Antagonistic Activity of Lactobacillus acidophilus LB against Intracellular Salmonella enterica Serovar Typhimurium Infecting Human Enterocyte-Like Caco-2/TC-7 Cells

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To gain further insight into the mechanism by which lactobacilli develop antimicrobial activity, we have examined how Lactobacillus acidophilus LB inhibits the promoted cellular injuries and intracellular lifestyle of Salmonella enterica serovar Typhimurium SL1344 infecting the cultured, fully differentiated human intestinal cell line Caco-2/TC-7. We showed that the spent culture supernatant of strain LB (LB-SCS) decreases the number of apical serovar Typhimurium-induced F-actin rearrangements in infected cells. LB-SCS treatment efficiently decreased transcellular passage of S. enterica serovar Typhimurium. Moreover, LB-SCS treatment inhibited intracellular growth of serovar Typhimurium, since treated intracellular bacteria displayed a small, rounded morphology resembling that of resting bacteria. We also showed that LB-SCS treatment inhibits adhesion-dependent serovar Typhimurium-induced interleukin-8 production.

Salmonella spp. are the etiologic agents of a variety of diseases globally defined as salmonellosis. Infections range in severity from self-limiting gastroenteritis to life-threatening systemic enteric fevers to septicemia. Studies have shown that salmonellae initiate infection by invading and multiplying within epithelial intestinal cells and Peyer’s patches. Salmonella enterica serovar Typhimurium interacts with microvilli of the intestinal brush border (9, 16), inducing the formation of surface appendages (17) and promoting the synthesis of bacterial proteins (10). During the entry process, protrusion of the host cell membrane occurs, and the bacteria are completely surrounded by “splashes” of membrane, indicative of macropinocytosis (11). Changes in the distribution of cytoskeletal components, resulting from signaling (for a review, see reference 13), have been reported during Salmonella invasion (11, 12, 15). Cytoskeletal rearrangements and membrane ruffling involve the small guanosine triphosphate-binding protein CDC42Hs (3). Invasion of M cells in vivo and of epithelial cells and macrophages in vitro requires a type III secretion system encoded on the Salmonella SPI1 pathogenicity island located at centisome 63 (7). After entry, bacteria reside in vacuoles and obtain nutrients from the host eucaryotic cells (14), allowing intracellular growth of the microorganisms (20).

We have documented the antagonistic activity, in vitro and in vivo, of Lactobacillus acidophilus LB against enterovirulent bacteria involved in gastrointestinal disorders. For example, this strain causes a significant inhibition of enteropathogens’ association with and entry into cultured human intestinal cells (4–6). Moreover, we have recently provided evidence that strain LB secretes a heat-stable antimicrobial compound(s) different from lactic acid (5). The aim of this study was to gain further insight into the antagonistic activity of L. acidophilus LB against S. enterica serovar Typhimurium, in particular against bacteria localized within cultured human enterocyte-like Caco-2/TC-7 cells, a model of the mature enterocyte of the small intestine (23).

MATERIALS AND METHODS

Bacterial strains and growth conditions. S. enterica serovar Typhimurium strain SL 1344 (9) was used as the indicator strain. Bacteria were cultured in Luria broth (Difco Laboratories, Detroit, Mich.) at 37°C. L. acidophilus LB was isolated from a human stool specimen (Lacteol Laboratory, Houdan, France). LB bacteria were grown in DeMan, Rogosa, Sharpe (MRS) broth (Biokar Diagnostic, Beauvais, France) for 18 h at 37°C. Spent culture supernatant of LB (LB-SCS) was obtained by centrifugation of the culture at 10,000 × g and 4°C for 30 min. Centrifuged LB-SCS was passed through a sterile 0.22-μm-pore-size filter unit (Millex GS; Millipore, Molsheim, France). Filtered LB-SCS was assessed for the absence of bacteria by plating on tryptic soy agar. A concentrated (10-fold) suspension of the LB-SCS was obtained by freeze-drying. The pH values of different LB-SCS preparations ranged from 5 to 4.5. As a control, LB broth was adjusted to pH 4.5 with HCl (MRS-HCl) as previously described (2, 4–6). As a second control, MRS was adjusted to pH 4.5 with lactic acid (MRS-LA; final concentration, 0.00 mM).

