Probiotics and Immune Function: Insights into Mechanisms of Modulation of Mucosal Immunity by Selected Lactobacilli

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The therapeutic and preventive effects of fermented milk products containing selected strains of lactic acid bacteria on diseases such as infections, gastrointestinal disorders, and food allergy have often been reported (1). Some lactic acid bacteria, such as *Lactobacillus johnsonii* Lai, also show immunostimulatory properties in healthy subjects by enhancing innate immune defenses (2). Furthermore, positive effects on intestinal microbial ecology were shown in a recent human double-blind placebo-controlled study, in which the number of *Clostridium perfringens*-positive subjects was reduced by *L. johnsonii* Lai (3). These studies provide evidence that regular consumption of products containing probiotic bacteria may enhance immune response and positively affect the indigenous microflora. This is certainly of benefit to healthy consumers, but also increases resistance to immune-related diseases; this is extremely important in immunocompromised populations, such as the elderly.

Immunostimulation by lactic acid bacteria is dependent on the number of live bacteria transiently colonizing the small bowel. Thus survival in the gastrointestinal tract, especially resistance to gastric pH and bile salts, is a prerequisite for immunomodulatory effects. Adherence to intestinal epithelial cells also is a valuable property; if this can be established, even temporarily, it will result in a competitive advantage for the probiotic and prolong its effect. Adhesion of lactic acid bacteria has been widely demonstrated in vitro, by using intestinal epithelial cell lines such as Caco-2 and HT-29, and constitutes one of the selection criteria for probiotic strains (4). However, there have been few reports on the mechanisms underlying the modulation of mucosal or systemic immunity by lactic acid bacteria. In this chapter, we discuss some aspects of recent work on how luminal signals in the intestine, delivered by probiotic bacteria, can modify the activation of the mucosal immune system.
THE INTESTINAL MUCOSA

Mucosal surfaces represent large areas of interface between the host and the external environment. Physiologically, they can be sterile, as in the distal pulmonary tree, or colonized, as in the distal gastrointestinal tract. Mucosal mechanisms of defense have evolved common strategies for all mucosal surfaces (5), but, in the case of a colonized mucosa, there are additional characteristics. Whereas a strong response against invasive pathogens must be mounted, unresponsiveness or hyporesponsiveness to food antigens or indigenous bacteria must be guaranteed. This lack of immunologic response is an active process, based on various mechanisms, which globally are called oral tolerance.

Gut mucosal defenses are able to cope with environmental antigens or infectious agents, without triggering constant and severe inflammation that would result in tissue damage. Thus fine tuning of responses to maintain a continuous low-grade activation of the mucosal immune system is mandatory. Both endogenous mediators and luminal factors, including those derived from bacteria, are implicated in intestinal homeostasis. The integrity of the mucosal barrier is a basic requirement for host survival, both from a nutritional and a defensive point of view.

IMMUNE-MEDIATED DEFENSE MECHANISMS

Antibody Production at Mucosal Surfaces

The best-understood defense system of the intestinal mucosa is the production of secretory immunoglobulins (sIgs) against intestinal damaging agents such as toxins, pathogenic bacteria, and viruses. The prominent germinal centers of the gut-associated lymphoid tissue (GALT) are the main lymphopoietic sites for mucosal B cells, with a preferential commitment to immunoglobulin A (IgA) production. Germinal center development depends on antigenic challenge, mainly of microbial origin. According to their affinity for specific antigens, B cells migrate into the germinal centers, where they undergo somatic mutation of the Ig genes, leading to increased affinity for the specific antigens.

In the GALT, Ig isotype switching occurs predominantly toward the IgA isotype. CD4+ T cells expressing CD40 ligand and producing interleukin (IL)-4, IL-10, and IL-5, colocalize with B cells in the germinal centers, and participate actively in the process of isotype switching (6). Terminally differentiated B cells will migrate to the lamina propria compartment, where IgA is secreted and transported through the epithelial layer toward the intestinal lumen by the polymeric Ig receptor or secretory component. When sIgA reaches the intestinal lumen, it reacts with specific antigens preventing the physical interaction of noxious agents with the mucosal surface. This process is called immune exclusion and does not imply activation of inflammatory processes. Production and secretion of IgA is further regulated at the lamina propria by (a) endogenous mediators, such as transforming growth factor β (TGF-β) and IL-5, produced mainly by regulatory T cells (7); and (b) intestinal bacterial colonization (8).
Stimulation of Immunoglobulin A Production by *L. johnsonii* La1

