

Probiotics and Lung Immune Responses

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Abstract

There is increasing interest in the potential for microbe-based therapeutic approaches to asthma and respiratory infection. However, to date, clinical trials of probiotics in the treatment of respiratory disease have met with limited success. It is becoming clear that to identify the true therapeutic potential of microbes we must move away from a purely empirical approach to clinical trials and adopt knowledge-based selection of candidate probiotics strains, dose, and means of administration. Animal models have played a key role in the identification of mechanisms underlying the immunomodulatory capacity of specific bacteria.

Microbe-induced changes in dendritic cell phenotype and function appear key to orchestrating the multiple pathways, involving *inter alia*, T cells, natural killer cells, and alveolar macrophages, associated with the protective effect of probiotics. Moving forward, the development of knowledge-based strategies for microbe-based therapeutics in respiratory disease will be aided by greater understanding of how specific bacterial structural motifs activate unique combinations of pattern recognition receptors on dendritic cells and thus direct desired immune responses.

Keywords: beneficial microbes; airway; allergy; respiratory infection

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Probiotics and Allergic Airway Inflammation

Probiotics are defined as live microorganisms that, when administered in adequate amounts, confer a health benefit on the host (1). Organisms investigated for potential beneficial effects are most frequently *Lactobacillus* or *Bifidobacterium* species. However, additional types of bacteria, including nonpathogenic forms of *Escherichia coli* and *Bacteroides*, as well as certain yeasts, such as *Saccharomyces*, have been suggested to have probiotic potential. Although organisms must be viable to meet the definition of probiotic, there is evidence that killed organisms, and even components of bacteria, can mimic certain potentially beneficial effects of candidate probiotics on host biology.

In recent years, evidence has emerged suggesting that microbial exposure, either naturally in the environment or through dietary supplementation in the form of

probiotics, may protect against and/or reduce the severity of allergic disease. For example, there is evidence that the protective effect of the farming environment on development of atopic sensitization, hay fever, and asthma is related to the wider range of microbial exposures in children living on farms compared with urban-dwelling peers (2). This is supported by animal studies demonstrating that specific bacteria that are abundant in cowsheds, *Acinetobacter lwoffii* F78 and *Lactococcus lactis* G121, can attenuate allergic responses in mice (3).

Significant attention has been given to clinical investigations of early-life probiotic treatment and the prevention of allergic disease development, with mixed results (4). However, there have been a limited number of clinical trials addressing the therapeutic potential of probiotics in subjects with asthma (5). In those trials that have been conducted, none have demonstrated significant effects of probiotic

administration on asthma-related outcomes. Therefore, there is currently no evidence to recommend probiotics as therapy or adjuvant treatment in asthma. However, a problem with existing clinical trials of probiotic therapy in asthma, and with many probiotic trials in general, is a lack of strong scientific rationale for the selection of the candidate probiotic organism, the dose given, or how the organism is administered. To maximize the chance of success in future clinical trials, we need to better understand how certain organisms can influence lung immune responses. To this end, preclinical studies in animal models can play an important role in allowing us to identify the mechanisms that underlie the ability of certain bacteria to modulate immune responses in the airway.

To date, animal models have provided strong evidence indicating that oral administration of a number of different microbes can attenuate allergen-induced

allergic airway response in adult mice (6–10).

It is clear, however, that the finding that oral administration of a particular microbe can modulate lung immune responses does not mean that other members of that genus, or even species, will have similar effects. Immunomodulatory activity may depend on strain-specific properties. The mechanisms underlying the capacity of bacteria in the intestine to modulate immune responses at distant tissues sites, including the airway, are unknown but likely rely on the existence of what has been termed the common mucosal immune system.

