Cross-Talk between Probiotic Bacteria and the Host Immune System\textsuperscript{1,2}

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Abstract

Among the numerous purported health benefits attributed to probiotic bacteria, their capacity to interact with the immune system of the host is now supported by an increasing number of in vitro and in vivo experiments. In addition to these, a few well-controlled human intervention trials aimed at preventing chronic immune dysregulation have been reported. Even though the precise molecular mechanisms governing the cross-talk between these beneficial bacteria and the intestinal ecosystem remain to be discovered, a new and fascinating phase of research has been initiated in this area as demonstrated by a series of recent articles. This article summarizes the status and latest progress of the field in selected areas and aims at identifying key questions that remain to be addressed, especially concerning the translocation of ingested bacteria, the identification of major immunomodulatory compounds of probiotics, and specific aspects of the host-microbe cross-talk. The interaction with immunocompetent cells and the role of secretory IgA in gut homeostasis are also evoked. Finally, a brief overview is provided on the potential use of recombinant DNA technology to enhance the health benefits of probiotic strains and to unravel specific mechanisms of the host-microbe interaction. J. Nutr. 137: 781S–790S, 2007.

Modulation of host immunity is one of the most commonly purported benefits of the consumption of probiotics. Increasingly growing, but still limited, clinical evidence exists to support this concept. Nevertheless, general claims regarding probiotic modulation of host immunity overstate our current knowledge of both the fate of ingested probiotic products and their specific effects on molecular and cellular components of the immune system, even though progress has recently been made in analyzing possible mechanisms involved in host-microbe interactions. The direct antagonism toward infectious organisms by probiotics, although a clearly important application, is generally not featured in this article and has been reviewed recently (1–5). This article summarizes the status of the field in selected areas referring to specific examples. It aims at identifying the major gaps that remain in our knowledge and outlines possible avenues to fill those gaps rather than reviewing the abundant literature in this research area. Complementary information can be found in a number of recent reviews (6–9).

Fate of ingested bacteria in the gastrointestinal tract

It is commonly suggested that probiotics must “persist and multiply” in the target ecosystem to be effective. However, the interaction of orally ingested probiotics with the intestinal epithelium or other immunologically active intestinal cells has just begun to be rigorously studied. A number of studies with a variety of probiotic strains have been conducted to determine the extent to which probiotics “colonize” or, more correctly, transiently persist in the intestine. The combined results demonstrate conclusively that ingested strains do not become established members of the normal microbiota but persist only during periods of dosing or for relative short periods thereafter (10–14). There is also evidence that common probiotic strains differ in their degree of persistence (10,15). This may reflect in part their capacity to resist the harsh conditions encountered in the upper digestive tract.

Presumably, to modulate immunity, probiotic organisms must “talk” to immune cells that are endowed with recognition receptors or that are otherwise sensitive to probiotic-derived products (e.g., metabolites, cell wall components, DNA) (Fig. 1). There is no a priori reason that introduced strains would need persist and multiply to encounter intestinal immune cells. In fact, general acceptance that “colonization or persistence” is required.
for probiotics to be efficacious typically illustrates that perceived benefits of probiotics are often ill-defined. The field instead needs to consider specific immunological applications, whether prophylactic or therapeutic, and then proceed to address mechanisms by which ingested probiotic organisms might be used to prevent or treat enteric disorders. Such studies will require the formulation of detailed hypotheses regarding the way orally ingested probiotics interact with specific types of host immune cells.

Given the diversity of inflammatory or immune responses that can be mounted by the intestinal epithelium, association of probiotics with epithelial cells might be sufficient to trigger signaling cascades that ultimately activate underlying immune cells in the lamina propria. Alternatively, probiotics may also release soluble factors that themselves trigger signaling cascades at the level of the epithelium or associated immune system (16–18) (Fig. 1).