Fermented milk products containing probiotic bacteria, such as *L. johnsonii* La1 [10^10 colony-forming units (CFU)/ml, daily dose] were shown to have immune adjuvant effects, as demonstrated by a significant increase in total serum IgA in human adult volunteers. Furthermore, consumption of *L. johnsonii* La1 in conjunction with an attenuated oral *Salmonella typhi* vaccine (Votif) promoted the specific immune response, as assessed by a significant increase of Ty12a-specific serum IgA (9).

It has been reported that the human indigenous microflora is only partially covered by IgA-specific antibodies and even less so by IgG and IgM (10). An important proportion of the microflora (close to 50%) is not covered by antibodies. These findings seem to show that the partial unresponsiveness to the autochthonous microflora may appear after a transient immune response takes place, which is suggested by the gnotobiotic animal model. Conversely, the effect of ingested bacteria, such as probiotics, for maintaining activation at the germinal center level is not known. However, they could contribute to it and thereby promote an IgA response that is specific not only against bacterial antigens but also against bystander antigens sampled through the follicle-associated epithelium containing the M cells.

Intestinal Epithelial Cells

Intestinal epithelial cells are considered to be a component of the mucosal immune system. They participate in the initiation and regulation of the mucosal immune response to bacteria by interacting with immune cells of the GALT, lamina propria lymphocytes, and intraepithelial lymphocytes. It has been shown that intestinal epithelial cells may change phenotype as a result of stimulation by soluble mediators, such as interferon γ (IFN-γ), derived from intraepithelial lymphocytes (11). This agrees with the concept that activated intestinal epithelial cells express higher levels of human leukocyte antigen (HLA) class II molecules (12), classic class I and nonclassic HLA class Ib molecules such as CD1d (13), the intercellular adhesion molecule 1 (ICAM-1), complement factors, and cytokine receptors (14). On stimulation, they are able to produce a wide range of immunomodulatory cytokines (15). In addition, they can actively participate in the local reaction against pathogens, exerting a form of innate immunity. Moreover, the endogenous microflora seems to have a modulatory effect on the mucosal immune homeostasis and therefore on the mucosal mechanisms of defense. The importance of microflora-derived host protection is evident by the higher susceptibility of germ-free animals to intestinal infections. Intestinal epithelial cells are now thought to be implicated in the recognition of components of the intestinal microflora, including food-derived probiotic bacteria, and the transduction of bacteria-derived signals to resident mucosal immune cells.

We summarize data obtained with different human *in vitro* models on the molecular mechanisms of bacterial interaction with intestinal epithelial cells.
MODULATION OF THE MUCOSAL IMMUNE RESPONSE BY COMMENSAL BACTERIA

Regulation of the Immune Phenotype of Intestinal Epithelial Cells In Vitro

Nonpathogenic bacteria normally do not invade the host. Therefore the signal for modulation of mucosal immune homeostasis has to be "processed" in the intestinal epithelial cells in various ways: by release of soluble mediators that will translocate through the epithelial layer to neighboring immune cells; by modification of the luminal ecology because of their metabolic activity; and by changes in epithelial phenotype and function.

Relevant intestinal epithelial cell immune markers can be grouped into molecules involved in (a) antigen presentation: major histocompatibility complex (MHC) class II, Cd1, which is an early event of the immune response; (b) cross talk between intestinal epithelial cells and lymphocytes: ICAM-1, Fas, IFN-γ receptor; and (c) soluble mediators such as cytokines and chemokines: IL-8, tumor necrosis factor α (TNF-α), and monocyte chemoattractive protein 1 (MCP-1), all of which promote the recruitment and activation of immune cells in the different intestinal microenvironments.