The Common Mucosal Immune System

The concept of the common mucosal immune system holds that activated lymphocytes are able to migrate from one mucosal site to another. This system has been well assessed in animals, with demonstrations of repopulation of gut and lung with IgA-containing cells after transfer of lymphocytes either from bronchus-associated lymphoid tissue, Peyer patches, or mesenteric lymph nodes (MLN) (11). The MLN are central in regulating the common mucosal immune system, having a critical role in induction of tolerance/immunity and gating of communication between the gut mucosa and systemic immunity (12). Although commensal or probiotic bacteria can be carried to the MLN by intestinal dendritic cells (DC), commensal/probiotic-associated DC do not enter the thoracic duct lymph or reach the systemic circulation. Therefore, the influence of microbe-associated DC on the immune environment in the MLN, particularly on the development of T cells and B cells that can enter systemic circulation, is likely central to the ability of probiotic organisms to attenuate allergic inflammation throughout the body. Early indications that beneficial microbes could stimulate the common mucosal immune system were provided by Perdigon and colleagues (13), demonstrating that, in mice, oral administration of a number of lactic acid bacteria lead to a dose-dependent increase in IgA⁺ cells in both the intestine and the bronchus-associated lymphoid tissue. Recent studies (14) have identified that feeding mice with *Lactobacillus*

rhamnosus JB-1 induces significant changes in the immune environment of the MLN, decreasing proinflammatory cytokine production and, perhaps most critically, increasing the numbers of T-regulatory cells (Treg). It is suggested that the altered immune environment, after exposure to the bacteria, influences the response to subsequent antigen challenge at mucosal sites, including the airway.

Regulatory T Cells

Diverse populations of Treg cells play an important role in regulating Th2 responses to allergen and maintaining functional tolerance (15). Indeed, the resolution of Der p1-induced allergic inflammation in mice is dependent on CD4⁺CD25⁺Foxp3⁺ regulatory cell recruitment to the lungs (16).

There is now strong evidence linking the immunomodulatory function of certain commensal bacteria, and components thereof, to induction of Treg cells and their associated cytokines (7, 17, 18). Mazmanian and colleagues demonstrated that oral ingestion of polysaccharide A (PSA) derived from *Bacteroides fragilis* protects animals from experimental colitis through induction of IL-10-producing CD4⁺ T cells (19), and DC cocultured with PSA promoted the generation of an IL-10-producing Treg cell population when incubated with naive T cells. Attenuation of the allergic airway response after oral *L. rhamnosus* JB-1 treatment in mice is associated with a significant increase in the proportion of functional CD4⁺CD25⁺Foxp3⁺ regulatory cells in the spleen and mediastinal lymph node (7). Similarly, MacSharry and colleagues (9) demonstrated increased lung Foxp3⁺ T cells and decreased inflammation after antigen challenge in mice treated with a *Bifidobacterium longum* strain. A causal relationship between microbe-induced Treg cell activation and reduced airway inflammation is suggested by a number of studies. Lyons and colleagues (8) tested a range of candidate probiotics for the ability to inhibit allergic airway inflammation. The capacity to attenuate the allergic airway response was restricted to the only strain that induced an increase in circulating Foxp3⁺ Treg cells. It also clear that probiotic-induced Treg cells have the capacity to reduce airway inflammation, as demonstrated by the ability of

CD4⁺CD25⁺ cells adoptively transferred from *L. rhamnosus* JB-1-fed nonsensitized mice to reduce the airway inflammation in ovalbumin-sensitized animals (7). More recently, it has been demonstrated that depletion of Treg cell using anti-CD25 antibodies can prevent *L. rhamnosus*-induced down-regulation of the allergic airway response in mice (10).

Probiotics appear to induce a regulatory response that does not require prior exposure of Treg cells to a specific allergen (7). Once activated, Treg cells can suppress effector T cells in an antigen-nonspecific way called “bystander suppression” (15), and *in vivo* transfer studies demonstrate that Treg cells can create a regulatory milieu that promotes the outgrowth of new populations of Treg cells with antigen specificities distinct from those of the original population (15). In this way, certain lactic acid bacteria (LAB) may induce Treg cells in the gut-associated lymphoid tissue that can spread to the airways in response to immune challenge and inflammation.

Dendritic Cells

DC are antigen-presenting cells that play a decisive role in determining immunity or immune tolerance; this determination is based on the maturation or activation state, the subset of DC, and the microenvironment at the time of antigen uptake (20). DC are among the first immune cells to encounter bacteria in the intestine and can directly present antigens from commensals to the MLN (21). DC can ingest and retain small numbers of live commensal bacteria for several days (21). This ingestion of commensal bacteria induces a tolerogenic phenotype, so that the DC's interaction with T and B cells promotes and maintains a noninflammatory immune response through mechanisms that include direct suppression and deletion of T cells and the induction of a range of Treg cell subtypes. Thus, although Treg cells may be major effectors of immune regulation mediated by some microbes, the phenotypic changes in DC following interaction with bacteria are likely to be critical in orchestrating these immune responses. Microbes have diverse influences on DC phenotype and function. Certain bacteria are immunostimulatory, whereas others induce tolerogenic responses. To date, little

is known regarding what determines the influence of a particular bacterial strain on DC function, but it is likely the result of distinct combinations of receptor-mediated cell-signaling pathways activated by specific patterns or mosaics of microbe-associated ligands.