Certainly much attention has been given to the adhesive properties of probiotic organisms, and ability to adhere to host cells or mucus is commonly considered to be a requirement for probiotics. However our perceptions about probiotic adhesion, especially to epithelial cells, have been derived almost entirely from in vitro studies, which very partially mimic the complexity of the intestinal ecosystem. Our knowledge of the mucus gel and its importance as a defensive entity is significantly limited because conventional fixation of intestinal tissues (with aldehyde fixative) results in detachment and loss of surface mucus. The significance of this experimental limitation was demonstrated by Matsuo and coworkers (19), who used Carnoy’s solution (ethanol- and acetic acid-based) to guarantee the preservation of surface mucus in paraffin sections of human colon samples.

Bacteria were observed within laminated arrays of sialo- and sulfomucins in an outer layer, indicating the importance of the mucus gel in preventing direct adherence of gut bacteria to the epithelial surface. This raises the question of the importance of epithelial adhesion and the physiological significance of in vitro systems often based on epithelial cell lines that do not produce mucus. However, these simplified systems are useful and important tools to identify possible signaling pathways and molecular markers, which could be studied further in animal models or human intervention trials. Certainly much additional work is needed to determine whether certain strains are able to reach and adhere to the epithelium in vivo, eventually forming a biofilm, as well as to identify the physiological consequences of such action. These questions might best be addressed with recombinant or mutated probiotic strains overexpressing or lacking genes that encode putative adhesion factors or with specific transgenic knockout mouse strains.

Nonetheless, a large number of in vitro studies have been reported that examined epithelial cell responses to adherent probiotic strains. Initially, these studies demonstrated the ability of probiotic strains to regulate the secretion of a variety of cytokines and pro- or anti-inflammatory molecules, especially in cocultures of intestinal cell lines and immune cells (20–22). Refinement of analytical methods has led to the identification of cell signal transduction proteins specific for gram-positive probiotic strains as compared with pathogenic bacteria (23,24). Recent in-depth mechanistic studies revealed complex steps involving transcription factor shuttling between the cytosol and nucleus of epithelial cells (25–27). To better account for the physiological context of the observed responses, it appears critical to design more sophisticated in vitro models involving.
multiple cellular partners (21) or ex vivo culture models (e.g., Ussing chambers) (28) using samples derived from healthy or diseased intestinal tissues. This would enable the particular role of probiotic strains in the context of specific immunological or inflammatory conditions to be examined. Nevertheless, observations derived from such systems will have to be confirmed in vivo, as they may not account for factors such as the peristaltic movement of the bowel or the interaction with the enteric nervous system.

**Bacterial translocation in the gastrointestinal tract**

The impact of bacterial adhesion on translocation across the epithelium represents another recurrent question. Translocation of commensal bacteria to mesenteric lymph nodes (MLN) has been clearly demonstrated (29–32) and presumably is central to the development and activation of the intestinal immune system. This work should be expanded to screen a wide range of well-characterized and labeled probiotic strains, considering that some strains may be capable of modulating tight junctions and thereby crossing the epithelium. Also needed are noninvasive methods for measuring bacterial translocation because this will make it possible to evaluate the importance of this process in terms of immunological responsiveness to probiotic or commensal bacteria.

Sampling of luminal bacteria by dendritic cells (DC), which have been shown to anchor between epithelial cells (33,34) through receptors for the tight junction protein they express, may also occur. It was demonstrated that dendritic protrusions can cross the epithelial junctions to “capture” bacteria from the lumen. It has also been suggested that DC may sample translocated bacteria that enter the lamina propria because of a low degree of physiological leakiness in the epithelial barrier.

An alternative pathway for crossing the epithelium relies on bacterial adhesion to M cells covering the Peyer’s patches, and physiologically relevant M-cell lines do not exist. Rapidly restored on the introduction of even single bacterial species (39–42). The development of the localized mucosa-associated immune system is only in part genetically determined: it is also functionally dependent of the bacterial microbiota (43). Not clear, however, is the extent to which antigenic components of bacterial cell walls mediate the state of physiological inflammation that characterizes the stable association between a mammal host and its resident microbiota.