Stimulation of the human intestinal cell line HT-29 in vitro by using a nonpathogenic Escherichia coli increased the expression of ICAM-1 (CD54) and IFN-γ receptor (CD119). Furthermore, when E. coli was combined with IFN-γ, constitutively produced by intraepithelial lymphocytes, a synergistic effect was detected for the expression of MHC class II molecules (HLA-DR), ICAM-1, Fas, and IFN-γ receptor (Table 1). In addition, the proinflammatory cytokine/chemokines TNF-α and IL-8 (Fig. 1) were induced by the gram-negative bacteria, and the induction was significantly increased when E. coli were combined with IFN-γ. Lactic acid bacteria (L. johnsonii Lai), in contrast, did not show any agonistic effect with respect to the onset of proinflammatory cytokines. However, the combination of lactic acid bacteria and IFN-γ increased the expression of IFNγ receptor (16).

### TABLE 1. **Modulation of surface antigens on HT-29 cells by nonpathogenic bacteria**

<table>
<thead>
<tr>
<th>Stimulus</th>
<th>HLA-DR (CD119)</th>
<th>ICAM-1 (CD54)</th>
<th>FAS (CD95)</th>
<th>IFN-γR (CD119)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No treatment</td>
<td>0</td>
<td>5</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>0</td>
<td>26°</td>
<td>5</td>
<td>26°</td>
</tr>
<tr>
<td><em>Lactobacillus johnsonii</em> Lai</td>
<td>0</td>
<td>5</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>9</td>
<td>20°</td>
<td>10</td>
<td>ND</td>
</tr>
<tr>
<td><em>E. coli</em> + IFN-γ</td>
<td>26°</td>
<td>80</td>
<td>16°</td>
<td>39°</td>
</tr>
<tr>
<td>Lai + IFN-γ</td>
<td>15°</td>
<td>27°</td>
<td>14°</td>
<td>ND</td>
</tr>
</tbody>
</table>

Flow-cytometric analysis of modulation of surface antigen expression on HT-29 cells after bacterial challenge. Results are expressed in mean fluorescence intensity (MFI) subtracted with the MFI obtained with the isotype control antibody. Data are representative from one experiment. 1 x 10^6 cfu/ml bacteria; IFN-γ, 25 U/ml.

° Significant change (p < 0.05) compared with IFN-γ single treatment.

°° Significant change (p < 0.05) compared with basal expression.

HLA, human leukocyte antigen; ICAM, intracellular adhesion molecule; ND not done.
The fact that lactic acid bacteria alone or in combination with IFN-γ did not induce any of the proinflammatory cytokines suggests that lactic acid bacteria could participate in tissue protection against the deleterious effect of an ongoing inflammatory process. Bacterial-epithelial cell contact was mandatory for the induction of intestinal epithelial cell phenotypic changes, giving support to the importance of adherence to intestinal epithelium as a selection criterion for probiotic bacteria.

The regulation of the immune phenotype with regard to specific molecules involved in cell-to-cell interactions, playing a key role in the homeostasis of the immune system, seems to suggest a role for intestinal epithelial cells in the regulation of the cellular environment at the intraepithelial compartment and the lamina propria.

<table>
<thead>
<tr>
<th>Ctrl</th>
<th>IFN-γ</th>
<th>La-1</th>
<th>E.coli</th>
<th>La-1/IFN-γ</th>
<th>E.coli / IFN-γ</th>
<th>MW</th>
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**FIG. 1.** Potentiating effect of interferon γ (IFN-γ) to induce proinflammatory cytokines in HT-29 cells after stimulation with nonpathogenic bacteria. Absence of proinflammatory cytokines, tumor necrosis factor (TNF-α), interleukin (IL)-8, and monocyte chemoattractive protein 1 after stimulation of HT-29 cells with *Lactobacillus johnsonii* La1. Reverse transcription–polymerase chain reaction analysis of TNF-α, IL-8, and MCP-1 messenger RNA expression in undifferentiated HT-29 cells after bacterial challenge: *Escherichia coli*, *L. johnsonii* La1, and *L. sakei* (24 h, 10⁶ CFU/ml); IFN-γ (25 U/ml); (ctrl), no treatment. continues
FIG. 1. *Continued.*
Interaction of Nonpathogenic Bacteria with Mixed Mucosal Cell Populations: Human Caco-2/Leukocyte Cocultures In Vitro

There is increasing evidence that bacterial signals to the host must be processed by a network of different mucosal cells, resulting in an integrated response that dictates the host reaction against a constantly changing microbial environment in the intestine.