It is an attractive concept that by using microbial-based treatment to control the maturation of DC, the outcome of an immune response can be modulated. Kwon and colleagues (22) identified that regulatory DC expressing high levels of IL-10, transforming growth factor- β , COX-2, and indoleamine 2,3-dioxygenase (IDO) drive the generation of CD4⁺Foxp3⁺ Treg cells after administration of a mixed-strain probiotic preparation in mice. The enzyme IDO is the rate-limiting step in the conversion of tryptophan to immunoactive kynurenines. DC expressing IDO contribute to the generation and maintenance of peripheral tolerance by depleting autoreactive T cells and by inducing Treg cell responses (23). Overall, it appears that the ability of certain microbes to promote IDO activity, in addition to IL-10 expression by DC, may be important in the generation of a regulatory immune response and the establishment of a tolerance. Perhaps significantly, the maintenance of a clinically unresponsive state after aeroallergen exposure in atopic individuals has been associated with increased IDO activity and IL-10 production (24). However, it is clear that multiple immunoregulatory components contribute to the tolerogenic capacity of DC after exposure to microbes. Recently, it was demonstrated that feeding *L. rhamnosus* JB-1 to mice leads to an increase in regulatory/tolerogenic phenotype and function of DC in the MLN (14). In this case, the increased capacity of *L. rhamnosus* exposed DC to drive Treg cell formation appeared to be dependent on bacteria-induced expression of the immunomodulatory enzyme heme oxygenase 1 (14).

Heme oxygenase is the rate-limiting enzyme for heme metabolism and catalyzes heme to biliverdin, carbon monoxide (CO), and free iron (Fe²⁺). There are three known isoforms, the inducible HO-1, constitutive HO-2, and the relatively newly discovered isoform HO-3. It has been identified that the inducible isoform, HO-1, is involved in immune regulation. Overexpression of HO-1 in DC

leads to increased secretion of IL-10 and reduced capacity of the cells to trigger effector immune responses (25). George and colleagues identified that HO-1 expression by antigen-presenting cells is required for the function of CD4⁺CD25⁺ Treg cells (26). In several allergy models, HO-1 is found to reduce local inflammatory cell infiltration, suppress inflammatory cytokines, and enhance IL-10 expression (27). HO-1 has been demonstrated to attenuate ovalbumin-induced allergic airway inflammation through up-regulation of Foxp3⁺ Treg cells (27). In recent studies, it was demonstrated that feeding mice with *L. rhamnosus* led to increased HO-1 expression by DC in the MLN, and this effect was mimicked by direct *in vitro* exposure of bone marrow-derived DC to the bacteria (14). The observed increase in HO-1 expression occurred almost exclusively in those DC shown to be associated with JB-1 or components of the bacteria, suggesting that direct interaction of the bacteria and DC is required to mediate the phenotypic and functional changes. Furthermore, pharmacological inhibition of HO-1 prevented the *L. rhamnosus*-induced increase of Foxp3⁺ T cells in the MLN of mice (14).

The mechanism of action of HO-1 in inducing Treg cells is unknown but likely involves heme degradation products acting individually or in combination. CO promotes the development of tolerogenic DC as well as directly inhibiting T-cell proliferation (28), whereas ferritin, produced in response to free Fe²⁺, induces CD4⁺ Treg cells (29). Furthermore, there is a functional relationship between HO-1 and IDO. One of the products of tryptophan metabolism by IDO, 3-hydroxyanthranilic acid, can enhance HO-1 expression leading to CO production that in turn increases IDO expression and activity (30). The breaking system for this auto-amplifying loop is likely HO-1-driven starvation of available heme, essential for the catalytic activity of IDO. A positive feedback loop has also been described between HO-1 and IL-10 expression in DC (31). Thus, the functional relationship between HO-1, IDO, and IL-10 may be key in establishing the immunoregulatory response observed after exposure to specific microbes.