**Immunomodulatory compounds of probiotic bacteria**

The immunostimulatory properties of commensal bacteria are best exemplified by studies with gnotobiotic animal models, which demonstrate that essentially all aspects of the intestinal immune system are underdeveloped in germ-free animals but rapidly restored on the introduction of even single bacterial species (39–42). The development of the localized mucosa-associated immune system is in part genetically determined: it is also functionally dependent of the bacterial microbiota (43). Neurological inflammation and the host (47). Recognition of microbe-associated molecular patterns is known to be mediated by pattern recognition receptors, including the Toll-like receptor family (TLRs), that signal the presence of specific microorganisms to the host (47). For example the lipoteichoic acids of gram-positive bacteria, pathogenic or nonpathogenic, are able to activate cellular responses via TLR2 (48–50). On another hand, Traversos et al. (51) reported that the peptidoglycan of both gram-positive and gram-negative bacteria is not sensed through TLR2, TLR2/1, or TLR2/6 but most likely through an intracellular receptor (Nod1/Nod2); however, no probiotic bacteria were included in this study. More recently, Mazmanian et al. showed that the ubiquitous gut microorganism *Bacteroides fragilis* could activate maturation of the developing immune system through the wnt signaling surface polysaccharide PSA (52).

As mentioned above, it has been established that the effect of probiotic bacteria may also result from soluble factors that alter epithelial permeability (16), inhibit the inflammatory cascade (17), or mediate activation/maturation/survival of dendritic cells (53). Native DNA carrying specific unmethylated CpG motifs could similarly provide some basis for the discrimination among different bacterial species in the gastrointestinal tract. DNA isolated from the probiotic mixture VSL#3 containing 8 lyophilized lactic acid bacterial strains (*Bifidobacterium longum*, *Bifidobacterium infantis*, *Bifidobacterium breve*, *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus delbrueckii* subsp. *bulgaricus*, *Lactobacillus plantarum*, and *Streptococcus salivarius* subsp. *thermophilus*) elicited noninflammatory responses from epithelial and immune cells (54). In addition to inhibition of IL-8 secretion from epithelial cells and attenuation of *Bacteroides vulgatus*-induced interferon-γ from mouse cells.
splenocytes, it was found that VSL#3 DNA inhibited systemic TNF-α production and improved the histological score of inflammation in IL-10 knockout mice (54). In a similar approach and also using the VSL#3 mixture, Rachmilewitz et al. (55) reported that the chromosomal DNA of this probiotic preparation was responsible, via TLR9 signaling, for the antiinflammatory effect observed in a mouse Dextran sulfate-induced colitis model. In their experimental setting, nonviable y-irradiated probiotics were equally effective as live ones. Signaling through TLR-5 has also been reported to occur; for example, the commensal *E. coli* strain MG1655 and its associated flagellin were shown to trigger proinflammatory responses in enterocytes both in vitro and ex vivo (56).

Altogether, these results shed light on the potency of probiotic bacteria to regulate immune responses and highlight a complex interaction between the host immune system and different bacterial compounds, including chromosomal DNA and cell wall components as well as soluble metabolites (Fig. 1). Studies of this type may ultimately lead to a better understanding of the molecular basis of the variation in immunomodulation capacity that clearly exists among various lactic acid bacterial strains (57–60). The use of transgenic knockout mice invalidated for specific receptors or transcriptional regulators will also help to unravel key host factors mediating the response to microbial stimuli (see below).

**Interaction of probiotics with immunocompetent cells**

Tolerance and homeostasis in the intestine are maintained by specialized subsets of lymphocytes. Subsets of CD4⁺ T cells have drawn most of the attention so far, and several phenotypes have been described, depending on the type of cytokines or surface molecules they express. At least 3 subsets of regulatory CD4⁺ T cells have been characterized that may play a role in gut homeostasis: Th3, Tr1, and CD25⁺ (61,62). There also seem to be roles for other T-cell types, including NK T cells (63) and γδ-intraepithelial lymphocytes (IEL) (64,65), but the proof of their direct involvement is in need of additional study. Recently, the presence in the gut of evolutionarily conserved mucosal-associated invariant T cells that are MR1 (monomorphic major histocompatibility complex I-related molecule)-restricted and require the presence of the commensal microbiota for their expansion in the lamina propria has been documented (66), but their function remains to be elucidated.