To investigate such interactions, a human in vitro model was established with Caco-2 cells and peripheral blood mononuclear cells, by using a trans-well culture technique (17). The immune response to different nonpathogenic bacteria was assessed by determining cytokine expression in intestinal epithelial cells and leukocytes. The proinflammatory cytokines TNF-α, IL-8, and MCP-1 were induced in Caco-2 cells on challenge with nonpathogenic *E. coli* and *Lactobacillus sakei* (Fig. 2). In contrast,

![FIG. 2. Differential induction of chemokines by nonpathogenic bacteria in leukocyte-sensitized Caco-2 cells. Determination of specific gene transcripts for interleukin (IL)-8 and monocyte chemoattractive protein 1 in Caco-2 cells after stimulation of Caco-2/leukocyte cocultures with nonpathogenic *Escherichia coli*, *Lactobacillus johnsonii* La1, and *L. sakei* (16 h, 10⁶ and 10⁷ CFU/ml). Controls: lipopolysaccharide (1 μg/ml), IL-1β (10 ng/ml), no treatment (medium). Results represent one of three independent experiments.](image)
**FIG. 3.** Significant induction of transforming growth factor β (TGF-β) messenger RNA in leukocyte-sensitized Caco-2 cells by *Lactobacillus johnsonii* La1. Reverse transcription–polymerase chain reaction analysis of TGF-β–specific gene transcripts in Caco-2 cells after stimulation of Caco-2/leukocyte cocultures with nonpathogenic *Escherichia coli, Lactobacillus johnsonii* La1, and *L. sakei* (16 h, 10^6 and 10^7 CFU/ml). Controls: lipopolysaccharide (1 μg/ml), interleukin 1β (10 ng/ml), no treatment (medium). Results represent one of three independent experiments.

*L. johnsonii* La1 did not stimulate the production of these cytokines, but upregulated the expression of TGF-β (Fig. 3). Responsiveness of intestinal epithelial cells to nonpathogenic bacterial signals was dependent on the presence of peripheral blood mononuclear cells. In addition, the underlying immune cells responded in a discriminative manner to different bacteria, although the bacteria had no direct access to this compartment. As depicted in Fig. 4, *E. coli* and *L. sakei* exclusively induced TNF-α and IL-1β protein secretion from leukocyte-sensitized cocultures, whereas no induction of these proinflammatory cytokines occurred with *L. johnsonii* La1. These results strengthen the hypothesis that bacterial signaling at the mucosal surface is dependent on epithelial–immunocyte cross talk, which seems responsible for the innate reaction that can distinguish between different nonpathogenic microorganisms. This discriminative response occurred in both compartments, probably orchestrated by cell secretory products that are not yet entirely identified. These results also indicate that, depending on the lactobacillus strain, a more proinflammatory (*L. sakei*) or a more

**FIG. 4.** Absence of secretion of the proinflammatory cytokines tumor necrosis factor α (TNF-α) and interleukin 1β (IL-1β) from *Lactobacillus johnsonii* La1–challenged Caco-2/leukocyte cocultures. Stimulation of Caco-2/leukocyte cocultures with nonpathogenic *Escherichia coli, L. johnsonii* La1, and *L. sakei* (16 h, 10^6 CFU/ml). Secretion of TNF-α (A) and IL-1β (B) into the basolateral compartment was determined by enzyme-linked immunosorbent assay technique (bar chart, pg/ml). Reverse transcription–polymerase chain reaction analysis was used to determine the expression of TNF-α (A) and IL-1β (B) specific gene transcripts in Caco-2 cells. Values are given as mean ± SD of triplicates.
immune-regulatory (*L. johnsonii* La1) type of immune response might be stimulated at the mucosal site.

The results presented provide direct evidence of the beneficial effect of specific probiotic strains on intestinal immune homeostasis. This knowledge presents the food industry with unique possibilities for improving gut homeostasis by nutritional interventions.

**New Generation of Probiotic Bacteria with Potential Application in Prevention of Gastrointestinal Disorders and Allergy**

Various bifidobacteria from the Nestlé Culture Collection (NCC), including species of *Bifidobacterium lactis, B. adolescentis*, and *B. breve*, are currently being investigated for their cytokine profile by using Caco-2/leukocyte cocultures. Those strains that do not induce any of the proinflammatory cytokines, TNF-α, IL-8, or MCP-1, are of particular interest for use as probiotics with antiinflammatory effects (Fig. 4). The data obtained from *in vitro* assays can be combined with the antipathogenic properties of some of the strains (for example, antisalmonella, antirotavirus) to select for potential applications in preventing or treating diarrhea. In addition, bifidobacteria with antiinflammatory effects have strong potential as supplements in infant formulas. More recently, bifidobacteria were shown to be of increasing interest in elderly people, who harbor reduced numbers of bifido strains in their microflora and often have low-grade chronic inflammation. Supplementation of the common diet with any dairy product containing selected bifidobacteria could be beneficial in terms of "correcting" the microflora and could be a valid contribution to the daily energy intake.