Caco-2/TC-7 cell culture. The TC7 clone (Caco-2/TC-7) (1), established from the parental Caco-2 cell line (23), was used. Cells were routinely grown in Dulbecco modified Eagle’s medium (DEMEM) (25 mM glucose) (Life Technologies, Cergy, France), supplemented with 20% heat-inactivated (30 min, 56°C) fetal calf serum (Boehringer, Mannheim, Germany) and 1% nonessential amino acids (Life Technologies) as previously described (2, 4–6). For maintenance purposes, cells were passaged weekly, using 0.02% trypsin in Ca2+–Mg2+-free phosphate-buffered saline (PBS) containing 3 mM EDTA. Experiments and maintenance of the cells were carried out at 37°C in a 10% CO2–90% air atmosphere. The culture medium was changed daily. For assays of S. enterica serovar Typhimurium infection, Caco-2/TC-7 cells were used at postconfluence after 15 days of culture (i.e., they were fully differentiated cells).

Determination of penetration of S. enterica serovar Typhimurium into Caco-2/TC-7 cells. For Caco-2/TC-7 cell monolayer infection, serovar Typhimurium strain SL1344 was cultured at 37°C for 18 h in Luria broth. A cell infection assay was conducted as previously reported (2, 4, 5). Briefly, prior to infection, the Caco-2/TC-7 monolayers, prepared in 24-well tissue culture plates (TPP) (ATGC, Paris, France), were washed twice with PBS. Bacteria were suspended in the culture medium, and 1 ml of this suspension was added to each well of the culture at 10,000 cells/well. The plates were incubated at 37°C in an atmosphere of 10% CO2–90% air for different infection time periods and then were washed three times with sterile PBS.

Internalization of serovar Typhimurium organisms was determined by quantitative measurement of numbers of bacteria located within the infected monolayers, using the aminoglycoside antibiotic assay (4, 5). After incubation, monolayers were washed twice with sterile PBS and then incubated for 60 min in medium containing 30 μg of gentamicin/ml. Bacteria that adhered to the Caco-2/TC-7 brush border were rapidly killed, whereas those located within Caco-2/TC-7 cells survived. The monolayer was washed with PBS and lysed with sterilized H2O2. To determine the number of viable intracellular bacteria, appropriate
dilutions were plated on tryptic soy agar and bacterial colony counts were performed.

For determination of penetration by *S. enterica* serovar Typhimurium into Caco-2/TC-7 cells, the latter were grown on 1-cm² filters mounted in a culture chamber (Costar culture plate inserts; 3-μm pore size) (10⁵ cells per chamber), which delineates an apical (luminal) and a basolateral (serosal) reservoir (18). Bacteria (5 × 10⁴ CFU/ml) were inoculated onto the apical surface. After incubation, monolayers were washed twice with sterile PBS and then incubated for 60 min in medium containing 50 μg of gentamicin/ml, which kills only the extracellular bacteria. The numbers of bacteria in the basolateral medium were monitored over time.

Each assay was conducted in triplicate with three successive passages of Caco-2/TC-7 cells.

Antagonistic activity against serovar Typhimurium infection in Caco-2/TC-7 cells. The activity of LB-SCS against *S. enterica* serovar Typhimurium SL1344-induced cell alterations in vitro was determined under two sets of experimental conditions. In one experiment, pretreatment of SL1344 with LB-SCS was carried out for 1 h at 37°C before cell infection was conducted. After centrifugation (5,500 × g, 10 min, 4°C), the bacteria were washed with PBS and resuspended in the Caco-2/TC-7 cell culture medium for the cell infection process (5 × 10⁶ CFU/ml).

In the other experiment, Caco-2/TC-7 cells, grown on filters mounted in a culture chamber, were infected with *S. enterica* serovar Typhimurium SL1344 (5 × 10⁷ CFU/ml, 1 h, 37°C) to determine the activity of LB-SCS against this intracellular pathogen. After infection, monolayers were washed twice with sterile PBS and then extracellular salmonellae were killed by treatment with gentamicin (50 μg/ml, 1 h, 37°C). Monolayers were washed twice with sterile PBS and subjected to LB-SCS (twofold concentrated) treatment for 1 h at 37°C. In all experiments, determinations of the viable cell-associated and intracellular bacteria and of penetration (sorting in basolateral medium) of *serovar Typhimurium* were conducted as described above.