Probiotics and Lung Infection

The need for new and improved strategies to tackle infectious disease has led to an examination of the therapeutic potential probiotic-induced modulation of the mucosal immune response. Evidence from clinical studies suggests that certain microbes may decrease the incidence of bacterial and viral respiratory infections, whereas there is stronger evidence that probiotic treatment can reduce the severity of duration of infections in human subjects (32). Certainly the clinical evidence supporting the use of probiotics in protecting against respiratory viruses is much better than for therapy in allergy and asthma. Consequently, it has been suggested that the focus of probiotic therapy in asthma should be directed at identifying organisms capable of reducing viral infections that may contribute to development or exacerbation of the disease.

Animal studies clearly demonstrate that certain lactobacillus and bifidobacteria strains can significantly reduce infection with respiratory pathogens. This protective effect of probiotics is generally associated with up-regulation of alveolar macrophage and/or natural killer (NK) cell activity in the airway mucosa (33–35).

Alveolar macrophages provide the first line of defense against organisms that reach the lower airways. The ability of orally administered *Lactobacillus casei* to dose-dependently enhance the phagocytic activity of alveolar macrophages (36) likely contributes to the accelerated recovery of the innate immune response and improved outcomes after *Streptococcus pneumoniae* respiratory infection in malnourished mice and in young mice infected with *Pseudomonas aeruginosa*.

NK cells are the main components of host-nonspecific cell-mediated immunity, recognizing and helping to control a wide range of pathogens, including viruses, bacteria, and intercellular parasites. Koizumi and colleagues (37) demonstrated that feeding mice with *Lactobacillus pentosus* significantly enhanced NK activity of spleen cells and induced NK1.1-positive NK and NK T cells to produce IFN- γ . The increase in IFN- γ production did not occur through direct action of *L. pentosus* on NK cells but was dependent on IL-12 produced by CD11c⁺ DC after a toll-like receptor (TLR) 2- and/or TLR4-dependent

interaction between the DC and the bacteria. Fink and colleagues (38) also provided evidence that specific lactic acid bacteria inducing high levels of IL-12 in DC promote amplification of a type 1 response via potent stimulation of IFN- γ production in NK cells. Significantly, combining IFN- γ -inducing and noninducing LAB completely abrogates DC-mediated IFN- γ production by NK cells. Such findings provide a note of caution that the effects of mixed-strain probiotic preparations may not be the sum of the parts.

Probiotic–Host Interactions

It is likely that the antiinflammatory efficacy of a bacterial strain results from a combination of signaling pathways activated as a result of a specific pattern of microbe-derived ligands interacting with the corresponding pattern recognition receptors on host cells. Little is known, however, concerning the nature of the microbe–host cell interactions or how these interactions could be manipulated to obtain stronger regulatory responses.

Bacterial components such as capsular polysaccharides, lipopolysaccharide, lipopeptides, and the CpG motif of bacterial DNA act as ligands for TLR and other pattern recognition receptors such as nucleotide-binding oligomerization domain containing proteins and lectins. The specific array of motifs expressed by a particular organism likely results in distinct immunological responses by activating unique patterns of receptor signaling.

Although it is likely that the immune response to probiotic bacteria results from the combined action of numerous signaling pathways, there is evidence that single isolated components can mimic the beneficial effects of whole organisms (19). Grangette and colleagues (39) demonstrated that a mutant strain of *Lactobacillus plantarum* (Dlt[−]) that incorporates much less D-alanine in its teichoic acids had a dramatically reduced ability to induce secretion of proinflammatory cytokines from peripheral blood mononuclear cells while significantly increasing IL-10 production. These studies highlight the fact that microbe-associated membrane patterns

are not generic, and investigations of their immunoregulatory effects must use components isolated from the specific strain of interest.

Conclusions

To date, clinical trials of microbe-based treatments for allergic disease have used a largely empirical approach leading, perhaps not surprisingly, to mixed results at best (5). Determining the immune pathways and bacterial characteristics critical to the beneficial effects of microbial exposure in respiratory infection and allergic inflammation will allow for the development of knowledge-based strategies that can be applied to clinical testing. This will include informed selection of potential immunomodulatory bacteria or microbe-derived compounds as well as identification of potential early biomarkers of treatment efficacy that could be assessed in small numbers of subjects before launching large-scale trials. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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