The microbiota has a positive impact on immune regulatory functions of the gut, and disruption of these immune regulatory functions by an imbalanced microbiota may lead to exacerbated effector responses and chronic inflammatory diseases (67). Typically, both UC and CD are characterized by a loss of tolerance to gut commensals (68,69), as illustrated for example by the observations that treatment with broad-spectrum antibiotics abolishes clinical symptoms (70). Some interest has therefore recently emerged to address the potential role of probiotics in the induction (or restoration) of regulatory-type immune responses in the gut. Experiments in rats and mice using several strains of *Lactobacillus* have shown an increase in proportion of CD25⁺ T cells in the lamina propria (71) and a decrease in T-cell reactivity (72–74). In a clinical study, the ingestion of *L. rhamnosus* GG was associated with a rise in mitogen-induced IL-10 from peripheral blood mononuclear cells that translated into high serum concentrations of IL-10 (75). However, this strain proved unprotective against IBD in humans (76). In vitro studies have suggested that undefined components of lactobacilli may have antiproliferative effects on T cells and suppressive effects on cytokine secretion by T cells (77). Such effects appear to implicate the emergence of a Tr1-like cell population capable of releasing TGF-β and IL-10 in the culture medium (78). However, the change in immune balance might also result from an indirect mechanism based on luminal modification of the antigen after treatment with probiotic strains (79). For example, a decrease in CD3-mediated secretion of the Th2 prototype cytokine IL-4 and suppression of T-cell proliferation were observed in mice exposed to milk caseins previously treated with *Lactobacillus rhamnosus* GG enzymes (80,81).

It is clear that the nature of the intestinal T-cell response is regulated by local DC populations that interact with these cells (82) and that, conversely, regulatory T cells interacting with DC restrain their maturation, thus amplifying tolerance (83,84). DC initiate immune responses in vivo by presenting antigens to T cells, whereas secretion of immunoregulatory cytokines influences polarization of T-cell responses (Th1, Th2, Th3, or regulatory T cells). The relative roles of DC and T cells in regulating immune tolerance to intestinal bacteria and in inflammatory sites where tolerance has been abrogated are ill-defined. It has been shown that *Lactobacillus* and *Bifidobacterium* strains differentially influence cytokine production by in vitro–matured DC, which suggests that the in vivo activity of regulatory T cells might be influenced by DC that have been exposed to specific commensal microorganisms including probiotics (85,86). Exposure of DC to a selection of probiotic bacteria in vitro was shown to instruct the DC to drive regulatory T cells to produce IL-10 (87). This capacity is not restricted to lactic acid or even gram-positive bacteria, as it was observed that *Bordetella pertussis* and *Vibrio cholerae* compounds can selectively commit DC to induce polarizing signals via different mechanisms (88). The demonstration that mucosal DC differ from systemic and spleen DC in their capacity either to suppress or prime immune responses (89–91) argues in favor of a mucosa-specific cross-talk between the intestinal microbiota and the host (92). In addition, human monocytes and monocyte-derived DC were shown to exhibit different patterns of cytokine release and receptor expression in response to exposure to gram-positive or gram-negative bacteria (93). These observations underline the necessity to isolate cell populations from the most appropriate tissue or fluid when pursuing ex vivo analysis of the immunomodulation capacity of probiotics.

Apart from a few studies (47,54,55), the wide range of existing animal models, particularly transgenic knockout mice with specific cellular or molecular deficiencies (e.g., B cells, T cells, TLRs), have merely been used to investigate immunological responses to either commensal or probiotic bacteria. In this respect, IL-12p40 promoter/luciferase transgenic mice (94) represent a valid tool to address the effects of particular bacteria on the modulation of the host immune response. Specifically, this model allowed identification of a subset of DC in the terminal ileum constitutively producing IL-23 under the influence of intestinal bacteria, which could explain clinical manifestation of CD in this part of the gut (95,96).

Most of the studies conducted so far have used a variety of “simplified” in vitro systems in which many potential players of the mucosal regulatory response were lacking. For example, the key role of the epithelial cell in the whole process would be better integrated using appropriate in vitro coculture systems (21,33). Special attention should be paid to the fact that the methods used for DC isolation and maturation may influence how they respond to microbial stimulus. In parallel, ex vivo studies that target individual cellular components of the mucosal immune system are now feasible, because of laser microdissection techniques associated with microarray technology (97,98),...
Although in vitro assays correspond to relatively flexible tools to initiate mechanistic studies, much remains to be done to establish their predictive value as to the targeted health benefit.