Each assay was conducted in triplicate with three successive passages of Caco-2/TC-7 cells.

**Immunofluorescence microscopy.** Monolayers of Caco-2/TC-7 cells were prepared on glass coverslips which were placed in 24-well tissue culture plates. After incubation, cell preparations were fixed for 10 min at room temperature in PBS-3.5% paraformaldehyde. Determination of F-actin cytoskeletal cell rearrangements was conducted by direct immunofluorescence microscopy, using fluorescein-phalloidin (Molecular Probes, Junction City, Oreg.). The coverslips were incubated with PBS-0.2% Triton X-100 for 4 min before incubation with fluorescein-phalloidin for 45 min at 22°C, after which the coverslips were washed three times with PBS.

For examination of intracellular *S. enterica* serovar Typhimurium after Caco-2/TC-7 cell infection (5 × 10⁷ CFU/ml), indirect immunofluorescence microscopy was performed with a polyclonal antibody directed against the *Salmonella* O antigen (diluted 1:100 in PBS) (Institut Pasteur, Paris, France). Coverslips were incubated with PBS-0.2% Triton X-100 for 4 min before application of the primary antibody, and after a 45-min incubation with Fluorescein-phalloidin for 45 min at 22°C, the coverslips were washed three times with PBS. Then a fluorescein isothiocyanate-conjugated secondary antibody was added, and after another 45-min incubation at 22°C the coverslips were then incubated with PBS.

**IL-8 assay.** For determination of interleukin-8 (IL-8) levels, monolayers of Caco-2/TC-7 cells were prepared in 24-well tissue culture plates. For some experiments, *serovar Typhimurium* bacteria were treated with LB-SCS for 1 h at 37°C prior to monolayer infection (5 × 10⁷ CFU/well). Under the other set of conditions, Caco-2/TC-7 cells were apically infected with *S. enterica* serovar Typhimurium (5 × 10⁷ CFU/ml) for 1 h and then treated for 1 h with LB-SCS. For this set of experimental conditions, after removal of the culture medium the cells were further incubated for 4 h in DMEM containing 50 μg of gentamicin/ml. Under all conditions, the culture medium in which cytokine levels were determined was first centrifuged for 20 min at 12,000 × g to pellet residual bacteria and cells. The IL-8 concentration was determined with a human IL-8...
immunoassay kit (Diaclone Research Biotest, Buc, France). In a preliminary experiment, we determined that LB-SCS does not interfere with the IL-8 immunoassays.

Data analysis. Results are expressed as means ± standard errors of the means (SEM). For statistical comparisons, Student’s t test was performed.

RESULTS

LB-SCS inhibits the intracellular lifestyle of S. enterica serovar Typhimurium SL1344 in Caco-2/TC-7 cells. When S. enterica serovar Typhimurium SL1344 (5 × 10⁷ CFU/ml) apically infected Caco-2/TC-7 cells, it efficiently entered the cells by 1 h postinfection (5 × 10⁶ CFU/ml; intracellular). Transcellular passage of serovar Typhimurium in Caco-2/TC-7 cells has been recently documented, and there is evidence of a basolateral sorting of S. enterica serovar Typhimurium SL1344 after apical infection (18). We observed here that in Caco-2/TC-7 cells infected with SL1344 for 1 h, bacteria, penetrating the cell monolayer through the apical domain, appeared in the basolateral medium by 8 h postinfection (Fig. 1). The activity of LB-SCS against the transcellular passage of serovar Typhimurium was examined. A highly significant decrease in basolateral sorting of viable serovar Typhimurium organisms was observed after the cell monolayers that had been infected with SL1344 for 1 h were treated with LB-SCS for 1 h. Two MRS controls were used. The first one was MRS adjusted to pH 4.5 with HCl (MRS-HCl) as previously described (2, 4–6). Since lactic acid was present in LB-SCS (5), the second control was MRS adjusted to pH 4.5 with DL-lactic acid (MRS-LA) (final concentration, 100 mM). As disclosed in Fig. 1, both the MRS-HCl and MRS-LA controls were inactive.

