EFFECT OF PROBIOTICS ON ALLERGIC IMMUNOPROFILE

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Abstract: *Several experimental results have lead to the theory that the pathogenesis of allergic diseases is determined by an imbalance between Th1/Th2 immune responses. It has been founded a Th2 immune response in most of the allergic diseases, which are defined by high levels of interleukin 4 (IL-4). Most of the studies have shown that decreasing Th2 cells cytokines by growing Th1 responses may be a positive switch against Th2 diseases like asthma and allergy. There are some results that confirm that probiotics might have a beneficial effect against allergic diseases by reducing TH2 cytokine production. Consequently, probiotics could restore the host capacity to limit the response against aeroallergens and the development of allergy. The results are very promising, and there is some experimental evidence from animals and humans to suggest their effectiveness. Basic science studies on each probiotic strain that includes their effects on the immune system followed by systematic evaluation of the effects of the most promising strains in specific allergic diseases are required before we can draw any definite conclusions regarding their effectiveness.*

INTRODUCTION

The most common allergic diseases are represented by asthma, rhinitis, and allergy. This results from interaction between several genetic and environmental factors. An acute immediate hypersensitivity appears when allergens are inhaled because of an immune response based on a genetic predisposition (atopy). The inflammatory process may be classified into early- and late-phase reactions. The immediate response is generally mediated by mast cell degranulation and the late phase is followed by the migration of neutrophil, eosinophil and lymphocyte into the inflammatory site. Respiratory allergic diseases are usually characterized by: airway hyperresponsiveness (AHR); reversible airway obstruction and mucus hypersecretion: airway inflammation.(1)

Different experimental studies have supported the theory that the pathogenesis of allergic diseases is determined by misbalance between Th1/Th2 immune responses, with an exaggerated Th2 immune response, meaning increased levels of interleukin (IL) IL-4, IL-5, IL-9 and IL-13. IL-4 and its structural homologue, IL-13, are prominent cytokines in asthma not only on account of their proinflammatory role, but also due to their effects on mucus hypersecretion and airway wall remodelling, as revealed in transgenic animal models. Th2 cytokines lead to the selection and activation of many effector cells, like eosinophils and mast cells.(2) All these together are very important in the evolution of chronic allergic inflammatory diseases. IL-4 has high levels in the serum and bronchoalveolar lavage of allergic patients. Peripheral blood mononuclear cells from atopic asthmatics increase the production of IL-4 as response to dust mite antigen. In allergic inflammation IL-4 is related with production of IgE by B lymphocytes. IgE-mediated immune responses are consolidated by IL-4 response by its ability to regulate IgE receptors from the cell surface.(3) An auxiliary mechanism by which IL-4 participate to airway obstruction in asthma is the influence of mucin gene expression and the hypersecretion of mucus. The expression of eotaxin is increased by IL4 and several inflammatory cytokines from fibroblasts that might participate to inflammation and lung remodelling in chronic asthma. An important biological activity of IL-4 in the evolution of allergic inflammation is the capacity to determine the differentiation of naive T helper type 0 (TH0) lymphocytes into TH2 lymphocytes. Although these TH2 cells are producing IL-4 (in a positive feedback loop), IL-5, IL-9 and IL-13, they are losing the ability to produce interferon- gamma. We can say that a unique biological activity of IL-4 is the induction of TH2 lymphocytes because IL-4 receptors and not IL-13 receptors are expressed on T cells.(3) It has been studied that Th1 lymphocytes and cytokines such as Interferon-gamma (IFN-γ) and IL-12 may suppress and counter Th2 responses of allergic diseases. Recent studies have shown that changing cytokine producing profile of Th2 cells by increasing Th1 responses may be a protection against Th2-related diseases like asthma and allergy. IFN-γ, the most important Th1 effector cytokine, has been demonstrated to be very important for the determination of allergic-related cronic diseases.(4) In fact, low IFN-gamma production lead to the evolution of allergic diseases, and individuals with chronic asthma have very reduced IFN-gamma production in response to allergen when compared to control patients.(5) IFN-γ has the power to participate in a several number of cell types that are implicated in Th differentiation. It determines IL-12 production by antigen presenting cells (APC), such as dendritic cells and macrophages.(6) IFN-γ also executes direct inhibitory effects on Th2 cytokines, decreasing the levels of IL-4 and IL-5

The suppressive effects of IFN-gamma on allergic disorders have been shown to be mediated by several mechanisms, such as: regulation of allergen presentation to T lymphocytes, differentiation of naive T cells toward Th1 phenotype and/or inhibition of Th2 cell recruitment/differentiation; suppression of Th2 cytokine release from activated T cells; inhibition of effector cell recruitment to the site of inflammation; induction of apoptosis in T cells and eosinophils; blockage of IgE isotype switch in B cells; induction of nitric oxide (NO) production.(7)