**Role of the secretory IgA in the gut homeostasis**

SlgA is the most abundantly produced immunoglobulin at the surface of mucous membranes in mammals. SlgA contributes to specific immunity against invading pathogenic microorganisms (99). In the gut, SlgA production depends on intricate mechanisms involving antigen sampling by M cells (100), processing by underlying antigen-presenting cells (101), T-cell activation (102), and B-cell switch in the Peyer’s patch and neighboring lamina propria (103) (Fig. 1). Multiple cytokines including IL-4, TGF-β, IL-5, IL-6, and IL-10 are instrumental to intestinal SlgA production, yet discrepancies between in vitro and in vivo data remain, leading to controversy as to their physiological function. The same set of cytokines are required for maintaining tolerance and IgA switch and production, thus establishing a link that can partly explain why mucosal SlgA are considered noninflammatory in the mucosal environment (104).

Commensal bacteria act as an important antigenic stimulus for the maturation of gut-associated lymphoid tissue (GALT) implicated in the induction of local immune responses (105,106). In what can appear as a paradox, probiotics and nonpathogenic commensals boost overall SlgA antibody responses and thereby trigger intestinal immune exclusion and subsequent elimination (107–110). The mechanisms whereby probiotics modulate immune responses leading to tolerance or SlgA activation appear to be highly dependent on the strains. Changes in the intestinal microbiota result in induction of specific mucosal SlgA responses through a pathway independent of T-cell help and subsequent antibody maturation (111). This ensures control of the endogenous microbiota through a broad spectrum of reduced-affinity SlgA, in contrast to the mechanisms involved in the recognition of pathogen antigens. The adaptive SlgA responses to the intestinal microbiota could allow the host to respond to fluctuations in commensal bacteria without eliciting a deleterious response and thus contribute to mucosal homeostasis (35,112). Additionally, the sampling of low amounts of antigen associated with SlgA may be important in inducing and maintaining tolerance to intestinal bacteria. SlgA capable of entering Peyer’s patches across M cells and target DC (113) may direct bacteria in the form of immune complexes into the GALT to permit continuous immune stimulation under non-inflammatory conditions (114).

The crucial role of SlgA in maintaining bacterial homeostasis is further reflected by its contribution to microbial biofilm formation in vitro (115). The potential role of biofilms in the complex bacteria-bacteria or bacteria-host interactions that take place in the gut remains largely unexplored. Biofilms have been proposed to ensure a mode of steady-state growth of the endogenous microbiota (116). SlgA-mediated biofilm formation might also explain why bacteria that bind SlgA have a selective advantage in the gut (117). The association of SlgA with biofilm formation in the gut has been demonstrated recently in a more physiological context in sections from rat, baboon, and human tissues (118).

SlgA were reported to be involved in multiple functions including bacterial binding (119,120), antibody anchoring at mucosal surfaces (121), and interaction with mucus (122). An intriguing recent study provided evidence that a 30-mer peptide comprising amino acids 38–67 from human secretory component found in mucosal and gland secretions (123) exhibits prebiotic properties when incubated with various bifidobacterial strains (124). This suggests a relevant function for free secretory component that may benefit gut bacteria. The bifidobacterial growth was stimulated 100 times more effectively than with equimolar amounts of the carbohydrate N-acetylglucosamine. The bifidogenic effect of milk might thus not be caused solely by its “free” sugar content as generally thought but can be contributed by SlgA known to be heavily complexed with carbohydrates (125).