Finally, *in vitro* assays and experimental animal models contributed to the selection of a new lactic acid bacterium from the *L. paracasei* group, which was shown to have different effect on Th1/Th2 functions compared with *L. johnsonii* La1. These preliminary results are currently under evaluation.

**CONCLUSIONS**

Intestinal epithelial cells permanently interact with the luminal content of the gut, including commensal bacteria and a cellular network of professional immune cells. Our experimental data suggest that intestinal epithelial cells play an important role in processing nonpathogenic bacteria–derived signals to the mucosal immune system. This is achieved by differential expression of molecules involved in cell-to-cell contact or by the secretion of soluble mediators, such as cytokines/chemokines, that will attract specific immune effector cells. Thus one appropriate function of intestinal epithelial cells is to adapt the physiologic reactivity of the host tissues to a highly changing intestinal content. Dysfunction of this interphase could promote discordance between the luminal signal and the initiated response. This could cause pathologic conditions owing to exaggerated responses to nondangerous signals such as food antigens,
resulting in food allergy or chronic inflammation (that is, inflammatory bowel disease). Fine tuning of this dynamic interphase probably depends not only on intestinal epithelial cell function but also on an intricate cell-to-cell cross talk, in which intraepithelial lymphocytes are further participants.

*Lactobacillus johnsonii* La1 revealed a low potential for inducing a proinflammatory response, but favored the induction of TGF-β expression in intestinal epithelial cells. TGF-β is a key factor implicated in the regulation of intestinal barrier function and is thought to mediate tolerance to the indigenous microflora through bystander suppression. These in vitro results support the observation of a current human study in healthy volunteers in which immunostimulation by *L. johnsonii* La1 was not linked to systemic proinflammation, as acute-phase proteins and receptors for IL-2 and IL-6 in serum did not increase above control levels during and after consumption of La1 (3).

The probiotic effects observed with *L. johnsonii* La1 are not linked to general, irreversible modifications of immune responsiveness that could have harmful effects, but rather to transient alterations that are beneficial to the host.

In conclusion, these probiotic products are safe for the general population and could be of further use in populations of specific ages or as supplementation in clinical nutrition.

ACKNOWLEDGMENTS

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REFERENCES

DISCUSSION

Dr. Iolascon: You use Caco-2 colon carcinoma cells. Might noncancer cells have a different pattern of expression? I believe you could use bacteria and look at expression profiles on the cells with the entire genome. What is the difference between live bacteria and dead bacteria on the probiotic effect?

Dr. Pfeifer: I come from the cell biology field, and I have been involved in establishing the first normal human cell lines for liver, skin, and intestine. This is my main research area, and in our laboratory, we now have the first normal colon cell line. We used Caco-2 cells first because that was a more established cell line, and we could compare data in the literature, but I can assure you that normal intestinal cells acted in basically exactly the same way. We also have results from explant cultures from humans. So we feel comfortable that our results are not an in vitro artifact. In relation to dead versus live bacteria, or probiotics versus postbiotics, we have looked at dead bacteria, and we do see certain effects, but in most of our experiments, these effects are reduced compared with those in live bacteria.

Dr. Zoppi: In your presentation you did not emphasize that intestinal bacilli are a component of an ecosystem in which there is a balance between the various species of microorganisms. What is the effect of your lactobacilli on the environment of the intestine in infants?

Dr. Pfeifer: We did not in fact test the La1 bacterium in infants; most of the studies were done in adult volunteers. However, it is not completely true that we did not consider the environment. In the clinical studies in which the bacterium is given, we are dealing with normal volunteers who have an established microflora. In that environment, with no antibiotics and with an absolutely normal diet—except that the subjects did not eat a fermented product for a period of 3 weeks—we could show first, that the La1 bacterium could survive and establish itself in the small intestine as well as in the colon, and second, that there was stimulation of the immune system, shown by the expression of more antibodies as well as by increased phagocytotic activity. So whereas in our in vitro experiments we did not have a normal environment for the purposes of simplicity, we did in fact test our bacteria in normal volunteers consuming a normal diet.