We conducted additional experiments to examine the development of LB-SCS activity. Considering the result above, we determined the level of viable intracellular serovar Typhimurium, as a function of time of LB-SCS treatment, in Caco-2/TC-7 cells that had been infected with SL1344 for 2 h (Fig. 2A). As shown in Fig. 2, the level of viable intracellular bacteria decreased regularly during the 2-h period of LB-SCS treatment. For example, when measured at 2 h, a 3-log decrease in viable intracellular serovar Typhimurium was observed, whereas a 1-log decrease was observed after treatment with MRS-HCl or MRS-LA under the same conditions.

We examined how intracellular S. enterica serovar Typhimurium evolved after LB-SCS treatment over a long period of time postinfection (Fig. 2B). For this purpose, a Caco-2/TC-7 cell monolayer that had been infected with SL1344 for 2 h was treated for 1 h with LB-SCS. In agreement with a recent study showing that serovar Typhimurium did not proliferate in nonphagocytic cells (21), we found that S. enterica serovar Typhimurium SL1344 did not proliferate in the nonphagocytic Caco-2/TC-7 cells. While examining how the level of intracellular bacteria evolves, we observed that a 4-log decrease in the level of viable intracellular serovar Typhimurium occurred during the first 3 h post-LB-SCS treatment; afterward, the level of intracellular bacteria remained stable through 20 h posttreatment. We observed that after a 1-h treatment with MRS-HCl or MRS-LA under the same conditions, only a 1.5-log decrease in the level of viable intracellular serovar Typhimurium occurred, and the level remained stable through 20 h posttreatment.

The behavior of intracellular S. enterica serovar Typhimurium SL1344 in the Caco-2/TC-7 cells was examined by a detailed microscopic examination of infected cells, in which intracellular bacteria were stained with rabbit anti-serovar Typhimurium O antigen polyclonal antibody (Fig. 3). In control infected cells, two bacterial morphologies were observed in randomly distributed cells. The bacteria were organized into long filaments, with division septa initiated but not completed, and in a large proportion of bacterial progeny a normal rod-shaped morphology, indicating proliferation, was evident. In
infected cells exposed to LBS-SCS (1 h of treatment), no bacteria were found to have organized into long filaments or to have significant progeny with a normal rod-shaped morphology. In contrast, intracellular bacteria displayed a small, rounded morphology resembling that of resting bacteria. In infected cells exposed to MRS-HCl or MRS-LA (1 h of treatment), most progeny of intracellular bacteria had a normal rod-shaped morphology, but bacteria were not organized into long filaments. This resembles one of the serovar Typhimurium morphologies observed in nontreated infected cells. 

Activity of LB-SCS against *S. enterica* serovar Typhimurium SL1344-induced apical F-actin rearrangements in Caco-2/TC-7 cells. It is well known that in epithelial cells, invading serovar Typhimurium SL1344 is surrounded by a large extension of the host cell membrane, correlating with the size and extent of an F-actin-dense region (11, 12, 15). We examined F-actin distribution at the apical domain in SL1344-infected Caco-2/TC-7 cells by fluorescein-phalloidin labeling and epifluorescence microscopy (Fig. 4). In the uninfected control cells, the fine, flocculated actin located centrally in the cells represents microvillus-associated F-actin (Fig. 4A). We found dramatic changes in the apical F-actin distribution in serovar Typhimurium SL1344-infected Caco-2/TC-7 cells, characterized by the disappearance of the fine, flocculated actin located centrally in the cells and the appearance of intense localized accumulations of F-actin (Fig. 4B and C).

Evolution of *S. enterica* serovar Typhimurium SL1344-induced F-actin accumulation upon MRS or LB-SCS treatment was examined (Fig. 4 and Table 1). For this purpose, cells that had undergone bacterial infection for 2 h were treated with LB-SCS for 1 h and F-actin accumulation was examined at 1 and 2 h posttreatment (4 and 5 h postinfection, respectively) (Fig. 4H and I). At 1 h post-LB-SCS treatment, F-actin accumulation remained evident but appeared more diffuse than in control infected cells (Fig. 4H). At 2 h post-LB-SCS treatment, no F-actin accumulation was found and the cells showed a normal F-actin distribution.

![Image of Fig. 4](http://aem.asm.org/...)