**Recombinant lactic acid bacteria with enhanced health effects**

The potential of lactic acid bacteria to act as a live mucosal delivery system has been investigated during the last 2 decades (126–130). Although strain-specific immunoadjuvant properties have been demonstrated for a number of *Lactobacillus* species (131), the intrinsic antigenicity of lactic acid bacteria seems to be rather low by mucosal routes. This has not prevented the use of these microorganisms as effective carriers for protective antigens. The most complete studies have been carried out with the C subunit of the tetanus toxin (TTFC). Both persisting (i.e., *Streptococcus gordonii, Lactobacillus plantarum*, and *Lactoba- cillus casei*) and nonpersisting (i.e., *Lactococcus lactis*) species have been investigated as live vaccine vehicle. The strains producing sufficient antigen concentrations induced high serum IgG concentrations after nasal or intragastric administration, which turned out to be protective in many instances. Also, local TTFC-specific SlgA were induced (132). This approach has now been extended to additional antigens (128–130).

In parallel to this work, Steidler et al. (133) demonstrated that host immune responses could be enhanced by codelivery of IL-2 or IL-6 and TTFC. The approach of delivering cytokines with known modulatory properties was further extended by the construction of recombinant *L. lactis* strains secreting murine IL-10 (134). The authors successfully demonstrated that these strains were able to prevent or treat inflammation in 2 murine colitis models. Notably, this effect was obtained with much lower doses of IL-10 than those required when the cytokine was used as a free polypeptide. Steidler et al. further constructed a safe (no antibioresistance marker and chromosomally integrated transgene) biologically contained strain secreting human IL-10 (135). Authorization to conduct a small human intervention trial (targeting IBD) with this strain has been obtained in the Netherlands, and the trial has recently been completed (136). The search for novel therapeutic approaches for acute and chronic colitis based on live recombinant lactic acid bacteria was also extended by the construction and in vivo evaluation of *L. lactis* strains secreting bioactive murine trefoil factors (TFF). TFF are excellent candidates to restore disrupted intestinal epithelial barrier, but they are mostly ineffective when administered orally. Vandenbroucke et al. (137) demonstrated that intragastric administration of TFF-secreting *L. lactis*, in contrast to purified TFF, led to effective prevention and healing of acute DSS-induced murine colitis and was successful in reducing established chronic colitis in IL-10−/− mice.

Additionally, production and mucosal delivery of different types of bioactive molecules such as single-chain Fv antibodies, allergens, or digestive enzymes have been achieved in lactic acid bacteria (130). Targeted diseases included microbial infections such as vaginal candidosis (138) and dental caries (139), allergies (140–143), autoimmune diseases (144,145), HPV-induced tumors (146), and metabolic defects such as pancreatic insufficiency (147). Moreover, efforts have been devoted to improve the efficacy of lactococci or lactobacilli as delivery systems. For example, mutants were generated that release intracellular...
compounds more efficiently (148), but their in vivo immunogene-
nicity has not been reported as yet. More recently, cell wall
mutants of *L. plantarum* and *L. lactis*, defective in alanine
racemase (*alr* gene), were constructed and characterized
(149,150). Using TTFC as a model antigen, Grangette et al.
(151) demonstrated that each of these mutants behaves as a
substantially improved antigen delivery system compared with
its wild-type counterpart. The potency of the *L. plantarum* Alr-
mutant was further confirmed using a weak immunogen, i.e., the
*Helicobacter pylori* urease B, as protective antigen (152).
Notably, in this study, a significant reduction in the pathogen
load in the mouse stomach was achieved after immunization
with the recombinant mutant strain, in contrast to results
obtained with its wild-type counterpart.

Although recombinant strains would not be accepted today
in functional foods, their future use in therapeutic approaches
can be foreseen provided that the benefit/risk balance is positive
for consumers. It might be expected that such strains would be
formulated as pharmaceutical preparations and prescribed by
medical doctors. By no means are they intended to be included in
retail products.

In addition to these “designed strains,” mutants in specific
genes encoding for potential probiotic functions (adhesion
factors to mucus, resistance to acid, specific cell wall compo-
nents, etc.) could be engineered to compare their biological
effect with that of their wild-type counterpart. This strategy
should help unravel mechanisms underlying the cross-talk
between probiotic bacteria and their host or identify key
probiotic compounds. Currently available and rapidly growing
genomic information should greatly facilitate this approach
(153,154). Grangette et al. (50) recently provided an illustration
of this approach. Based on in vitro tests (cytokine secretion
profile from stimulated human peripheral blood mononuclear
cells), these authors selected a mutant of *L. plantarum* impaired
in its capacity to incorporate d-alanine in teichoic acids (Dlt-
mutant), for its antiinflammatory potential. Notably, in correla-
tion with in vitro tests, the Dlt- mutant proved to be more
protective in a mouse model of colitis than the wild-type strain.
Finally, as mentioned above, fluorescently labeled (155) or
genetically tagged bacteria could be used to better explain the
fate of bacteria after ingestion, and this may help identify the
principal immune cells that recognize and process them.