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In recent years, more attention has been given to the intestinal microbiota and its influence on sensitization and the origins of allergic disease, as it may modulate immunologic and inflammatory systemic responses. The intestinal microbiota hypothesis has been proposed to explain the rising incidence of allergic disorders. Probiotics are living microorganisms that when administered to humans in certain doses may confer a health benefit. They have been proposed as immune-modulators of the allergic response by affecting phagocytosis and production of pro-inflammatory cytokines, and thus are being advocated as therapeutic and preventive interventions for allergic diseases. Based on findings that exposure to microbial flora early in life can change the Th1/Th2 balance, thus favoring a Th1 cell response, probiotics may be beneficial in preventing allergic diseases. Probiotics inhibit allergic diseases by suppressing the Th2 response. Interleukin IL-4, IL-5, and IL-13 are representative cytokines released by Th2 cells that are suppressed by probiotics

Experiments carried out in mice sensitized to ovalbumin have clearly indicated that after gastric administration of lactic acid bacteria (LAB) species, the specific IgE and TH2 profile–dependent inflammatory responses were inhibited. Moreover, recent reports suggest that Lactobacillus rhamnosus GG can reduce allergic disease symptoms in human subjects. The administration of this strain to breast-feeding mothers and to newborn babies led to a high inhibition (50%) of the risk of atopic eczema in babies. Recent in vitro experiments demonstrated that the stimulation of PBMCs or monocytes from healthy donors by a variety of LAB species enhanced the secretion of IL-12, which is a pivotal pro-TH1 cytokine involved in the control of allergic disease development.(8)

Determination of cytokine profiles (“immunoprofiles”) induced by probiotics in human peripheral blood mononuclear cells (PBMC) or dendritic cells (DC) has been applied in several studies for the characterization of probiotics. Notably, a strain of Lactobacillus paracasei selected on the basis of its ability to induce IL-12 and inhibit IL-4 secretion in an experimental model showed a benefit in a subsequent clinical trial in humans suffering from allergic rhinitis. Alternatively, researchers recently showed that co-culture of specific probiotic strains with PBMC from human allergic donors decreased IL-13 production along with strain-specific effects on induction of Th1 cytokines and cell surface markers. Different studies have shown that Th2 response in allergic individuals is inhibited by the lactobacilli L. plantarum, L. lactis, L. casei and L. rhamnosus GG. These strains reduce IL-4 and IL-5 production by PMBC when human cells are preincubated with lactobacilli before the stimulation with specific allergens. For this mechanism is required the presence of monocytes and is dependent on Th1 cytokines (IL-12, IFN-γ).(9) Using a food allergy model to study Th2 response in mice, Shida et al. reveal that peritoneal injection of heat-killed L. casei Shirota determine an increase in serum IL-12 and a switch in the cytokine profile from Th2 to Th1 (less IL-4 and IL-5 and more IFN-g This lead to lower secretions of IgE and IgG1 antibodies by splenocytes, preventing systemic anaphylactic reaction.(10) A double-blind clinical study in children who were allergic to cow’s milk also showed that the administration of L. rhamnosus GG for four weeks increased IFN-γ production in PBMCs after stimulation with anti- CD3/anti-CD28. At the same time, it suppressed secretion of IL-4, normally produced in large quantities after stimulation of the CD4+ T cells in allergic children.(11) In a recent study, it was showed that Lactobacillus rhamnosus ATCC 7469 strain can modulate the Th1/Th2 balance by reducing TH2 cytokine (IL4) release and enhancing TH1 cytokine production (IFN gamma), so different strains of probiotics could be promising line of treatment for allergy.

Probiotics play an important role in modulating the immune system by an anti-inflammatory action, all the results depending on strain, the immunological parameters measured, and the type of cells involved.

CONCLUSIONS

The precise mechanisms behind the favourable effects of probiotics on allergy are not entirely known. Several mechanisms have been observed in vitro and in animal studies. In addition to modulation of the intestinal microbiota, probiotics have been observed to improve the barrier function of the intestinal mucosa, reducing leakage of antigens through the mucosa and thereby exposure to them. Direct modulation of the immune system may be through the induction of antiinflammatory cytokines. The intestinal microbiota participates in the development of the postnatal immune system such as oral tolerance and immunity. The interaction of probiotics and enterocytes is the key to the initiation of immunomodulation. Allergy was recently described as being the result of a deficit of bacterial stimulation during childhood.

These results confirm and extend previous observations that probiotics might have a beneficial effect against allergic diseases by reducing TH2 cytokine production. Consequently, probiotics could restore the host capacity to limit the response against aeroallergens and the development of allergy.

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