**FIG. 4.** Evolution of the serovar Typhimurium SL1344-induced apical F-actin alteration in Caco-2/TC-7 cells upon LB-SCS treatment. High-magnification micrographs showing localization of F-actin labeled by fluorescein-phalloidin. Magnifications, ×100. (A) Control uninfected cells. The fine flocculated actin centrally located in the cells represents microvillus-associated F-actin. (B and C) Cells infected for 2 h with *S. enterica* serovar Typhimurium SL1344, incubated in DMEM for 1 h, and observed at 1 h (B) or 2 h (C) posttreatment. The localized dense spots of fluorescence represent F-actin accumulation resulting from a *Salmonella*-induced lesion. (D) Uninfected cells treated for 1 h with MRS-LA, showing no change in apical F-actin distribution. (E and F) SL1344-induced localized dense F-actin accumulation in cells 1 h (E) or 2 h (F) post-MRS-LA treatment. The randomly dispersed serovar Typhimurium-induced localized F-actin accumulations remain present and are of the same size and intensity as those of infected untreated cells. Identical results were obtained with LB-HCl treatment (data not shown). (G) Uninfected cells treated for 1 h with MRS-HCl, showing no change in apical F-actin distribution. (H and I) SL1344-induced localized dense F-actin accumulation in cells 1 h (H) or 2 h (I) post-LB-SCS treatment. The dispersed localized *Salmonella*-induced F-actin accumulations were reduced in intensity at 1 h post-LB-SCS treatment. At 2 h post-LB-SCS treatment, no F-actin accumulation was found and the cells showed a normal F-actin distribution.
TABLE 1. Evolution of S. enterica serovar Typhimurium SL1344-induced localized apical F-actin accumulations in control and treated Caco-2 cells*  

<table>
<thead>
<tr>
<th>Caco-2/TC-7 cell treatment group</th>
<th>Mean no. of accumulations (± SEM) observed at postinfection h:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control infected cells</td>
<td>2 4 5</td>
</tr>
<tr>
<td>Infected cells treated with MRS-HCl</td>
<td>20 ± 4* 12 ± 2*</td>
</tr>
<tr>
<td>Infected cells treated with MRS-LA</td>
<td>19 ± 5* 14 ± 2*</td>
</tr>
<tr>
<td>Infected cells treated with LB-SCS</td>
<td>12 ± 1.5** 4 ± 0.5**</td>
</tr>
</tbody>
</table>

* Caco-2/TC-7 cells were infected with 10^6 CFU of serovar Typhimurium/ml for 2 h. Infected cells were treated for 1 h with DMEM (control), LB-SCS, or MRS-LA. Localized F-actin rearrangements, revealed by direct immunofluorescence labeling with fluorescein-phalloidin, were counted at 2, 4, and 5 h postinfection. For treated cells, the observations at 4 and 5 h postinfection correspond to those at 1 and 2 h posttreatment, respectively. Results presented are the mean ± SEM of the localized apical F-actin accumulations per microscopic area (20 random microscopic areas were examined per monolayer) for nine monolayers resulting from three separate experiments (five repetitive cell passages). **, values for control and treated cells were not significantly different (Student's t test); ***, values for control and treated cells were highly significantly different (P < 0.01; Student's t test).

Effect of LB-SCS on S. enterica serovar Typhimurium SL1344-induced cytokine secretion in Caco-2/TC-7 cells. It is known that the association of serovar Typhimurium with epithelial cells in vitro is followed by the induction of chemotactic cytokine secretion (8, 19, 22). We examined whether the LB-SCS was able to modify Salmonella-induced IL-8 secretion (Fig. 5).

We exposed serovar Typhimurium (5 × 10^7 CFU/ml) to LB-SCS, MRS-HCl, or MRS-LA (1 h of treatment) prior to the cell infection. As shown in Fig. 5A, a marked decrease in SL1344-induced IL-8 secretion was observed when the Caco-2/TC-7 cells were infected with the LB-SCS-treated S. enterica serovar Typhimurium. Indeed, we found a highly significant (95%) decrease in IL-8 secretion compared with the control cell monolayer infected with untreated salmonellae. It was noticed that MRS-LA and MRS-HCl had intrinsic significant activity but that it was lower than that of LB-SCS.