The fact that probiotic bacteria interact with the host
immune system is now well accepted and illustrated by in vitro
and in vivo experiments and is becoming progressively
supported by human intervention trials. However, our current
understanding of the molecular mediators involved in the
cross-talk between beneficial or commensal bacteria and the host
remains fragmentary as compared with the knowledge devel-
oped for specific pathogens. Although mechanistic studies have
become more sophisticated in recent years, the information
remains limited. Different active compounds have been identi-
fied in a few probiotic strains, but their respective contribution
to specific immune effects remains to be analyzed in more detail,
as most of these compounds also exist in the endogenous
intestinal bacteria. The mucosal immune system has therefore
to process a significant number of similar signals and yet guarantee
immune homeostasis. Use of the rapidly evolving “omics”
technology will undoubtedly help progress in this area, as it will
provide a more holistic view of the cross-talk between partners.

**Conclusion**

In conclusion, it is evident that the analysis of the impact of
probiotics on the host immune system has entered a new and
fascinating phase of research and that this effort is likely to offer
novel and useful means to modulate host immunity for protec-
tion from, or treatment of, a wide variety of human and animal
disorders.

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**Literature Cited**

1. Allen SJ, Okoko B, Martinez E, Gregorio G, Dans LF. Probiotics for
treating infectious diarrhea (Cochrane Review). In: The Cochrane
Library Issue 3. (ISSN 1464–780X). Chichester, UK: John Wiley &

2. Servin AL, Coconnier MH. Adhesion of probiotic strains to the
intestinal mucosa and interaction with pathogens. Best Pract Res Clin

3. Bergonzelli GE, Blum S, Brussow H, Corthesy-Theulaz I. Probiotics as
a treatment strategy for gastrointestinal diseases? Digestion. 2005;72:
57–68.


5. Huebner ES, Surawicz CM. Probiotics in the prevention and treatment
of gastrointestinal infections. Gastroenterol Clin North Am. 2006;35:
355–65.


7. Mercenier A, Pavan S, Pot B. Probiotics as biotherapeutic agents:
present knowledge and future prospects. Curr Pharm Des. 2003;9:
175–91.

8. Prioult G, Nagler-Anderson C. Mucosal immunity and allergic
responses: lack of regulation and/or lack of microbial stimulation? Immu-

9. Iweala OF, Nagler CR. Immune privilege in the gut: the establish-
ment and maintenance of non-responsiveness to dietary antigens and


11. Tannock GW. Probiotic properties of lactic-acid bacteria: plenty of

12. Tannock GW. The bifidobacterial and *Lactobacillus* microflora of

istered *Lactobacillus murinus* to predominate and persist in the porcine

14. Klingberg TD, Budde BB. The survival and persistence in the human
gastrointestinal tract of five potential probiotic lactobacilli consumed
as freeze-dried cultures or as probiotic sausage. Int J Food Microbiol.

15. Rastall RA. Bacteria in the gut: friends and foes and how to alter the

Doyle J, Jewell L, De Simone C. Probiotic bacteria enhance murine and
human intestinal epithelial barrier function. Gastroenterology. 2003;121:
580–91.

17. Menard S, Candall C, Bambou JC, Terpend K, Cerf-Bensussan N,
Heyman M. Lactic acid bacteria secrete metabolites retaining anti-
inflammatory properties after intestinal transport. Gut. 2004;53:
821–8.

Supermutant of *Bifidobacterium breve* induces dendritic cell maturation,
activation, and survival through a Toll-like receptor 2 pathway. J Allergy


47. Cross-talk between probiotics and the immune system 787S


121. Driessen AJM, colleagues. Cross-talk between probiotics and the immune system 789S