Dr. Marini: When we were working with different kinds of probiotics in preterm babies, we found that on the first day, we had a high rate of colonization, but with continuous administration of the probiotic, the colonization declined. Simultaneously there was an increase in
specific IgA and IgM. So as usual, the body reacts against new things. However, we found that in spite of this, colonization could change for the better—for example, there was a reduction in anaerobic colonization. So I believe that probiotics can work even in the presence of host antibodies. I have a question: you said that killed bacteria were not so effective as live bacteria, but when there is mucosal damage or when the mucosa is very immature, as in preterm babies, is there a risk of bacterial translocation?

**Dr. Pfeifer:** I do not think I can completely answer that question because we did not do any clinical trials in preterm babies. If I had to make a choice, I would go for killed bacteria, even with their reduced effects, exactly because it is not certain whether translocation might occur under extreme conditions.

**Dr. Moro:** You discussed individual probiotics, which are similar but have different actions. What happens when you give a combination of these different types? Do they all have the same effects, is there a mixture of effects, or is there a change in their effects?

**Dr. Pfeifer:** What I have tried to show is that there are probiotics that determine very different patterns of physiologic and immune function response. Lai and the ST11 have quite different pathways. If you combine bacteria that have identical or very similar patterns of action, for example LT1 and BB12, then you get a synergistic effect. However, I do not think I would want to combine Lai with ST11, because they affect quite different pathways.

**Dr. Moro:** Is there any effect of these probiotics on normal immunizations?

**Dr. Pfeifer:** In one particular experiment, we tested the response to an oral vaccine. In this experiment, the group that received the LC1 had an enhanced immune response compared with the placebo group. This seems to mean that we should be able to support the vaccination response with the use of probiotics, but we have not done this in children yet.

**Dr. Veereman:** There are many clinical studies on *Lactobacillus* GG. Have you also studied this strain in vitro? Do you have any data on its effects?

**Dr. Pfeifer:** *Lactobacillus* Lai is a Nestlé strain, and we have a particular interest in studying its properties. But obviously we know the *Lactobacillus* GG very well and in fact, in many of our studies, we use it as a positive or negative control. From the literature on *Lactobacillus* GG, it is clear that Lai has common effects, but in addition to unique functions; for example, it has a positive effect on the nonspecific immune system that has never been shown for GG.

**Dr. Veereman:** Can companies have a patent on specific strains? Do you own particular strains, and do other companies own other strains?

**Dr. Pfeifer:** The Lai, which is in fact a strain of the LC1, is a Nestlé-patented strain.

**Dr. Endres:** You showed the switch from Th1 to Th2 cells in the prevention of food allergy, and Isolauri in Finland has shown, clinically at least, that there is a protective effect of *Lactobacillus* GG (1,2). In one of your slides, you showed that depression of IL-4 by *L. paracasei* ST11 was very effective, but I was not clear whether *Lactobacillus* GG also was investigated in that *in vitro* study. Is *L. paracasei* more potent than *Lactobacillus* GG?

**Dr. Pfeifer:** In that study by Isolauri, the infant formula was actually fermented with the *Lactobacillus* GG, and this probably led to the breakdown of specific allergenic epitopes—at least that is Isolauri’s hypothesis. So the mechanism whereby GG might induce a preventive effect on allergy is certainly different from that of ST11. There are some doubts about that study by Isolauri, as other workers have not been able to repeat the results. However, we believe that ST11 acts through a different mechanism from that of GG.

**Dr. Hernell:** You mentioned that adhesion is an important characteristic of probiotics, and I can understand the value of that in preventing infection by pathogens. Is it also necessary for immune function? If so, you would expect to have a dose response. Is anything known about that?
Dr. Pfeifer: We are not sure yet how important adhesion is for the immune response. The results that we have indicate that colonization of the small intestine has a positive effect on immune function. However, we have one probiotic that is as immunostimulatory as La1 but not so adherent. So it may be that adhesion is helpful but not essential for activation of the immune system in the small intestine.

REFERENCES