We observed that when the Caco-2/TC-7 cells were preinfected with SL1344 (5 × 10^7 CFU/well) and then treated with LB-SCS for 2 h, no change in the Salmonella-induced IL-8 secretion was observed compared with the control cell infected with the untreated pathogen (Fig. 5B).

**DISCUSSION**

As recently discussed (25), a major problem in antibiotic therapy is the ineffectiveness of these drugs against pathogens that have already entered a host cell. For example, several antibiotics are not able to penetrate host cells and are only effective against extracellular pathogens (26), whereas other molecules are effective against intracellular bacteria (25). For antibiotics capable of crossing the epithelial membrane, the problem resides in the capacity of the compound to reach the particular intracellular location in which the pathogen develops its intracellular lifestyle, which includes surviving, proliferating, intracellular movement, alteration of cell functions, and/or induction of cell apoptosis.

We have previously reported that the human L. acidophilus strain LB develops antimicrobial activity against a wide range of gram-negative and gram-positive pathogens in vitro and in vivo (2, 4–6). To gain further insight into the mechanism by which L. acidophilus LB inhibits Salmonella infection in vitro and in vivo (5), we have used polarized epithelial cell monolayers creating impermeable epithelial barriers, i.e., the cultured human adenocarcinoma cell line Caco-2/TC-7 (1), which is a model of the mature enterocyte of the small intestine (23). Attachment to the intestinal brush border (9, 16) prior to cell entry is a prerequisite for S. enterica serovar Typhimurium pathogenesis. Contact between the pathogen and the host cell is followed by synthesis of bacterial proteins, eliciting host cell signaling followed by profound cytoskeletal rearrangements, bacterium internalization, and intracellular bacterial proliferation (for a review, see reference 13). Observations in the present study complete our previous reports (4, 5) and explain...
how the LB-SCS antagonizes serovar Typhimurium infection in vitro and in vivo. Indeed, we demonstrated that LB-SCS treatment kills the intracellular salmonellae. Moreover, our results demonstrate that by killing the intracellular pathogen, the secreted antimicrobial compound(s) present in the LB-SCS promotes the decrease in serovar Typhimurium-induced cell lesions.

Many studies have demonstrated that the characteristic response of epithelial cells of the intestinal mucosa to bacterial adhesion is the release of a range of cytokines, such as IL-6, -7, -8, and -10 and tumor necrosis factor alpha (for a review, see reference 27). For example, infection of the human embryonic intestinal cell line INT407 by S. enterica serovar Typhimurium SL1344 induces host cell signal transduction involving a cascade of the three mitogen-activated protein kinases ERK, JNK, and p38 (19). Induction of these signaling pathways leads to the activation of the transcription factors NF-κB and AP-1, resulting in the production of proinflammatory cytokines such as IL-8. IL-8, a member of the C-X-C family of chemotactic cytokines, is a potent chemoattractant for polymorphonuclear leukocytes developing microbicidal activity involving both oxidative and nonoxidative pathways in host defense systems. We found here that infection of polarized Caco-2/TC-7 cells by serovar Typhimurium SL1344 is followed by the release of IL-8. We observed that LB-SCS treatment exerts the opposite effect on Salmonella-induced IL-8 secretion as a function of the experimental conditions. Inhibition of IL-8 secretion was found when SL1344 was treated with LB-SCS prior to cell infection. We have previously reported that under these conditions of infection the LB-SCS treatment inhibits the association of serovar Typhimurium with Caco-2 cells (5). Our present results demonstrate that inhibition of bacterial adhesion could promote the blockage of the adhesion-dependent, S. enterica serovar Typhimurium-induced IL-8 release (8, 19, 27). An opposite effect was observed when LB-SCS treatment was applied to SL1344-preinfected Caco-2/TC-7 cells, since no inhibition of serovar Typhimurium-induced IL-8 release was found. Under these conditions, S. typhimurium preliminarily interacted with and then penetrated the cell, inducing IL-8 production prior to LB-SCS treatment. Altogether, our results indicate that LB-SCS treatment did not interfere directly with IL-8 synthesis but could block adhesion-dependent cytokine production by acting directly against the pathogen.

In conclusion, we have obtained consistent data to explain how LB-SCS, containing a secreted antimicrobial compound(s), is able to inhibit the intracellular lifestyle of S. enterica serovar Typhimurium infecting human polarized intestinal cells.

REFERENCES