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Review Article

Can probiotics be used to treat allergic diseases?

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Abstract

Probiotics are proprietary formulations of specific microorganisms and quantified populations of live bacteria that are intended to confer a health benefit on the host. These different strains and combinations of microorganisms have a wide and varying range of clinical and immunologic capacities that can modify intestinal microbial populations in ways that can benefit the host. The enhanced presence of probiotic bacteria in the intestinal microbiota has been found to correlate with protection against atopy. The prevalence of allergic diseases such as asthma, allergic rhinitis, and atopic dermatitis has increased sharply over the past 2–3 decades in many countries, and allergies are now the most common chronic disease among children throughout the world. In the past few years, probiotics have been advocated for the management of allergic diseases in many parts of the world. So far, probiotics have shown more promise, albeit limited, in the primary prevention of allergic disease rather than in the treatment of established disease.

Keywords: allergic diseases; allergic rhinitis; asthma; atopic dermatitis; probiotics

1. Introduction

The rapid increase in immune-mediated disorders such as allergic disease is strongly linked to reduced early microbial exposure.[1,2] The intestine is the body's largest immune organ; most of the antibody-producing cells reside in the intestine.[3] The intestinal microbiota represents the body's greatest microbial exposure by a substantial extent, and in part works to provide stimulation of the immune system. The specific composition of the intestinal microbiota may affect the risk of developing allergic disease.[4–6] This finding provided the foundation for intervention studies designed to modify gut microbial composition for the treatment of allergic disease. The effects of beneficial bacteria (probiotics) or resistant starches or fiber (prebiotics) that selectively stimulate a limited number of beneficial bacteria have been evaluated in allergy treatment studies.[7,8] Several reviews have examined the evidence for prebiotics and probiotics in the treatment of allergic disease. However, in the current era of evidence-based medicine, there remains insufficient evidence to formally recommend probiotics for the prevention of allergic diseases or as part of the standard management for any allergic conditions in children.[9]

2. Terminology

An allergy is a hypersensitivity reaction initiated by immunological mechanisms. Such allergies are generally broken down into two groups: an antibody-mediated allergy or a cell-mediated allergy. Hypersensitivity causes objectively reproducible symptoms or signs, initiated by exposure to a defined stimulus at a dose tolerated by healthy individuals.

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Allergens are antigens that cause allergy.[10] These allergens can make contact with the immune system through various routes such as inhalation, ingestion, and skin contact, or enter directly into the body through an insect bite.[11] Atopy is a personal or familial tendency, usually in childhood or adolescence, to produce immunoglobulin E (IgE) antibodies in response to ordinary exposure to allergens (usually proteins) and to develop typical symptoms such as asthma, rhinoconjunctivitis, and eczema/dermatitis. However, not all cases are attributable to IgE mechanisms.[10,12,13] The mechanisms leading to the increased incidence of allergic diseases are not fully understood but are known to involve genetic factors as well as complex interactions between the host and allergen exposure—as well as other environmental stimuli such as the intestinal microbiota and infectious agents.[14–17]

3. The intestinal immune system

In the healthy gut, the immune system is able to create a balance between the level of protective mucosal immunity and systemic tolerance. Immune homeostasis in the gut develops as a relationship is established between the intestinal microbiota, luminal antigens, and the epithelial barrier.[18] Microbial colonization of the intestine begins after birth, where the sterile gut of the newborn is gradually colonized by environmental bacteria and by contact with the maternal intestinal flora and surroundings and possibly by genetic factors.[19,20] Exposure to microbial flora early in life allows for a change in the T helper 1 (Th1)/Th2 cytokine balance, favoring a Th1 cell response.[21] At birth, the immune system of an infant is not fully developed and tends to be directed toward a Th2 phenotype to prevent rejection *in utero*. The Th2 phenotype, however, leads to the stimulated production of IgE by B cells and thus increases the risk for allergic reactions through the activation of mast cells. Microbial stimulation early in life will reverse the Th2 bias and stimulate the development of Th1 phenotype and stimulate the activity of Th3 cells.[22] In this manner, their combined action will lead to the production of IgA by B cells. IgA contributes to allergen exclusion and will thereby reduce exposure of the immune system to antigens. Cytokines produced by the Th1 phenotype will also reduce inflammation and stimulate tolerance toward common antigens.[23]

4. Mechanisms of action of probiotics in allergic disorders

Although the exact etiology of allergic diseases remains ambiguous, the mechanisms by which microbial exposure affects the development and severity of allergic disease needs to be better understood. The hygiene hypothesis suggests that insufficient or aberrant exposure to environmental microbes is one of the causes of the development of allergy and their associated diseases.[24–26] As described above, allergic disorders are associated with a shift of the Th1/Th2 cytokine balance leading to activation of Th2 cytokines and the release of interleukin-4 (IL-4), IL-5, and IL-13 as well as IgE production.[21,27] Probiotics administration dramatically alters the gut microenvironment by promoting a change in the local microflora and in cytokine secretion, and can potentially modulate the Toll-like receptors and the proteoglycan recognition proteins of enterocytes, leading to the activation of dendritic cells and a Th1 response. The resulting stimulation of Th1 cytokines can suppress Th2 responses.[28] Other effects of probiotics that make them suitable for modulation of allergic disease include stimulation of mucosal IgA level as well as allergen-specific B and T cell responses.[29] Recent studies suggest that the bacterial–host interaction may induce the expansion of T regulatory cells and the expression of immunomodulatory cytokines such as IL-10 and transforming growth factor-beta; these interactions are very complex and involve networks of genes, Toll-like receptors, signaling molecules, an enhanced intestinal IgA response, and the mechanisms by which probiotics affect innate and adaptive immune responses and patterns of disease.[30–32]

5. Probiotic strains and effects

Probiotic microorganisms are generally lactic acid bacteria including *Lactobacillus acidophilus*, *Lactobacillus bulgaricus*, *Lactobacillus casei*, *Lactobacillus plantarum*, and *Lactobacillus rhamnosus.* The *Lactobacillus* species possess several important properties such as efficient adherence to intestinal epithelial cells to reduce or prevent colonization of pathogens, competitive growth, and production of metabolites to inhibit or kill pathogens and nonpathogens.[33] However, other bacterial species such as *Bacillus*, *Bifidobacterium* spp., and *Propionibacterium* spp. as probiotic strains have also been described in several commercial products.[34] The potential use of *L. casei* strain Shirota has also been described as a probiotic agent for stimulating immune responses and preventing enterobacterial infections,[35] and *Lactobacillus* GG is likewise used as an effective oral vaccine for rotaviruses.[36] Before the use of a probiotic is considered for hospitalized patients, a careful assessment of risk versus benefit must be made. Additionally, to ensure patient safety, probiotics should be properly handled during administration.[37]

6. Probiotics' role in allergic disorders

6.1. Probiotics in atopic dermatitis

Numerous animal and *in vitro* studies, as well as several human trials, suggest a beneficial effect of probiotics in allergic diseases. Several randomized studies demonstrated that when *Lactobacillus* GG or placebo was given to pregnant mothers with a strong family history of eczema, allergic rhinitis, or asthma and to their infants for the first 6 months after delivery, the frequency of developing atopic dermatitis in the offspring was reduced in 2 years, 4 years, and 7 years by 50%, 44%, and 36%, respectively.[38,39] However, after Lee et al[40] searched PubMed and the Cochrane database in 21 trials for review and quality assessment of probiotics in the prevention and treatment of pediatric atopic dermatitis, current evidence suggested that probiotics had a superior efficacy in