear cells, and redirect the immune system in a regulatory or tolerant mode.[25,26] Although the cytokine production types of various probiotics differ, the lactic acid bacteria isolated from healthy individuals principally stimulate non–inflammatory cytokines.[27] Certain probiotic strains are recently demonstrated to decrease proinflammatory cytokines by the pathway of Th17 cell suppression.[28,29]

Local and systemic anti–inflammatory effects: The local and systemic anti–inflammatory effect of probiotics is ascribed to amplified secretion of IL–10 by immune cells in the gut and the spleen of tested animals. Furthermore, a decline in the production of pro–inflammatory cytokines e.g. IFN–γ, TNF–α and IL–12 was demonstrated.[30,31] Similarly, oral LGG supplementation caused high IL–10 levels in atopic children, suggesting that particular probiotics might have systemic anti–inflammatory effects and perhaps improve regulatory or tolerance–inducing actions as well.[32]

Immune system regulation (Tolerogenic Dendritic and Regulatory T (Treg) cell development): Some strains of the Bifidobacteria were demonstrated to induce in vitro cultured neonatal dendritic cells to drive T cell responses and might therefore be used as nominees in primary prevention and therapy of allergy. Specifically, Bifidobacterium bifidum was detected to be most effective polarizer in vitro–cultured dendritic cells to impel Th1–type responses including augmented IFN–γ releasing T–cells with concurrent attenuation of IL–4–secreting T–cells.[33] Lactobacillus reuteri and Lactobacillus casei were also demonstrated to induce DC –SIGN (CD209) in monocyte–derived dendritic cells to thrust the development of Tregs.[34] Recent research suggested that one of the actions of probiotics might involve stimulation of differentiation of IL–10–dependent, TGF–β–bearing Tregs.[35,36] Moreover, T–cells induced by Bifidobacterium bifidum may drive dendritic cells as generators of more IL–10.[37]

Modification of other lymphocyte subgroups: In a study, Gerasimov et al evaluated the clinical effect of probiotics Lactobacillus acidophilus and Bifidobacterium lactis with prebiotic FOS on lymphocyte subgroups in preschool children with moderate–to–severe eczema. This study showed that the percentage/absolute count of the $CD4^+$ and the CD25T cells decreased; and the percentage/absolute count of CD8 –T cells augmented in the prebiotic+probiotic group at

the 8th week, compared with control group.[38] In another study; CD57T cells was found to be augmented significantly in control subjects after probiotic administration and was not altered in patients with atopic dermatitis.[39] However, in majority of probiotic studies, lymphocyte subpopulations were not changed by the probiotic supplementation.

Pattern–recognition receptor (Toll–Like Receptor: TLR) stimulation: Certain lactic acid bacteria strains e.g. Bifidobacterium bifidum, Bifidobacterium infantis and Lactobacillus salivarius were detected to be capable of stimulating TLR–2.[40] Oral Lactobacillus reuteri supplementation diminished main specifics of an asthmatic reaction, involving respiratory tract eosinophilia, cytokine levels, and hyper reactivity to methacholine by the pathway of TLR–9.[41] The TLR–mediated actions of probiotics entail immunoregulatory cytokines e.g. IL–10 and TGF–β and diverse subgroups of Treg cells, particularly CD4CD25FoxP3 T cells for TLR–4 stimulators and NKT cells for TLR–3 stimulators.[28,42]

In brief, promising actions of probiotics on immune system are being classified as local and systemic effects. Local effects of probiotics probably include intestine–stabilizing effect and systemic tolerance induction. Systemic actions contain anti–inflammatory effects caused by Th17 cell suppression and systemic TLR stimulation, induction of Th1 type immune reactions to allergens, stimulation of tolerogenic dendritic cells, besides Treg cell production.[1,2]

Conclusion

Better comprehension of the actions of various probiotic species on immune system and further research to understand into the etio–pathogenesis of the diverse manifestations of allergy in near future are necessary for the confirmation of particular species having anti–allergic potential.

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